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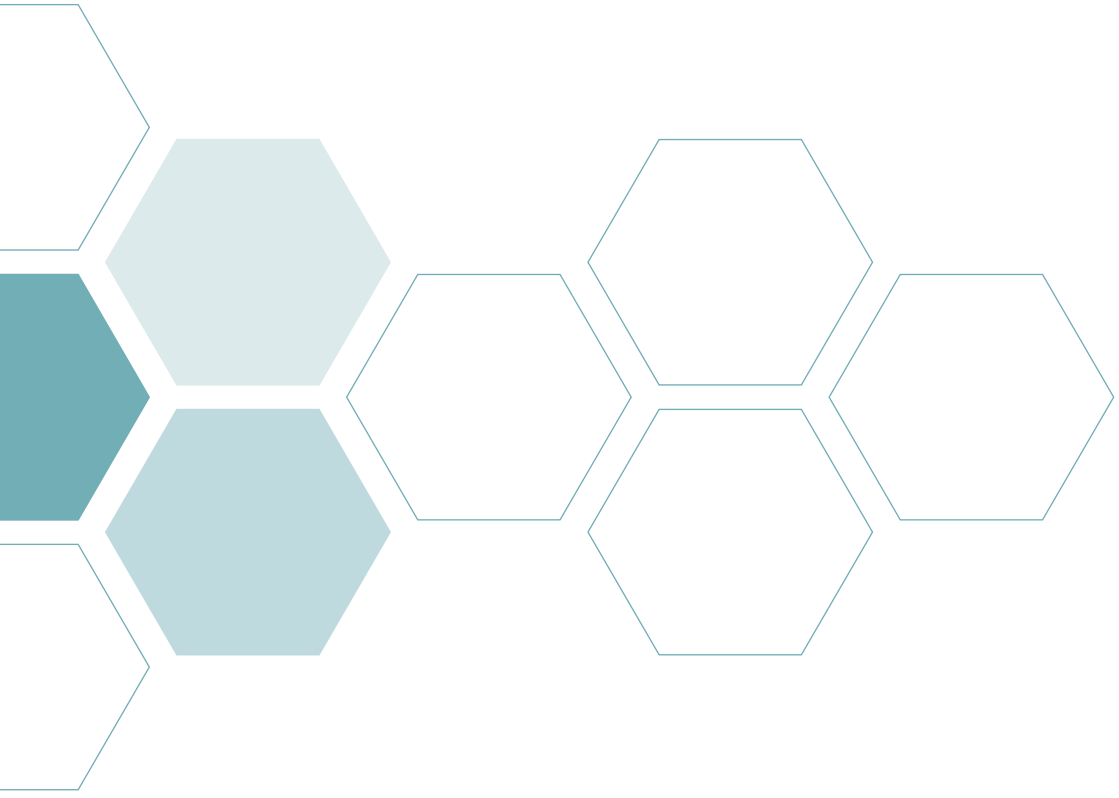

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Editorial Review Board

Advances in Management of Acute Coronary Syndrome (ACS): Guideline Recommendations for Novel Treatments in Dual Antiplatelet Therapy

Michael Miller, MD, FACC, FAHA

For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

Patients who have had an episode of acute coronary syndrome (ACS) are at risk for future events. Numerous interventions, including dual antiplatelet therapy, can reduce this risk significantly. The challenge for health care providers is engaging patients to embrace these interventions for the long term.

Key Points

- People who have had a myocardial infarction are at high risk for another event.
- Lifestyle, dietary, and various medications are important for reducing risk.
- The more interventions a patient can adhere to, the lower their risk of events.
- Dual antiplatelet therapy for at least 12 months after an event is important, and therapy should be continued out to 30 months in certain patients.

CARDIOVASCULAR DISEASE (CVD) IS THE leading cause of death from non-communicable disease and the leading cause of death in people less than 70 years old.[1] The obesity and diabetes epidemics are propelling this forward.

Atherosclerosis is the predominant cause of CVD. In the early stages, there is remodeling with vessel expansion to accommodate the soft plaque that develops. It is in the middle to late stages of plaque development that vessel expansion cannot be accommodated and leads to decreased blood flow and tissue oxygenation. Stable atherosclerosis with an approximate obstruction of 70 percent can result in exertional angina. As the atherosclerotic plaque continues to grow, it can become unstable or "vulnerable" and then rupture. Plaque rupture releases pro-coagulant chemicals – tissue factor, von Willebrand factor, and thrombin – which stimulate thrombosis, leading to complete vessel occlusion. Acute coronary syndrome (ACS), as the result of vessel obstruction, includes non-ST segment elevation myocardial infarction (NSTEMI), ST segment elevation myocardial infarction (STEMI), or unstable angina.

Patients who have had a myocardial infarction (MI) are at high risk for ischemic events for the long-term and thus should receive secondary prevention of atherothrombotic disease.[2] The highest risk is in the first 90 days after a MI. Risk stays high at about 22 percent out to one year after the event and is 17 percent beyond one year. Secondary prevention includes lifestyle and dietary interventions and medications which may include beta-blockers, lipid-lowering agents, antihypertensives, and antithrombotic therapies.

Exhibit 1 shows the goals of lifestyle and dietary interventions.[3,4] One additional lifestyle intervention that is not listed in Exhibit 1 is stress reduction. This can be accomplished through education, meditation, and yoga. Patients with CVD should have an individualized education plan to optimize secondary prevention.

Beta blockers are most effective in preventing events in those patients with impaired systolic

Exhibit 1: Lifestyle/Risk Factor Goals in Secondary Prevention[3,4]

Risk Factor	Goal
Smoking	Cessation
Total Dietary Fat / Saturated Fat	< 30% calories /< 7% calories
Fish/Omega 3	≥ 3 servings/week/1 g/day
Dietary Cholesterol	< 200 mg/day
Dietary Sodium	< 2,000 mg/day (DASH diet goal)
Physical Activity	> 30 min/day; 5 times/week (daily IIa)
Weight Loss/Maintenance	**Initial BMI** — **Weight Loss Goal** 25 to 27.5 — BMI < 25 (WC < 40in/35) > 27.5 — 10% relative weight loss
Blood Pressure	< 120/80 mmHg
LDL Cholesterol (primary goal)	Greater than 50% reduction from baseline < 70 mg/dL if possible
Triglycerides	< 175 mg/dL
Diabetes	HbA1c < 7.0%
BMI = body mass index; WC = waist circumference	

Exhibit 2: Guideline Recommendations for β-Blockade after MI[5-8]

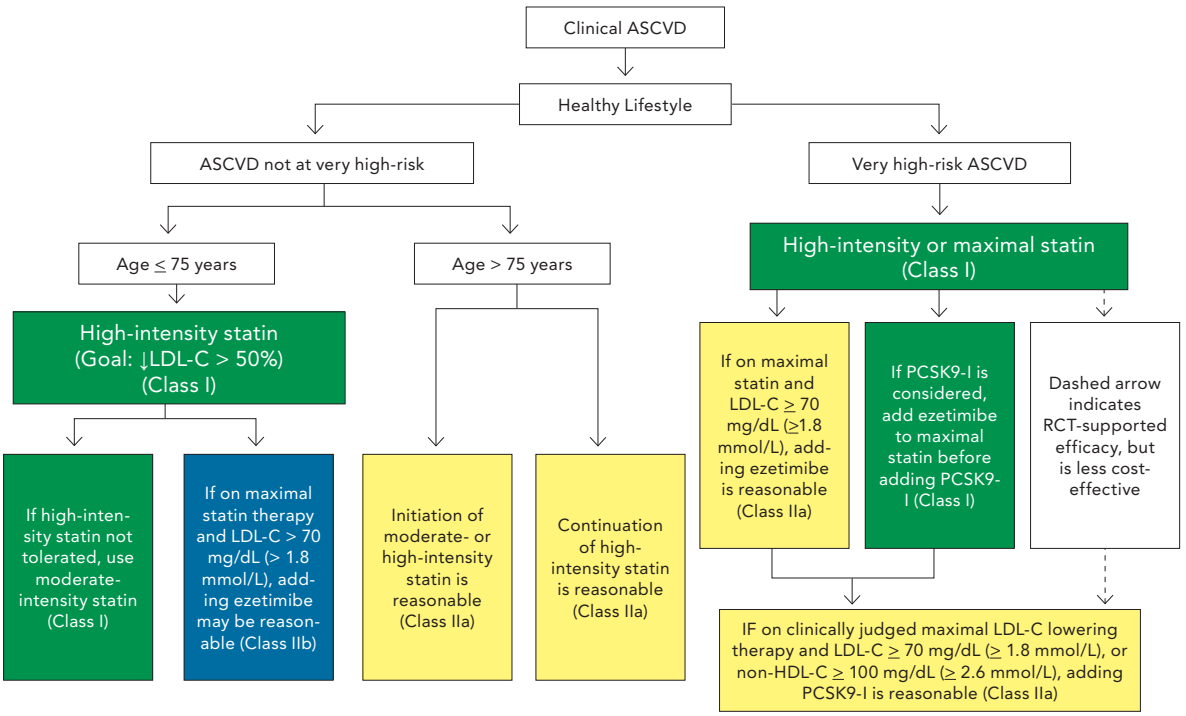
Society	Management	Recommended Duration
ACCF/AHA	NSTEMI/STEMI	Initiate in all patients without contraindications and continue in those with abnormal LV function (Ia) Reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS (Iia
European Society of Cardiology	NSTEMI/STEMI	Long-term in patients with LVEF ≤40% (heart failure or LV dysfunction) (Ia) Consider during hospital stay and thereafter in patients without contraindications (IIa)

ACCF/AHA = American College of Cardiology Foundation/American Heart Association
NSTEMI = non ST segment elevation myocardial infarction
STEMI = ST segment elevation myocardial infarction
LV = left ventricle
LVEF = left ventricular ejection fraction

function. Exhibit 2 outlines the ACCF/AHA and ESC recommendations for using beta blockers after an MI.[5-8] Beta blockers should be used for at least a year after a MI; the benefit declines after about three years of therapy. If left ventricular function is preserved, the beta blocker could be stopped at one year, but it should be continued in those with heart failure.

Lowering low-density lipoprotein cholesterol (LDL-C) has been shown in numerous studies to reduce CV events in the secondary and primary prevention setting. The lower the LDL-C is driven down, the lower the risk of CVD. If a patient has had a MI, the LDL-C can be lowered as low as the patient can tolerate; there is no longer a minimum LDL-C at which lipid-lowering therapy needs to be reduced. The 2018 guidelines for managing cholesterol relevant to secondary prevention are shown

Exhibit 3: 2018 ACCF/AHA Cholesterol Guidelines for Secondary Prevention[9]



ACCF = American College of Cardiology Foundation
AHA = American Heart Association
ASCVD = atherosclerotic cardiovascular disease
PCSK9-I = Proprotein convertase subtilisin/kexin type 9 inhibitor

in Exhibit 3.[9] Certain patients have very high risk for future events, which includes those with major atherosclerotic CVD (ASCVD) as demonstrated by recent ACS (within past 12 months), history of MI (other than recent ACS event), history of ischemic stroke, or symptomatic peripheral arterial disease. It also includes those with high-risk conditions (age ≥ 65, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes, hypertension, chronic kidney disease, current smoking, and persistently elevated LDL-C (≥ 100 mg/dl), despite maximally tolerated statin therapy and ezetimibe).

Antithrombotic therapy to prevent thrombosis includes antiplatelet agents and anticoagulation. Anticoagulation is primarily used in those patients who have atrial fibrillation. Antiplatelet agents including COX-2 inhibitors (aspirin) and P2Y12 agents (clopidogrel, prasugrel, and ticagrelor) are the agents used after an ACS event. In secondary prevention, aspirin alone leads to a 20 percent reduction in CV risk.[10] The P2Y12 agents are used in combination with aspirin in the post-ACS setting. There are pharmacokinetic and efficacy differences in the P2Y12 receptor antagonists, which can impact their selection (Exhibit 4). The major differences include long time to maximum platelet inhibition with clopidogrel, maximum platelet inhibition, and genetic variations which hinder the effectiveness of clopidogrel (CYP2C19) reduced-function allele. Prasugrel has been shown to be more effective in reducing events but does increase risk of bleeding compared to clopidogrel.[11] There are some exceptions to improved benefit with prasugrel, which includes those who have had a stroke, have low body weight, and are 75 years of age or older. Ticagrelor is more effective in reducing events and results in lower bleeding risk compared to clopidogrel.[12] Dual antiplatelet therapy (DAPT), comprising a P2Y12 inhibitor and aspirin, is better at reducing risk compared to aspirin alone for reducing CV risk in those with prior MI.[13,14] Typically, DAPT will be continued for 12 months after an ACS episode (Exhibit 5), and then therapy will be reduced to one antiplatelet agent, which is typically aspirin.[5-8,15,16] Patients who are at high risk for future events may benefit from prolonged DAPT out to 30 months, but the risk of bleeding also has to be considered before continuing beyond one year.[14,17] A DAPT score can be used to

Exhibit 4: P2Y Receptor Inhibitor Antithrombotics Used Post-ACS

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Cylcopentyl-triazolopyrimidine
Mechanism of action	Binds to the $P2Y_{12}$ ADP receptor	Binds to the P2Y12 ADP receptor	Selective antagonist of $P2Y_{12}$ receptor
Reversible effect	No	No	Yes
Pro-drug	Yes	Yes	No
Time to max inhibition, post loading dose	*2 to 4 hours	0.5 to 1 hour	1 to 2 hours
Max inhibition of platelet aggregation	40% to 60%	80% to 85%	> 90%
Metabolism	CYP 2C19/2B6/1A2	Primarily 3A4/2B6	CYP 3A4
Active metabolite(s) t1/2	30 minutes	~ 7 hours	9 to 11 hours
P-glycoprotein substrate	No	Unknown	Yes

*Depending on dose administered

Exhibit 5: Guideline Recommendations for Duration of DAPT after ACS[5-8,15,16]

Society	Management	Recommended Duration
AHA, ACCF, SCAI	Medical	Ideally up to 12 months
	PCI (DES)	At least 12 months
ESC	All	12 months Those with sirolimus- or paclitaxel-eluting stents may benefit from prolonged DAPT beyond 1 year. DAPT for 6 months might be sufficient
ACCP	Medical	12 months
	PCI	12 months After 12 months, recommend single antiplatelet therapy over continuation of DAPT

DAPT = dual antiplatelet therapy
AHA = American Heart Associaton
ACCF = American College of Cardiology Foundation
SCAI = Society for Cardiovascular Angiography and Interventions
ESC = European Society of Cardiology
ACCP = American College of Chest Physicians
PC = percutaneous intervention
DES = drug eluting stent

accurately identify patients with the greatest anticipated benefit versus harm from continuing DAPT beyond 12 months. A score of 2 or greater indicates that long-term therapy may be beneficial.[18]

A meta-analysis of nine randomized controlled trials evaluating patient-tailored multifactorial lifestyle interventions aimed at reducing more than one cardiovascular risk factor in patients with established CVD found that fatal CV events were reduced by 18 percent overall.[19] The more preventive therapies that a patient is on, the better the overall CV risk reduction.[20]

Keeping patients on all of these preventive therapies requires patient engagement for optimal adherence. In one trial, only 69 percent of patients were

persistent at six months post-MI and 31 percent discontinued at least one CV medication.[21]

Engaging patients in their care includes goal-directed patient care, personalized risk information, and web or smartphone-based device tools and interactions. A multidisciplinary team of a physician, nurse, clinical pharmacist, a nurse practitioner or physician's assistant, and a medical assistant is another way to increase achievement of secondary prevention goals and improve patient adherence and persistence.[22]

Conclusion

There are a large number of interventions which are effective in reducing the risk of CV events in those who have already had a MI. Each of the interventions needs to be maximized to meet goals, and patient engagement is necessary to ensure adherence. Extended duration of DAPT to decrease atherothrombosis requires individualization.

Michael Miller, MD, FACC, FAHA is a Professor of Cardiovascular Medicine, Epidemiology, and Public Health at the University of Maryland School of Medicine in Baltimore, MD.

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Novel Treatment Advances and Approaches in Acute Myeloid Leukemia (AML): Expert Strategies for Improved Clinical and Economic Outcomes

Amir T. Fathi, MD

For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

There have been significant advances in the treatment of acute myeloid leukemia (AML) in the past decade. Prior to these advances, essentially the only treatment for the disease was to reboot the bone marrow using potent chemotherapy regimens and with some cases hematopoietic stem cell transplant. It was unfortunate that not all patients could undergo these treatments because of underlying poor health or comorbidities. The new targeted therapies are being used in combination with chemotherapy in early disease to treat relapsed/refractory disease, and in combination with older medications to manage older patients.

Key Points

- The emergence of effective, targeted therapies is providing improved survival outcomes for patients with selected genetically mutated disease.
- Novel combinations of older therapies with targeted therapy for older patients allow treatment which is tolerable and enhances outcomes.

ACUTE MYELOID LEUKEMIA (AML), A CANcer of the blood and bone marrow with excess immature white blood cells, was first described in 1845 by John Hughes Bennet and Rudolf Virchow, who independently described cases of spleen enlargement, cytopenias, and suppuration, based on autopsy specimens. Virchow termed it "Weisses Blut," white blood, or leukemia. In 1868, Ernst Neumann first suggested the bone marrow as the origin of blood cells. The 1960s and 1970s brought the classification of leukemia by cell surface immunohistochemistry and chromosomal analysis. The 2000s have brought the identification of genetic mutations which drive the disease. Leukemia develops when there are genetic mutations in the myeloid cells, precursor cells of platelets, red blood cells and white blood cells derived from the hematopoietic stem cells. The genetic mutations prevent the myeloid cells from maturing normally and allow uncontrolled proliferation (Exhibit 1).

AML is the most common leukemia affecting adults. There are approximately 21,000 new cases each year in the United States (U.S.) and 10,500 deaths. The median age at diagnosis is 67. The traditional prognosis model of AML is based on patient age and medical comorbidities, whether the AML evolved from preceding marrow disease (e.g., myelodysplastic syndromes [MDS]), and the presence of certain molecular characteristics based on cytogenetic and mutational analysis. Exhibit 2 shows examples of some cytogenetic and mutational characteristics which predict prognosis.[1] Based on all of these factors, patients could have favorable, intermediate-1, intermediate-2, or adverse risk disease. Favorable disease has the longest disease-free survival after treatment and best overall survival (OS) and adverse risk disease has the shortest of these.[1] As more and more mutations have been identified in AML, prognostication has become much more complicated. Depending on the underlying mutations, each case of AML has a different course, prognosis, and optimum treatment.

There have been significant advances in the treat-

Exhibit 1: Bone Marrow Examples

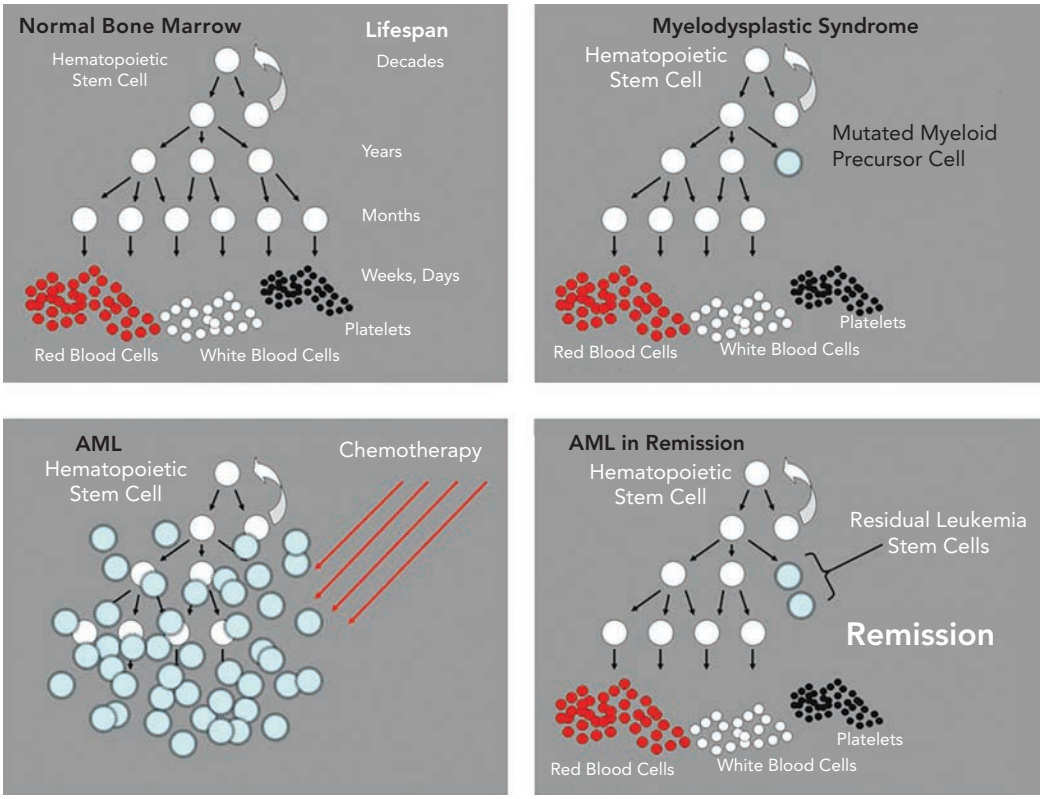


Exhibit 2: AML Molecular and Cytogenetic Risk Groups[1]

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3-ITD* (normal karyotype) Mutated *CEBPA* (normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3-ITD* (normal karyotype) Wild-type *NPM1* and *FLT3-ITD* (normal karyotype) Wild-type *NPM1* without *FLT3-ITD* (normal karyotype)
Intermediate-II	t(9;11)(q22;q23); *RPN1-EVI1* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21;q26.2) or t(3;3)(q21;q26.2); *RPN1-EVi1* t(6;9)(p23;q34); *DEK-NUP2314* t(v;q23); *MLL* rearranged -5 or del(5q) -7 abnl(17p) Complex karyotype*

AML = acute myeloid leukemia; ITD = internaltandem duplication
*Complex karyotype is defined as three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions: t(8;21), inv(16) or t(16;16), t(15:17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3)

Exhibit 3: Response to Enasidenib[8]

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (n = 209)
Overall Response (CR, CRp, CRi, mCR, PR)	59 (37%) [95%CI: 30%, 45%]	10 (42%) [22%, 63%]	7 (50%) [23%, 77%]	79 (38%) [31%, 45%]
CR	29 (18%) [95%CI: 13%, 25%]	4 (17%) [5%, 37%]	3 (21%) [5%, 51%]	37 (18%) [13%, 24%]
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	3 (1%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

CR = complete response; CRp = CR with incomplete platelet recovery; Cri = CR with incomplete hematologic recovery; mCR = marrow CR; PR = partial response; SD = stable disease; PD = progressive disease

ment of AML in the past decade. Treatment had essentially been the same since the 1960s using various chemotherapy regimens to treat every case the same by rebooting the bone marrow by destroying all the current cells and hoping that normal stem cells would begin replicating. Induction chemotherapy regimens (to induce remission) include cytarabine and daunorubicin or idarubicin with complete response (CR) rates of 75 percent (includes those needing two courses). Accordingly, about 25 percent of patients do not respond and have refractory leukemia. After induction that induces remission, consolidation therapy to attempt a cure is undertaken with either high-dose cytarabine or allogeneic hematopoietic stem cell transplant. Patients with a more favorable disease typically receive chemotherapy for consolidation because their leukemic cells are more sensitive to chemotherapy. Those with intermediate or adverse risk who can tolerate a transplant have one for consolidation. The five-year survival rate for AML is 27.4 percent. When relapse occurs, various chemotherapy regimens have been tried with varying success. The five-year survival rate with relapsed AML for those less than 55 years of age is 11 percent and 6 percent for those over 55.[2]

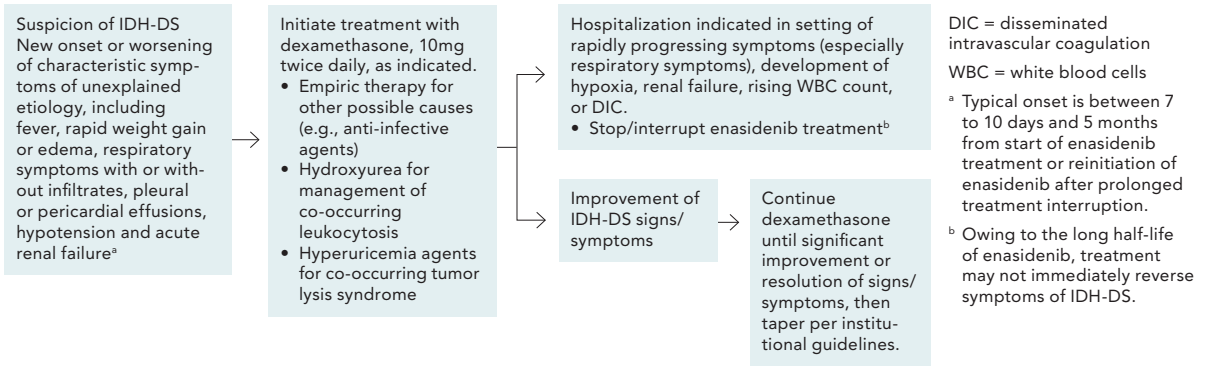
Several emerging therapies are changing the treatment landscape for AML. These therapies are targeting the underlying mutations which lead to the disease. Five new targeted therapies have been approved by the FDA since 2017.

Isocitrate dehydrogenase (IDH) is the first target of new therapies to discuss. IDH proteins, essential to the Krebs cycle, catalyze decarboxylation of isocitrate to α-ketoglutarate (α-KG) in the cytoplasm (IDH1) and mitochondria (IDH2). Mutant IDH enzymes catalyze α-KG to 2-hydroxyglutarate (2-HG), which is an onco-metabolite and which accumulates in IDH-mutant tumors. 2-HG suppresses key enzymes for bone marrow cell differentiation. Approximately 8 percent of patients with AML have IDH1 mutation.[3] A larger subset, approximately 15 percent, have IDH2 gene mutations.[4] Serum or urine 2-HG can be used as a noninvasive biomarker of disease activity for IDH-mutated AML.[5]

IDH inhibitors which target IDH mutations are now FDA approved for treating IDH-mutated AML. These agents allow differentiation of the bone marrow cells that were previously stuck being immature. Enasidenib (Idhifa®) is an oral, selective inhibitor of mutant-IDH2 enzymes. Treatment of IDH2-mutated AML produced impressive results in relapsed/refractory AML (R/R AML), untreated AML not eligible for chemotherapy, and MDS (Exhibit 3).[6] The overall response by IDH mutation type was 36 percent for R140Q and 42 percent for R172K. Median OS among relapsed/refractory patients was 9.3 months, and for the 34 patients (19.3%) who attained complete remission, overall survival was 19.7 months. There is minimal toxicity with this daily oral, non-chemotherapy agent. Enasidenib is currently FDA approved for treating R/R AML with an IDH2 mutation.

Ivosidenib (Tibsovo®) targets IDH-1 and produces results similar to enasidenib in those with

Exhibit 4: Diagnosis and Management of Isocitrate Dehydrogenase Differentiation Syndrome (IDH-DS)[8]



IDH-1 mutated AML. In patients with advanced IDH1-mutated R/R AML, ivosidenib at a dose of 500 mg daily was associated with a low frequency of grade 3 or higher treatment-related adverse events and with transfusion independence, durable remissions, and molecular remissions in some patients with CR.[7] Ivosidenib is FDA approved for treating adult patients with newly-diagnosed AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy and adult patients with R/R AML. Overall, even patients who do not achieve CR with the IDH inhibitors have some benefits, including reduced need for red blood cell transfusions, fewer clinic visits, fewer infections, and lower patient and caregiver treatment burden.

Differentiation syndrome can occur with IDH inhibitor treatment. This is too robust differentiation of cells, which leads to cytokine-mediated weight gain, plural effusions, pulmonary infiltrates, hypoxia, and fever. This is a potentially lethal clinical entity and occurs in 12 to 18 percent of enasidenib-treated patients with mutant-IDH2 R/R AML.[8] It can also occur with ivosidenib. Differentiation syndrome is treated with corticosteroids (Exhibit 4).[8]

FMS-like tyrosine kinase 3 (FLT3) inhibitors are another class of targeted agents. FLT3 is a tyrosine kinase enzyme that resides on the surface of cells and acts as a receptor. Ligand (FL) in the blood binds to the FLT3 receptor to turn it off. Normal precursor hematopoietic cells have FLT3 on the surface. When a FLT3 mutation is present, the FLT3 receptor is less sensitive to the ligand and thus the receptor is turned on all the time, allowing cells to constantly multiply. FLT3 mutations include internal tandem duplication (ITD) and tyrosine kinase domain (TKD). Approximately one-third of AML patients have a FLT3 mutation and have a highly proliferative disease (e.g., 200,000 white blood cells, leukemic deposits on the skin). This phenotype of the disease is prone to relapse if any leukemic cells remain after therapy.

The first agents developed to target FLT3 were aimed at numerous tyrosine kinases, including sorafenib (Nexavar®) and midostaurin (Rydapt®), and they have significant toxicity because of their nonspecific effects. The addition of midostaurin to standard chemotherapy significantly prolonged OS and event-free survival among patients with AML and a FLT3 mutation. Median OS was 74.7 months for the combination therapy group and 25.6 months for the group that received only chemotherapy.[9] Midostaurin is FDA approved for treating adults with newly diagnosed FLT3 mutation-positive AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

Gilteritinib (Xospata®) and quizartinib are the next generation, more specific FLT-3 inhibitor. In the FLT3-mutated R/R AML setting, the median OS in the gilteritinib group was significantly longer than the salvage chemotherapy group (9.3 months versus 5.6 months).[10] It is FDA approved for adult patients with FLT3 mutated-R/R AML. Quizartinib is still investigational but has also improved OS in patients with FLT3-ITD–mutated R/R AML compared with salvage chemotherapy.[11]

There are numerous ways to incorporate the targeted agents into traditional therapy. They can be given with chemotherapy for newly diagnosed disease (midostaurin), as monotherapy for relapse (enasidenib, ivosidenib), or for those newly diagnosed but unable to take chemotherapy (ivosidenib). A newer use of targeted therapy, which is not yet FDA

Exhibit 5: 2017 - 2018 FDA Approvals for AML

- 4/28/17: Midostaurin (Rydapt®)
  - For adult patients with newly diagnosed AML who have a FLT3 mutation
  - Companion diagnostic: LeukoStrat CDx FLT3 mutation assay.
- 8/1/17: Enasidenib (Idhifa®)
  - For adult patients with relapsed/refractory AML who have an IDH2 mutation
  - Companion diagnostic: RealTime IDH mutation assay.
- 8/3/17: CPX351/fixed ratio daunorubicin-cytarabine (Vyxeos®)
  - for the treatment of adults with two types of acute myeloid leukemia (AML): newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
- 9/1/17: Gemtuzumab ozogamicin (Mylotarg®)
  - For adults with newly diagnosed AML whose tumors express the CD33 antigen, and for treatment of patients two years or older with relapsed/refractory CD33+ AML.
- 7/20/18: Ivosidenib (Tibsovo®)
  - For adult patients with relapsed/refractory AML who have an IDH1 mutation.
- 11/21/18: Glasdegib (Daurismo®) and low dose cytarabine
  - For adult patients with newly diagnosed AML who are ≥ age 75 or are ineligible for induction due to comorbidity.
- 11/21/18: Venetoclax (Venclexta®) and hypomethylating therapy (or low dose cytarabine)
  - For adult patients with newly diagnosed AML who are ≥ age 75 or are ineligible for induction due to comorbidity.
- 11/28/18: Gilteritinib (Xospata®)
  - For adult patients with relapsed/refractory AML who have a FLT3 mutation.

approved, is as maintenance therapy at remission to prevent relapse, especially post-bone marrow transplant, and in those with FLT3 mutation. In an open label trial, sorafenib, initiated between days 45 and 120 after transplant and continued for twelve 28-day cycles in those with a first or second complete remission, improved OS compared to historical controls.[12] A randomized trial is ongoing examining this approach. The same approach is also being studied with IDH1 and IDH2 inhibitors.

Most patients with AML are older (>75 years of age), and the older the patient, the poorer their prognosis. There are many reasons for this, including poor performance status, heart and kidney disease, higher incidence of preceding bone marrow disease, higher rate of poor prognosis mutations, and higher rates of therapy-related morbidity and mortality. Older patients have a higher incidence of treatment-resistant disease, lower rates and duration of complete remission, and shorter median OS. They are also less likely to be eligible for allogeneic hematopoietic cell transplantation. The traditional induction/consolidation treatment paradigm is not possible for many older patients. Hypomethylating agents are a less intensive treatment which is increasingly used for less robust or older patients, in whom it is better-tolerated with a lower rate of toxicity than traditional aggressive chemotherapy regimens. This therapy is typically administered in the clinic and can lead to therapeutic responses, including transfusion independence, decrease in leukemic burden, and less commonly, remissions (~20%). However, responses are often transient, with leukemic progression and brief post-therapy survival.

Methyl groups which bind to DNA turn genes off and acetyl groups turn them on. In many patients with AML and MDS, genes are inappropriately turned off by methyl groups. The hypomethylating agents remove methyl groups and turn the genes important for blood cell maturation back on. Decitabine (Dacogen®) and azacitidine (Vidaza®), the two agents currently used, are very well tolerated; however, these agents can take several months to work.

The next evolution of therapy was to try to identify other things that could be given with

hypomethylating agents to improve remission rates. Vadastuximab talirine, an antibody toxin conjugate, was being studied in combination with these agents. Although early results looked promising, investigation of the agent was discontinued because of higher rate of death compared with placebo.

Venetoclax (Venclexta®) is an oral B-cell lymphoma two (BCL2) inhibitor which selectively binds and inhibits BCL2, a pro-apoptotic protein, leading to the initiation of apoptosis. Although potent as a single agent for chronic lymphocytic leukemia, as monotherapy it is not as impressive against AML. In the pivotal clinical trials evaluating venetoclax in combination with hypomethylating agents, the rates of complete CR plus CR with incomplete hematological recovery were 54 percent and 67 percent, respectively, and the median OS was 10.4 months and 17.5 months, respectively, comparing favorably with outcomes in clinical trials evaluating hypomethylating agents. The most common adverse events with venetoclax combinations are gastrointestinal symptoms, which are primarily low grade and easily manageable, and myelosuppression, which may require delays between cycles, granulocyte colony-stimulating factor (G-CSF) administration, or decreased duration of venetoclax administration per cycle. Based on the Phase II study results, the FDA approved venetoclax in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy; the Phase III trial results have not yet been published.[13]

Conclusion

Currently, there are several reasons for an optimistic outlook in treating AML. Improved outcomes are due to better prognostication, patient selection, and supportive care. In addition, the emergence of effective, targeted therapies and novel combinations for older patients that can maintain tolerability and enhance outcomes has had much impact. There is hope that the next decade will bring more approved AML therapies than in the last four decades combined.

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Optimizing Switching and Sequencing Strategies for Improved Clinical and Economic Outcomes in the Management of Multiple Sclerosis

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

There are numerous disease-modifying therapies which can alter the natural course of multiple sclerosis. The best choice of therapy for an individual patient requires shared decision-making between the clinician and patient which considers many patient, disease, medication, and access factors. Those patients with risk for progression and disability need more aggressive therapy.

Key Points

- Clinicians need to consider disease, medication, access, and patient factors when selecting therapy.
- They also need to address modifiable risk factors for disease activity and progression.
- Adherence to the therapeutic regimen and follow-up is important to clinical success.
- Patients need to buy into the choice of therapy and understand the risks versus benefits.
- Adherence with the chosen therapy is important.
- Patients should be monitored closely and therapy adjustments should be made based on tolerability and efficacy.

MULTIPLE SCLEROSIS (MS) IS A LIFELONG, complex, heterogenous, neurodegenerative disease that has a major impact on quality of life and productivity. Patients have many neurological symptoms, but worry most about becoming disabled. A major goal in treating MS, once it is diagnosed, is prevention of disability.

The principles for treating the disease are:

1. Treat as soon as possible [ideally at the clinically isolated syndrome (CIS) stage].
2. Consider disease activity and prognostic (demographic, clinical, MRI) profile when choosing therapy.
3. Follow patients closely.
4. Switch therapies for poor response.

Early treatment is important because the patient can never recover any function that is lost if effective treatment is delayed. It is important to personalize therapy for an individual patient given their prognosis.

Comprehensive care for a MS patient involves treating clinical attacks/relapses, chronic disease-modifying therapy (DMT), symptomatic therapy, and addressing wellness, health-maintenance, and vascular risk-factors. Because of the complexity of the therapeutic landscape, a multidisciplinary team is necessary to deliver comprehensive care. Multiple issues are addressed by various team members with empowerment for patients, families, and the care team. Comprehensive care improves patient communication with the care team, adherence to treatment, continuity of care, and quality of life. A comprehensive care team may be able to identify breakthrough disease early.

A wellness/health maintenance program is im-

Exhibit 1: Prognostic Factors in MS

	Good	Poor
Race	Caucasian	Black
Age at Onset	Young (< 35 years)	Older (≥ 35 years)
Gender	Female	Male
Smoker	No	Yes
Subtype	Relapsing	Progressing
First Attack	Optic neuritis, Sensory, Unifocal	Motor, Cerebellar, Sphincter, Multifocal
Recovery from Clinical Attack	Complete	Incomplete
Attack Rate	Low	High (≥2 in one year)
Disability at Five Years	No	Yes
MRI Lesions	Cerebral	Brainstem, cord
Lesion Load	Low	High
Enhancement	Absent	Present

portant because increasing evidence shows health maintenance changes or improves central nervous system (CNS) reserve, function, and repair. A wellness/health maintenance plan can be considered a DMT for MS. Components involve high-normal vitamin D levels, vitamin B12 levels of 400 pg/mL or more, regular aerobic exercise, weight loss if appropriate, no smoking, limited alcohol and salt, healthy diet, regular mental and social stimulation, good sleep hygiene, stress management, normalized vascular risk factors (blood pressure, lipids, and hemoglobin A1C), and monitoring of bone density and other health issues related to the underlying disease or its treatment.

Choosing a DMT involves determining the prognosis (Exhibit 1), which impacts how aggressive therapy needs to be. Disease, access, patient, and medication factors also have to be considered. Disease factors include the frequency and severity of relapses, duration since MS onset, lesion burden on MRI, lesion location, residual deficits, and the expanded disability status scale (EDSS) score. Access factors include formulary restrictions and out-of-pocket costs, which can be significant for the MS DMTs. Most insurers have a required stepped-care approach, which many clinicians do not agree with. Unfortunately, however, it must be considered when choosing therapy. Patient factors include potency/safety preference, risk tolerability, monitoring requirements, route of administration preferences, age, plans for future pregnancy, comorbidities, ability to come to appointments (such as frequently for infusions), employment/insurance coverage, and impairments impacting monitoring or adherence.[1] Medication factors include contraindications, prior treatments, dosing schedule, route of administration, and costs.

Treatments need to be based on shared decisions with the patient. When patients engage in shared decision-making, they learn about their health and understand their health conditions, recognize that a decision needs to be made and are informed about the options, understand the pros and cons of different options, have the information and tools needed to evaluate their options, are better prepared to talk with their health care provider, are able to collaborate with their health care team to make decisions right for them, and are more likely to follow through on their decision (adherence).[2] It is important for clinicians to set realistic expectations (decrease relapses, slow or prevent disability, reduce MRI activity) with the patient; none of the current treatments are a cure for MS, and many of them must be continued long term for benefit.

The treatment landscape for MS is very broad and continues to expand. There are now 20 distinct DMTs, including generics, which cover 10 different mechanisms of action. All are FDA approved for relapsing-remitting forms of MS (RRMS), one is approved for primary-progressive MS (PPMS), and two are approved for secondary-progressive MS (SPMS). All of them have been shown to be effective in reducing the frequency of MS attacks, reducing the number of new brain lesions on MRI scan, and in slowing the rate of disability progression. The chemotherapy agent mitoxantrone is FDA approved

Exhibit 2: Adverse Events with DMT[14,15]

Fingolimod/Siponimod

- New heart block, arrhythmia, or symptomatic bradycardia
- Macular edema
- Hepatotoxicity
- Infections
- PML
- Pulmonary Effects: Reductions FEV_1 and DLCO
- Hypertension
- Reactivation/rebound in MS activity when discontinued

Teriflunomide

- GI: Nausea, diarrhea
- Alopecia
- Hepatotoxicity
- Teratogenic in animal models
- Transient acute renal failure
- Hyperkalemia
- Hypertension

Dimethyl Fumarate

- GI: Abdominal pain, nausea, emesis, and diarrhea (transient)
- Flushing (transient)
- Proteinuria
- Rash/pruritus
- Hepatotoxicity
- Lymphopenia
- PML

Ocrelizumab

- Infusion reactions

Natalizumab

- Hypersensitivity reactions
- Hepatotoxicity
- PML
- CNS herpes virus infections
- Reactivation/rebound in MS activity when discontinued

Alemtuzumab

- Infusion reactions
- Infections
- Secondary autoimmunity
- Immune thrombocytopenia
- Rare cases of antiglomerular basement-membrane disease
- Possible increased risk of malignancies
- Melanoma
- Lymphoproliferative disorders
- Stroke

FEV_1 = forced expiratory volume; DLCO = diffusion lung capacity for carbon monoxide; PML = Progressive Multifocal Leukoencephalopathy; GI = gastrointestinal

for treating RRMS, but it is rarely, if ever, used.

Interferon beta and glatiramer, both injectable, are the first agents that were FDA approved for MS. Both are immune modulators, rather than immune suppressants. The advantages of these agents are long-term experience, minimal safety and modest tolerability concerns, and they are the safest DMTs for use prior to pregnancy. Long-term benefits have been observed on disability progression compared to the natural history of the disease. The disadvantages are the need for injection, which patients do not always like, and they provide modest benefit compared to the newer agents. Head-to-head trials show no differences in clinical efficacy between interferon beta and glatiramer.[3,4] The annualized relapse rates (ARR) with the two classes are about 0.3 in contemporary randomized controlled trials.[5-8] They reduce disability progression and the ARR about 30 percent.

Fingolimod (Gilenya®) is an oral sphingosine-1-phosphate (S1P) receptor modulator that binds subtypes S1P 1, 3, 4, and 5. SIP-1 receptor binding after phosphorylation results in internalization and loss of signaling function necessary for activated lymphocytes to leave lymphoid tissue and enter circulation. Effector memory cells in tissues are not affected, thus preserving immune surveillance. S1P receptors in glial cells allow for potential effects in the CNS. In experimental autoimmune encephalitis in an animal model, fingolimod administered into the brain causes enhanced remyelination and axonal protection; it is unknown whether similar effects occur in MS. Fingolimod is an oral medication that has better efficacy than interferon or glatiramer and is very well tolerated. It produces about a 50 percent reduction in ARR compared to interferon.[9-11] Extension trials have shown sustained low ARR (~0.16), reduction in MRI activity, and reduction in rate of brain volume loss in those on continuous fingolimod.[12,13] There are adverse events and contraindications which have to be considered with fingolimod. Exhibit 2 lists the major adverse events of selected DMTs.[14,15] The fingolimod adverse events and contraindications are primarily related to the effect of the drug on S1P receptors in the heart. There are numerous cardiovascular contraindications to fingo-

limod use: recent (within 6 months) myocardial infarction, unstable angina, cerebral vascular accident, transient ischemic attack, decompensated heart failure requiring hospitalization; class III/IV heart failure; history of Mobitz type II second-degree or third-degree AV block or sick sinus syndrome, unless patient has pacemaker; baseline QTc ≥500 ms, and treatment with class Ia or class III antiarrhythmic drugs.[15] The patient must be monitored for several hours after the first dose for bradycardia.

Teriflunomide (Aubagio®) is an oral inhibitor of dihydroorotate dehydrogenase in mitochondria, the rate-limiting enzyme in the de novo pyrimidine synthesis pathway. Teriflunomide has a selective cytostatic effect on rapidly dividing cells, including proliferating lymphocytes and may interfere with T lymphocyte cell antigen-presenting cell interaction, resulting in decreased T-cell activation. It has a very long half-life in the body; there is an accelerated elimination protocol using cholestyramine in the case of serious adverse events or the desire to become pregnant. The most clinical benefit is seen with the 14-mg dose. Reduction in ARR (30% to 35%), risk of disability progression (14-mg dose only), and new MRI lesions have been shown, and this agent is generally well tolerated.[16,17]

Dimethyl fumarate (Tecfidera®) is a twice-daily oral agent with efficacy in reducing relapses (ARR ~ 0.18), risk of disability, and new MRI lesions.[18,19] It enhances release of nuclear-related factor E2 [erythroid-derived 2] (Nrf-2), allowing translocation of Nrf-2 to the cell nucleus. It leads to inhibition of endothelial expression of ICAM-1, VCAM-1, and E-selectin. The induction of Nrf-2–mediated antioxidative pathways in astrocytes and microglia has the potential to have neuroprotective effects. This agent causes the most adverse events on a day-to-day basis, but the initial tolerability issues are usually transient. The twice-daily dosing can reduce adherence compared with a once-a-day oral agent\ like fingolimod.

Natalizumab (Tysabri®), a monthly intravenous infusion, is one of the most effective agents for MS. It is a selective monoclonal antibody directed at α4β-1 integrin expressed on all white blood cells, with the exception of neutrophils. It blocks attachment of activated lymphocytes to VCAM-1 on endothelial cells and subsequent migration into the CNS. In the trials, the AAR was 0.23 versus 0.85 with placebo. Natalizumab reduced risk of sustained progression of disability by 42 percent over two years. The cumulative probability of progression was 17 percent in the natalizumab group and 29 percent in the placebo group.[20] It reduced MRI activity of the disease by 90 to 95 percent. There is possible rebound of MS activity when natalizumab is discontinued, which requires early initiation of alternate DMT. It is well tolerated in most cases; progressive multifocal leukoencephalopathy (PML), which can be lethal, is the major adverse event of concern. The main risk factors for PML are duration of treatment, prior immunosuppressive therapy, and infection with the John Cunningham (JC) virus. In patients who are negative or low positive for JC virus infection, natalizumab is an option.

Alemtuzumab (Lemtrada®) targets CD52 antigen expressed on B and T lymphocytes, resulting in a long-lasting depletion of T cells. B cells return within a few months, which may be related to the autoimmune phenomena that can occur with this agent. This agent is given for a few days, stopped, and then repeated a year later; no additional doses are given. Compared to interferon beta, there was a 54.9 percent risk reduction for ARR (0.18 versus 0.39).[21] Sustained disability was no different at the end of six months. Compared to interferon beta in patients who had failed first-line treatment, there was a reduction in ARR of 49.6 percent (0.26 versus 0.52), a reduction in risk of EDSS worsening sustained at six months by 42 percent, and an increase in patients with confirmed disability improvement (22% versus 9%).[22] Antiviral prophylaxis for herpes simplex and varicella virus infection is required with each treatment cycle. Autoimmune diseases such as Hashimoto's thyroiditis can occur years after this agent is given. The risk management program for this agent requires certified infusion centers and prescribers, monthly complete blood count and urinalysis for 48 months following the last infusion, thyroid tests every three months for 48 months following the last infusion, and annual dermatologic exams. In 2018, a black box warning about a rare, but serious, risk of stroke and blood vessel wall tears was added to the package labeling. There had been 13 cases in five years, with 12 patients reporting symptoms within one day of administration.

Ocrelizumab (Ocrevus®) is an intravenous anti-CD20 monoclonal antibody that targets mature B cells; this was the first agent approved to specifically target B cells. It is given every six months. In RRMS compared against interferon beta, it reduced ARR (0.16 versus 0.29), MRI activity by 95 percent, and significantly delayed clinical disability.[23] In a four-year extension phase of the RRMS trial, there was sustained reduction in disease activity (ARR and disability progression), delayed cognitive decline, improved cognitive function, and reduced nerve damage and inflammatory biomarkers in the cerebrospinal fluid. It is a potent agent with efficacy similar to natalizumab, but there are

Exhibit 3: Siponimod versus Placebo in Secondary-Progressive MS[25]

Measure	Result
Primary Endpoint	
Three-month confirmed disability progression	21.0% reduction versus placebo *(P = 0.013)*
Secondary Endpoints	
Six-month confirmed disability progression in patients with no relapses two years prior to entry	18% reduction versus placebo (20.3% versus 23.6%; HR = 0.82)
Six-month confirmed disability progression	26.0% reduction versus placebo *(P = 0.006)*
Annualized relapse rate	55.5% reduction versus placebo *(P < 0.0001)*
T1 Gd+ lesion number	86.6% reduction versus placebo *(P < 0.0001)*
New T2 lesion number	81.0% reduction versus placebo *(P < 0.0001)*
T2 lesion volume change from baseline	79.1% reduction versus placebo *(P < 0.0001)*
Twelve-item MS walking scale	39.7% improvement versus placebo *(P < 0.0001)*
Percent brain volume change	23.4% improvement versus placebo *(P < 0.0001)*

no comparative trials between these two agents. It is becoming used much more often because of its efficacy and good tolerability.

Until recently, there were no effective DMTs specifically approved for primary-progressive or secondary-progressive disease. Ocrelizumab has also been studied for PPMS against placebo and is now FDA approved for this indication. PPMS is difficult to study because the rate of disease progression is very slow. Ocrelizumab reduces progression by 24 percent.[24]

Siponimod (Mayzent®), an oral selective S1P 1 and 5 receptor antagonist, was FDA approved for SPMS, RRMS, and CIS in early 2019. Data from the trial in SPMS is shown in Exhibit 3.[25] This agent is very similar to fingolimod, but it is more selective in S1P binding, so it has fewer adverse events. It does not have a requirement for first dose cardiovascular monitoring. The one issue with this agent is that CYP2C9 genotype testing is required before use. Those with a CYP2C9*3/*3 genotype cannot metabolize this agent and should not receive it. Those with one *3 gene should receive a reduced dose. Siponimod's place in therapy is not yet known, but it will likely replace fingolimod use, except in those with a problem genotype.

A second agent for SPMS, cladribine (Mavenclad®) was approved by the FDA in 2019. It also has an approval for RRMS. It is an oral purine antimetabolite that has prolonged effects on T cells and transient effect on B cells. An annual course of 3.5 mg/kg is given over five days in two successive months for two years. In a clinical trial, it reduced ARR by 57.6 percent compared to placebo (0.14 versus 0.33, P < 0.0001), increased the percentage of patients who were relapse free (79.7% versus 60.9%), and decreased the percentage with three-month confirmed disability progression by 33 percent.[26] The efficacy was maintained in a two-year placebo extension. Two- thirds of patients have no further disease activity out to five years after treatment completion.

Ozanimod is an investigational S1PR 1/5 receptor modulator that will likely be approved in the next couple of years. In an RRMS trial, it reduced ARR, new brain lesions, and brain volume loss compared to interferon. Several other agents are also under investigation. With all these choices of therapies, clinicians must make a decision with the patient which therapy to initiate. The best drug for a given patient is one that suppresses disease activity, is tolerable, causes no adverse events, is accessible, and allows the patient to continue a high quality of life. Once a therapy is selected, treatment goals, expectations, and a monitoring plan need to be defined. Clinicians need to educate patients on identifying symptoms of relapse and the importance of calling at the time of occurrence. The American Academy of Neurology guidelines for initiating therapy are shown in Exhibit 4.[1]

Monitoring of DMT includes disease symptoms suggesting clinical relapse or worsening, adverse events, and periodic MRI testing to detect new disease activity and suboptimal response. The Consortium of MS Centers has published guidelines for using MRI in diagnosis and follow-up monitoring.[27] For CIS follow-up, in those with high-risk of progression to MS, an MRI study with gadolinium is recommended at six to 12 months after diagnosis.

Exhibit 4: American Academy of Neurology Guidelines Initiating Therapy[1]

- Counsel patients on DMT at a separate treatment visit.
- Discuss and incorporate patient preferences in DMT decision.
- Educate patients on realistic DMT expectations.
- Evaluate patient readiness for DMT and counsel on its value.
- Counsel on effects of co-morbidities, adverse health behaviors on MS course.
- Evaluate barriers to adherence and counsel on its importance.
- Discuss DMTs for CIS and prescribe for patients with > 2 brain lesions characteristic of MS.
- Offer DMT to patients with relapsing forms of MS with evidence of recent relapse or MRI activity.
- Monitor for DMT AE, efficacy, tolerability, adherence.
- Monitor pregnancy plans and counsel regarding risks and contraception while on DMT.
- Counsel men regarding teriflunomide or cyclophosphamide risks of teratogenicity or infertility before initiating.
- Do not use mitoxantrone due to AE severity and frequency unless potential therapeutic benefits greatly outweigh risks.
- Prescribe alemtuzumab, fingolimod, ocrelizumab or natalizumab for patients with highly active MS.
- Offer ocrelizumab to patients with primary progressive MS likely to benefit, unless risks outweigh benefits.

DMT = disease-modifying therapy
CIS = clinically isolated syndrome
AE = adverse events
Guidelines have not been updated to include siponimod or cladaribine

For those who are low risk, the MRI can be done at 12 to 24 months after diagnosis. In established MS, imaging should be done if no recent prior imaging is available (e.g., in cases of new patient referrals), postpartum to establish a new baseline, before starting or switching DMT, six to 12 months after switching DMT (to establish new baseline on therapy), every one to two years during unchanged DMT to assess for subclinical disease, and in cases of unexpected clinical deterioration or to reassess original diagnosis. Gadolinium is helpful, but not essential, in established MS because new T2-lesions can be identified on well-performed standardized MRI imaging (unless T2-lesion burden is high).

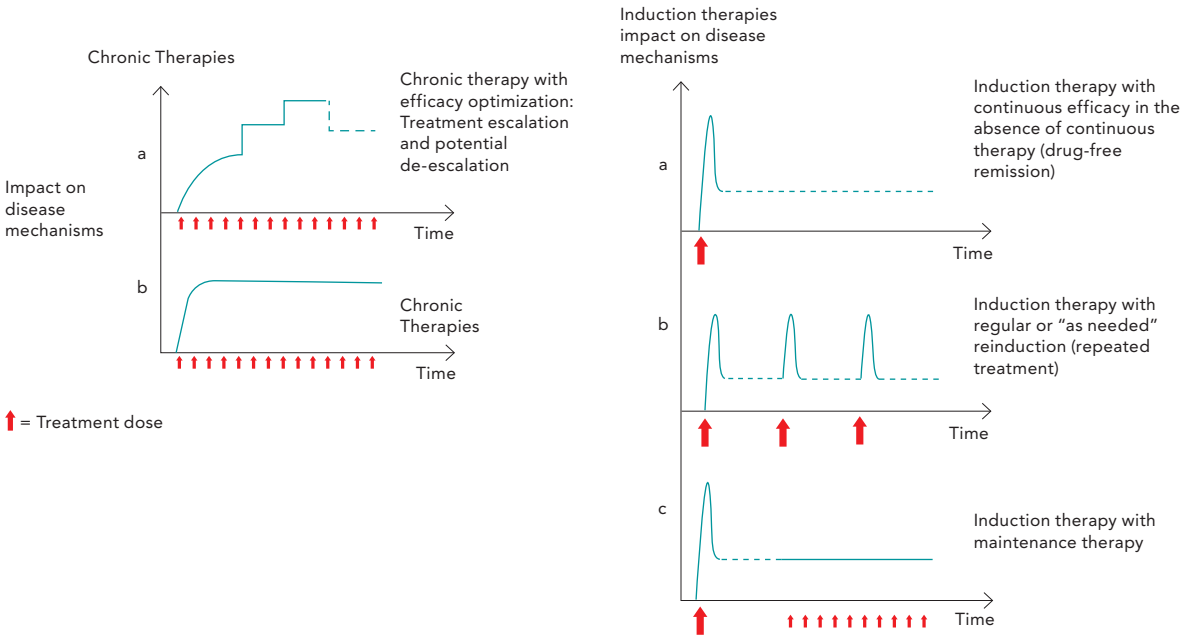
Treatment failure in MS management is difficult to define. Most patients are not completely free of disease activity during therapy. Disease activity may occur shortly after DMT initiation and before DMT is fully effective. Many clinicians obtain repeat MR imaging three to six months after a DMT is started to establish a new baseline, but the optimal timing for monitoring disease activity remains uncertain. Clinicians should consider treatment failure and switching DMTs when patients experience one of the following: ≥1 relapse, ≥2 unequivocally new MRI lesions, or increased disability on neurologic examination over one year of therapy.[1]

When switching treatment, a DMT with a different mechanism of action and more robust efficacy profile should be chosen. All of the newer DMTs appear to be more efficacious than interferon beta or glatiramer in RRMS.[1] Alemtuzumab should generally be reserved for patients with inadequate responses to two or more DMTs because of serious safety issues.[1]

In addition, when therapy is changed, the washout period should be as short as possible because of possible rebound of disease activity. Rebound has been shown with fingolimod and natalizumab. No washout or short duration (0 to 4 weeks) are reasonable for patients coming off most agents that are given continuously. Teriflunomide should involve cholestyramine washout until the serum level is less than 0.02 mcg/mL.

Expansion of DMT options with various potencies now present questions of what is the best treatment strategy. Currently, an optimization or escalation treatment paradigm is the norm, where initial therapy is started with monitoring for evidence of breakthrough disease and switching to an alternate class agent if breakthrough occurs. Initial therapy may involve first-generation or newer higher-potency agents. An induction treatment paradigm involves giving the highest potency agents or a bone marrow transplant to achieve rapid disease control and possibly reset the immune system. For example, alemtuzumab might produce a durable therapeutic response as a consequence of a permanent rebalancing of the immune system. Subsequent maintenance therapy could be given with an agent with higher safety and possible maintenance of immune reset by

Exhibit 5: Comparing Treatment Strategies[30]



prolonged immune modulating effects. Therapy after induction may only be needed periodically for recurrent inflammation. Exhibit 5 compares the various possible approaches.[28] Trials are ongoing to examine the induction approach.

Conclusion

Clinicians need to consider many different issues when selecting therapy. A health maintenance program to address modifiable risk factors for disease activity and progression is very important. It is also important for clinicians to stress adherence to the therapeutic regimen and follow up. Patients need to buy into the choice of therapy and understand the risks versus benefits. Patients should be monitored closely and therapy adjustments should be made based on tolerability and efficacy.

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Improving Clinical and Economic Outcomes with Personalized Treatment in the Management of Advanced Non-Small Cell Lung Cancer (NSCLC)

Joshua Bauml, MD

For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

The approach to managing advanced non-small cell lung cancer (NSCLC) has changed dramatically over the last few years and continues to evolve. Much of this change is due to the use of immunotherapy and targeted therapies. These therapies are significantly improving survival for this incurable stage of lung cancer.

Key Points

- Patients who have advanced NSCLC without EGFR or ALK mutations and PD-L1 expression less than 50 percent receive chemo-immunotherapy for first-line treatment.
- Those with advanced NSCLC without EGFR or ALK mutations and PD-L1 expression 50 percent or greater receive immunotherapy or chemo-immunotherapy.
- Patients with EGFR, ALK, ROS1, or NTRK alterations receive targeted therapy first-line.

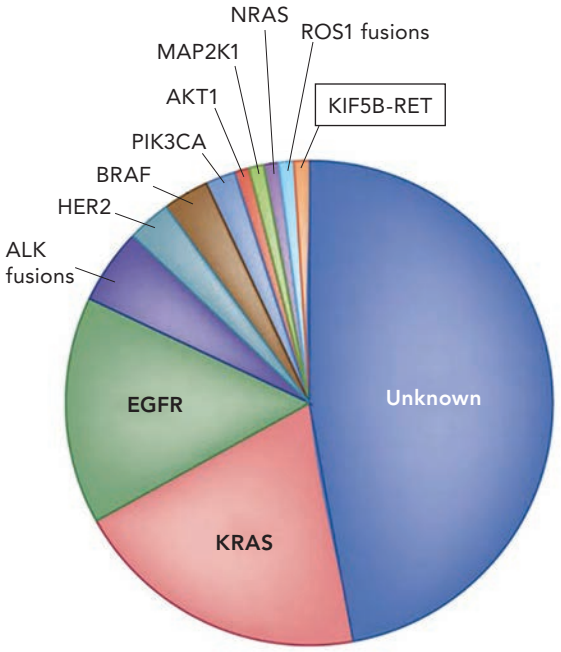
THE INTRODUCTION OF IMMUNOTHERAPY is one contributor to the dramatic changes in how advanced non-small cell lung cancer (NSCLC) is managed. Cancer cells which the immune system should consider foreign and destroy have many different ways to evade detection. Immunotherapy is stimulating the immune system to recognize and kill cancer cells.

T cells, whose primary job is to destroy foreign cells, have checkpoints on them which allows the T cells to recognize normal cells. One of these checkpoints is programmed death one (PD-1). Normal cells have programmed death ligand one (PD-L1) on their cells, so the T cells can recognize and not destroy them. Tumors can express PD-L1 on their surface, turn off T cells, and thus evade the immune system. Checkpoint inhibitors block the interaction between PD-1 and PD-L1, allowing T cells to remain active against tumor cells.

The first immunotherapy approved for advanced NSCLC was pembrolizumab (Keytruda®), an anti-PD-1 agent, which changed the first-line management of the disease. In patients who had greater than 50 percent expression of PD-L1 on their tumor, pembrolizumab improved overall survival (OS) and progression-free survival (PFS) compared to standard platinum doublet chemotherapy.[1] In the long-term follow-up data from this study, the median OS was 30.0 months compared to 14.2 months with chemotherapy. This is a dramatic improvement in OS given that five years ago the median OS with metastatic NSCLC was about one year. Pembrolizumab was better tolerated than chemotherapy. The incidence of high-grade adverse events (AEs) with immunotherapy was half the rate with chemotherapy. Immunotherapy is not free of AEs; by unleashing the immune system with this therapy, it can begin attacking normal tissues. The incidence of grade 3 to 5 immune-related AEs was 9.7 percent in this trial. Immune-related AEs have to be recognized early and treated aggressively, or they can be fatal.

Another pembrolizumab trial enrolled patients

Exhibit 1: Molecular Profile of Adenocarcinoma NSCLC



with lower levels of PD-L1 expression (>1%) and again there was an improvement in median OS.[2] An analysis of only those patients with 1 to 49 percent expression found no statistical difference in outcomes. Although pembrolizumab is FDA approved for advanced NSCLC with PD-L1 expression >1 percent, the benefit of this agent is in those who have 50 percent or greater expression. Thus, only patients with 50 percent or greater expression should be receiving pembrolizumab monotherapy.

The combination of pembrolizumab and platinum-based chemotherapy (platinum + pemetrexed) was studied in those with advanced nonsquamous NSCLC without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alterations. The triple combination produced an improvement in OS, regardless of the level of PD-L1 expression, and was beneficial even in those with less than 1 percent expression.[3] Overall, there was not a dramatic increase in AEs with the triple combination, but there were more patients who had to stop all treatments because of toxicity. Now patients with advanced non-squamous NSCLC without EGFR or ALK mutations and PD-L1 expression less than 50 percent receive chemo-immunotherapy. Those with 50 percent or greater expression can receive immunotherapy or chemo-immunotherapy.

Atezolizumab (Tencentriq®) is another PD-L1 checkpoint inhibitor immunotherapy. The IMpower study looked at carboplatin and paclitaxel with atezolizumab, bevacizumab, or both in Stage IV nonsquamous NSCLC. There was a modest survival benefit with the four-drug regimen, which led to FDA approval.[4] The paclitaxel component is a little harder for patients to tolerate than pemetrexed, and additionally the bevacizumab contributes significantly to the toxicity rates overall. This trial allowed patients with EGFR or ALK mutations who had failed prior tyrosine kinase inhibitor (TKI) therapy. Because this is the only regimen for which there is data in the TKI failure setting, this is the patient population who could be considered for this four-drug regimen.

KEYNOTE-407 examined carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab in advanced squamous NSCLC. Again, there was an OS benefit, regardless of the PD-L1 status, with the addition of pembrolizumab (15.9 versus 11.3 months).[5] Thus, patients with squamous disease can receive chemo-immunotherapy.

Nivolumab (Opdivo®), another anti-PD-1 immunotherapy with or without ipilimumab (Yervoy®), an anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) checkpoint inhibitor was compared to histologically selected chemotherapy in advanced NSCLC without EGFR or ALK mutations.[6] This trial used tumor mutational burden (TMB) instead of PD-L1 expression. In those with high TMB, there was a PFS ben-

Exhibit 2 Benefit of Targeted Therapies in a Targeted Age[9]

Genotype/Therapy	Median OS	95% CI
Oncologic driver + targeted therapy	3.49 years	3.02 - 4.33
Oncologic driver + no targeted therapy	2.38 years	1.81 - 2.93
No targeted therapy	2.08 years	1.84 - 2.46

efit, but nivolumab/ipilimumab was not associated with an improvement in OS over chemotherapy among patients with TMB high or low. Nivolumab/ipilimumab has not been FDA approved for first-line treatment of NSCLC. Nivolumab monotherapy is indicated for patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. It appears that guiding treatment decisions based on TMB is not the answer to the best biomarker for immunotherapy.

Immunotherapy is relatively well tolerated, but serious toxicities do occur and currently the therapy is very expensive. As more immunotherapy approaches emerge, it will be critical to understand how best to use them, and this is unlikely to be a "one-size-fits-all" approach. Clinicians need a good biomarker for selecting immunotherapy. What is needed is a biomarker that can convey the same confidence in choosing therapy as a biomarker such as EGFR mutation. It has been determined that someone who has an EGFR mutation will respond to targeted therapy aimed at that marker.

PD-L1, as a biomarker, is based on determining how immunologically active the tumor is, but it is an imperfect biomarker. It is heterogeneously distributed within tumors, and the positive areas change over time.[7] How to define negative for PD-L1 is another issue. Each of the immunotherapies was developed and marketed with a specific assay for PD-L1, which vary significantly from each other.

TMB is another possible biomarker of immunotherapy response; however, as previously discussed, it was not very useful in the nivolumab trial. Mutational load is associated with a greater number of potential neoantigens in the tumor than the immune system can recognize. TMB is already known to be an important biomarker for cytotoxic T lymphocyte antigen-4 (CTLA-4) checkpoint inhibitors. It is originally assessed with whole exome sequencing. Emerging studies have shown correlation of response with clinically available next-generation sequencing panels, but each panel must be validated. The other issue with TMB is that not all mutations are created equal. The type of mutation impacts the neogenicity of the tumor. Insertion deletion mutations with frameshift can generate many more neoantigens than other mutations, which may have a larger impact on response to immunotherapy.[8] This may explain the discordance between PD-1 blockade efficacy and overall TMB.

Combining PD-L1 and TMB is also a possibility. Although this combination is helpful, high PD-L1 and high TMB only occurs in about 20 percent of patients. The combination would not be helpful for selecting therapy in the other 80 percent. Treatment based on molecular profile is the other half of treating NSCLC. Exhibit 1 shows the major mutations that are found in adenocarcinoma type lung cancers. EGFR mutations occur in about 15 percent of nonsmokers who develop lung cancer. KRAS mutations are common; however, at this time, there are no approved targeted therapies. Currently, there are five genes with FDA approved therapies for patients with alterations: EGFR mutation, ALK translocations, ROS1 translocations, BRAF mutation, and NTRK translocations. Approximately 50 percent of the time, the molecular mechanism of the disease is unknown, so targeted therapy is not appropriate. If a patient has a known oncogenic mutation and receives targeted therapy, they have a much better survival compared with the patient with an oncogenic mutation and no available targeted therapy, or no identified mutation (Exhibit 2).[9] The expected survival is now even better than what was shown in this trial; a patient with ALK translocation treated with targeted therapy will live three to five years. Clinicians have to know what type of lung cancer a patient has in order to determine the most effective, appropriate treatment, and this requires genetic biomarker testing.

Choosing the appropriate test for biomarkers is important. Previously, single tests for each biomarker of interest had to be conducted with the limited amount of tissue from a biopsy, and there was a

waiting time for results before the next test could be done. Next-generation sequencing (NGS), which tests for a multitude of mutations at the same time, solves the tissue availability and time problem. NGS is the most tissue efficient process. The problem is now how is the clinician going to use this huge onslaught of data. Selecting the right NGS tests is also important. Conditions such as ALK fusion are not detected well with DNA-based NGS. RNA- based NGS is much better identifying these. In some practices, adenocarcinoma tumors are tested by both DNA and RNA NGS. It is important to note that some panels report ALK, ROS1, and NTRK, but they are checking for mutations, not translocations. Mutations in ALK, ROS1, and NTRK may be relevant for resistance to TKI therapy, but not for choice of initial therapy.

Any patient with metastatic adenocarcinoma of the lungs should be tested for genetic alterations. Most patients will not have a targetable alteration; however, for that group who does, it makes a big difference in survival. In addition to a survival benefit, those patients who do have a targetable alteration should receive targeted therapy first because the response rate and quality of life is much better than with other therapies. Testing is somewhat expensive, but using therapies in a more targeted fashion is certainly more cost effective than giving everyone immunotherapy.

EGFR mutations are seen in 10 to 15 percent of Caucasian patients and in 30 to 35 percent of East Asian patients. This mutation is strongly associated with epidemiology; it is typically seen in female never or light smokers. The most common mutations are exon 19 deletion and L858R. Tyrosine kinase inhibitors (afatinib, erlotinib, gefitinib, osimertinib) are given orally, have a very high response rate compared to chemotherapy, and have minimal adverse events compared to chemotherapy and immuno-chemotherapy. Osimertinib is a second-generation TKI designed to overcome the most common mechanism of TKI resistance (T790M), but it is also more effective as first-line therapy over gefitinib and erlotinib.[10] It also causes less rash and liver toxicity than the first-generation TKIs and is now standard of care first-line therapy for EGFR-mutated NSCLC.

NTRK fusion abnormalities are rare. Detection via DNA NGS is complex because of large introns. NTRK fusion is more commonly seen in rare cancers – salivary, secretory breast cancer, congenital nephroma, and infantile fibrosarcoma, but it is seen in 0.18 percent of adenocarcinoma NSCLC.[11] Larotrectinib (Vitrakvi®) is the available targeted therapy for NTRK fusion-positive cancers, including NSCLC.[12]

Conclusion

Chemotherapy or immuno-chemotherapy are standard of care for patients with NSCLC not harboring a molecular target. Available immunotherapy biomarkers have poor predictive capabilities but emerging biomarkers may lead to better outcomes and more efficient care. NGS can identify numerous genetic alterations but not all of them may have a targeted therapy. If a molecular target is present that has a targeted therapy, it is important that targeted therapy be used first.

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Exploring New Pathways and Emerging Data for Better Control and Management in the Personalized Treatment of Severe Asthma

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

There are new therapeutic approaches for severe asthma that improve outcomes, including exacerbations and oral steroid dependence. The patient selection for biologics is evolving, but it typically involves being uncontrolled on triple therapy and having biomarkers of eosinophilic asthma.

Key Points

- Severe asthma is difficult to control.
- Biologic therapies targeting underlying pathology for eosinophilic asthma are available.
- Biologic agents reduce exacerbations and, for some of the agents, reduce oral steroid dependence.
- Reducing steroid dependence is especially important because of the long-term adverse event risk.

SEVERE ASTHMA IS A SUBSET OF DIFFICULT to treat asthma patients. These patients remain uncontrolled despite high-dose inhaled corticosteroids combined with long-acting beta agonists (LABAs), montelukast, theophylline or systemic steroids (Exhibit 1).[1]

The goal of asthma management is disease control. Asthma control is defined by current clinical condition (symptoms, short-acting beta agonist use, night waking, activity limitation, and lung function) and features associated with future risk (exacerbations in past year, ever admitted to critical care for asthma, accelerated decline in lung function, and adverse events of treatment).[2,3] Consistently controlled asthma is important because lack of control increases risk of future asthma exacerbations, which are a key risk outcome and cost driver in asthma management.[4] In one trial, those with exacerbations had 3.5-fold increase in costs compared to those without exacerbations.[5]

Much has been learned about the pathophysiology of severe asthma in the past 20 years. Most patients with severe asthma have type 2 inflammation driving their lung disease. T helper two (Th2) cells mainly secrete the prototypical cytokines interleukin four (IL-4), IL-5 and IL-13, and stimulate type 2 immunity, which is characterized by high antibody titers and eosinophilia.[6,7] Airway eosinophils have been shown to drive type 2 inflammation and correlate with reduced lung function (FEV_1) in asthma and asthma exacerbations.[8] Type 2 inflammatory responses in the lungs often start in childhood and are driven by interaction between epithelial cells in the lung and environmental stimuli — such as viral respiratory tract infections or exposures to oxidants, such as cigarette smoke or other airborne pollutants. Activated airway

Exhibit 1: Asthma Definitions (ATS/ERS Guidelines)[1]

Difficult to Treat Asthma

- Uncontrolled asthma despite high-dose inhaled corticosteroids or other controllers.

OR

- Requires such treatment to remain controlled.

Severe Asthma

- Subset of difficult to treat asthma patients
- Remain uncontrolled despite high-dose inhaled steroids combined with:
  - *Long-acting beta agonist (LABA) montelukast, theophylline or systemic steroids for prior 6 months.*

epithelial cells produce IL-25, IL-33 or thymic stromal lymphopoietin (TSLP), which initiates a pathogenic cascade of Th2 cell proliferation.

Exhibit 2 details the most important clinical phenotypes of severe uncontrolled asthma.[7] Most patients with severe asthma have eosinophilic asthma, which is either allergic or non-allergic. Eosinophil levels and exhaled nitric oxide (FeNO) are biomarkers of eosinophilic asthma. Eosinophil levels correlate with decline in lung function and risk of future disease exacerbations, and FeNO levels are an indirect marker of eosinophilic inflammation. A rarer form of severe asthma is neutrophilic asthma, which is not responsive to steroids.

Asthma management uses a control-based asthma management cycle.[3] This cycle begins with assessment (accurate diagnosis, symptoms, and risk factors). Treatment with pharmacologic therapy and environmental controls is initiated and then treatment response is assessed. The cycle is a loop where response to therapy is assessed at each visit and therapy is adjusted as appropriate to achieve disease control.

Inhaled corticosteroids (ICS), which have long been the mainstay controller medication for asthma, suppress type 2 inflammation.[6] Regular use of ICS leads to a reduced risk of exacerbations and death from asthma.[9] A significant barrier to optimal asthma control has been underutilization of ICS.[10] Underutilization can be under-prescribing and patient nonadherence. Unfortunately, the majority of patients with severe asthma are not adherent with their prescribed ICS; most are only taking 50 percent of the prescribed dose.

Health literacy has been shown to impact asthma controller medication adherence.[11] In an Asthma in America survey, only about one in three (34%) patients said that the underlying cause of asthma could be treated; half (50%) thought it was possible to treat only symptoms; the rest (16%) were not sure. The percentage who were aware that the underlying cause can be treated corresponded to the assumptions of the general public, suggesting that asthma patients are no better informed about their condition than individuals without asthma.[10]

Some possible adherence solutions are patient education to improve health literacy and reviewing inhaler device technique. Newer options on the horizon are adherence tracking devices on inhalers which can transmit data to providers. The first will be for rescue albuterol inhalers. Frequent use of a rescue inhaler is a marker of uncontrolled asthma. FeNO levels can also be used as a marker of adherence. The cleverest solution may be the use of on-demand rescue albuterol in combination with ICS or a low-dose inhaled budesonide/formoterol combination. This approach is now recommended by the Global Initiative for Asthma guidelines instead of prescribing rescue albuterol alone for mild asthma.[3]

Achieving control with severe asthma requires optimizing medication therapy, treating comorbid conditions which can exacerbate the disease, and modifying environmental risk factors. Optimizing medications requires addressing that the patient is on appropriate medication, adding medications if control is not achieved, and ensuring medication adherence. Environmental risk factors include aeroallergen sensitization (i.e., animals, dust mites), occupational exposures, traffic pollutants (e.g., fine particulate matter), indoor pollutants, and tobacco smoke. Environmental controls such as mattress encasings are effective for preventing asthma emergency room visits and hospitalizations.[12]

Clinicians should assess asthma control after addressing medications, comorbid conditions, adherence, and environmental factors. If the patient has a good response to ICS, therapy is continued and monitored. If there is a poor response, therapy is added in a stepwise manner (Exhibit 3).[3] For

Exhibit 2: Severe Uncontrolled Asthma – Clinical Phenotypes[7]

	Allergic-eosinophilic	Nonallergic-eosinophilic	Neutrophilic
Frequency	Very common	Very common	Uncommon
Causes	Indoor and outdoor aeroallergens, occupational causes	Aspirin exacerbated (AERD) or no ASA sensitivity Idiopathic	Infections, smoke, pollutants, irritants, occupational agents
Biomarkers	Blood eosinophils ≥ 300 FeNO ≥ 20 ppb	Blood eosinophils ≥ 300 FeNO ≥ 40 ppb ↑ Sputum eosinophils	≥ 40-60% sputum neutrophils
Clinical Features	Onset in childhood, associated with allergic rhinitis, atopic dermatitis, **asthma exacerbations**.	Onset in adulthood, chronic rhinosinusitis, nasal polyps and obstruction, **asthma exacerbations**.	Poor response to inhaled corticosteroids, purulent mucus, reduced lung function

ASA = aspirin
FeNO = exhaled nitric oxide

the severe asthma patient who is not controlled on high-dose ICS, LABAs, long-acting antimuscarinics (LAMAs), and oral steroids daily or periodically, inflammatory phenotype-based biologics should be considered. The goals of adding biologic therapy are to achieve asthma control, reduce exacerbations, and reduce oral steroid requirements.

Five monoclonal antibodies have been FDA approved for treating severe asthma: omalizumab (Xolair®, anti-IgE), mepolizumab (Nucala®, binds IL-5), reslizumab (Cinqair®, binds IL-5), benralizumab (Fasenra®, blocks IL-5α receptor), and dupilumab (Dupixent®, inhibits IL-13 and IL-4 common receptor). Omalizumab was the first agent approved, and it binds free IgE to prevent mast cell activation. It is indicated for the allergic asthma phenotype with elevated IgE levels. Treatment with omalizumab produced a 25 percent reduction in the rate of asthma exacerbations in severe patients uncontrolled on ICS/LABA.[13] It has no consistent oral steroid sparing effect and works better in patients with high peripheral eosinophils (≥300) or high exhaled nitric oxide (≥20 ppb).

The anti-IL-5 agents are FDA approved for add-on therapy of severe asthma with an eosinophilic phenotype. Importantly, the anti-IL-5 agents lack efficacy for non-eosinophilic asthma. Mepolizumab and benralizumab produce about a 50 percent reduction in exacerbations and 50 percent reduction in oral corticosteroid use (Exhibit 4).[7,14,15] Reslizumab produces a 50 percent reduction in exacerbations, but data in oral steroid-dependent patients are not yet available. A disadvantage of reslizumab is administration by intravenous infusion, unlike the other two which are subcutaneous injections that patients can do at home.[16]

Exhibit 3: Pharmacologic Approach to Asthma[3]

1. Optimize LABA-inhaled corticosteroids
2. Add leukotriene antagonist
3. Add long-acting antimuscarinic (LAMA)
4. Add oral steroids (e.g., low-dose prednisone)
5. Consider biologic agent (monoclonal antibody)

Dupilumab treatment produces increases in forced expiratory volume (FEV_1) and a 50 percent reduction in exacerbations, and is oral steroid sparing. In steroid-dependent patients, there was a 28 percent decrease in oral prednisone dose versus placebo with a 59 percent decrease in exacerbations.[17] A disadvantage of dupilumab is every two-week dosing compared with longer dosing intervals for the anti-IL-5 agents. An advantage of dupilumab is that this agent appears to work in patients with lower eosinophil levels.

Biologics appear to have the most promising effects in eosinophilic (type 2 inflammation) asthma. More data are available on using in oral steroid dependent asthma for mepolizumab, benralizumab, and dupilumab. The biologics likely have a major impact on hospitalizations and death, but this data still needs to be determined.

Some questions with using the biologics in severe asthma remain. At this time, there are no comparative data between biologics; therefore, whether one is better than another is unknown. Optimal patient selection for biologics is not yet known but is typically based on evidence of eosinophilic asthma that

Exhibit 4: Anti IL-5 Monoclonal Antibodies for Eosinophilic Asthma[7]

Mepolizumab (binds IL-5)	Benralizumab (binds IL5 receptor)	Reslizumab (anti IL-5 cytokine)
Subcutaneous 100 mg monthly Ages ≥ 12 Studied in those with blood eosinophils ≥150, 53% ↓ exacerbation rate 50% ↓ oral steroid versus placebo Reduces blood eosinophils FEV_1 improved by 100 ml Works best in those with ≥ 300 eosinophils and two or more exacerbations annually Safety: herpes zoster, anaphylaxis	Subcutaneous 30 mg q 8 weeks (q4 for first 3 doses) Ages ≥12 Studied in those with blood eosionophils ≥300 50% ↓ exacerbation rates 50% ↓ oral steroids versus placebo Safety: anaphylaxis 3%	Intravenous dosing by weight (3 mg/kg) monthly Studied in uncontrolled asthmatic on medium-high inhaled steroids with ≥400 eosinophils and ≥1 exacerbation/year No data in oral steroid dependent patients 50% to 60% reduction in exacerbations versus placebo FEV_1 improved by 100 ml Safety: rare anaphylaxis

IL = interleukin; FEV_1 = forced expiratory volume in 1 second

is uncontrolled on triple therapy or is steroid dependent. Additional biologics are on the horizon. Agents in development for severe asthma include anti-TSLP, anti-IL 33 (regulates T2 and non-T2 inflammation), anti-IL25, and prostaglandin DP2 (PGD2) receptor antagonists.

Conclusion

Severe asthma is difficult to control, but there are now therapies targeting underlying pathology for eosinophilic asthma. These biologic agents have been shown to reduce exacerbations and, for some of the agents, reduce steroid dependence. Reducing steroid dependence is especially important because of the long-term adverse event risk.

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Exploring the Evolving Treatment Paradigm in the Management of Inflammatory Bowel Disease

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

It is an extraordinarily exciting time for clinicians who manage patients with inflammatory bowel disease. There are a number of newer treatment options which can help many patients with moderate-to-severe disease into remission and maintain that remission for extended periods. Many more options will be coming to the market in the next few years.

Key Points

- Treatment of IBD is based on the risk profile of the disease.
- High-risk disease should be treated aggressively, with a biologic agent with or without an immunomodulator, as early as possible in the disease process to prevent damage to the gastrointestinal tract.
- Using the newer therapies that are targeted to the underlying inflammatory process is important to improving outcomes in this disease.

THERE ARE APPROXIMATELY 1.6 MILLION cases of inflammatory bowel disease (IBD) in the United States. Approximately 50 percent are ulcerative colitis (UC) and 50 percent are Crohn's disease (CD). CD can involve any part of the gastrointestinal tract from the mouth to the anus, while UC begins in the rectum and works its way backward through the intestines. Males and females are equally affected. The typical age for diagnosis of CD is 15 to 35 years and about five to ten years later for UC. IBD results from a disordered immune response to gut contents in genetically predisposed individuals. This is a chronic, lifelong disease, without a medical cure. Surgical intervention is required in approximately two-thirds of CD patients and in as many as one-third of UC patients.

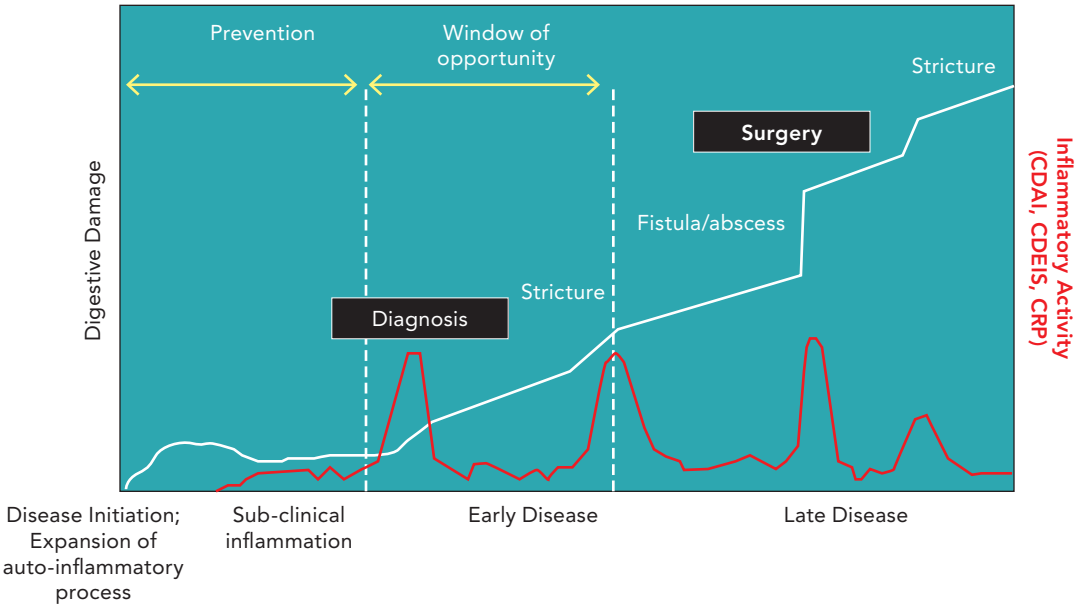
IBD is a complex genetic disorder. In genome-wide searches, multiple genes have been identified that increase or decrease the risk of development. There is 50 percent concordance in monozygotic twins for CD and 6 to 18 percent for UC. The lifetime risk of developing IBD in first-degree relatives of those affected is 8.9 percent for offspring, 8.8 percent for siblings, and 3.5 percent for a parent. Seventy-five to 80 percent of multiple affected families are concordant for disease type (i.e., CD or UC).

Northern Hemisphere countries have much higher rates of IBD compared with those in the Southern Hemisphere, and there has been a significant increase in the cases around the world, which appears to be an effect of urbanization and industrialization.

IBD has significant symptoms that impact quality of life. Both UC and CD cause diarrhea and abdominal pain. Weight loss, fever, and perianal disease are more common with CD. UC causes bloody stools, which prompts patients to seek care and leads to an earlier diagnosis than with CD.

The diagnosis of IBD utilizes clinical, laboratory, endoscopic, radiologic and histologic features, gastrointestinal specific complaints, and extraintestinal

Exhibit 1: Natural History of Crohn's Disease[1]



CDAI = Crohn's Disease Activity Index
CDEIS = Crohn's Disease Endoscopic Index of Severity
CRP = C-reactive protein

manifestations. Extraintestinal manifestations can include 'colitic' arthritis, ankylosing spondylitis, sacroiliitis, primary sclerosing cholangitis, pyoderma gangrenosum, erythema nodosum, uveitis, episcleritis, and autoimmune anemia.

It is important that an early diagnosis of IBD, particularly CD, be made as there is a window of opportunity to prevent inflammatory complications of the disease (Exhibit 1).[1] It is hoped that with an early diagnosis and subsequent tight disease control of inflammatory activity that there will be minimal digestive system damage and reduced need for surgery.

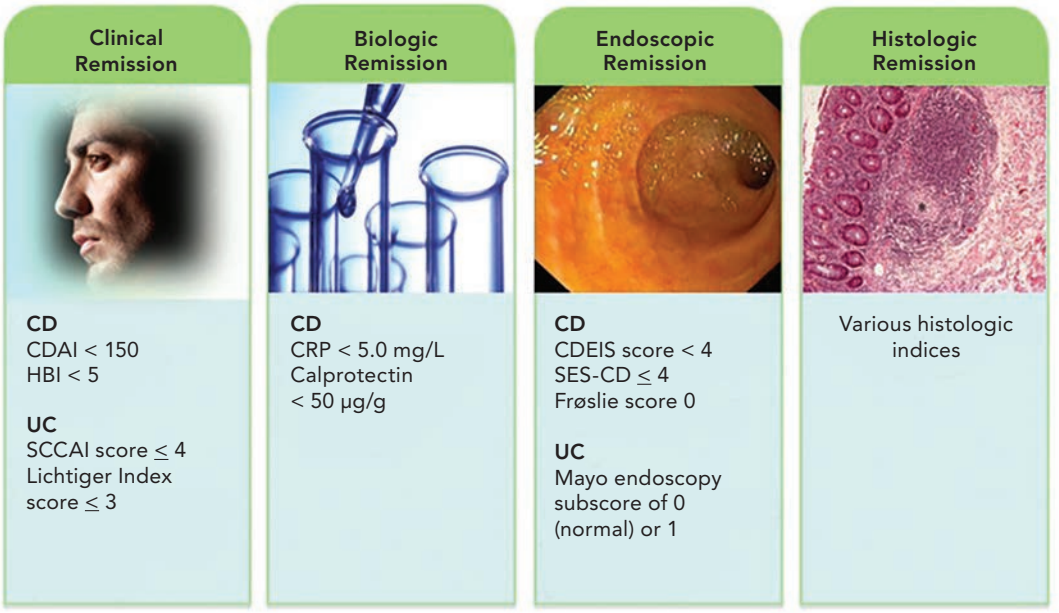
The therapeutic targets in IBD have evolved. The old paradigm was to treat based on symptoms, but symptoms are not a good way to determine if a patient's disease is under control because symptoms do not always correlate well with underlying inflammation.[2] The new paradigm is to treat based on objective markers of inflammation to achieve disease remission. Remission can be defined as clinical, biologic, endoscopic, or histologic (Exhibit 2). Clinical remission alone is no longer acceptable. The goal is now treat-to-target, as in other chronic diseases, by going beyond just symptomatic improvement or remission using clearly defined and objective biomarkers and endoscopy/radiology to demonstrate GI mucosal healing to prevent progressive bowel damage and complications.[3,4] Mucosal healing after therapy has been shown to predict improved outcomes in CD, including reduced need for surgery.[5]

With treat-to-target, therapy is initiated and the patient is followed up every 12 weeks for symptom and biomarker measurement and every 26 weeks for endoscopy or imaging. If the target of deep remission is met, therapy continues with ongoing monitoring on this same schedule. If the target is not met, medication adherence must first be addressed. If and when adherence is adequate, then the dose of the given therapy is maximized if possible. Only then is therapy changed. The treating-to-target approach leads to superior endoscopic and deep remission in CD.[6]

The options for treating IBD include corticosteroids (prednisone, budesonide EC, budesonide MMX), mesalamine (oral and topical, mesalamine, sulfasalazine, balsalazide), methotrexate, thiopurines, JAK inhibitors (tofacitinib), and biologics. The approved biologics include anti-tumor necrosis factor inhibitors (anti-TNF, infliximab, adalimumab, certolizumab and golimumab) as monotherapy or with concomitant immunomodulator, anti-integrins (vedolizumab), and anti-interleukin 12/23 (anti-IL 12/23, ustekinumab). The biologics and JAK inhibitors target the specific underlying issues that lead to and perpetuate inflammation.

For UC, patients are stratified based on risk of colectomy in order to choose therapy. Those at low

Exhibit 2: Definitions of Remission in IBD



CAI = Clinical Activity Index
CDAI = Crohn's disease activity index
CDEIS = Crohn's disease endoscopic index of severity
CRP = C-reactive protein
HBI = Harvey-Bradshaw Index
SES = simple endoscopic score
UCDAI = Ulcerative colitis disease activity index

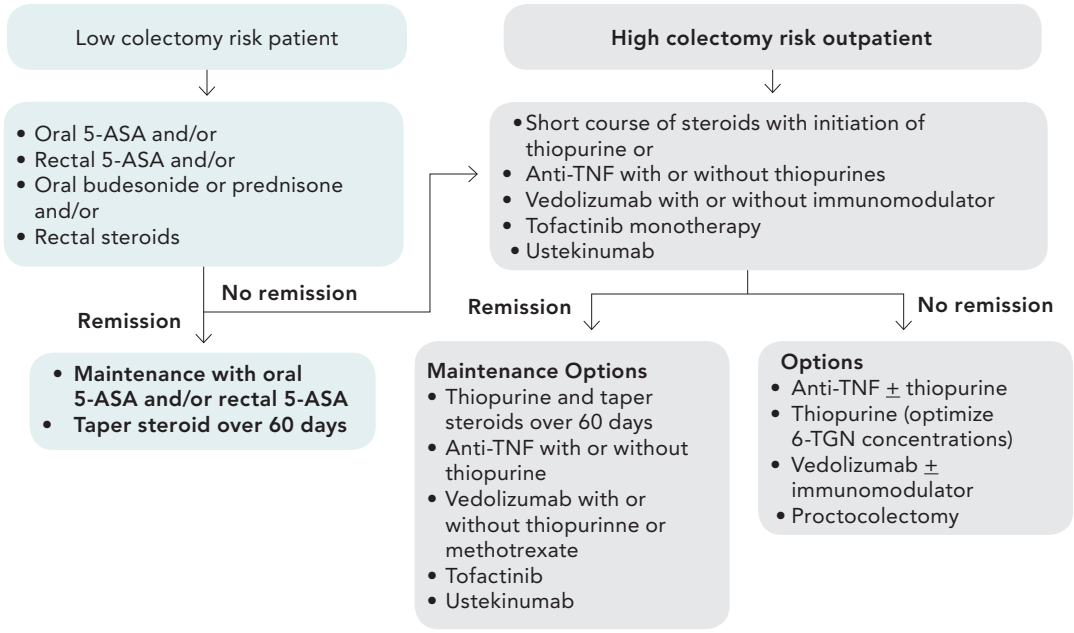
risk for colectomy include those with limited anatomic extent and mild endoscopic disease. High-risk markers for colectomy include extensive colitis, deep ulcers in the gastrointestinal tract, age < 40, high C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), steroid-requiring disease, history of hospitalization, *C. difficile* infection, and cytomegalovirus (CMV) infection. As many as 25 percent of high-risk individuals will lose their colon within two years of diagnosis, if they are not treated aggressively. Exhibit 3 shows a treatment algorithm for UC based on low risk versus high risk.[7] Treatment should be titrated to induce remission and then is continued to maintain the remission.

There are several factors that may prompt a clinician to choose one medication over another for UC. Infliximab, which is given intravenously, is the most potent anti-TNF agent, so it may be chosen for the patient who has very active disease. Vedolizumab, which appears to be the safest biologic, may be chosen for the patient with concomitant diseases, or who is older. The anti-TNF inhibitors are most effective when used in combination with immunomodulators. This class can increase risk of infection and lymphoma (when combined with immunomodulators). Tofacitinib is the only oral agent among the newer targeted anti-inflammatories, so some patients may prefer it over subcutaneous or intravenous injectable products. A unique risk of tofacitinib is herpes zoster infection.

CD can also be risk stratified to determine therapy. High-risk features in CD include age less than 30 at diagnosis, extensive anatomic involvement, perianal and/or severe rectal disease, deep ulcers, prior surgical resection, and stricturing and/or penetrating disease.[8] Exhibit 4 shows a treatment algorithm for CD again based on low risk versus high risk.[8] As with UC, CD treatment should be titrated to induce remission and then should be continued to maintain the remission. With either form of IBD, if therapy is discontinued the disease will likely flare-up.

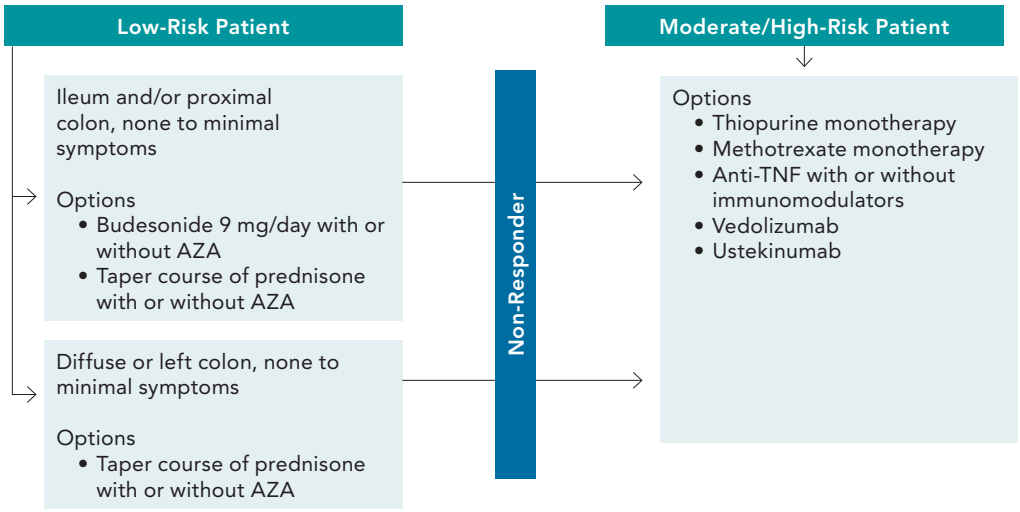
In CD, there is stronger evidence for clinical remission with the anti-TNF agents, and they lead to more rapid remission than with vedolizumab. Vedolizumab has an advantage in maintenance of remission, and better results are seen in those patients who are anti-TNF agent naïve. Vedolizumab is gut selective and has a very good safety profile.

Exhibit 3: Clinical Pathway for UC[7]



5-ASA = 5-aminosalicylate
TGN = thioguanine nucleotide
TNF = tumor necrosis factor

Exhibit 4: Clinical Pathway for Crohn's Disease[8]



Ustekinumab has been shown to be successful in both anti-TNF agent naïve and resistant patients, and its safety appears superior to anti-TNF agents. Its onset of action is between the anti-TNF agents and vedolizumab. Ustekinumab is a good choice if the patient also has psoriasis.

Optimizing therapies in IBD to achieve target goals includes therapeutic drug monitoring. This means measuring trough drug levels and anti-drug antibodies. If antibody levels are high, the agent currently being used should be switched because its effects are going to be neutralized by the antibodies. If

Exhibit 5: Emerging Therapies for IBD

Class	Investigational
Integrin inhibitors and MAdCAM-1 inhibitors	AJM 300 Etrolizumab SHP 647
S1P modulators	Etrasimod Ozanimod
Interleukin inhibitors	Brazikumab Guselkumab Mirikizumab Risankizumab
JAK inhibitors	Filgotinib Upadacitinib TD-1473
Microbiome modifiers	Fecal microbiota therapy

the patient has low trough levels, the dose should be increased. If the patient has adequate drug levels and still has inflammation, the class of agent needs to be changed because that particular agent's mechanism of action is not effective in this particular patient.

Numerous factors affect the pharmacokinetics of the TNF inhibitors and thus can affect therapeutic success with these agents. Concomitant immunosuppressives can decrease clearance of the TNF inhibitors, while anti-drug antibodies, low serum albumin, high baseline CRP, high baseline TNF concentration, high body mass index, and male gender are all factors which can increase clearance.[9] Infliximab, because it is dose-based on weight, is a good choice in patients who are overweight.

Adverse events of concern with agents include immunogenicity (anti-TNF, vedolizumab), cytopenias and hepatotoxicity (anti-TNF, thiopurines, methotrexate), heart failure exacerbation (anti-TNF), infection risk (anti-TNF, corticosteroids, thiopurines, tofacitinib), osteoporosis (corticosteroids), and malignancy (anti-TNF, thiopurines).[10-12] Corticosteroids are the class of drugs used to treat IBD that are associated with the overall highest rate of adverse events. Because of these adverse events, corticosteroids, although very effective, should only be used for remission induction.

Numerous agents are on the horizon for treating IBD (Exhibit 5), with many new targets being discovered in the inflammatory process of this disease. The future of managing IBD also includes serum and fecal biomarkers and genomic testing for diagnosis, treatment selection, and therapeutic response.

Because treatment of IBD has become much more complicated with all the new medications, patients with more than mild disease should be cared for by an IBD specialist rather than a generalist gastroenterologist. This may mean referring a patient to a specific physician in a gastroenterology practice or a university-based setting. The IBD management team should include physicians, physician extenders, nurses, surgeons, nutritionists, mental health professionals, and pharmacists.

Data suggest that IBD patients do not receive preventive services at the same rate as general medical patients. To improve the care delivered to IBD patients, health maintenance issues need to be co-managed by both the gastroenterologist and the primary care team. The American College of Gastroenterology has developed guidelines on preventive care in IBD.[13] Those with IBD are at risk for long-term medication adverse events, which requires monitoring; an example is monitoring vitamin D levels and bone density measurement for osteoporosis. It is also important for patients to get appropriate vaccines, especially if receiving immunosuppressive therapies, and cancer screenings. Checklists have been developed which can help clinicians ensure that appropriate health maintenance care is instituted. An example by the Crohn's and Colitis Foundation can be found at http://www.crohnscolitisfoundation.org/science-and-professionals/programs-materials/health-maintenance-checklist.pdf.

Conclusion

Treatment of IBD is based on the risk profile of

the disease. For those with high-risk disease, aggressive therapy with a biologic agent, with or without an immunomodulator, is needed as early as possible in the disease process to prevent damage to the GI tract. Because IBD is a chronic disease, treatment must be continued to maintain remission. Using the newer therapies that are targeted to the underlying inflammatory process is important to improving outcomes in this disease, but therapy does need to be optimized.

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Optimizing Clinical and Economic Outcomes in the Management of Moderate-to-Severe Rheumatoid Arthritis

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

Rheumatoid arthritis is an aggressive, systemic disease which can be treated effectively in most patients, but not cured. For greater than 90 percent of patients, therapy is lifelong. There are now numerous disease-modifying therapies targeting various components of the underlying immune pathophysiology, which can put the disease into remission

Key Points

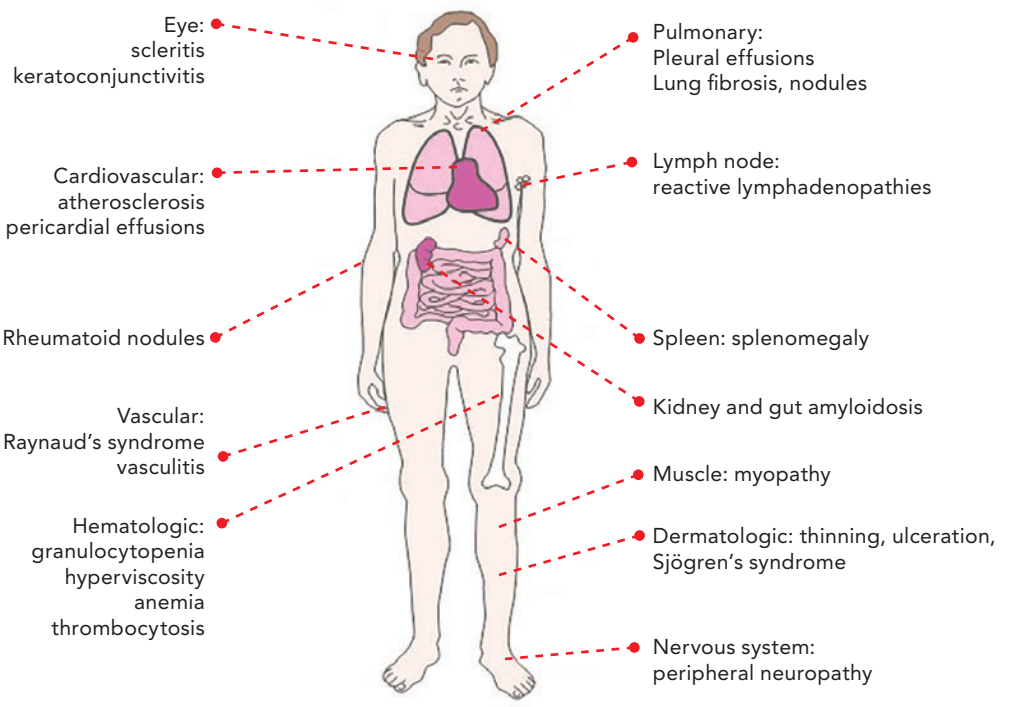
- It is important to achieve the lowest disease activity possible in order to maintain function and quality or life, and to prevent early death.
- Methotrexate is effective in 30 percent of patients, while 70 percent require additional therapy.
- Thirty percent will achieve true sustained remission, and 70 percent will achieve sustained low disease activity.
- Continuous communication between the rheumatologist and the patient is necessary to obtain the best disease control with the least toxicity.
- Limited patient access to medication because of insurer limitations is a major roadblock to effective disease control.

RHEUMATOID ARTHRITIS (RA) IS A SYSTEMIC autoimmune inflammatory disease which can be severely painful and disabling (Exhibit 1). The management of RA should use a treat-to-target approach, with a goal of remission or very minimal disease activity. Treat-to-target is incorporated into American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommendations for the treatment of RA.[1-3]

The primary goal of treating patients with RA is to maximize long-term health-related quality of life through the control of symptoms, prevention of structural damage, prevention of early death, normalization of function, and the participation in social and work-related activities. Abrogation of inflammation is the most important way to achieve these goals. Treat-to- target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA. The treatment of RA must be based on shared decision-making between the patient and rheumatologist. Continuous communication between the rheumatologist and patient and medication adjustments are necessary to obtain the best disease control with the least toxicity.

The primary target for treatment of RA should be a state of clinical remission. Clinical remission is the absence of signs and symptoms of significant inflammatory disease activity. While remission should be a clear target, low disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease.[1,2] The use of validated composite measures of disease activity, which include joint assessments, are needed in routine clinical practice to guide treatment decisions and identify

Exhibit 1: RA is a Multisystem Disease (it's not just the joints)



remission in a systematic manner. The choice of the composite measure of disease activity and the target value should be influenced by comorbidities, patient factors, and drug-related risks. Approximately 30 percent of patients will achieve a true sustained disease remission, with 70 percent able to achieve sustained low disease activity.

At each visit, clinicians should discuss the patient's symptoms fully, including joint symptoms, systemic symptoms, and patient important considerations such as degree of their pain, fatigue, and limitations of activity. They should perform a full physical examination and joint count to determine if there is other organ involvement and the state of the arthritis. Pertinent laboratory tests to assess the inflammatory state and whether there are systemic complications of therapy include, at a minimum, a complete blood count (CBC) and chemistries evaluating the liver and kidneys. A validated metric should be calculated at each visit to gauge the response to therapy. This can include a clinical measure (Clinical Disease Activity Index, Simple Disease Activity Index, Disease Activity Score in 28 joints) and a patient-reported measure, such as the Health Assessment Questionnaire -Disability Index (HAQ-DI) or Routine Assessment of Patient Index Data 3 (RAPID3). If the patient has not reached remission or very low disease activity, their medication is adjusted, taking into consideration patient preferences, comorbidities and, unfortunately, patient access to medication. All of this takes time and cannot be accomplished in 10-minute visits. Twenty-minutes is the average time needed for a comprehensive patient visit.

Patients need to understand that the likelihood of improvement is high with treatment, but a cure is doubtful. The importance of taking medication as prescribed for continued control of disease activity has to be emphasized to each patient – if they do not take the medications they are prescribed, the treatment cannot work. The importance of reporting adverse events as soon as possible and doing labs as required should also be conveyed to the patient.

Biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted-synthetic DMARDs (tsDMARDs) have revolutionized the treatment of RA by better targeting the underlying inflammatory pathology of the disease compared to the nonspecific suppression of the immune system of the traditional DMARDs, such as azathioprine and leflunomide. The bDMARDs target cytokines extracellularly by blocking cell surface receptors, binding to and neutralizing cytokines, or by activation of anti-inflammatory pathways. Tocilizumab and sarilumab are interleukin 6 (IL-6) receptor antagonists. IL-6 is a pleiotropic cytokine with multiple biological activities. Originally identified

Exhibit 2: Efficacy of bDMARDs/tsDMARDS in Clinical Trials[1,2]

Drug	ACR20	ACR50	ACR70	DAS < 2.6	â HAQ	Radiologic
ETN	✓	✓	✓	✓	✓	✓
IFX	✓	✓	✓	✓	✓	✓
ADA	✓	✓	✓	✓	✓	✓
CZP	✓	✓	✓	✓	✓	✓
GOL	✓	✓	✓	✓	✓	✓
ABA	✓	✓	✓	✓	✓	✓
TCZ	✓	✓	✓	✓	✓	✓
SAR	✓	✓	✓	✓	✓	✓
RTX	✓	✓	✓	✓	✓	✓
ANA	✓	✓	✓	NR	✓	✓
BAR	✓	✓	✓	✓	✓	✓
TOF	✓	✓	✓	✓	✓	✓

ACR20/50/70 = American College of Rheumatology composite measure of 20%, 50%, or 70% improvement
DAS = disease activity score; HAQ = Health Assessment Questionnaire; ETN = etanercept; IFX = infliximab
ADA = adalimumab; CZP = certolizumab; GOL = golimumab; RTX = rituximab; ABA = abatacept;
TCZ = tocilizumab; SAR = sarilumab; ANA = Anakinra; NR = not reported; BAR = baracitinib; TOF = tofacitinib

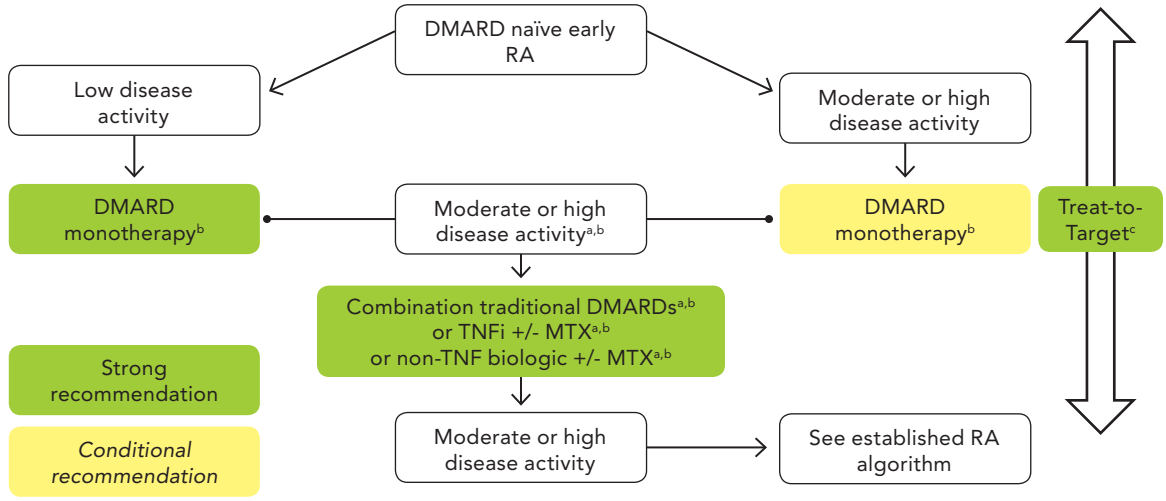
Exhibit 3: Efficacy in Various Patient Populations[1,2]

Drug	MTX-naïve	Early RA	Monotherapy	MTX-IR	MTX-IR
ETN	✓	✓	✓	✓	ND
IFX	✓	✓	✓	✓	ND
ADA	✓	✓	✓	✓	ND
CZP	✓	✓	✓	✓	✓
GOL	✓	ND	No	✓	✓
ABA	✓	✓	✓	✓	✓
TCZ	✓	ND	✓	✓	✓
SAR	ND	ND	✓	✓	✓
RTX	ND	ND	No	✓	✓
ANA	NR	ND	✓	✓	ND
BAR	✓	✓	✓	✓	✓
TOF	✓	✓	✓	✓	✓

ABA = abatacept; ADA = adalimumab; ANA = anakinra; CZP = certolizumab pegol;
EETN = etanercept; GOL = golimumab; IFX = infliximab; IR = inadequate responder;
HAQ = Health Assessment Questionnaire; ND = not determined; NR = not reported;
RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor;
BAR = baricitinib; TOF = tofacitinib; MTX = methotrexate

as a B-cell differentiation factor, IL-6 induces the final maturation of B cells into antibody-producing cells. It regulates the humoral immune response to antigens. The available bDMARDs in the United States (U.S.) include tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, adalimumab, certolizumab, golimumab), anti-CD20 inhibitor (rituximab), co-stimulation blocker of CD80/86:CD28 (abatacept), and IL-6 receptor antagonists (tocilizumab, sarilumab). All of the

Exhibit 4: American College of Rheumatology Early RA Treatment Algorithm[1]



[a]Consider adding low-dose steroids (<10mg/day of prednisone/equivalent) in patients with moderate or high RA disease activity when starting disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure.

[b]Also consider using short-term steroids (defined as < 3 months of treatment) for RA disease flares.

[c]Treatment target should ideally be ACR/EULAR remission or low disease activity if remission not possible.

TNFi = tumor necrosis factor inhibitor
MTX = methotrexate

bDMARDs are injectable monoclonal antibodies.

The tsDMARDs are orally administered small molecules that target intracellular signaling pathways.[4] The Janus kinase (JAK) inhibitors, tofacitinib and baricitinib, are the only tsDMARDs available at this time. These agents have been shown to be equivalent (tofacitinib) or superior in efficacy (baricitinib 4 mg) to TNF inhibitors.[5,6]

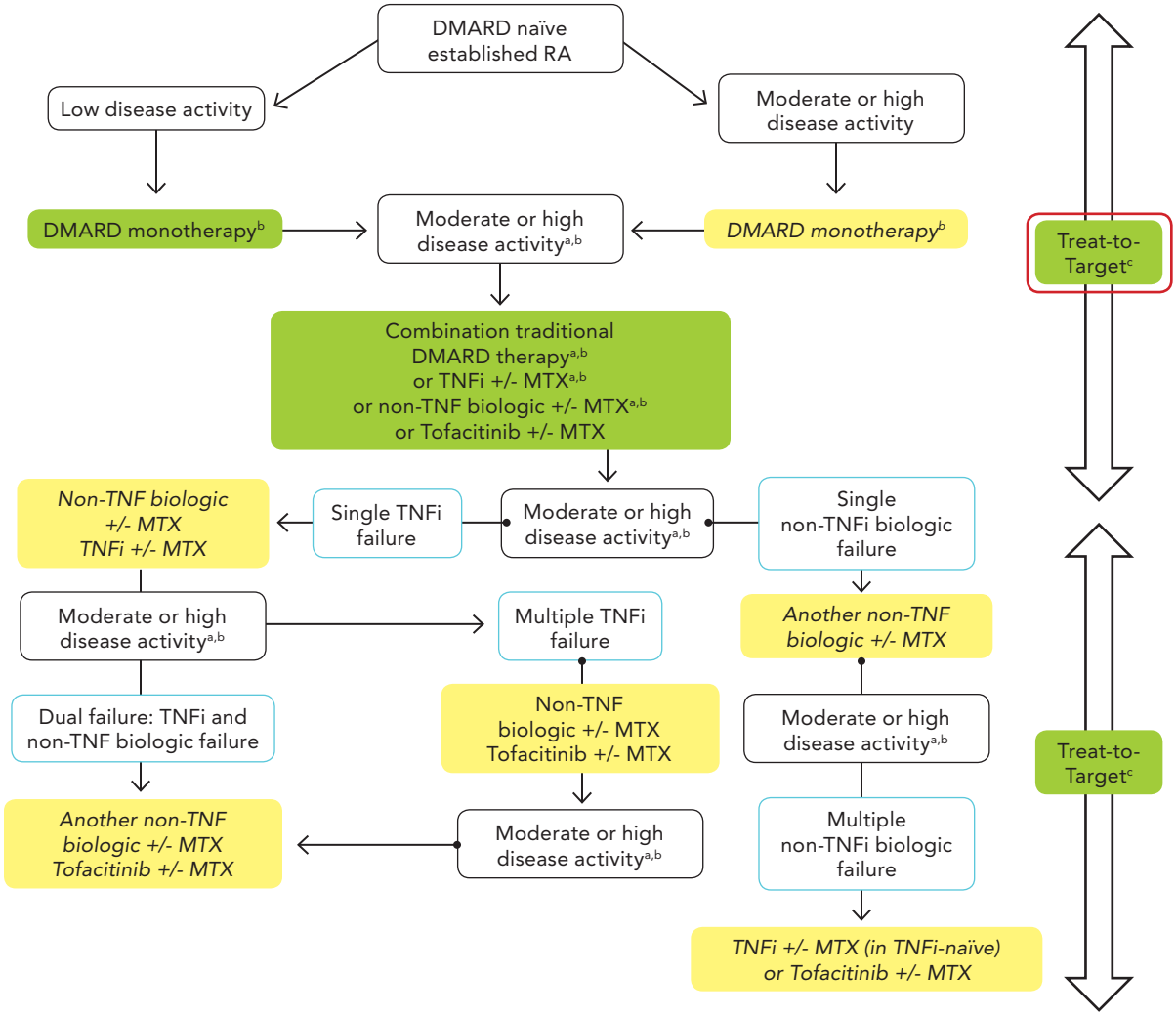
The bDMARDs and tsDMARDs are all effective for reducing symptoms, maintaining or restoring physical function, and slowing or halting radiographic progression (Exhibit 2).[1,2] They also have been studied in various patient populations (Exhibit 3).[1,2]

Limitations for using the bDMARDs and tsDMARDs are cost, not all patients obtain remission with a given agent, and concern about adverse events. Superior clinical and radiologic responses are obtained when most of the bDMARDs are used in combination with methotrexate (MTX), thus patients have to be on two therapies, which can both cause adverse events. IL-6 antagonists and JAK inhibitors are preferred if monotherapy is necessary because MTX use is not possible or tolerated. Factors for selecting among all these therapies include payer restrictions, patient choice, depth of response needed, speed of onset of effect, and co-morbidities. Insurer limitations on the use of the newer DMARDs are a major roadblock to effective disease control. The requirements for step therapy are especially problematic if a patient has severe disease, which is almost always going to require a bDMARD or tsDMARD and MTX for control.

The safety profiles of the bDMARDs and tsDMARDs are similar. The rates may be different, but the adverse events of concern are generally the same across all these agents. Serious infections, opportunistic infections, anemia, neutropenia, and lymphopenia are all issues. Unique adverse events with the JAK inhibitors include thromboembolic events, modest increase in serum creatine, and occasional increase in creatine phosphokinase.

The ACR treatment algorithms for early DMARD naïve disease and established disease are shown in Exhibits 4 and 5.[1] In both early and established disease, the guidelines recommend the treatment target should ideally be ACR or EULAR remission criteria or low disease activity if remission is unobtainable. If possible, all patients should begin on an effective dose of MTX (> 15 mg). Methotrexate is effective in achieving low disease activity in 30 percent of patients, while 70 percent of patients will require additional therapy. Patients should be seen three months after starting MTX. If there is a good response (significant reduction of CDAI/DAS28) and no adverse events, the MTX is continued. If there are tolerability issues, therapy should be switched to

Exhibit 5: Established RA Algorithm[1]



[a]Consider adding low-dose steroids (<10 mg/day of prednisone/equivalent) in patients with moderate or high RA disease activity when starting traditional DMARDs and in patients with DMARD failure or biologic failure

[b]Also consider using short-term steroids (defined as < 3 months of treatment) for RA disease flares.

another traditional DMARD or IL-6 or JAK inhibitor monotherapy. If remission is not achieved but the MTX is tolerated, a bDMARD or a tsDMARD should be added. There is low likelihood of response to addition of other traditional DMARDs. Any bDMARD or tsDMARD, that the patient prefers and to which they have access, can be utilized. Therapy is then evaluated every three months and adjusted until the patient reaches ACR/EULAR remission or lowest disease activity possible with acceptable tolerability. Once the disease is in remission, therapy can be tapered down by reducing the dose or the dosing frequency; however, it cannot be discontinued completely in the majority of patients.

Poor prognostic factors for severe RA include moderate-to-high disease activity despite traditional DMARDs (MTX, leflunomide, etc.), elevated acute phase reactants (Erythrocyte Sedimentation Rate [ESR] and C-Reactive Protein (CRP), high swollen joint count, seropositivity of rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA), presence of erosive disease of the joints, and inadequate disease control with two or more traditional DMARDs.[2] These patients definitely need to be on the most effective therapies, which are the bDMARDs or tsDMARDs.

Conclusion

RA is an aggressive, systemic disease which can be treated well in most patients, but not cured. For

more than 90 percent of patients, therapy is lifelong. It is important to achieve the lowest disease activity possible in order to maintain function, quality of life, and prevent early death. MTX monotherapy is effective for some patients, but the majority of them require the addition of a bDMARD or a tsDMARD. About 70 percent of patients will be able to achieve low disease activity, and 30 percent will reach true sustained remission. Limited patient access to medication because of insurer limitations is a major roadblock to effective disease control. Continuous communication between the rheumatologist and patient is necessary to obtain the best disease control with the least toxicity.

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Recent Advances in the Treatment and Management of Moderate-to-Severe Atopic Dermatitis: What's New in Biologic Therapies

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For a CME/CEU version of this article, please go to /www.namcp.org/home/education, and then click the activity title.

Summary

Treatment of atopic dermatitis (AD) is the most exciting arena currently in dermatology. Those who have been trying to care for these patients over the years have been seriously limited in therapies for those with moderate-to-severe disease. The new biologic therapy is providing unprecedented control of this skin disease.

Key Points

- AD is the most common chronic inflammatory skin disease.
- Crisaborole, an effective nonsteroidal topical agent which is well tolerated, is available for mild-to-moderate AD.
- Dupilumab, an effective biologic therapy, is now available for moderate-to-severe AD.
- Multiple additional biologics and other classes of therapy are on the horizon.

ATOPIC DERMATITIS (AD) IS THE MOST common chronic inflammatory skin disease, often starting in childhood, and it is a lifelong disease in many patients. AD manifests as eczematous rashes, itch, bacterial colonization and secondary infections and can have an intermittent or persistent course. Additionally, it is the leading cause of non-fatal disease burden of skin conditions.

AD occurs in approximately 20 percent of school-aged children and in 10 percent of adults; however, it may occur in as many as 30 percent of adults.[1] Up to 10 percent of those affected may develop the disease as an adult.[2] Studies have also shown that as adults, 50 percent of those with childhood AD retain some component of the disease.

An intact, healthy skin barrier is a critical first-line of defense against various microbes, irritants, and allergens. AD is a skin barrier disease that is thought to be the result of immune dysregulation within the skin. A major factor in maintaining an intact skin barrier is filaggrin. There is decreased filaggrin due to genetic mutations and type 2 helper T cells (Th2) mediated down regulation, which results in increased epidermal hyperplasia, decreased lipids in the skin, and decreased stratum corneum hydration. In addition, filaggrin breakdown products play an important role in acidifying the stratum corneum. An increase in the pH of the stratum corneum activates a number of serine proteases. A pH-induced increase in serine protease activity leads to both barrier breakdown and precipitates additional Th2 inflammation. The skin in AD has defects, even when it looks entirely normal.

Without adequate moisture, the skin is dry, red, and readily irritated. Alterations in proteases, pH changes in the skin, and irritants lead to scratching and skin trauma. This skin trauma allows allergens and bacteria to cross over into the skin and invoke

an immunologic response. It is helpful to think of the barrier defects in AD as resembling a whiffle ball; the skin is covered with holes that let the water in the skin "out" and the trigger factors "in." The skin barrier abnormality in AD is not just an epiphenomenon (a secondary or additional symptom or complication arising during the course of a malady), it is the initiator of the pathogenesis of the disease state. Overall, AD is a complex interplay between the skin barrier, allergy/immunology, and pruritus (Exhibit 1).[3] Treatment of AD requires repairing the skin barrier disruption, reducing itching, and replenishing skin moisture.

Intense pruritus is one of the most challenging aspects of disease management. Histamine 4 receptors are highly expressed on keratinocytes in lesioned skin of AD. Stimulation of these receptors promotes keratinocyte proliferation, inhibits keratinocyte differentiation, impairs skin barrier, and induces itching.[4] New antihistamines for managing itch in AD are being investigated as the currently available antihistamines are not particularly effective for itch management.

Itching is the one aspect of AD that most bothers parents of children with this skin disease. A reduction in skin hydration by 10 percent is crucial for the induction of itch.[5] Nighttime loss of sleep due to itching and scratching is a major issue for children and their parents; children may wake up an average of 36 times nightly, disrupting both their sleep and the sleep of their parents. About 30 percent of parents report that their children with AD climb into bed with them because of the itching and inability to sleep.[6] Parents of children with AD lose one to one and a half hours of sleep every night.

Moisturization of skin is important to managing itching. Chilled noxzema is a cost-effective way to help control itching and may be applied as often as needed. It "replaces" the sensation of itching with a cooling, tingling sensation and does not need to be washed off.

Beyond itching, AD, like other systemic inflammatory diseases, has impact on mortality. In adults, 10-year mortality is increased post hospitalization for AD compared to the general population, but is reduced compared to psoriasis.[7] There is also an increased risk of coronary artery disease, myocardial infarction, and suicide with moderate-to-severe AD.[8-11] It addition to its impact on sleep, AD has significant impact on overall quality of life.[12]

AD is also a financially costly disease. Overall health-related cost of AD is estimated at $5.2 billion in the United States (U.S.) each year.[13] That breaks down to $349 per patient per month in costs. Eighty-six percent of pediatric dermatology admissions to the hospital are for AD.[14] Overall, there is clear multi-dimensional burden with this disease.

Interestingly, prenatal folic acid and iron supplementation offer protection against AD development in the first six years of life.[15] Maternal folic acid supplementation is associated with DNA methylation that continues for many years after exposure. DNA methylation of genes regulating immune response may explain the benefit of folic acid on AD. Additionally, lack of adequate iron and folate in gestation may impair differentiation of a normal immune system, and folic acid plays an important role in strengthening the epithelial barrier.

It is important to note that although AD is predominately a disease of childhood, the majority of studies of therapeutic agents have only been conducted in adults. More recent agents, such as crisaborole which is discussed later, have been studied and are approved for use in pediatric populations.

Crisaborole (Eucrisa®), a topical benzoxaborole phosphodiesterase type 4 (PDE4) inhibitor, is FDA approved for AD. Crisaborole blocks cytokine synthesis by increasing and maintaining cyclic adenosine monophosphate (cAMP) levels and subsequently protein kinase A levels which negatively modulate signaling pathways that lead to cytokine production. This agent has physiological properties from the boron component that allow for skin penetration, but it does not have systemic absorption. Crisaborole reduces inflammation and itching and repairs the skin barrier.[16] It is indicated to treat mild-to-moderate AD in adults and children two years of age and older.

Crisaborole is a well-tolerated agent. The most common adverse effect is burning sensation at the application site. During studies of crisaborole, the rates of topical adverse effects remained very low over two years of treatment.[16] Topical steroid-like adverse reactions, such as application site atrophy and telangiectasia, did not occur during the crisaborole studies.

Topical tacrolimus, which has been available since 2000, has fallen out of favor because of a black box warning about possible cancers related to long-term use, but a possible use for tacrolimus ointment is in management of atopic keratoconjunctivitis. In a single-center, retrospective study in 18 patients, topical application to the eyelids decreased ocular symptoms and significantly decreased the need for topical steroids to the eyelids.[17]

The first targeted biologic agent for this disease was approved by the FDA in March of 2017. Dupilumab (Dupixent®), a fully human monoclonal antibody targeted therapy, is indicated for adults and children 12 and older with moderate-to-severe AD. It is an interleukin four alpha (IL-4α) receptor antagonist which inhibits signaling of IL-4 and IL-13, the TH2-derived cytokines that are impor-

Exhibit 1: Schematic of Pathology of Atopic Dermatitis[3]

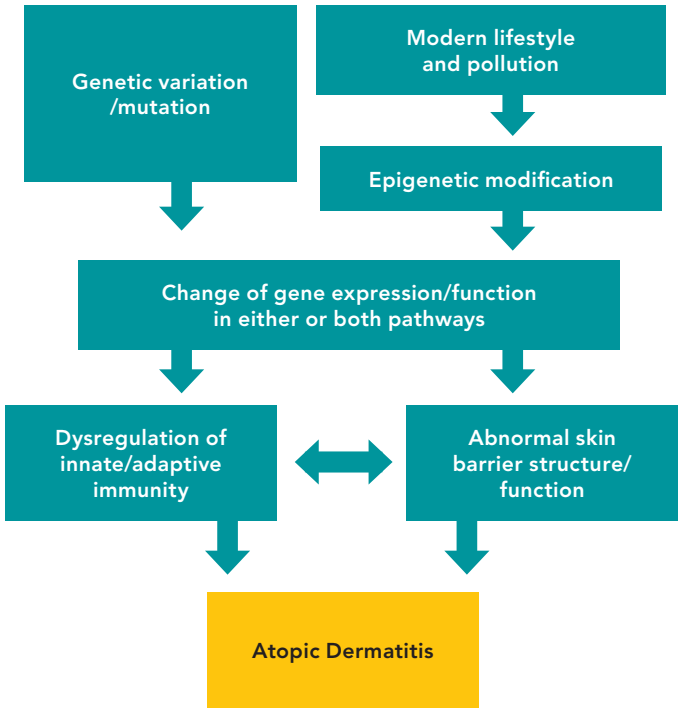
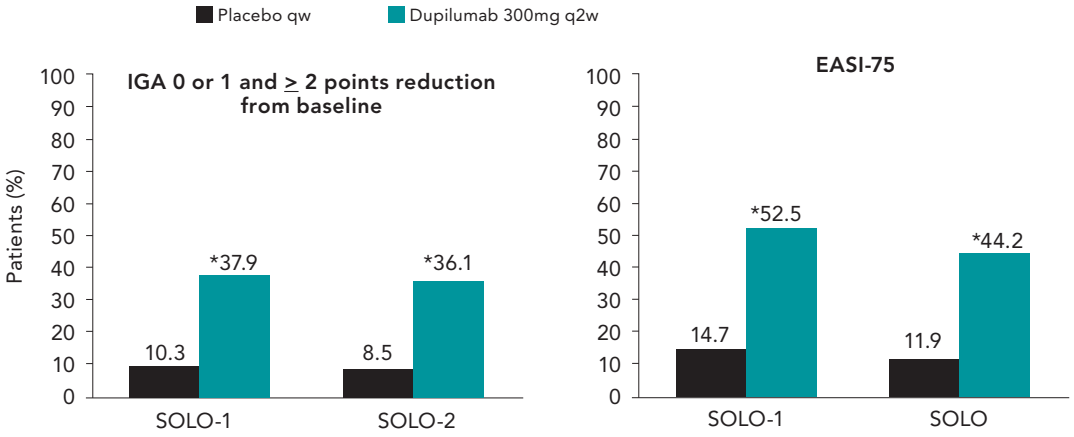


Exhibit 2: Efficacy of Dupilumab in Moderate to Severe AD at Week 16 Compared with Placebo[22]



*P< 0.0001 versus placebo
Only data from 300 mg every two weeks shown. Study also included 300 mg every week.
IGA 0 or 1 = Investigator Global Assessment clear or almost clear
EASI-75 = Eczema Area and Severity Index 75 percent improvement

tant drivers of AD pathology. IL-4 and IL-13 are inhibitors of epidermal differentiation and natural antimicrobial peptides, are elevated in acute and chronic skin lesions of AD, and both interact with the IL-4 receptor. Additionally, patients with AD have increased numbers of CD4- and CD8+ cells that release these two cytokines.

Dupilumab has been studied in the treatment of adults and adolescents with moderate-to-severe AD as monotherapy and in combination with topical

Exhibit 3: Efficacy of Tofacitinib Topical[30]

Primary Measurement	2% TOFACITINIB OINTMENT; BID (n=34)	PLACEBO OINTMENT; BID (n=31)	P value
% Change in EASI Score at week 4	-81.7	-29.9	< 0.0001

Secondary Measures	2% TOFACITINIB OINTMENT; BID (n=35)	PLACEBO OINTMENT; BID (n=34)
% Achieving PGA Clear or Almost Clear	71.4	20.6
% PGA Clear or Almost Clear and ≥ 2 Grade/Point Improvement	65.7	11.8

corticosteroids.[18-24] Patients may have AD hotspots that require the addition of topical corticosteroids to get it under control. In three randomized Phase III pivotal trials of 2,119 adult patients with inadequately controlled moderate-to-severe AD, measures of skin clearing (Eczema Area and Severity Index [EASI] and Investigator Global Assessment [IGA]) and severity of disease were significantly improved at 16 weeks compared to placebo (Exhibit 2).[22]

In one study where some patients underwent a skin biopsy, dupilumab treatment resulted in changes in the AD molecular disease profile.[20] It improved the AD molecular disease profile in a dose-dependent manner, and expression of genes upregulated in AD lesions were decreased in treated patients. Additionally, the molecular changes paralleled improvements in clinical scores.

Dupilumab also has an impact on symptoms and quality of life. It reduced peak itch at 16 weeks relative to placebo, by 1.1 to 3.2 points in all doses except the 100 mg dose. It also improved sleep, health-related quality of life, and reduced anxiety and depression symptoms.[21]

Another option for severe disease in pediatrics when dupilumab is not an option is methotrexate given once a week. Because of the known risk of lymphoma, it is typically only used from one to two years. In a case review, 76 percent of patients (n = 55) showed improvement with methotrexate and 50 percent of patients had minor adverse effects such as GI upset.[25]

Clinicians and managed care need to get ready for an onslaught of new AD targeted agents. Other topical PDE4 inhibitors like crisaborole, including OPA-15406, are under investigation for mild-to-moderate AD. OPA-15406 ointment has rapid onset anti-inflammatory and anti-pruritic effect and has been shown to be especially effective in selective inhibition of PDE4 subtype B.[26] A small number of children of age 10 and above were included in the published trials.

As with dupilumab, many of the investigational biologic agents target IL-4 and IL-13, but a few also target IL-31, which is thought to be important in mediating itching. Lebrikizumab and nemolizumab are two examples of investigational biologics for AD. Lebrikizumab, a humanized monoclonal antibody that targets IL-13 with high-affinity binding, is being studied for moderate-to-severe AD. It inhibits heterodimerization of the IL-13 alpha/IL-4 alpha complex. Positive outcomes were shown in a recent Phase II study.[27]

Nemolizumab antagonizes the IL-31 receptor A which blocks IL-31 signaling on various cells, including peripheral neurons. IL-31, the itch cytokine, is significantly upregulated in AD lesions. Levels of IL-31 have correlated with disease activity, compromised barrier function, and the itch-scratch cycle. Nemolizumab decreased itching on a visual analogue scale by 20 to 40 percent more than placebo.[28]

Janus kinase (JAK) inhibitors are another promising novel drug class for moderate-to-severe AD.[29] These inhibit the activity of one or more of the JAK family of enzymes and thus interfere with the JAK-STAR signaling pathway and block cytokine signaling. Tofacitinib (Xeljanz®), a JAK3 inhibitor that is already FDA approved for rheumatoid arthritis, psoriatic arthritis and ulcerative colitis, blocks IL-2. IL-4, IL-15, IL-21, and TH2 cell differentiation. Although given orally for the approved diseases, topical tofacitinib is in Phase III trials for AD. In a Phase II study, tofacitinib 2 percent ointment applied twice a day significantly improved EASI

score, physician global assessment, and affected BSA (Exhibit 3).[30] Interestingly, itching improved by day two of therapy. Tofacitinib topical was well tolerated with more adverse effects being observed in the placebo vehicle (55.9%) group compared to tofacitinib (31.4%). Other JAK inhibitors that are being studied in adult AD include ruxolitinib (Jakafi®, JAK1/JAK2), filgotinib (JAK1), and baricitinib (Olumiant®, JAK1/JAK2).

Conclusion

Atopic dermatitis is more common in the pediatric population, but most medication treatment trials have been in adults. An effective biologic treatment for moderate-to-severe AD which targets the underlying pathophysiology is now available for both adults and adolescents. Additionally, numerous other biologics and JAK inhibitors are on the horizon for treating this disease.

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Expanding Options in the Treatment of Prostate Cancer: The Impact of Prognostic Biomarkers on Patient Outcomes

Henry M. Garlich

For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

The cost of oncology care is concerning for managed care. One way which plans can possibly save money is by forming strategic partnerships with laboratories and providers to ensure appropriate use of genetic tests to guide therapy. For prostate cancer in particular, this may lead to reduction in use of treatments for low-risk disease.

Key Points

- Managed care can consider forming strategic partnerships with genetic testing companies to increase access and improve use of genetic testing.
- One area to target is prostate cancer where genetic testing can distinguish between low-risk disease which can be managed with active surveillance and higher-risk disease which should be treated definitively with surgery or radiation.
- Appropriate use of genetic testing may lead to cost savings from reduced use of surgical and radiologic interventions.

TOTAL AND PRIVATE HEALTH CARE SPENDing is greater in the United States (U.S.) than in the United Kingdom, Germany, Sweden, France, the Netherlands, Switzerland, Denmark, Canada, Japan, and Australia. Government health care spending in the U.S. is similar to that of these other countries and is even less than some of them. Despite all this spending, the quality of care in the U.S. ranks last among the listed countries. Part of this cost is waste, with the U.S. health care system wasting at least $750 billion yearly. This waste includes unnecessary services, inefficiently delivered services, excess administration costs, missed prevention opportunities, and fraud. Blue Shield of California is working with clinicians and strategic partners, such as genetic testing manufacturers, to eliminate low-value care and lower costs without harming quality of care.

One area of opportunity to reduce waste and improve quality of care is in prostate cancer care. Prostate cancer is the number one cancer in men in terms of the number of new cases diagnosed annually, and it is the second leading cause of death among men.[1] There are more than 175,000 new cases diagnosed each year. Prostate cancer is the third most costly cancer to treat.[2] As shown in Exhibit 1, up to 40 percent of the treatment spend on prostate cancer ($4.8 billion) may be inappropriate.[3,4] Much of the inappropriate care in prostate cancer is the overuse of surgical or radiation procedures, rather than using active surveillance.

The traditional pathway for diagnosis of prostate cancer has multiple problems (Exhibit 2). There is a lack of patient and physician confidence that a prostate biopsy alone provides accurate information for risk assessment and appropriate treatment decision-making. Historically, there is a 25 to 30 percent discordance between a biopsy Gleason Score (marker of aggressiveness) and the score assigned from speci-

Exhibit 1: Identifying Waste in Prostate Cancer Treatment Spend[1,2]

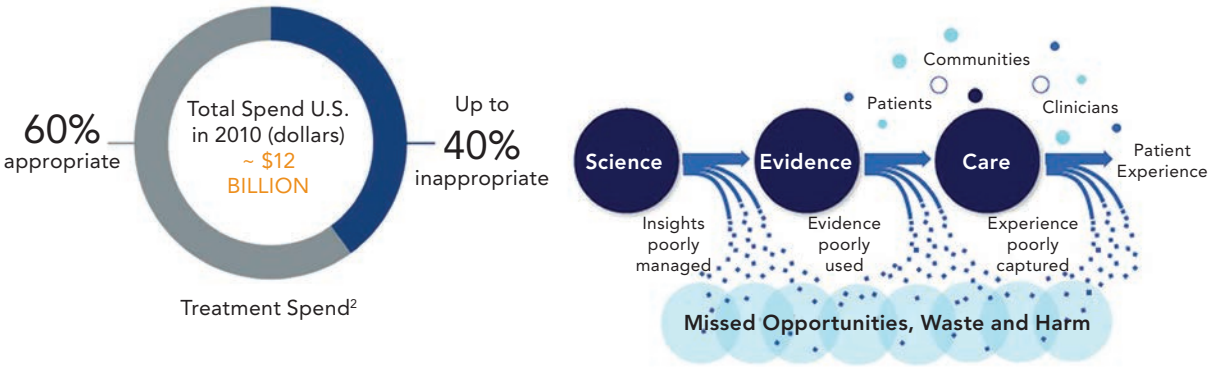
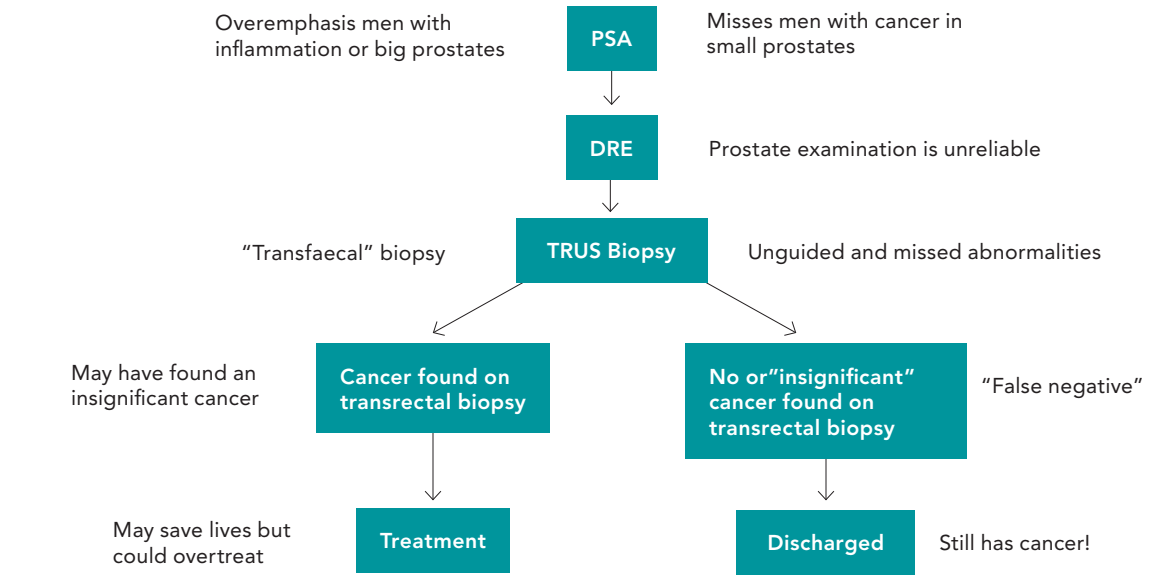


Exhibit 2: Traditional Diagnostic Pathway has Multiple Problems



PSA = prostate specific antigen
DRE = digital rectal exam

mens obtained during a radical prostatectomy. The clinical uncertainty in the ability of biopsy tissue alone to discriminate indolent disease from aggressive cancer contributes to widespread overtreatment of low-risk prostate cancer.

There is widespread concern that the early detection of prostate cancer through screening programs has led to the overtreatment of localized disease.[5-7] Approximately 80 percent of all patients with localized prostate cancer receive definitive treatment, including radical prostatectomy, radiation therapy, androgen deprivation therapy, or some combination.[8] This occurs despite a risk of treatment-related complications and the fact that the vast majority of prostate cancers do not cause death, even when initial treatment is conservative. Overall, there is no

Exhibit 3: The Power of Molecular Tumor Testing to Differentiate between Two Similar Cases

Clinical Features 62 years old PSA: 3.2 Gleason: 3 + 3 = 6 Stage: T1c **Proposed Treatment** Radical Prostatectomy		**Clinical Features** 62 years old PSA: 4.0 Gleason: 3 + 3 = 6 Stage: T1c **Proposed Treatment** Radical Prostatectomy
Consistent with AUA low-risk	**Molecular Tumor Testing**	Considerably more aggressive than AUA low-risk
1%	**10-year Prostate Ca Mortality**	5%
Active Surveilance	**Active Treatment**	Radical Prostatectomy
$0[1]	**Initial Treatment Cost**	$10,739[1]
$893[2]	**Annual Follow-up Cost**	$771[2]

Exhibit 4: Partnership with Labs

Coding

- Identity code stacking and appropriate use of Tier 2 and unlisted codes
- Prevent code shopping
- Work with labs to utilize SOMN

Clinical Collaboration

- Provide genetic consulting and education
- Share data and clinical evidence
- Provide medical expertise
- Medical policy and CED

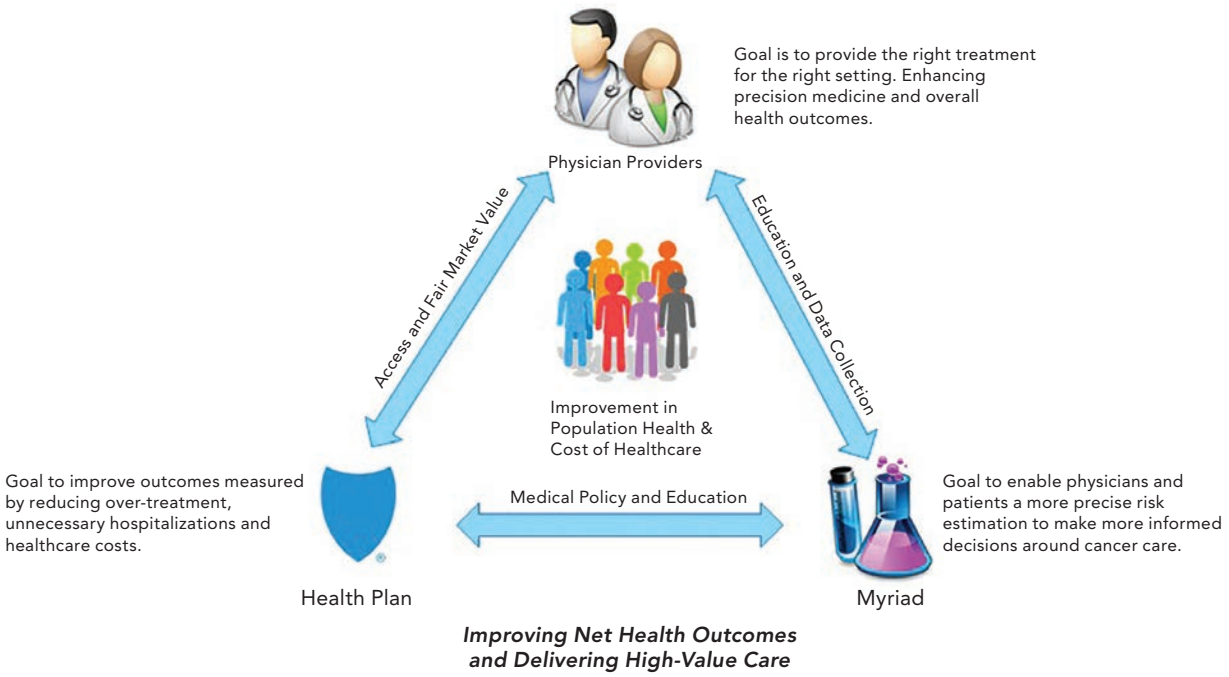
Fair Market Pricing

- Negotiate contracted fair market rates based on available data
- In-network versus OON fee schedule
- Advances in technology reduce pricing

difference in mortality outcomes between active surveillance and definitive treatment. Definitive treatment can cause complications including infection, urinary incontinence, sexual dysfunction, and depression. Risk stratification using typical prognostic factors leaves physicians and patients with uncertainty about the aggressiveness of the cancer, resulting in under-use of active surveillance.[8,9]

Thus, there is a need for more precise risk stratification tools that allow for more informed decision-making at the time of diagnosis. Gene expression assays can fill an evidence-based need for a prognostic indicator that distinguishes between aggressive and indolent tumors more accurately than clinical

Exhibit 5: Triad of Collaboration



Improving Net Health Outcomes and Delivering High-Value Care

and pathologic features, enabling physicians to confidently tailor optimal treatment strategies for patients. The National Comprehensive Cancer Network (NCCN) guidelines state that men with low or favorable intermediate-risk disease may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, Prolaris, or ProMark.[9] The tumor-based molecular assays provide prognostic information independent of the NCCN or the Cancer of the Prostate Risk Assessment (CAPRA) risk groups. Exhibit 3 illustrates the power of molecular testing to steer appropriate patients to less invasive and less costly treatment.

There are many reasons for insurers to provide access to the tumor-based molecular assay tools. One is to promote active surveillance in appropriate patients and stem the overuse of radical prostatectomy and intensity-modulated radiation therapy. Use of the assay can improve risk stratification by incorporating individual underlying tumor biology. Cost savings can be seen by increasing the use of active surveillance, while decreasing the use of immediate treatment. Cost savings can be both for the patient in terms of co-pays and cost-sharing and for the plan. By identifying those with more aggressive tumors, treatment can be initiated, which decreases progression rates.

Plans can have various aspects of collaboration with laboratories to improve use of the molecular assays (Exhibit 4). Insurers have to find a laboratory which provides quality testing with analytic and clinical validity to collaborate with. Because of lack of national standards for many of these assays, laboratories have been willing to work with plans to establish the usefulness of their assays.

Blue Shield of California instituted a program of collaboration between the insurer, providers, and a laboratory company to improve net health outcomes and deliver high-value care to those diagnosed with localized prostate cancer (Exhibit 5). Blue Shield began covering the test a few years ago and has been collecting data on the collaboration. Preliminary results from the program found that active surveillance increased 18 percent, radial prostatectomies decreased 8 percent, and intensity-modulated radiation therapy decreased 14 percent. Cause and effect that the test itself led to the changes cannot be determined yet from this data; however, insurers cannot wait for a randomized controlled trial to determine the benefit. Most providers are already using these tests, even if they are not covered by insurance. Patients are paying out of pocket, or the institutions are subsidizing the costs. Insurers can work with laboratory companies to allow access, evaluate costs, determine if there are cost savings, and determine if the tests are an asset to providers.

Conclusion

Providing access to tumor molecular assays has the potential to reduce invasive procedure use and thus costs in managing low-risk prostate cancer. More insurers need to cover these tests and work with their providers to reduce waste in the care of these patients. Insurers need to partner with laboratories to begin to manage the high cost of cancer care.

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Expanding the Role of Biosimilars: Key Advances in the Treatment Landscape

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

More biosimilars are being approved every year by the FDA, and several are finally on the market. The uptake of biosimilars has been slow in the United States (U.S.), but this may accelerate as more experience is gained. Biosimilars are leading to significant cost reductions and improved patient access in the European Union. Whether this same success can be seen in the U.S. is not yet known.

Key Points

- Biologics are complex drugs that cannot be made "generic."
- A biosimilar is a biologic demonstrated to be highly similar to a reference product through appropriate comparative, head-to-head quality, non-clinical and clinical studies.
- The comparability exercise used to demonstrate that a biosimilar is "highly similar" to a reference biologic is scientific, robust, and regulated.
- Several biosimilars are now approved in the U.S., with more under FDA review and many more under development.

WHEN DISCUSSING BIOSIMILARS, IT IS IMportant to start with a few definitions. According to the U.S. Code of Federal Regulations, a biologic is any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man. Biologics are derived from living sources, including bacteria, viruses, humans or animals. Biologics in this discussion can be thought of as therapeutic proteins. Biologics have very different characteristics compared to typical chemical or small molecule drugs (Exhibit 1), which makes them difficult to duplicate.[1] Unlike producing small molecule drugs, the manufacturing process for biologics is complex. Some example biologics include human insulin, epoetin alfa, and rituximab.

Globally, biologics share of total prescription medicine sales is increasing significantly and are a major driver of rising medication costs. In 2017, biologics represented 2 percent of all U.S. prescriptions, but accounted for 37 percent of net drug spending. Since 2014, biologic drugs accounted for 93 percent of the growth in net drug spending.

The FDA defines a biosimilar as a biological product that is highly similar to a U.S.-licensed reference biological product for which there are no clinically meaningful differences in safety, purity, or potency of the product.[2] Exhibit 2 shows where the FDA allows biosimilar to be different from the reference product.[3]

Intended copies of biologic products ("me-too biologics") are copies of already licensed biological products that have not met the regulatory criteria for biosimilars and are not available in the U.S. A biobetter is a biologic that has been structurally and/or functionally altered to achieve an improved or different clinical performance and must go through the full development and approval process. No biobetters have been approved in the U.S.

Two basic principles that have allowed development of biosimilars include that biologics undergo natural variability with time and that an identical copy of a biologic cannot be made.[4] The biosimilar does not need to be exactly like the reference biologic because the reference biologic is not identical to itself over time. Exhibit 3 shows the number of manufacturing changes to several biologics which have occurred since their initial FDA approval.[5] Small modifications in manufacturing may result in gradual changes. Despite differences, when the products are within a

Exhibit 1: Differences Between Chemical Drugs and Biologics[1]

	Chemical Drugs	Biologics
Size	Small, low molecular weight	Large, high molecular weight
Structure	Simple, well-defined	Complex, heterogeneous
Mannufacturing	• Reproducible chemical reactions • Identical copies can be made	• Living cells or organisms • Impossible to ensure identical copies
Characterization	Completely characterized	Impossible to fully characterize molecular composition
Stability	Stable	Unstable, sensitive to external conditions
Immunogenicity	Mostly non-immunogenic	Immunogenic

Exhibit 2: FDA Specifications for Biosimilars versus Reference Biologic[3]

Biosimilar Product Specification	Comparison with Reference
Formulation	May be different
Delivery device/container	May be different
Routes of administration	May optain licensure for fewer than all routes of administration for which reference product is licensed
Conditions of use	May obtain licensure for fewer than all conditions of use for which reference product is licensed
Strength	Must be the same

prespecified acceptable range, a biologic product is marketed with no change in label. If large alterations occur, analytical studies (and possibly additional clinical studies) are required to compare the post-change product with the existing pre-change product.[6]

To demonstrate biosimilarity, the biosimilar sponsor submits evidence that the candidate biosimilar is not significantly different from the reference product. The clinical efficacy and safety of the biologic molecule has already been demonstrated by the reference product. The goal is not to replicate unnecessary clinical trials but to use smaller-scale direct comparisons and extrapolation. When a biosimilar is approved, there should not be an expectation that there will be differences in safety and efficacy. The process of biologic and biosimilar approval is through the Public Health Service Act instead of the Food, Drug, and Cosmetics Act, which outlines the approval process for small molecule medications. Each undergoes a different approval process (Exhibit 4). The biosimilar development program objective is to establish biosimilarity based upon the totality of evidence, not to re-establish clinical benefit. The highly similar designation is determined based on analytics and clinical pharmacology data. The determination of no clinically meaningful differences is based on targeted clinical trials in a sensitive population (i.e., the indication for which difference is likely to be detected).

Some issues relevant to biosimilars are extrapolation, interchangeability, immunogenicity, and naming. Extrapolation is where the indications for

Exhibit 3: Reference Biologics and Post-Approval 'Life Cycle' Changes[5]

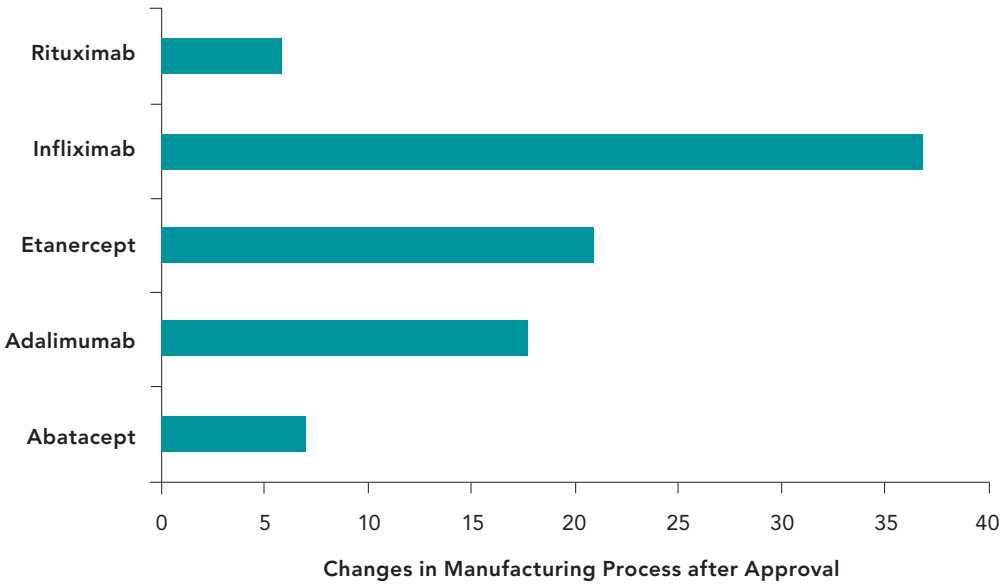
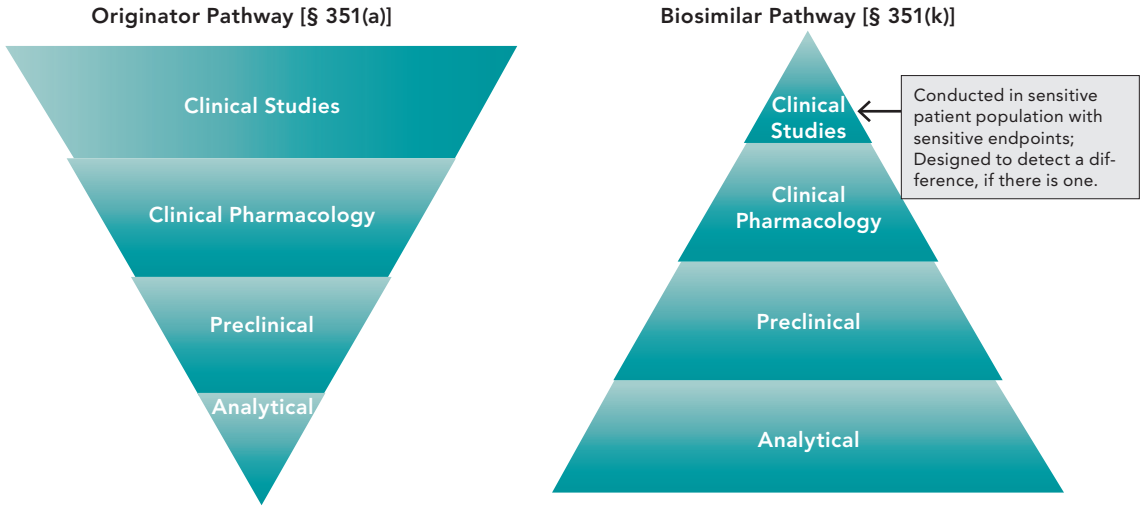


Exhibit 4: Biosimilar Pathway Represents a Paradigm Shift from Standard Originator Registration Pathway



a biosimilar are the same as those for the reference product, even though studies are not required to be done with the biosimilar for each indication. The approved indications for the biosimilar are justified based on the total data package. Interchangeable or interchangeability means that two products can be directly interchanged (i.e., if a prescription is written for Reference drug A and there are is an interchangeable biosimilar B, no intervention with the original prescriber is required for a substitution of A with B to be made subject to individual state regulations).

Interchangeable is a FDA designation that requires different data standards than 'biosimilarity' alone. It requires dedicated switching study and post-marketing monitoring. Any biological product under consideration for substitution must first be approved by the FDA as "interchangeable." No currently approved biosimilars have an interchangeable designation.

Immunogenicity is a concern with all biologics, not just biosimilars. The consequences of immunogenicity are loss of efficacy through neutralization of the administered biologic agent by antibodies against biologic and general immune responses (allergy, anaphylaxis). A comparative parallel, head-to-head study is required to assess immunogenicity of a biosimilar.

There has been controversy about the naming of biosimilars. Some experts believe that biosimilars should have the same exact nonproprietary name as their respective reference in order to communicate that these products are "highly similar" and to facilitate adoption and substitution of interchangeable biologics.[7,8] This approach makes it hard to trace adverse events to a specific product. The other side believes that biosimilars should each have a distinct nonproprietary name to distinguish them from the originator and other biosimilars to improve pharmacovigilance for adverse events and to recognize that these are distinct products. This approach can lead to confusion about whether they are "highly similar," may impede adoption of biosimilars, and can lead to issues with substitution. The FDA Guidance on Naming established that there will be a core nonproprietary name and distinguishing suffix (devoid of meaning and composed of four lower case letters) for each biosimilar. Newly approved originator or biosimilar products will have the distinguishing suffix; older biologics do not have the suffix For example, infliximab (Remicade®) is a reference product and infliximab-abda (Renflexis®) is a biosimilar. The core name will group similar biologics in electronic systems, and having the suffix for all products reduces perception that biosimilars are inferior to the reference product. The goal of this naming structure is to facilitate pharmacovigilance and prevent inadvertent substitution. Inadvertent substitution may lead to unintended alternating or switching of biological products that have not been determined by the FDA to be interchangeable.

Uptake of biosimilars has been greater in Europe than in the U.S. Safety and efficacy of approved and marketed biosimilars in Europe has been consistent with experience with the reference biologics, with no specific safety issues identified. In an updated European Commission report on the impact of biosimilar competition, consistent average price reduction in therapy areas where biosimilars have been introduced was shown across the European Union.[9] Increased biosimilar competition affected not only the price for the directly comparable product, but for the whole product class. Some countries within the European Union had a low usage/availability in specific classes in 2015; however, price reductions seemed to significantly increase access for patients to biological medicines by 2017.

As of November 2019, the FDA had approved 24 biosimilars, and 10 are currently marketed: epoetin alfa-epbx (Retacrit®), filgrastim-sndz (Zarxio®), filgrastim-aafi (Nivestym®), tbo-filgrastim (Granix), infliximab-dyyb (Inflectra®), infliximab-abda (Renflexis®), pegfilgrastim-jmdb (Fulphila®), pegfilgrastim-cbqv (Udenyca®), and trastuzumab-anns (Kanjinti™). Legal issues have entangled many of the others. The U.S. remains, by far, the world's largest pharmaceutical market, including biologics, so there will be some pressure to get the legal issues resolved. Among biosimilars that have entered the market, price reductions and market penetration have been limited. For example, filgrastim-sndz, the first biosimilar to be approved, entered the market in September 2015 at only a 15 percent discount off the reference's list price and by the end of 2016 had acquired just 20 percent of the U.S. filgrastim market.[10] Infliximab biosimilars are available at a 25 percent discounted price relative to the reference biologic, and have acquired about 7 percent of the U.S. infliximab market.[11] Prices for infliximab have been declining and the biosimilars got a boost when United Healthcare added the biosimilars as preferred for its Medicare Advantage plans, over the reference product (Remicade®). Exhibit 5 shows some of the barriers to biosimilar uptake and possible solutions.[12]

One area of particular interest and anticipation for marketed biosimilars is oncology. Biologics represent approximately 50 percent of the pharmaceutical market in oncology and play a critical role in clinical care for supportive care (myeloid growth factors, erythropoietin stimulating agents) and in active therapy (monoclonal antibodies, antibody drug conjugates, interferons, and immunotherapy). Many of the most expensive drugs are used in oncology. Trastuzumab-anns has recently entered the market and rituximab-abbs (Truxima®) was launched in late 2019. There is potential for enormous impact of biosimilars on costs and availability of biologics in oncology.

The biosimilar segment of the pharmaceutical industry is exploding. Some 700 biosimilars are at varying stages of development, and more than 660 companies are involved. Many patents of blockbuster and budget-busting biologics are expiring, but biosimilar developers will not have it easy. The companies behind the brand-name products will continue to protect their turf with rebates and marketing. Eventually, there may be three to five biosimilar products for each reference biologic competing against one another.

Exhibit 5: Barriers to Biosimilar Uptake[12]

Barrier	Result	Proposed Strategy
Regulatory Policy		
Approval process Interchageability Extrapolation	Prescribers are uncertain if clinical evidence is adequate and if products are interchangeable or if indications can be extrapolated.	Rigoroius educational programs by manufacturers and policy makers on FDA processes for approving biosimilars and how pharmacovigilance programs are implemented.
Economics		
Reimbursement models Pricing Payers	Complex and dynamic CMS reimbursement rules for biosimilars create confusion for billing offices. Economic impact on patients and providers is difficult to evaluate. Providers may not be able to adopt biosimilars if payers prefer innovator products.	Simplify coding and reimbursement processes and work with payers on demonstrating the value that biosimilars bring to market, such as lowering costs and improving access.
Perception		
Treatment goals Patient acceptance	Prescribers may be more willing to accept biosimilars when treating for palliative intent rather than curative intent. Patients may be reluctant to accept what they view as "generic" products.	More educational programs that focus on acknowledging behavioral economics as a concept that effects prescribing. Incentivizing prescribers to use biosimilars using various payer-based vehicles.

CMS = Centers for Medicare and Medicaid Services; FDS = U.S. Food and Drug Administration

Conclusion

Biologics are complex drugs that cannot be made "generic." A biosimilar is a biologic demonstrated to be highly similar to a reference product through appropriate comparative, head-to-head quality, non-clinical and clinical studies. The comparability exercise used to demonstrate that a biosimilar is highly similar to a reference biologic is scientific, robust, and regulated.

Biosimilar uptake continues to increase in Europe, and no specific safety issues have been identified for approved and marketed biosimilars. Several biosimilars are now approved in the U.S., with more under FDA review. Incorporation of biosimilars into U.S. clinical practice offers opportunity for health care cost savings and increased patient access to biologic therapies but has been slow to develop.

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New Advances in the Diagnosis and Treatment of Narcolepsy

Thomas Roth, PhD

For a CME/CEU version of this article, please go to /www.namcp.org/home/education, and then click the activity title.

Summary

Narcolepsy, a chronic sleep disorder, has major impact on affected patients. Several treatments are available which improve daytime sleepiness, nighttime sleep, and cataplexy. Treatment often requires combination therapy.

Key Points

- Narcolepsy is a neurodegenerative autoimmune disorder, resulting in destruction of hypothalamic neurons producing the neuropeptide orexin.
- Combination therapy with a stimulant and an anticataplectic agent is often used.
- Sodium oxybate treats both excessive daytime sleepiness and cataplexy, but has to be dosed twice during the night.
- Future therapies are targeting the immune system and orexin deficiency.

NARCOLEPSY IS A CHRONIC SLEEP DISORDER characterized by overwhelming daytime drowsiness and sudden attacks of sleep. Hallmark symptoms of narcolepsy include excessive daytime sleepiness (EDS), cataplexy, vivid hallucinations upon falling sleep or awakening from sleep, and brief episodes of total paralysis upon falling asleep or awakening from sleep. EDS is the most common initial symptom, occurring alone in about 46 percent of patients and with other symptoms in 33 percent of patients.[1] Over 60 percent of patients present with only one hallmark symptom; less than 10 percent of patients present with all four hallmark symptoms.

Cataplexy is a sudden transient complete or partial loss of muscle tone accompanied by full conscious awareness, typically triggered by emotions such as laughing, crying, or terror. Cataplexy is present in the majority of patients with narcolepsy (64% to 90%).[2] Cataplexy is not just a collapse at the knees, it can involve the eyes, head, or jaw. The first episode of cataplexy typically occurs several weeks or months after the onset of EDS, although it may be delayed for decades.[1] In approximately 10 percent of cases, cataplexy is the first symptom of narcolepsy to appear. Cataplexy is often misdiagnosed as a seizure.[3] Other symptoms of narcolepsy are disturbed nighttime sleep and mental fog. Wake and sleep cycles are poorly consolidated in narcolepsy, which leads to disturbed nighttime sleep.

The syndrome was first described in the 1870s and stimulants were first used in the 1930s. In the 1980s an association with human leukocyte antigens (HLA) was found, tying the syndrome to the immune system. More recent advances provide compelling evidence that narcolepsy is a neurodegenerative autoimmune disorder, resulting in destruction of hypothalamic neurons producing the neuropeptide orexin. In 2009 and 2010, there was a dramatic increase in narcolepsy cases in Northern Europe and China, especially in children. This increase was traced to vaccination against pandemic H1N1 Influenza A (pH1N1) with a specific vaccine (Pandemrix®) in Europe and natural infection with pH1N1 in China.[4] Influenza and the associated vaccination are specific environmental

Exhibit 1: Differentiating Narcolepsy from Idiopathic Hypersomnia[10,11]

- **Narcolepsy**
  - Naps are more refreshing
  - Higher propensity to fall asleep (higher Epworth Sleepiness Scale [ESS] scores)
  - Patients experience more frequent and longer nocturnal awakenings
- **Idiopathic Hypersomnia**
  - Naps are typically not refreshing
  - Nocturnal sleep is typically longer (> 10 hours) and not punctuated by awakenings
  - Tendency for improvement in ESS over time
  - High frequency of comorbid psycho-affective complaints

triggers for the as yet unidentified autoimmune process leading to narcolepsy onset.

The sleep-wake cycle is governed by a complex, multilevel neuronal system in the brainstem, thalamus, hypothalamus, and basal forebrain. Neurons in the hypothalamus producing orexin stabilize the activity of other key neuronal groups involved in the control of sleep and waking. Many neurochemically distinct systems interact to regulate wakefulness and sleep. Wakefulness is promoted by brainstem and hypothalamic neurons producing acetylcholine, norepinephrine, dopamine, serotonin, histamine, and orexin. Each of these arousal systems is capable of increasing wakefulness, but coordinated activity in all these pathways is required for complete alertness and cortical activation. Because orexin promotes wakefulness and inhibits rapid eye movement sleep, its absence in narcolepsy permits inappropriate transitions between wakefulness and sleep.

Narcolepsy occurs in one in 2,000 people in the general population in the United States (U.S.) and narcolepsy with cataplexy occurs in one in 3,000.[2] Narcolepsy is relatively rare compared to other sleep disorders including obstructive sleep apnea (15% of general population), insomnia (1 in 10), and restless leg syndrome (RLS) (1 in 50 adolescents, 1 in 13 adults).[5-8]

Diagnosis begins with a review of the patient's clinical and family history. Key features to query for in the clinical history are age at onset, duration of symptoms, length of naps and their recuperative quality, duration and quality of nocturnal sleep, and family history. A sleep diary can be helpful in gaining some of this information. The age of onset of EDS and cataplexy in narcolepsy peaks in the late teens; the other symptoms (if present) lag by four to five years.[9] Naps tend to be restorative with narcolepsy and sleep is disturbed at night.

Numerous other sleep disorders must be ruled out when diagnosing narcolepsy. These include obstructive sleep apnea, chronic insomnia, RLS, idiopathic hypersomnia, shift work sleep disorder, and insufficient sleep syndrome. Obstructive sleep apnea, chronic insomnia and RLS tend to begin much later in life than narcolepsy. Exhibit 1 compares the features of narcolepsy and idiopathic hypersomnia.[10,11]

Most cases of narcolepsy are sporadic, but multiplex families have been observed. Just over 20 percent of patients with narcolepsy have one or more first-degree relatives with narcolepsy.[12] Compared with the general population, the relative risk of narcolepsy among first-degree relatives of patients with narcolepsy was 74.6. Risk of other sleep disorders (adjustment sleep disorder, insufficient sleep syndrome, and nocturnal eating/drinking syndrome) are also significantly increased among first-degree relatives of patients with narcolepsy compared with the general population.

Tools for diagnosis include the Epworth Sleepiness Scale (ESS), sleep laboratory evaluation [polysomnography, Multiple Sleep Latency Test (MSLT)], and the International Classification of Sleep Disorder (ICSD-3) criteria. The ESS measures daytime sleepiness (Exhibit 2).[13] In addition to narcolepsy, moderate to severe daytime sleepiness can occur with obstructive sleep apnea, Parkinson's disease, and depression. Polysomnographic findings include short nocturnal rapid eye movement (REM) sleep latency, disruptive nocturnal sleep, and periodic leg movements.[14] Intrusion of REM sleep into wakefulness is a hallmark of narcolepsy. Fifty percent of the time those with narcolepsy have less than 60 minutes for sleep onset REM periods. Signs of disruptive nocturnal sleep include increased proportion of stage 1 sleep, increased wake after sleep onset, and lower sleep efficiencies. Periodic leg movements (> 10/hour) occur in approximately 40 percent of subjects with cataplexy. Polysomnography is insensitive in diagnosing narcolepsy; the MSLT is required. The MSLT measures how fast someone falls asleep.

Exhibit 2: Epworth Sleepiness Scale[13]

Scale Values

0 = would never doze

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

Situation	Chance of Dozing
Sitting and reading	_____
Watching television	_____
Sitting inactive in a public place	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car while stopped for a few minutes in traffic	_____

Score > 10 = excess daytime sleepiness

Sleep latency of 10 minutes or more is considered "normal;" those with narcolepsy tend to be at eight minutes or less (median 6.5).[15] In the International Classification of Sleep Disorder, narcolepsy type 1 is distinguished by sleepiness plus cataplexy and a positive multiple MSLT, or sleepiness plus cerebrospinal fluid orexin deficiency. Narcolepsy type 2 requires sleepiness and a positive MSLT and the absence of type-1 markers.[16] The hypersomnia and/or MSLT findings must not be better explained by another sleep, neurologic, mental, or medical condition, or by medicine or substance use.

Other diagnostic tools for this syndrome include human leukocyte antigen (HLA) testing and orexin assays in cerebrospinal fluid. HLA DRB1*15 and DQB1*0602 genotypes are associated with narcolepsy. DQB1*0602 is strongly associated with presence and severity of cataplexy. It is present in 76 percent of patients with cataplexy compared with 41 percent of those without cataplexy and in 24 percent of the general population.[17] Because DQB1*0602 is common in patients without narcolepsy, it is not definitive for diagnosing narcolepsy as much as its absence argues against a diagnosis of narcolepsy.[18] DQB1*0602 positivity is less helpful in familial narcolepsy than in sporadic narcolepsy.

Narcolepsy is underdiagnosed. It is estimated that that 50 percent or more of patients with narcolepsy are undiagnosed.[19] For those who do get diagnosed, there can be a significant delay.[20,21] Since 1980, the median is 3.5 years (range, 1.5 to 7.25 years). More recently diagnosis has occurred more rapidly with increased awareness and improved tools for diagnosis. The time to diagnosis is shorter when cataplexy is a presenting symptom.

Treatment begins with behavioral strategies (Exhibit 3).[1,22,23] Various stimulants are used to manage EDS. This includes modafinil, sodium oxybate, methylphenidate, amphetamine/methamphetamine/dextroamphetamine, and selegiline. Solriamfetol is a non-stimulant for managing EDS. All but selegiline are FDA approved for treating EDS in narcolepsy. Cataplexy can be treated with sodium oxybate, selegiline, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), or selective serotonin reuptake inhibitors (SSRIs). Only sodium oxybate is FDA approved for managing cataplexy. The antidepressants are REM sleep suppressants, which is why they benefit cataplexy and reduce the number of cataplectic attacks.

Many patients require treatment with a wake-promoting agent and an anticataplectic; however, clinical trial evidence supporting combination therapy efficacy is limited. The most common combination in the U.S. has been a SNRI, or a SSRI with modafinil, or an amphetamine derivative. To date, only one study evaluating combination therapy (modafinil plus sodium oxybate) has been published. Modafinil and sodium oxybate can potentiate each other because of different mechanisms of action and lead to better daytime wakefulness.[24] Combination therapy can also consist of a short-acting and a long-

Exhibit 3: Behavioral Strategies for Narcolepsy[1,22,23]

- Take short, regularly scheduled naps.
- Adhere to a consistent sleep/wake schedule.
- Exercise for at least 20 minutes per day at least four or five hours before bedtime.
  - Regular exercise for prevention of obesity important in children with narcolepsy.
- Maintain a comfortable, adequately warmed bedroom environment.
- Engage in relaxing activities (e.g., warm bath) before bedtime.
- Avoid alcohol and caffeine-containing beverages for several hours before bedtime.
- Avoid smoking, especially at night.
- Take advantage of patient support groups (www.narcolepsynetwork.org).

acting psychostimulant to achieve alertness quickly, maintain alertness for longer periods of time, and avoid insomnia as an unwanted side effect. Importantly, tolerance does not develop with any of the medications for narcolepsy; therefore, patients can effectively take them for years.

Modafinil (Provigil®, generics) has lower potency than amphetamine, few peripheral side effects, and lower addictive potential than amphetamines. It is a Schedule IV controlled substance. Its mechanism of action is debated, but probably involves dopamine transmitter inhibition and some histaminergic activity. It is available as a racemic mixture; the R-isomer has a longer half-life and is in development as a single isomer product.

Sodium oxybate (Xyrem®) is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. It is indicated for the treatment of EDS and cataplexy in patients with narcolepsy who are seven years of age and older. Because of the risks of CNS depression, abuse, and misuse, sodium oxybate, a Schedule III controlled substance, is available only through a restricted distribution program called the XYREM REMS Program, using a central pharmacy that is specially certified. Prescribers and patients must enroll in the program. Sodium oxybate is thought to act via GABA B or specific gamma-hydroxybutyrate receptors. It reduces dopamine release at night and likely causes secondary dopamine increase during day. Besides the prescribing restrictions and abuse potential, bi-nightly dosing is necessary. Half of the prescribed dose is given at bedtime and the other half is given 2.5 to 4 hours later, which requires the patient to set an alarm to get up and take the dose. The initial starting dose is 4.5 grams, which can be increased to 9 grams. The bedtime dose has immediate effects on disturbed nocturnal sleep; sodium oxybate is the only narcolepsy agent that improves nighttime sleep. Therapeutic effects on cataplexy and daytime sleepiness are often delayed. Interestingly, at a dose of 9 grams per day, the ESS scores can normalize for some patients.[25] Overall, this agent reduces EDS, increases daytime alertness, improves night sleep, and reduces the number of cataplectic attacks.

Solriamfetol (Sunosi®) was approved for EDS from narcolepsy and obstructive sleep apnea in early 2019. It is a norepinephrine–dopamine reuptake inhibitor (DNRI) and is derived from phenylalanine. Solriamfetol significantly improves mean Maintenance of Wakefulness Test (MWT) sleep latency (at 4 weeks, 9.5 versus 1.4 min, $P < 0.0001$; at 12 weeks, 12.8 versus 2.1 min, $P < 0.0001$) and mean change in ESS (4 weeks, -5.6 versus -2.4, $P = 0.0038$; 12 weeks, -8.5 versus -2.5, $P < 0.0001$).[26] At 12 weeks, this agent, which is given in the morning when the patient awakes, improved wakefulness out to nine hours.[27]

Patients want a medication that provides consistent and adequate control of the daytime sleepiness without the hard crash and one that would require one dose taken at bedtime resulting in eight hours of restorative sleep. This ideal agent is not yet available. Numerous agents with various different mechanisms of action are in development. This includes immune-modulating therapies, thyrotropin-releasing hormone analogues, orexin agonists, and histaminergic H3 antagonists/inverse agonists. There are at least five companies investigating orexin agonists.

Conclusion

Narcolepsy, a neurodegenerative autoimmune disorder resulting in orexin deficiency, often requires

combination therapy with a stimulant and an anticataplectic agent to manage EDS and cataplexy. Sodium oxybate is the only FDA approved agent that treats both EDS and cataplexy, but it has to be dosed twice during the night, which is difficult for patients. Future therapies are targeting the immune system and orexin deficiency.

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Integrating New and Emerging Targeted Therapy into the Treatment of Ovarian Cancer: Expert Strategies for Improved Patient Outcomes

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

After almost a decade without significant progress, there has recently been a flurry of changes to the treatment paradigm for advanced ovarian cancer. PARP inhibitors are now FDA approved for maintenance in first-line and later-line therapy and for treatment in late-lines of therapy. Bevacizumab is also approved for treatment and maintenance. The treatment landscape is likely to dramatically change again in the next few years when ongoing studies are completed.

Key Points

- Chemotherapy plus anti-VEGF treatment is now a standard of care in all disease settings.
- Olaparib is approved for primary maintenance.
- Rucaparib and niraparib are approved for secondary maintenance.
- Numerous new therapies are on the horizon.

OVARIAN CANCER IS AN UNCOMMON tumor, which is primarily diagnosed in women 55 years of age and older. The median age of diagnosis is 61. The name ovarian cancer is a misnomer because the primary site of origin is likely the fallopian tube, and most are serous tumors. The etiology is unknown, but is not talc related.

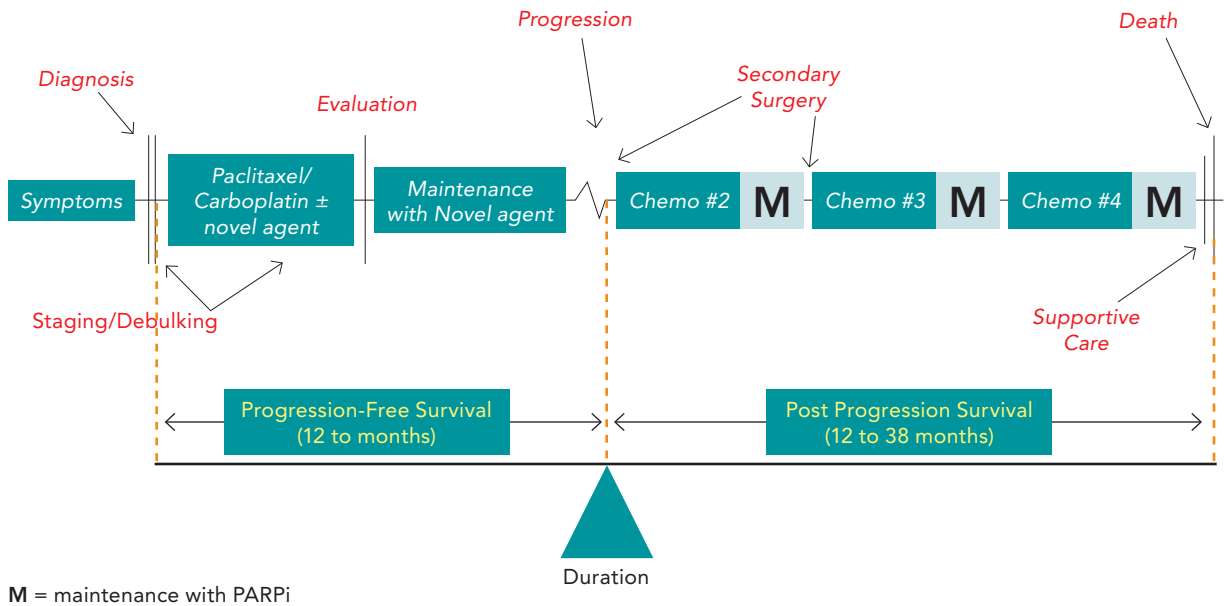
This cancer is defined by TP53 tumor suppresser gene mutations, alterations in function, or total loss. TP53 changes are found in more than 90 percent of cases; precancerous lesions with the TP53 changes have been shown to develop in the fallopian tube epithelium. Because there are so many different things going on with TP53, it makes targeting therapy difficult. Primarily, ovarian cancer is a disease of gene copy numbers rather than gene mutations. However, germline breast cancer (BRCA) mutations are found in 20 to 25 percent of ovarian cancer cases.

Ovarian cancer is very difficult to prevent, as the spread of cancer cells within the circulation occurs even before tumors in the ovaries are detected. Seventy-five percent of ovarian cancers are advanced Stage III or Stage IV (metastatic) at the time of diagnosis.

In 2018, there were 22,240 new cases in the United States (U.S.) and 14,070 deaths.[1] The incidence of ovarian cancer (number of new cases per year) has been steadily falling since 2001, while the prevalence (number people alive with the disease) has increased. Prevalence has likely increased because patients are living longer with the disease. With improved therapies, patients are now living longer with recurrence than the time they live from initial treatment to recurrence. The five-year survival rate is 47.4 percent.

The principle interventions for ovarian cancer

Exhibit 1: Ovarian Cancer Treatment Path



M = maintenance with PARPi

are surgery and chemotherapy, but the risk of recurrence is high (~70%), and there are no curative options in recurrence. Exhibit 1 shows the typical treatment path for a patient with ovarian cancer. The goal is to give the most active treatment at the initial diagnosis. Since 1996, adjuvant chemotherapy for advanced disease has been paclitaxel and cisplatin. Numerous alterations to this chemotherapy backbone have been investigated, but nothing thus far has superseded this combination.

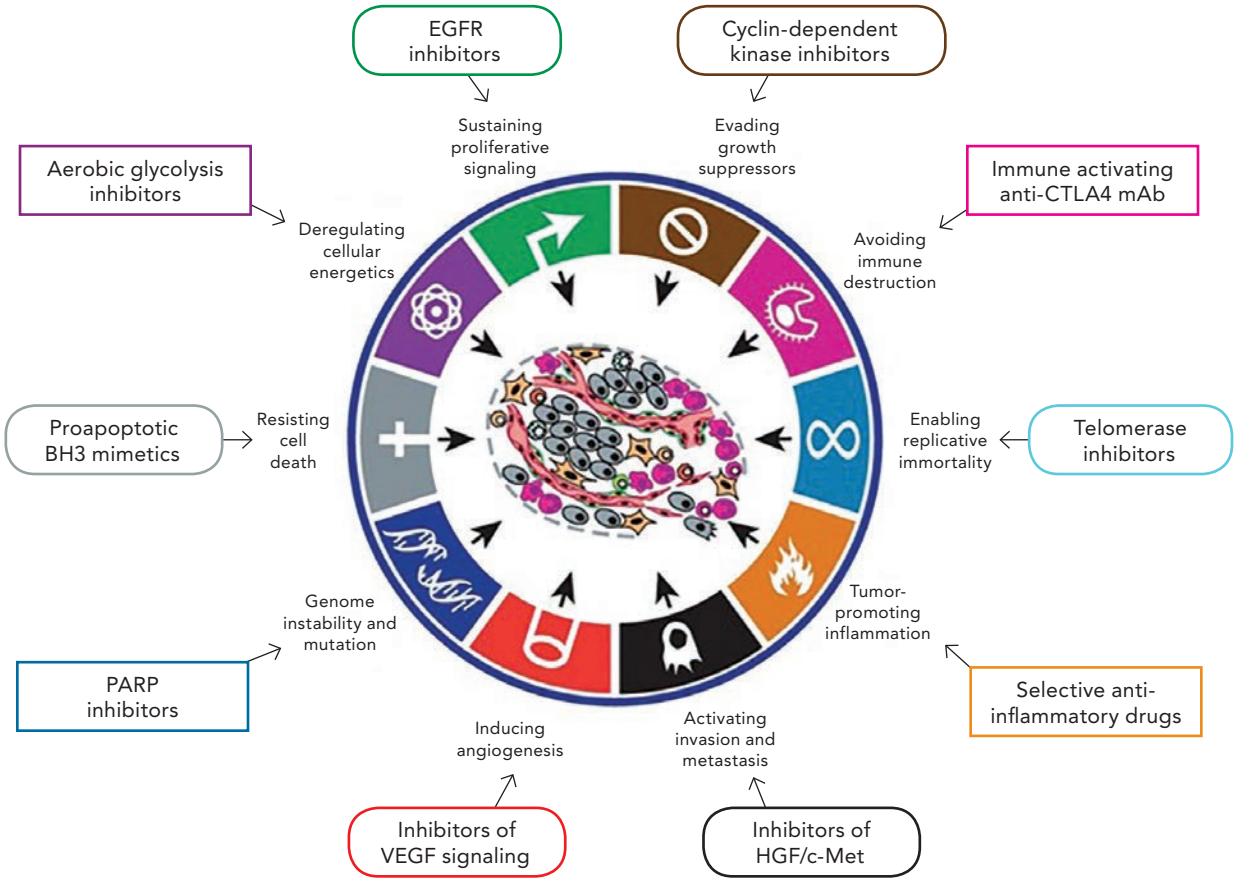
Adding novel agents as adjuvants to chemotherapy has also been investigated. Currently, chemotherapy plus a novel agent and then novel therapy maintenance is the standard of care. The future is likely novel therapy, then chemotherapy/novel, and then novel therapy. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent, targets the growth of blood vessels in tumors and ovarian cancer is very highly vascularized. Bevacizumab is now FDA approved for use in combination with carboplatin and paclitaxel, followed by bevacizumab monotherapy maintenance for Stage III or IV disease after initial surgical resection.

The rate of response is greater than 75 percent to initial chemotherapy regimens. This includes complete response (CR) and partial response (PR). An assessment operation after initial chemotherapy finds pathological disease in over 40 percent of clinical CR patients; this is disease that is subclinical and cannot be seen on scans. Clinical CRs have greater than 50 percent recurrence risk at two years. Pathological CRs have more than 40 percent risk at two years. Primary maintenance with a novel agent is an appropriate option for CRs and documented PRs. Of all the options that have been studied thus far, none have improved overall survival (OS); however, bevacizumab, pazopanib, a selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumor growth and inhibits angiogenesis, and poly (ADP ribose) polymerase inhibitors (PARPi) provide progression-free survival (PFS) benefits. Treatment with a PARPi may provide an OS advantage but that is yet to be determined.

PARPi help repair single-strand breaks in DNA when it becomes damaged. DNA damage may be caused by many things, including exposure to UV light, radiation, certain anticancer drugs, or other substances in the environment. Without PARP-based repair, double-strand breaks occur, which can be fixed with homologous recombination. In cells with homologous recombination deficiency (HRD), there is no way to repair the damage that is caused by blocking PARP with a PARPi, and thus cells die. BRCA mutations lead to HRD and, as noted previously, occur in 20 to 25 percent of ovarian cancer cases.

Olaparib (Lynparza®), a PARPi, is FDA approved for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced ovarian cancer who are in complete or partial response to first-line platinum-based chemotherapy.

Exhibit 2: Therapeutic Targets in Ovarian Cancer[7]



In the trial that lead to FDA approval for this indication, 60.4 percent of patients treated with olaparib were progression free at three years compared with 26.9 percent of placebo-treated patients.[2] At a median 41 months follow-up, median PFS with olaparib had not been reached versus 13.8 months with placebo. Olaparib was well tolerated in the study, with quality of life scores equal for the olaparib and placebo groups. It is also approved for maintenance therapy after chemotherapy for recurrence and as treatment for recurrence in patients with gBRCAm or sBRCAm disease that has already been treated with three or more chemotherapy regimens.

Overall, primary treatment of ovarian cancer is an optimal radical resection combined with adjuvant platinum-based chemotherapy, followed by maintenance therapy with a novel agent. Bevacizumab and olaparib have recently been FDA approved for this indication. As noted previously, even with a CR to chemotherapy, disease is likely present. The so-called maintenance therapy is really a second-line treatment that is targeting those remaining cells rather than waiting for them to regrow sufficiently to be detected by scans.

Many trials of first-line treatment with maintenance are ongoing. Some of these are triple-therapy trials with immunotherapy, PARPi, and anti-angiogenesis agents. Two of the trials are olaparib/pembrolizumab/bevacizumab and olaparib/durvalumab/bevacizumab.

Recurrent ovarian cancer is very common and options are plentiful, with six median regimens given in the U.S. Recurrence typically occurs at 18 to 24 months after initial treatment. Nothing is a cure in the recurrent setting. Traditional classification of recurrence has either been platinum-sensitive or platinum-resistant (less than six months since last treatment). Recurrent disease is now defined by histology, the number of prior regimens, molecular signature (BRCA/HRD status) and the platinum-free interval. The longer the patient has been treatment free before recurrence, the better the survival.

Platinum-sensitive recurrent disease is treated with a platinum-based regimen and then maintenance.

Bevacizumab is now FDA approved for maintenance in the recurrent setting. In the BRCA-mutated population, platinum-based therapy is the best way to cause DNA damage that can then be treated with PARPi to lead to tumor cell death. Rucaparib (Rubraca®), olaparib, and niraparib (Zejula®) have all been evaluated as maintenance after second-line chemotherapy and beyond in those with germline or somatic BRCA mutation and have similar efficacy.[3-5] PARPi maintenance improves PFS, and all three are FDA approved for this indication. These agents are tripling the time to recurrence, which is one of the factors in increasing the prevalence rates of ovarian cancer.

Numerous agents have been studied for platinum-resistant recurrent ovarian cancer, but none are very effective. For platinum-resistant disease, the best options include weekly paclitaxel with or without bevacizumab (best activity, but adverse events of hair loss and neuropathy), pegylated liposomal doxorubicin (Doxil®, most convenient for patients), or gemcitabine and cisplatin (good activity). The addition of bevacizumab to chemotherapy provides an improvement in objective response rates, a three-month improvement in PFS, and a 3.3-month improvement in OS.[6] Clinical trials are also an option in this setting.

In the past, many treatment efforts have targeted the cancer cells, but now most of the investigation is aiming at the many different therapeutic targets in the microenvironment in which the cell grows (Exhibit 2).[7] Only the PARPi and VEGF inhibitors are currently FDA approved for ovarian cancer, but the other areas are all being studied.

Checkpoint inhibition immunotherapy is under investigation for treating ovarian cancer; however, the published trials have been disappointing so far. Numerous trials are ongoing. The group that immunotherapy might benefit are those with BRCA mutation/HRD which typically has more somatic mutations than ovarian cancer without this. The combination of an immune checkpoint inhibitor plus a PARPi holds the most hope for significant benefit in those with BRCA mutation/HRD. Another small subgroup (3% to 5%) that may benefit are those with micro-satellite instability (MSI); checkpoint inhibitors are FDA approved for treating any cancer with high levels of MSI.

Conclusion

Ovarian cancer is a heterogenous disease with an evolving treatment landscape and survivorship. Chemotherapy plus anti-VEGF treatment is now a standard of care in all disease settings. Three PARPi are approved for maintenance and treatment, and more are on the way soon. Target discovery has led to a flood of clinical trial development options. Most promising are combinations of angiogenesis inhibitors, PARPi, and immune checkpoint inhibitors. Data from frontline and recurrent disease trials are soon to report, which will change the therapeutic landscape significantly.

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Evolving Considerations in the Treatment of Metastatic Bladder Cancer: A Closer Look at the Role of Immunotherapy

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

As with many other cancers, the availability of immunotherapy has dramatically changed how metastatic bladder cancer is treated. Immunotherapy is an option in both the first-line and second-line treatment setting and is being investigated for several other uses in non-metastatic disease. One targeted therapy is now available for metastatic bladder cancer with a specific genetic mutation, and more of these are likely to be approved in the future.

Key Points

- Chemotherapy with gemcitabine and cisplatin is still the preferred first-line treatment of metastatic bladder cancer.
- In cisplatin ineligible patients, immunotherapy (pembrolizumab or atezolizumab) is the option if programed death ligand 1 (PD-L1) positive, or gemcitabine/carboplatin if PD-L1 negative.
- For platinum refractory disease, immunotherapy or targeted therapy with erdafitinib are the treatments of choice.

THE TREATMENT OF METASTATIC BLADDER cancer (also called urothelial carcinoma) has evolved dramatically over the past few years. In 1985, the first reports of chemotherapy efficacy in this disease were reported. Gemcitabine was first used in 1997. Cisplatin in combination with gemcitabine became standard chemotherapy for metastatic disease around 2000. Traditional chemotherapy for metastatic disease leads to 50 to 55 percent of treated patients having tumor regression and an additional 33 percent with stable disease. The problem with chemotherapy is a short durability of response. The median progression-free survival (PFS) is 7.5 months and overall survival (OS) is 14 months with this combination.

Unfortunately, a large percentage of patients with metastatic disease are not cisplatin eligible because of poor renal function.[1] This is especially true for those 60 years of age and older where approximately 50 percent of patients are not eligible. Those who are not cisplatin eligible have typically been given gemcitabine/carboplatin, but it is less effective in terms of response rates and OS compared with gemcitabine/cisplatin.[2] Over 60 percent of patients who receive gemcitabine/cisplatin will be alive at 12 months compared with 37 percent who receive gemcitabine/carboplatin.

Second-line chemotherapy before immunotherapy was taxanes combined with pemetrexed. The response rates were low (5% to 28%), PFS was approximately two to three months, and OS was six to nine months.[3-5]

Because of limited responses to chemotherapy in second-line therapy, other avenues of treatment have been investigated. One which is successful is the use of immunotherapy because bladder cancer typically has a high mutational burden.[6] The level of mutational burden predicts the response to immunotherapy because the mutated cells have cell surface markers which can be recognized by the T

Exhibit 1: Immune Checkpoint Inhibitors in Platinum-Refractory Setting[8-14]

	Pembrolizumab	Durvalumab	Nivolumab	Avelumab	Atezolizumab
ORR	21% (PD-L1+ (CPS ≥10%) 21.6%)	18% (PD-L1+ 27.6%)	20% (PDL1 >5% 28.4%; PDL1 >1% 23.8%)	17% (PD-L1+ 24%)	13%
OS (months)	10.3	18.2	8.7	6.5	8.6
PFS (months)	2.1	1.5	2	1.5	2.1
12 months survival	44%	55%	43%	47%	39%
Grade 3/4 TRAE	15%	7%	18%	8%	16%

Important: Data is not from head to head trials
ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TRAE = treatment-related adverse events

cells, which have been activated by the therapy.

A new era of bladder cancer treatment began in 2016 with the approval of the first immunotherapy for this disease. Currently, five checkpoint inhibitor immunotherapies against programmed death (PD) have been FDA approved for treatment of locally advanced or metastatic urothelial carcinoma following platinum-based therapy (second-line treatment). Two of these (pembrolizumab [Keytruda®] and nivolumab [Opdivo®]) are anti-PD-1 agents, and the other three (atezolizumab [Tecentriq®], durvalumab [Imfinzi®], and avelumab [Bavencio®]) are anti-PD-ligand 1 (PD-L1) agents. In the first trial published with immunotherapy in bladder cancer, about 50 percent of patients responded with at least some tumor reduction with a relationship between response and the amount of the tumor PD-L1 expression.[7] Approximately one-third of patients with metastatic bladder cancer will have high PD-L1 levels (≥1%).

Checkpoint inhibitors were initially studied in patients who were platinum refractory. They improve OS in metastatic bladder cancer that has become platinum refractory (Exhibit 1).[8-14] In addition to an overall response rate of approximately 20 percent, another 20 percent will have stabilization of their disease. For example, OS is 10.3 months with pembrolizumab compared with 7.3 months for second-line chemotherapy. Importantly, at 12 and 24 months significantly more immunotherapy-treated patients are still alive. The tail end of the survival curve is most important to look at when examining the benefits of immunotherapy; this is where durable disease control or cure can be identified. One trial of atezolizumab was disappointing because it was no better than chemotherapy; therefore, it is difficult to justify using this agent when there is level 1 data with pembrolizumab and with other agents also having good supporting data.

Checkpoint inhibitors have also been studied in the first-line metastatic setting for those patients who cannot receive cisplatin-based chemotherapy. Both pembrolizumab and atezolizumab improve OS in this setting (Exhibit 2).[2,15-17] Pembrolizumab is FDA approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10), as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status. Atezolizumab is FDA approved for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area), as determined by an FDA-approved test, or are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status. Thus, PD-L1 testing is required in the front-line setting.

Exhibit 2: Immune Checkpoint Inhibitors in Front-Line Cisplatin Ineligible Setting Compared to Carboplatin[2,15-17]

	Pembrolizumab	Atezolizumab	Carboplatin
ORR	29%	23%	36%
CR	7%	9%	4%
OS (months	11.5	15.9	9.3
PFS (months)	2	2.7	2
Landmark Survival	48% (12 months)	57% (12 months)	37%

Important: Data is not from head to head trials
ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TRAE = treatment-related adverse events

Exhibit 3: Current Treatment Paradigms Metastatic Urothelial Carcinoma

- First Line Setting
  - Cisplatin eligible
    - gemcitabine/cisplatin
  - Cisplatin ineligible
    - immunotherapy (pembrolizumab or atezolizumab) if PD-L1+
    - gemcitabine/carboplatin if PD-L1-
  - Chemotherapy unfit
    - immunotherapy (pembrolizumab or atezolizumab)
- Platinum refractory
  - 5 immunotherapies (pembrolizumab level 1 evidence)
  - erdafitinib (FGFR3 or FGFR2 mutation)

Once immunotherapy was FDA approved in the front-line setting, many clinicians began using it instead of gemcitabine/carboplatin in those not cisplatin eligible. Data from two ongoing trials of the combination of chemotherapy (gemcitabine/cisplatin or carboplatin) in combination with immunotherapy (pembrolizumab or atezolizumab) prompted clinicians to again make a change in treatment selection. These trials had an immunotherapy alone arm in PD-L1 negative patients; however, this arm of the trial ceased due to inferior survival. Clinicians now use immunotherapy in the front-line cisplatin ineligible setting if the patient's tumor is PD-L1 positive. Once the final results from this trial are known, practice may evolve into combination chemotherapy/immunotherapy in all front-line patients.

Overall, immunotherapy is well tolerated with a low rate of grade 3 or 4 adverse events. Compared to the adverse events of platinum-based chemotherapy, it is much better tolerated, with less impact on quality of life.

As with many other cancers, various genetic mutations are being identified in bladder cancer, which may be targets for therapy. One of these is fibroblast growth factor receptor 3 (FGFR3) mutations. Treatment with erdafitinib (Balversa®), an oral FGFR3 kinase inhibitor, in patients with this mutation resulted in an overall response rate (ORR) of 40 percent, an additional 39.4 percent with stable disease, a median duration of response of 5.6 months, and OS of 13.8 months.[18] This agent was approved by the FDA in April 2019 for treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC), which has susceptible FGFR3 or FGFR2 genetic alterations, and who have progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Bladder cancers with FGFR pathway upregulation and with FGFR3 alterations may be "immune cold" and appear to be associated with poor response to anti-PD-1/PD-L1 therapies.[19] With additional experience, the use of FGFR3 inhibitors may move earlier in the therapy paradigm.

Exhibit 3 shows the current treatment paradigm

for metastatic bladder cancer. Treatment selection depends on the line of therapy and the patient's ability to receive specific chemotherapy. The burden of disease and symptomatology also impact selection. Chemotherapy will bring the disease under control faster than immunotherapy and should be selected treatment for someone with a large disease burden, or who is very symptomatic.

There are many other signals beyond PD-L1 which lead to T-cell activation and inhibition; therefore, combinations of immunotherapy that target multiple signals are under investigation. Durvalumab and tremelimumab, an investigational cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, and nivolumab and ipilimumab (Yervoy®), another CTLA-4 inhibitor, have been studied in metastatic bladder cancer.[20] The final results of these trials are awaited but the early results of nivolumab/ipilimumab appear better than nivolumab alone. Perioperative and adjuvant (post-chemotherapy) immunotherapy are also being studied.[21]

Immunotherapy along with radiation therapy (RT) for bladder preservation in early disease is also being studied. Options under investigation include combining RT with a radiosensitizer (gemcitabine, or cisplatin, or 5-flurouracil/mitoxantrone) compared to RT radiosensitizer and atezolizumab; RT combined with avelumab; and RT with cisplatin and pembrolizumab.

A therapy that will likely be important for patients with liver metastases, who have traditionally had very poor prognosis and lack of response to treatment, is enfortumab vedotin. This antibody-cytotoxic drug conjugate, which has received an FDA breakthrough designation, produced an ORR in patients with liver metastases of 39 percent in early trials. In September 2019, the FDA granted a priority review of this agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have previously received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting and a PD-1/PD-L1 checkpoint inhibitor. It is also being studied in combination with pembrolizumab.

Conclusion

Dramatic changes in metastatic bladder cancer treatment have already been seen, and more changes are on the way. Combinations of chemotherapy and immunotherapy as first-line treatment and more agents for molecular subsets of bladder cancer will likely become standard of care in the next few years.

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Individualizing Treatment in the Management of Advanced Breast Cancer: How Novel Therapies are Changing the Treatment Paradigm

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

The treatment of metastatic breast cancer is no longer a one-size-fits-all approach. Various patient factors along with biomarkers are used to personalize therapy. This individualization increases the chances of a successful outcome.

Key Points

- Therapy for metastatic breast cancer is selected based on patient specific-factors, actionable biomarkers, and logistical considerations.
- There are now multiple therapies available which can be selected based on identified biomarkers.
- Poly (ADP-ribose) (PARP) inhibitors are one targeted therapy that improves progression-free survival in metastatic breast cancer with germline breast cancer 1 and 2 (BRCA 1 and 2) mutations.

PERSONALIZED MEDICINE IN BREAST CANcer means choosing the right medicine for the right patient at the right time. Deciding factors on selecting the appropriate medication include patient specific factors (co-morbidities, pre-existing toxicities such as neurotoxicity, disease burden, prior therapies, and adherence concerns), actionable biomarkers (estrogen receptors, progesterone receptors, human epidermal growth factor receptor 2 [HER2], programmed death ligand 1 [PD-L1], phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha [PIK3CA], and breast cancer gene mutations [BRCA1/2]), and logistical considerations (timing, cost/insurance concerns, biomarker test turnaround, obtaining medications). An example of therapy selected based on actionable biomarkers is alpelisib (Piqray®), a phosphoinositide 3- kinase (PI3K) inhibitor, FDA approved for advanced breast cancer patients in postmenopausal women and men whose tumors have the PIK3CA mutation and are hormone receptor-positive and human epidermal growth factor 2 (HER2) negative. PIK3CA mutations are found in about 30 to 40 percent of breast cancers.

The typical flow of planning for therapy starts with a patient with prior breast cancer treatment presenting with symptoms suggestive of metastatic disease. Radiologic imaging (CT scans, bone scans, PET) and labs (liver function tests, complete blood count, tumor markers) are initially done. If this initial testing suggests metastatic disease is happening, the next step would be a diagnostic biopsy of the metastatic site is performed to confirm the recurrence (i.e., this is the same type of tumor that was initially treated). At a minimum, hormone receptor and HER2 biomarker testing are done; these recep-

Exhibit 1: Targeted SOC Therapy Examples

- ER+ disease: Consider use of CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) or everolimus in combination with endocrine therapy.
  - ESR1 mutation: Favor fulvestrant over aromatase inhibitor.
  - PIK3CA mutation: Apelisib.
- HER2+ disease: Prioritize use of taxane + trastuzumab+/-pertuzumab, TDM1, lapatinib, neratinib.
- Triple negative disease: Standard chemotherapy versus Nab-paclitaxel + atezolizumab (PD-L1+) in first-line.
- BRCA 1/2 germline mutation: olaparib, talazoparib.

ER = estrogen receptor
CDK = cyclin dependent kinase
ESR = estrogen receptor gene
PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
HER = human epidermal growth factor
TDM1 = trastuzumab emtansine
BRCA = breast cancer

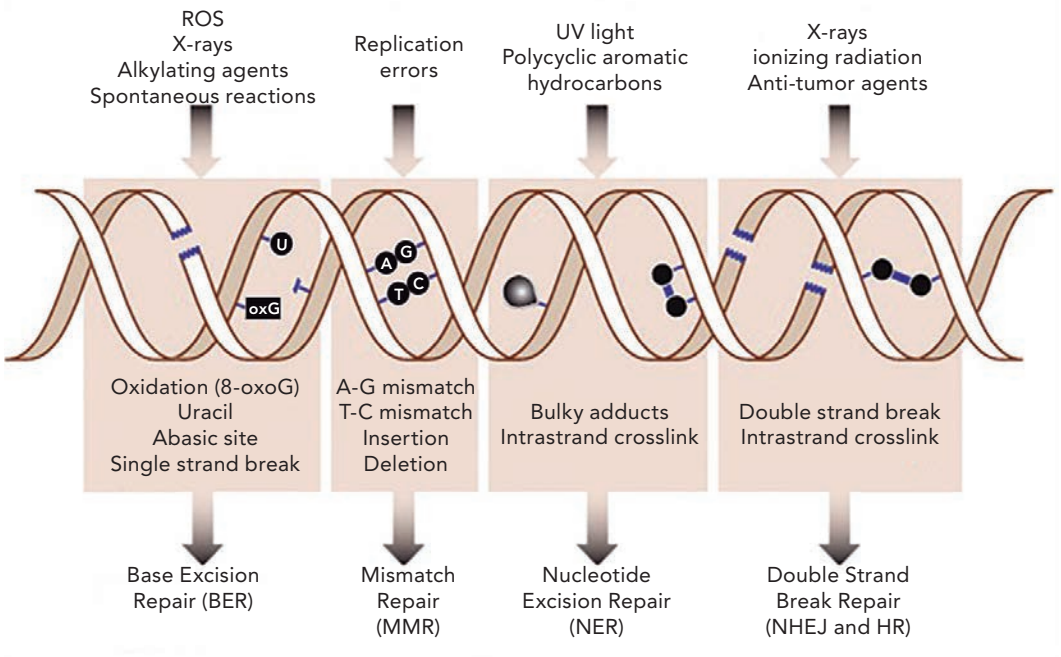
tors change in about 25 percent of cases from what was seen in the initial episode. Often, the patient requires or desires prompt initiation of therapy upon learning their diagnosis.

Various issues can occur during treatment planning. One is selection of testing and turn-around. There has been a proliferation of next-generation sequencing (NGS) genetic assays, both commercial and in-house, at major medical centers. Depending on the genes of interest, a test may be conducted in house or sent out for testing. The typical turn-around is two to three weeks which can delay the initiation of treatment. Once the results of testing are obtained, they must be interpreted. Physicians at academic medical centers may be more familiar with interpreting the test results than community oncologists. In addition, larger medical centers have tumor boards which can guide the selection of therapy based on the actionability of genetic test results. Those without such a board have to depend on the commercial assay report for determining the appropriate therapy. More often than not there are therapy possibilities identified on testing; this may be an FDA-approved agent for breast cancer, the off-label use of an agent approved for another cancer, or in a clinical trial. Having sufficient tissue available for genetic testing can sometimes be an issue; a second biopsy may be needed. Another major issue is the consent process for germline testing, which is required by many states. There has to be genetic counseling on the impact of the test results not only on cancer treatment but also on other areas the test results might impact, such as risk for other diseases, employability, or privacy concerns. Most medical centers use in-house genetic counselors. In the community, this may not always be available because there are too few genetic counselors. Some of the test manufacturers are trying to obtain telephone consent.

Exhibit 1 shows targeted standard of care therapy for the major biomarkers and mutations tested for in advanced breast cancer. For example, for patients with estrogen receptor-positive metastatic disease, cyclin dependent kinase 4/6 (CDK 4/6) inhibitors are combined with endocrine therapy to block the effects of estrogen. In a patient with an estrogen receptor 1 (ESR1) mutation, the traditional agents (aromatase inhibitors), which either block the production of estrogen or block the action of estrogen on receptors, are not effective; however, an agent like fulvestrant, which degrades the estrogen receptor itself, is effective. Another example of targeted therapy is the use of PARP inhibitors in breast cancer 1 and 2 (BRCA 1/2) germline mutation. BRCA 1/2 are involved in repairing DNA damage in cells.

DNA mutation and damage are routine, daily events, with more than one million events per day. It is caused by endogenous (metabolic damage, replication errors) or exogenous (chemicals, ionizing radiation, UV light, viruses) factors. Cells must successfully repair DNA damage or they become old (senescence), die (apoptosis), or immortal (cancer). Exhibit 2 illustrates the five mechanisms of DNA repair. Mismatch repair (MMR) excises incorrect nucleotides during replication of microsatellite re-

Exhibit 2: DNA Repair Pathways



ROS = reactive oxygen species
NHEJ = non-homologous end-joining
HR = homologous repair

gions by DNA polymerase (proofreading errors), DNA oxidation, DNA alkylation, or platinum adducts. Defective MMR, which occurs because of mutations in the MSH2-6 and MLH1-3 genes, results in microsatellite instability (MSI high) which is associated with checkpoint immunotherapy response in some tumors. MMR deficiency is associated with Lynch syndrome/hereditary nonpolyposis colorectal cancer. Base excision repair (BER) takes out specific incorrect nucleotides and replaces them with correct ones. Genes that control this process are XRCC1, APE1, PARP (single-strand DNA repair), and DNA polymerases. Nucleotide excision repair (NER) is the pathway for removing bulky or distorting DNA lesions. This process is more complex than BER and is controlled by XPA-G, ERCC1, CSA/B, and DNA polymerase genes. Homologous recombination (HR) fixes double-strand breaks accurately during the S and G2 phase of the cell cycle, using the undamaged sister chromatid. Genes for this process are Rad51, BRCA1/2, and Exo1. Non-homologous end-joining (NHEJ) is an error prone process of joining double-strand breaks throughout the cell cycle and involves the Ku70-80, DNA-PKc, and XRCC4 genes.

Deficiencies in one or more DNA repair pathways can sensitize cells to DNA damaging therapeutic agents. BRCA1/2 defects sensitize cells to the DNA damaging effect of PARP inhibitors. Over time, compensation through mutations by another pathway can impact resistance to DNA damaging therapeutic agents. Genomic instability in one or more DNA repair pathways can lead to activating mutations in key growth pathways, inactivating mutations of key tumor suppressors, or alterations in protein structures that can affect fitness of cancer cell clones during therapy. Greater genomic abnormalities may render cancer cells more recognizable by the host immune system as foreign (neoantigens). Targeted DNA damaging agents include PARP inhibitors (olaparib, talazoparib, veliparib, niraparib, and rucaparib), Wee1 inhibitors, ATR inhibitors, and CHK1/2 inhibitors. Only the PARP inhibitors are FDA approved; the rest are investigational.

BRCA-mutated cells are HR deficient and thus dependent on other pathways for DNA repair. Women with germline BRCA mutation are at risk for developing breast and ovarian cancer. A germline mutation means that all cells in the body have this same defect as compared to somatic BRCA mutations which can occur in individual tumor cells. Treatment of someone with BRCA germline mutated breast cancer with a PARP inhibitor leads to inhibition or trapping of PARP at single-strand

DNA breaks, leading to double-strand breaks and stalling cell division at DNA replication forks. Repairing double-strand breaks requires HR, which BRCA-mutated cells do not have, so PARP inhibitors cause "synthetic lethality" in BRCA-mutated cells.

Two of the FDA approved PARP inhibitors have an indication for treating BRCA 1/2 germline mutated metastatic breast cancer – olaparib and talazoparib. Olaparib monotherapy was studied in a randomized, open-label, Phase III trial compared with standard single-agent chemotherapy in patients with a germline BRCA mutation and HER2 negative metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease. Olaparib monotherapy provided a significant benefit over standard therapy; median progression-free survival was 2.8 months longer and the risk of disease progression or death was 42 percent lower with olaparib monotherapy than with standard therapy.[1] The response rate was 59.9 percent in the olaparib group and 28.8 percent in the standard therapy group. The rate of grade 3 or higher adverse events was 36.6 percent in the olaparib group and 50.5 percent in the standard therapy group, and the rate of treatment discontinuation due to toxic effects was 4.9 percent and 7.7 percent, respectively. Those with BRCA 1 or platinum naïve disease appear to benefit more with olaparib.

The trial that led to FDA approval of talazoparib for breast cancer was a randomized, open-label, Phase III trial in which patients with advanced breast cancer and a germline BRCA 1/2 mutation and no more than three prior lines of chemotherapy received either talazoparib or standard single-agent chemotherapy. Median progression-free survival was significantly longer in the talazoparib group than in the standard therapy group (8.6 months versus 5.6 months; $P<0.001$).[2] The interim median hazard ratio for death was 0.76 ($P = 0.11$). The objective response rate was higher in the talazoparib group than in the standard therapy group (62.6% versus 27.2%; $P<0.001$). Hematologic grade 3-4 adverse events (primarily anemia) occurred in 55 percent of the patients who received talazoparib and in 38 percent of the patients who received standard therapy; nonhematologic grade 3 adverse events occurred in 32 percent and 38 percent of the patients, respectively. Patient-reported outcomes favored talazoparib.

There are no head-to-head comparison trials with the PARP inhibitors in metastatic breast cancer for efficacy or adverse events. Both agents cause significant rates of hematologic adverse events. Talazoparib is more likely to cause hair loss than olaparib. Overall survival data with PARP inhibitor treatment in the metastatic setting have not been reported.

PARP inhibitors are being studied in earlier lines of treatment and in various combinations. For example, niraparib is being studied in the pre-surgical setting (neoadjuvant therapy) and olaparib as adjuvant therapy. The combination of a PARP inhibitor with checkpoint therapy or anti-angiogenesis is also under investigation.

The cost of olaparib and talazoparib is significant, with costs ranging from $13,000 to $15,000 monthly; thus, patients with large cost of share or non-commercial insurance have access issues. These agents still cause significant toxicity, but not much more than chemotherapy. Nausea and anemia are the most common adverse events. As an oral medication, there is less impact on the patient's quality of life than chemotherapy and presently they are primarily used in BRCA 1/2 germline mutated breast cancer patients as a line of therapy similar to chemotherapy. Germline testing is likely to increase in breast cancer patients who have not typically met criteria for testing (i.e., do not have the usual risk markers of family history of breast or ovarian cancer) to identify candidates for PARP inhibitors. The PARP inhibitors are not as effective for patients with somatic BRCA mutation. BRCA 1/2 mutations may not be the only marker for the selection of PARP inhibitors. There is a need for more research to identify additional biomarkers for PARP inhibitor benefit to improve the cost/benefit ratio.

Conclusion

The availability of next-generation sequencing and other genetic testing has expanded the known biomarkers that can be used for selecting therapy in metastatic breast cancer. Personalized medicine in this setting means incorporating biomarkers and patient factors to select the best therapy. For patients with a BRCA 1 or 2 germline mutation, this will mean a PARP inhibitor.

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Novel Treatment Advances and Approaches in the Management of Hepatocellular Carcinoma (HCC): Expert Strategies for Improved Patient Outcomes

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For a CME/CEU version of this article, please go to www.namcp.org/home/education, and then click the activity title.

Summary

The treatment options for advanced hepatocellular carcinoma (HCC) have expanded dramatically in the past few years. Each of the approved therapies provide some survival benefit, but they are not cures. The choice of first-line therapy for advanced disease is currently a tyrosine kinase inhibitor but, like many other cancers, treatment choices can change rapidly.

Key Points

- Tyrosine kinase inhibitors are the primary first-line treatment for advanced HCC.
- Immunotherapy has emerged as a second-line treatment option and will likely move into the first-line setting.
- Costs of treating HCC are significant, and one area contributing to the total cost is management of immunotherapy adverse events.
- Identification of those at risk for developing HCC and appropriate surveillance is important.
- Treatment of hepatitis C infection and alcoholism are two important prevention strategies.

HEPATOCELLULAR CARCINOMA (HCC) IS THE sixth most common cancer globally.[1] There are more than 800,000 new cases each year. HCC is third leading cause of cancer-related mortality. The incidence and mortality from primary hepatobiliary cancers has been increasing. One contributor to the rising incidence of HCC is rising rates of nonalcoholic steatohepatitis (NASH) from obesity.

Cirrhosis is the cause of 80 percent of cases of HCC.[2] Cirrhosis can be secondary to hepatitis C and B virus infections (HCV, HBV), alcohol, and NASH. Approximately 20 percent of HCC cases occur without preexisting cirrhosis and are related to HBV, NASH, age (> 80 years), and fibrolamellar HCC.

Staging is essential to assess the resectability of the tumor mass, choose an appropriate therapy, and predict the prognosis of HCC patients. In addition to the stage, choice of therapy is based on the severity of the underlying liver disease, availability of treatment resources, and clinical expertise. Child-Pugh scoring determines the severity of liver disease on the basis of serum albumin, bilirubin, prothrombin time, ascites, and encephalopathy. Very early stage and early stage disease are treated with resection, ablation, or liver transplantation. Intermediate stage is treated with chemoembolization. Unfortunately, HCC is often diagnosed at advanced stages when highly effective therapies are limited. Advanced stage disease is where the majority of advances have been made with targeted therapies. First-line therapy for advanced stage disease is treatment with sorafenib and lenvatinib, which are oral tyrosine

Exhibit 1: Comparison of FDA Approved Agents

Agent	Mechanism of Action	Target(s)
Sorafenib	TKI	VEGFR2, VEGFR3, PDGFR, FLT-3, c-kit and RAF
Lenvatinib	TKI	VEGFR1, 2 and 3, FGFR 1, 2, 3 and 4, PDGFR alpha, c-Kit, and RET
Regorafenib	TKI	VEGFR 2 and 3, RET, c-kit, PDGFR and RAF
Cabozantinib	TKI	VEGFR, MET, and AXL
Ramucirumab	VEGFR antagonist	VEGFR2
Nivolumab	PD-1 receptor antagonist	PD-1
Pembrolizumab	PD-1 receptor antagonist	PD-1
Atezolizumab + Bevacizumab	PD-L1 antagonist VEGF antagonist	PD-L1 VEGFR

TKI = tyrosine kinase inhibitor
VEGFR = vascular endothelial growth factor receptor
PD-1 = programed death one
PD-L1 = programmed death ligand one

kinase inhibitors (TKIs) that have antiangiogenic events (Exhibit 1). Second-line agents include additional TKIs (regorafenib, cabozantinib, and ramucirumab) and immunotherapy. The estimated survival time with a diagnosis of advanced HCC is eight to 12 months with sorafenib and 14 months with lenvatinib as first-line therapy and eight to 10 months with second-line therapy.[3]

Sorafenib (Nexavar®) was the first agent to show a survival benefit (10.7 months versus 7.9 months with placebo) in patients with advanced stage HCC with good performance status and liver function (Child-Pugh A).[4] An oral agent, it became standard of care for first-line treatment after its FDA approval in 2007. Treatment with sorafenib causes several adverse events – diarrhea, alopecia, hand-foot skin reaction, and weight loss – which can occasionally be grade 3 or worse.[5]

Lenvatinib (Lenvima®) is the second oral TKI approved for treating advanced HCC. When compared to sorafenib, it was shown to produce better median progression-free survival (PFS), overall response rate (ORR), and median time to progression, but not median overall survival (OS).[6] The patients included in this trial had unresectable, advanced stage HCC, good performance status, Child-Pugh A status, and had no prior systemic treatment. The ORR in this trial for lenvatinib (24.1%) was the highest seen in monotherapy for advanced HCC trials. It is also approved for first-line therapy.

Atezolizumab (Tecentriq®), a programmed death ligand one (PD-L1) inhibitor, in combination with bevacizumab, an intravenous vascular endothelial growth factor (VEGF) inhibitor, have been studied in a Phase 1b study as first-line therapy in advanced stage or metastatic HCC that was treatment naïve.[7,8] In the report of data from the first 20 patients, the combination produced a 61 percent ORR, 65 percent PFS at six months, and 86 percent of the patients were still alive at six months. Because of the benefits seen in this trial, the combination received FDA breakthrough designation as first-line treatment for advanced or metastatic HCC in mid-2018, but it does not yet have FDA approval for HCC treatment. The addition of bevacizumab appears to produce additional immunomodulatory events and a more favorable tumor microenvironment, potentiating the efficacy of atezolizumab. A Phase III study comparing the combination against sorafenib as first-line for advanced or metastatic HCC is currently enrolling subjects.

Regorafenib, which is sorafenib with an additional fluoride atom, became standard of care in the second-line for patients progressing on sorafenib when it was approved in early 2017. It produces a 2.8 months improvement in OS compared to placebo

(10.6 months versus 7.8 months).[9] The most common grade 3 or 4 adverse events with regorafenib include hypertension, hand-foot skin reaction, fatigue, and diarrhea.

Immunotherapy became the standard of care in the second-line setting when nivolumab (Opdivo®), a programmed death one (PD-1) inhibitor, was approved by the FDA in September 2017 because of the complete and partial response rates (3% and 12%, respectively) seen in the approval trial. Prior therapies primarily only produced stable disease in advanced HCC instead of complete or partial responses. Nivolumab was observed in a Phase I/II study and produced an ORR of 20 percent in patients treated with nivolumab 3 mg/kg.[10] Median duration of response was 9.9 months and responders had median OS of 18 months which is impressive for second-line treatment. The most common adverse events (AEs) associated with nivolumab treatment were fatigue, itching, rash, diarrhea, and increased liver/pancreatic enzymes. Grade 3 or 4 AEs included increased liver and pancreatic enzymes. Benefit was seen early in this trial, irrespective of HCV or HBV infection status and PD-L1 expression status on tumor cells. Patients reported quality of life as stable from baseline to week 25. The FDA accelerated approval of nivolumab for patients who have progressed on sorafenib. A conventional approval is pending based on completion of the Phase III study results.

Pembrolizumab (Keytruda®), another PD-1 inhibitor, was studied in advanced HCC previously treated with sorafenib in a non-randomized, open-label Phase II trial (KEYNOTE-224).[11] A 17 percent ORR was seen along with duration of response beyond six months in 89 percent, 4.9-month median PFS, and median OS of 12.9 months. Twenty-four percent of subjects had grade 3 treatment-related AEs, and there was one case of grade 4 treatment-related hyperbilirubinemia. In addition, one patient death associated with ulcerative esophagitis was linked to treatment, and three patients had immune-mediated hepatitis. Pembrolizumab received accelerated FDA approval based on the open-label trial. In the KEYNOTE-240 study Phase III trial, pembrolizumab compared with placebo for second-line therapy did not meet its primary endpoint. However, OS, PFS, and ORR were consistent with KEYNOTE-224. The manufacturer is still analyzing the data from this trial.

Immunotherapy is being further investigated in ongoing studies. The CheckMate-459 study is comparing nivolumab against sorafenib as first-line therapy. Immunotherapy will likely move into the first-line setting for advanced HCC in the near future.

Cabozantinib is another TKI which has been evaluated in the second-line and third-line setting and is FDA approved for this indication. In a double-blind study, there was a 2.2-month improvement in OS compared to placebo.[12] When the data was split out to only look at the second-line setting patients (only prior sorafenib), the OS was better (4.1 months). Dose reductions are required in the majority of patients due to AEs.

Another agent which has been evaluated in the second-line setting is ramucirumab (Cyramza®), a VEGFR2 antagonist that specifically binds VEGFR2 and blocks binding of VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D. The study of this agent only included patients with high levels of alpha-fetoprotein (AFP, $\geq$ 400 ng/mL), a biomarker which indicates poor prognosis. Ramucirumab improved OS (8.5 months versus 7.3 months) and PFS (2.8 versus 1.6) versus placebo.[13] Ramucirumab is now FDA indicated for the treatment of patients with HCC who have an AFP of $\geq$ 400 ng/mL and have been treated previously with sorafenib.

Based on the available data, selecting first-line therapy can be somewhat difficult for clinicians. Based on the trial comparing lenvatinib to sorafenib, the two agents appear very similar and clinicians could choose either. Lenvatinib may be the better choice in patients with a large grade l tumor burden because of the higher response rate. The trial comparing the two agents excluded patients with greater than 50 percent liver involvement and those with macrovascular invasion, which is a population that needs response the most. The preferred agent in this case is unknown. Potential AEs can be another point for choosing therapy. Grade 3 and 4 hypertension rates tend to be higher with lenvatinib, and hand-foot syndrome is higher in those receiving sorafenib. The choice of first-line therapy also impacts the available options for second-line therapy. All the second-line agents have been tested post-sorafenib. The Barcelona Clinic Liver Cancer (BCLC) guidelines have sorafenib as first-line therapy with lenvatinib as an option, with the caveat that no second-line therapies after lenvatinib failure have been studied.[14]

Prior sorafenib therapy probably has an impact on the efficacy of subsequent therapy. Immune dysfunction exists in advanced HCC. Removal of immunosupressive cells can restore antitumor efficacy.[15] Sorafenib is immunomodulatory by enhancing effector T cell function.[16] There are some data to suggest that lenvatinib is also immunomodulatory. Exhibit 2 summarizes some of the factors which favor one agent over the other in the first-line setting.

The choice of second-line therapy is also diffi-

Exhibit 2: Selecting First-Line Therapy in Advanced HCC

Factors	Data
Desire tumor shrinkage	Higher response rate with lenvatinib (24% versus 9%)
Uncontrolled hypertension	Higher risk with lenvatinib (any grade 42% versus 30%)
Hepatitis B	Better OS with lenvatinib (13.4% versus 10.2%)
Western population	Better OS with sorafenib
Purist: Impact on second-line	All second-line tested only post sorafenib

cult because of the number of available agents. It is important to define sorafenib failure; the benefit of this agent has to be maximized by reducing the dose to manage AEs prior to discontinuing treatment. There is not yet mature data to recommend a particular sequence of first-line and second-line agents for maximum OS. At this time, performance status and liver function are major drivers in selecting therapy. Sometimes the agent chosen reflects a clinician's practice setting. If they are also treating colon cancer, they may be more familiar and comfortable with regorafenib and its AE management, whereas someone who also treats lung cancer may be more likely to prescribe immunotherapy. The availability of follow-up support and monitoring with clinical pharmacists or physician extenders for oral therapies may also impact treatment selection.

Because immunotherapy takes the brakes off of the immune system, immune-related adverse events (irAEs) can occur. These irAEs can be life threatening and many require hospitalization. These hospitalizations contribute to the increasing cost of oncology care. One survey of 26 cancer centers found a significant increase in hospital admissions due to irAEs over the period of 2011 to 2015.[17] During this period of time, there were 343 hospitalizations for suspected irAEs; the majority (65%; N = 223) were confirmed irAEs that required treatment with immunosuppression or therapy discontinuation. The mean hospital length of stay was 6.3 days (range 1 to 31 days), readmission rate for another irAE 25 percent, total readmission rate 61.7 percent, and inpatient mortality was 8 percent. The most common irAEs were enterocolitis (43.9%), pulmonary (16%), hepatic (15%), neurological (8.9%), endocrinopathies (7.1%), rheumatological (4%), dermatological (3%), cardiovascular (3%), renal (1.8%), and allergy (1.3%). The majority of oncologists surveyed felt very uncomfortable managing irAEs, and 48 percent felt that irAE complications should be managed by a different service.[17]

In a soon to be published article, a Markov model approach was utilized to evaluate the cost-effectiveness of different treatment sequences for advanced HCC. The model allowed for nine possible states and the transition probabilities (in one-month increments) were derived from study data for the individual medications. For the first drug in the sequence, the states included: treatment (1), treatment with toxicity (2), discontinuation due to toxicity (3), progression (4), and death (5). Patients in state 1 could move to any of the five states; patients in state 2 could move to any other state; patients in states 3 and 4 transitioned to treatment on the second drug (states 6 – 8) or to state 5; and patients in state 5 (death) remained there. Exhibit 3 shows the cost- effectiveness ratio (CER) for various sequences of first-line and second-line therapies with all the CERs higher than accepted $100,000 – $150,000 per QALY.[18]

In a cost analysis using U.S. Department of Defense data, the majority of HCC patients sequenced from first-line sorafenib to second-line nivolumab.[19] Second-line therapy was split between TKIs, immunotherapy, and chemotherapy. Advanced HCC patients initiating first-line systemic therapy had poor prognosis and less than 20 percent received second-line therapy. A majority of patients (76%) either died prior to receiving second-line therapy, or discontinued first-line therapy without switching to second-line. HCC-related total costs comprised approximately 67 percent of total all-cause costs for the patients. Costs of prescription systemic therapy amounted to 32 percent of total all-cause costs. Although survival rates in first-line sorafenib were lower relative to the overall first-line systemic population, lack of clinical detail around staging (e.g., Child-Pugh scores) made it difficult to confirm whether more advanced patients were more likely to be treated with sorafenib. Median survival of approximately six months for first-line sorafenib

Exhibit 3: Twelve-Month Cost of Sequencing Therapies for First-Line and Second-Line Treatment of HCC[18]

Treatments: 1. First Line 2. Second Line	Average QALY	Average Cost	CER	Toxicity Rate	Average Survival (months)	12-Month Survival Rate
1. Sorafenib 2. Regorafenib	0.623	$149,556.15	$239,951.23	0.473	8.58	0.510
1. Sorafenib 2. Cabozantinib	0.632	$153,450.85	$242,726.61	0.475	8.67	0.530
1. Sorafenib 2. Pembro	0.653	$132,465.46	$202,830.03	0.394	8.71	0.536
1. Lenvatinib 2. Regorafenib	0.688	$156,909.95	$228,064.31	0.439	9.09	0.569
1. Lenvatinib 2. Cabozantinib	0.693	$159,547.17	$230,111.62	0.437	9.15	0.584
1. Lenvatinib 2. Pembro	0.709	$143,473.86	$202,447.19	0.376	9.18	0.587

QALY = quality of life year; CER = cost effectiveness ratio

was higher than other real-world studies. The author concluded that there is unmet need in first-line advanced HCC for therapies that can prolong survival and reduce costs.

A study of the costs in the Veterans Administration system found that the mean three-year total cost of care in HCC patients was $154,688 compared with $69,010 in matched cirrhotic controls, yielding an incremental cost of $85,679.[20] Almost 65 percent of this cost difference was from increased inpatient costs.

Early detection and prevention of HCC development is, in principle, the most impactful strategy to improve patient prognosis and may reduce health care costs. However, a one-size-fits-all approach to HCC screening for early tumor detection, as recommended by clinical practice guidelines, is utilized in less than 20 percent of the target population.[21] Additionally, the performance of screening modalities, including ultrasound and alpha-fetoprotein, is suboptimal. Furthermore, optimal screening strategies for those with hepatitis C that has been cured and those with non-cirrhotic NASH remain controversial.[21] Antiviral therapies can be effective etiology-specific HCC chemo-preventive interventions, but viral cure does not eliminate HCC risk, and therefore requires continued risk assessment, screening, and/or additional chemo-preventive interventions are needed. HCC prevention approaches should target those with alcoholism and HCV infection because both are treatable and treatment reduces risk.

Health plans can use claims data to identify which of their members have HCC and which have the conditions that put them at risk for HCC. The data can tell the plan at what state patients are being diagnosed and which therapies their members with HCC are receiving. Claims data can also show if at-risk members are getting the recommended surveillance with AFP and periodic ultrasound testing. Identifying the members at risk for HCC and the current rates of surveillance can lead to a strategy to identify HCC at earlier stages.

Numerous treatment regimens are under investigation for various states of HCC treatment. Combinations of sorafenib and pembrolizumab, sorafenib and nivolumab, lenvatinib and pembrolizumab, cabozantinib and atezolizumab, and atezolizumab and bevacizumab are all being studied in first-line therapy for advanced disease. A trial comparing nivolumab and sorafenib for first-line therapy has been completed, but has not yet been reported. Other trials are examining the best way to measure response to immunotherapy, to switch therapies, to sequence the various agents, and choose patients based on biomarkers.

Conclusion

Tyrosine kinase inhibitors are the primary first-line treatment for advanced HCC, with immunotherapy

being frequently used as a second-line treatment option. Immunotherapy will likely move into the first-line setting after ongoing trials are published. The cost of treating HCC is significant, and one area driving costs is management of immunotherapy adverse events. Identification of those at risk for developing HCC and appropriate surveillance is an important way to identify patients earlier in the disease process when it might be curable. Treatment of hepatitis C infection and alcoholism are two important prevention strategies.

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A Unicorn and a Trojan Horse
An Overview of the Genesis, Formation, and Work of NAMCP's Value Based Care Council

Michael A. Ford, RPh, Executive Director

THE NUMBER ONE RULE IN DRAWING attention to an article is to conceive a title that has a degree of intrigue. More on the title in a moment, but let's first provide some backstory as to the reason for this article.

Today's media, politicians, and others focus on the price of prescription drugs as if they are just a commodity. In the opinion of this writer, the optics of high prescription drug prices are driven in part through more of the cost share of this portion of insurance coverage being shifted to patients who are now paying a larger portion of the cost of the medications. There are also other dynamics impacting these optics, which will not be a focus of this article, such as rebates and profits incurred by other entities and their relative impact on price inflation. The classification of a commodity may hold true for some generic forms of medication, however, there are many medications (often within the same therapeutic class) that are clinically and therapeutically differentiable based on their respective value proposition. While there is a trend to view prescription drugs as a commodity, this mindset can prevent the realization of the full value that can be derived from many prescription medications.

Depending on the resource, prescription drugs account for anywhere from 14 percent to 20 percent of the dollars spent on health care. When considering that approximately 80 percent of people who see any healthcare practitioner end up on a prescription medication, it is paramount that the optimum value is derived from that same medication. It is also important to note that adherence rates are abysmal, with adherence dropping, on average, to well below 20 percent after 18 months, regardless of the therapeutic class. It is extremely difficult to realize the full value proposition of a drug if approximately 80 percent of patients quit taking their medication after 18 months.

Let's go back to the title of the article. When it comes to the unicorn, this is in reference to the elusive search as to what form value-based care might actually end up looking like in the future, as it continues to go through metamorphosis. It's extremely important to note, that no matter the form, the need to extract the most value from pharmaceuticals, as well as from medical devices and diagnostics, will be imperative. In order to maximize the extraction of that value, we should first look in the belly of the Trojan horse, which is a reference to the formulary and associated medical policy for coverage. While these two strategies are currently in place as standard methods for pharmacy benefit and medical management, there are numerous opportunities to improve processes and better coordinate the two in order to enhance the ability to effectively leverage that spend so as to optimize outcomes while decreasing overall costs.

For all of the above reasons, the NAMCP Medical Directors Institute decided in late 2018 to create the Value Based Care Council (VBCC). The VBCC mission supports empowering Medical Directors with information and resources to assist them in making value-based decisions that support achieving the Triple AIM of improved outcomes and the patient experience while reducing overall costs. The goal is to improve the integration of cost, quality, and access in the clinical decision-making process so as to enhance the effectiveness and efficiency of extracting value from the associated spend in order to optimize outcomes.

The VBCC consists of two components, the Executive Leadership Advisory Committee (ELAC) and the Founding Charter Members (FCM). The ELAC is comprised of approximately 12 Medical Directors, Chief Medical Officers, and Directors of Pharmacy from various disciplines from around the country, while the FCM is comprised of representatives of various health-related industries, also from around the country. It is through this vehicle of the VBCC that these components collaborate in an effort to provide tools and resources with practical utility for Medical Directors in order to achieve both the mission and goals of the council. With this collaboration, the VBCC provides a unique forum whereby both medical leadership and industry work together, which helps improve communication, enhance trust and credibility, as well as serve as a vehicle of advocacy for all parties. If you would like more information about the VBCC, please contact (e-mail), Will Williams at: wwilliams@namcp.org.

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