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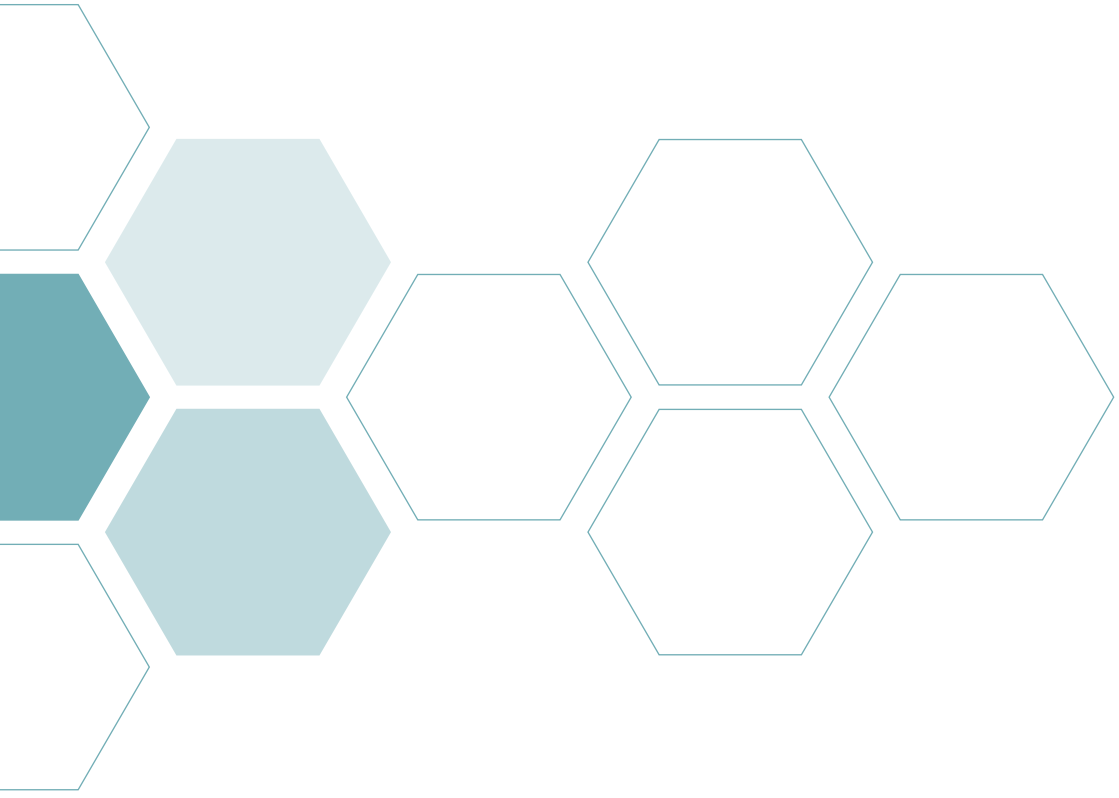

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Clinical Advances in Idiopathic Pulmonary Fibrosis: New Treatment Goals and Strategies

David J. Lederer, MD, MS

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

Summary

Idiopathic pulmonary fibrosis (IPF) is a rare but devastating disease. There are now oral medications which slow the rate of lung function decline. Data on other benefits of these medications are now emerging.

Key Points

- Antifibrotics are a good choice for most patients with IPF.
- Both pirfenidone and nintedanib slow progression of IPF.
- Counseling and careful monitoring are required to optimize outcomes.
- New data are showing hospitalization and mortality benefits.

IDIOPATHIC PULMONARY FIBROSIS (IPF) IS a progressive disease of peripheral lobular fibrosis of unknown cause, characterized by thickening of the alveolar walls. It is a disease of older adults. Approximately 0.5 percent of adults in the United States (U.S.) over 65 years old have IPF. Approximately one new case is diagnosed per 1,000 adults over the age of 65 each year. More than 200,000 Americans are thought to be affected. It is a high-impact disease with disabling exertional dyspnea and cough that causes severe functional limitation and impaired quality of life. The median survival time from diagnosis is 3.8 years.

There are several dilemmas in the diagnosis and care of IPF. It is difficult to recognize and diagnose, even for some pulmonologists. Many clinicians who are not familiar with the disease believe there is nothing to do for these patients. It is considered to be a rare disease, there is lack of provider and public awareness, and there is limited research funding. Another major dilemma is lack of understanding as to what causes the disease; multiple mechanistic pathways have been implicated via animal models, but there is little data on humans.

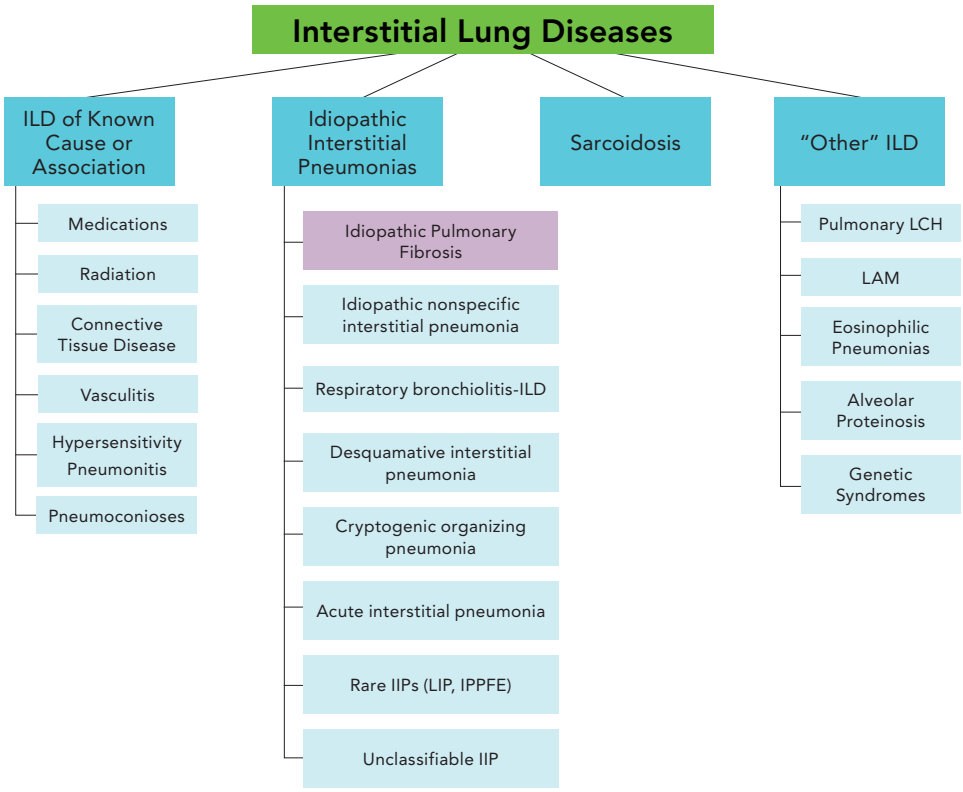
IPF is just one of the many interstitial lung diseases (ILD), (Exhibit 1).[1,2] As shown in Exhibit 2, an interstitial lung disease workup should be triggered by symptoms of dyspnea or non-productive cough, even if otherwise explained, and one or more findings.

A high-resolution CT is best for diagnosing IPF. It will show the usual interstitial pneumonia (UIP) pattern that is classic for IPF. The diagnosis of IPF also requires ruling out other causes of ILD (Exhibit 1).

Once diagnosed, general management of IPF includes smoking cessation, if appropriate, supplemental oxygen, pulmonary rehabilitation, weight management, age-appropriate vaccinations, ILD support groups, patient education, and advocacy group involvement. Definitive treatment of IPF includes lung transplantation and medications. There are now two FDA approved therapies for IPF which will be discussed. Clinical trial enrollment is also an option for many patients.

Vascular endothelial growth factor (VEGF), fi-

Exhibit 1: Interstitial Lung Diseases[1,2]



broblast growth factor (FGF), and platelet-derived growth factor (PDGF) have all been implicated in the development of IPF. Nintedanib (Ofev®) is an oral tyrosine kinase inhibitor that targets all three. In a one-year trial of patients with IPF with forced vital capacity (FVC) greater than 50 percent predicted (moderate to severe disease) comparing nintedanib to placebo, there was a 68.4 percent reduction in the rate of loss function as measured by FVC.[3] On average, patients with IPF lose 0.2 L of FVC each year; in this trial and others, patients lost 0.1 L/year.[3,4] Importantly, even with therapy, lung function continues to decline. There was also a lower incidence of acute exacerbations in the nintedanib group compared with placebo (2.4 vs. 15.7 per 100 patient-years, P = 0.02) and a small improvement in quality of life with nintedanib treatment; however, there were no significant mortality benefits.[3] In two other one-year trials of this agent, there was a slowing in lung function decline by FVC (~100 ml benefit).[4] One of the trials found a significant benefit in the time to the first exacerbation, while there was no significant difference in the other trial. No benefits on quality of life or mortality were seen in these two trials. Diarrhea, nausea, and vomiting are the most common adverse effects with nintedanib.

Pirfenidone (Esbriet®) is an oral drug with anti-inflammatory, antifibrotic, and antioxidant effects. It blocks PDGF and reduces fibroblast proliferation. Studies have shown lung function, mortality, and physical function (six-minute walk) benefit of pirfenidone, with minimal adverse effects.[5,6] In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9 percent in the proportion of patients who had an absolute decline of 10 percentage points or more of the predicted FVC or who died. The proportion of patients with no decline in FVC had a relative increase of 132.5 percent, there was a reduced decline in the six-minute walk distance, and there was improved progression-free survival with pirfenidone treatment. Mortality due to IPF was reduced 68 percent with pirfenidone treatment compared with placebo. The most common adverse effects with pirfenidone are nausea, poor appetite, diarrhea, gastroesophageal reflux, and photosensitive rash.

The IPF management guidelines strongly recommend oxygen and lung transplantation as treatments for IPF.[7] The most recent version of the guidelines conditionally recommends nintedanib, pirfenidone,

Exhibit 2: What Should Trigger an ILD Evaluation?

At least one from each column

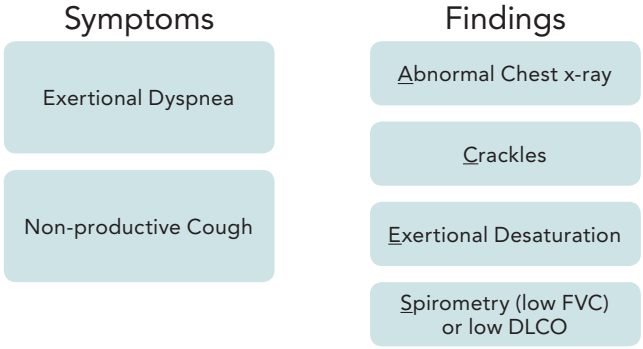


Exhibit 3: Antifibrotics for IPF

	Nintedanib	Pirfenidone
FDA-approved dose	150 mg by mouth twice daily	801mg by mouth three times daily
Common side-effects	Diarrhea	Anorexia, nausea, photosensitivity
Enzyme metabolism	Ester cleavage (major) CYP 3A4 (minor)	CYP 1A2 (major) Other CYP enzymes (minor)
Cautions	• Risks of both bleeding and arterial thrombosis • Rare risk of gastrointestinal perforation • Avoid anticoagulation and pro-thrombotic drugs • Drug-induced liver disease has been reported	• Fluvoxamine and high-dose ciprofloxaxin can raise pirfenidone levels • Omeprazole and smoking can lower pirfenidone levels
Need for liver function test monitoring	Yes	Yes
Clinical strategies to maximize tolerability	Anti-diarrheals Temporary dose reductions to 100mg twice daily	Slow dose titration over 14 days Should be taken with food Antacids Antiemetics Sun avoidance strategies

pulmonary rehabilitation, and antacid therapy. A conditional recommendation is a recommendation for use in most patients, but not necessarily in all patients. Antacid therapy is used to reduce GI reflux, which has been implicated in worsening IPF and possibly even contributing to the development of the disease. Antacid therapy is controversial because use of proton pump inhibitors increases the risk of pulmonary infections and other long- term issues.

Additional data on nintedanib have been published since the last guideline update. Tolerability in the real world in sicker folks than found in the trials is similar to what was found in the randomized controlled trials.[8] This agent seems to work equally well for patients with early disease (FVC > 90% predicted) and even if honeycombing is absent on HRCT.[9,10] Nintedanib may prevent acute exacerbations (in those with FVC 50 – 70% predicted) and may reduce on-treatment mortality (based on pooled analyses and meta-analyses).[11,12]

There are also new data for pirfenidone. It also is tolerated well in sicker patients and seems to work equally well for those with FVC > 80 percent predicted.[8,13-15] Interestingly, it seems to continue to work even after disease progression occurs on therapy.[16] Long-term safety data has shown no unsuspected signals.[15] It reduces respiratory-related hospitalizations and may reduce mortality (based on

pooled analyses and meta-analyses).[17,18]

In selecting who to treat with which agents, it is important to remember that the interventions that help the most are not medications; the most helpful are supplemental oxygen, pulmonary rehabilitation, treatment of mood and anxiety disorders, social support, and education. Clinicians also have to decide when to treat patients with medications. Patients should meet the diagnostic criteria in the published guidelines.[1,2,7]

The antifibrotic medications slow disease progression and might delay hospitalization and death. Overall, pirfenidone and nintedanib reduce lung function decline by about 50 percent over one year. They do not improve dyspnea or cough, pulmonary function, oxygen requirements, quality of life, nor exercise capacity. The two agents appear to be equally efficacious.

The major difference between the agents is adverse effects. To improve tolerance of IPF medications, patient counseling and several interventions can be done. Taking pirfenidone with a full meal, slow titration over 14 days, antacid therapy (but not omeprazole), and antiemetics (ondansetron) for some patients will decrease the nausea and appetite loss related to this medication. Most patients taking nintedanib will require loperamide to control diarrhea. Temporary dose reductions to 100mg twice daily can also help to reduce diarrhea.

Hepatic function monitoring is required with both medications. Baseline liver function tests and then monthly testing for several months followed by periodic testing is required for all patients. Exhibit 3 compares the two medications.

Conclusion

Antifibrotics are a good choice for most patients with IPF, but not for all. Both pirfenidone and nintedanib slow progression of IPF. These medications are generally well tolerated. Counseling and careful monitoring are required to optimize outcomes. New data on hospitalization and mortality benefits of these agents are encouraging.

David J. Lederer, MD, MS is an Associate Professor of Medicine and Epidemiology at Columbia University Medical Center in New York, NY.

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New Frontiers in the Management of Hepatocellular Carcinoma (HCC): Exploring Novel Treatment Advances and Approaches

David E. Kaplan, MD, MSc, FACP, FAASLD, AGAF

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

Summary

Although early stage hepatocellular carcinoma is curable in some patients, advanced disease is not. There are several local/regional treatments and systemic therapies. Each provides some survival benefit, but there is a need for more treatments for advanced disease.

Key Points

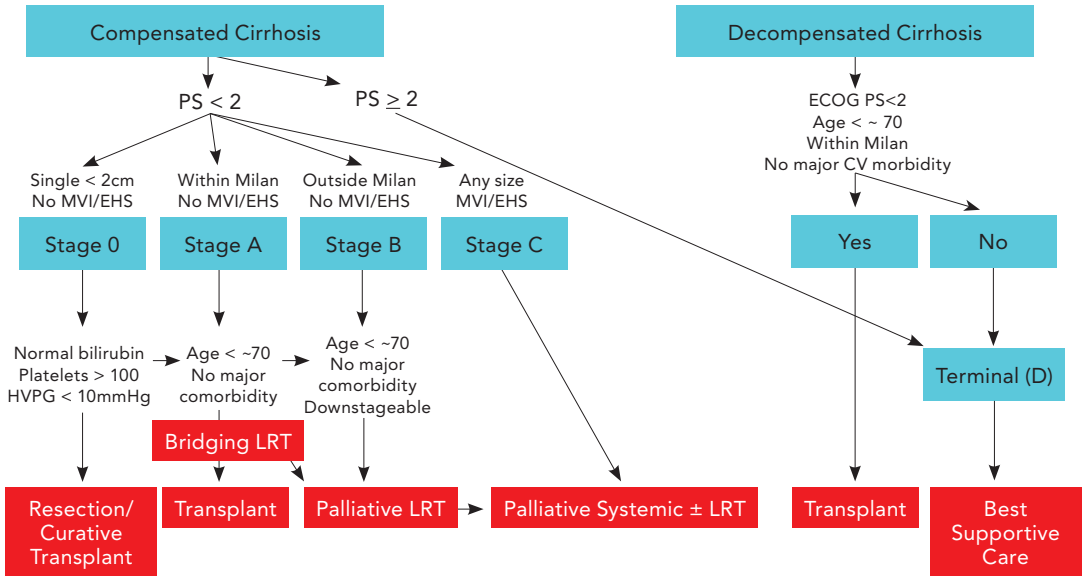
- Cirrhosis is the primary cause of HCC.
- The presence of cirrhosis complicates the treatment of HCC.
- Advanced disease is treated with local/regional therapies and systemic agents (tyrosine kinase inhibitors and immunotherapy).
- There are two first-line tyrosine kinase inhibitors and one second-line agent, with more to come for both lines.
- Immunotherapy is currently approved as second-line therapy in advanced disease, but it will likely become a second-line agent.

HEPATOCELLULAR CARCINOMA (HCC) IS the most common primary liver malignancy. It arises from transformed hepatocytes, and 90 percent of cases are associated with cirrhosis of all causes. HCC is generally asymptomatic until advanced and incurable because there are no nerves inside the liver. Mortality in patients with HCC is primarily caused by hepatic failure secondary to cirrhosis rather than the cancer itself. It can be diagnosed with imaging rather than biopsy in more than 95 percent of cases. Unique from other solid tumors, selected patients are cured by transplantation.

Most patients with HCC have two separate diseases – cancer and cirrhosis. Patients can have a good liver but bad cancer or a bad liver and good cancer. Some with advanced cancer have compensated liver disease and may look well; extrahepatic spread is relatively rare with HCC and rarely symptomatic. Those with advanced cirrhosis typically have multifocal hepatocarcinogenesis and high recurrence rates. The effects of cirrhosis, including portal hypertension, thrombocytopenia, and impaired hepatic function, limit treatment choices. Thus, having compensated liver disease with HCC is typically much better in terms of survival than having advanced cirrhosis and HCC.

For many years, HCC was primarily a disease of developing countries because of the high prevalence of hepatitis B viral infections. In the past 25 years, there has been a marked increase in prevalence in the developed world, primarily related to the hepatitis C virus (HCV). The United States (U.S.) had a dramatic 75 percent increase in HCC cases between 1990 and 2016.[1] Within the U.S. veteran population, there was a 250 percent increase in incidence of HCC from 2002 to 2012, mostly attributable to the aging cohort of veterans with HCV-related liver disease.[2] Alcohol and nonalcoholic fatty liver disease (NAFLD) contributed minimally to the increased incidence. Most patients were aged 60 to 69, two-

Exhibit 1: Treatment of Hepatocellular Carcinoma[4]



PS = performance status, MVI/EHS = macrovascular invasion or extra hepatic spread, HVPG = hepatic venous pressure gradient, LRT = local regional therapy

thirds were Caucasian, and 24 percent were African American (reflecting a disproportionate impact of HCV on black veterans).[2]

Although traditionally most patients were thought to present with advanced disease, an improved focus on identifying those with hepatitis C or B infection may be leading to earlier diagnosis. In a U.S. veteran population, the majority of patients presented with very early to intermediate disease. Almost 36 percent of patients presented in the very early or early stage, 32 percent with intermediate, and 31 percent with advanced or terminal disease.[2] The stage at presentation has an impact on overall survival (OS). Median OS for early stage disease is three years, for intermediate it is a little over a year, and for advanced it is less than six months.

Like most cancers, HCC is a costly disease to manage, with costs varying by the stage of the disease. In one trial, again in the Veterans Administration population, costs for those with advanced disease were $269,312 per year.[3]

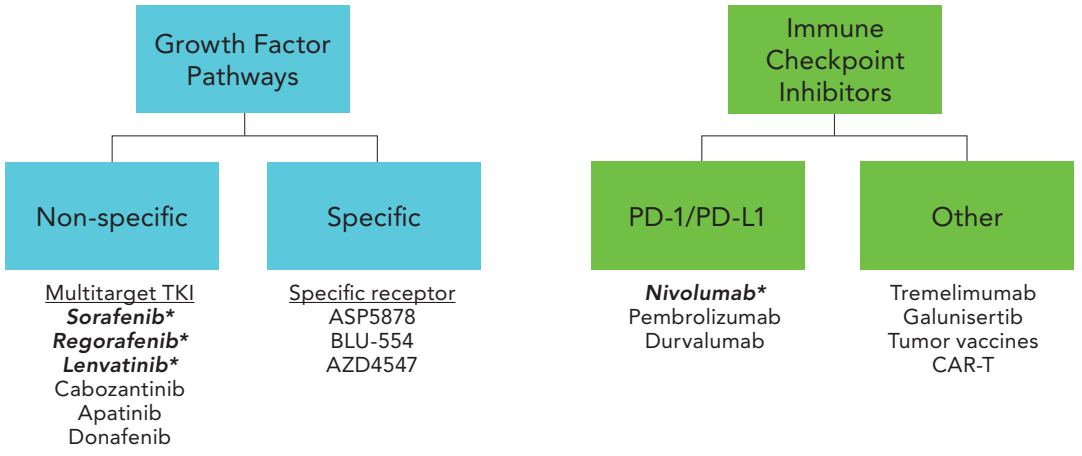
Staging HCC is different than with other solid tumors, which is typically done with TMN staging (tumor size, metastases, and node positivity). Most clinicians in the U.S. use the Barcelona Clinic Liver Cancer (BCLC) staging system, which initially considers whether compensated or decompensated cirrhosis is present (Exhibit 1).[4] Other considerations in staging and treatment include performance status, age, and tumor size.

For those with decompensated cirrhosis (ascites, encephalopathy, and bleeding varices) who have poor performance status, cardiovascular disease, or are over 70, best supportive care is recommended. For those with decompensated cirrhosis but who have tumors within the Milan criteria (single tumor 5 cm or smaller or up to 3 tumors less than 3 cm) and are in better physical shape, they may be listed for a liver transplant and be cured with a successful transplant.

For those with compensated cirrhosis, staging depends on performance status, tumor size/number, and macrovascular invasion or extra hepatic spread (MVI/EHS). Those with Stage 0 disease can be cured with resection or a liver transplant. All other stages of HCC are considered unresectable.

Resection, ablation, and liver transplantation are curative treatments for HCC. Resection and ablation are associated with high five-year recurrence rates due to the persistence of underlying cirrhosis and the oncogenic drivers of that milieu. There is a 70 percent five-year recurrence and 55 to 70 percent five-year survival with resection.[5] Ablation with radiofrequency, microwave, chemical, or stereotactic body radiation therapy (SBRT) is effective for HCC less than 3 to 4cm and is a minimally invasive, outpatient procedure. There is no bilirubin cutoff for allowing ablation. It does not cure cirrho-

Exhibit 2: Advanced Unresectable HCC – Broad Categories of Agents



** FDA Approved for HCC*

sis and is subject to anatomic restrictions. There is a 70 percent five-year recurrence and 40 to 50 percent five-year survival with ablation.[5] Now with the high numbers of people experiencing a cure of HCV, it is possible that recurrence rates after resection or ablation may decline; however, this remains to be seen.

Transplantation is the curative treatment of choice for selected relatively small unresectable HCCs. It cures cirrhosis, and there is a less than 15 percent recurrence rate. The five-year survival after transplant is greater than 70 percent.[6] While transplant offers a durable cure of HCC and cirrhosis with a very low five-year recurrence risk, demand far exceeds supply and many patients have contraindications to transplantation in the form of physical and mental health comorbidities.

Local/regional therapy (LRT) is also an option for intermediate disease. Embolotherapy allows delivery of anticancer therapy directly to the tumor-feeding arterial blood supply while sparing the healthy hepatic tissue mainly supplied by the portal vein. Variants include transarterial embolization (TAE), transarterial chemoembolization embolization (TACE), and transarterial radioembolization (TARE, Yttrium-90 [Y90]). There are differences in the techniques for embolotherapy; however, no one approach is thought to be superior and all improve median OS.

Treatments for advanced unresectable HCC are LRT and palliative systemic therapies. LRT for advanced disease includes Y90, SBRT, and proton therapy. Systemic therapies include tyrosine kinase inhibitors (TKI) and immunotherapy; these are usually used after a patient has had LRT and has progressed. Data are accumulating that LRT in early advanced stage disease in well-compensated cirrhosis can be equivalent to systemic therapy with a TKI.[7] Y90 radiotherapy was recently tested in locally advanced, inoperable HCC head-to-head against sorafenib, a TKI, and showed non-significant survival differences, although it had a more favorable side effect profile and patient quality of life (QOL) indicators.[8] Radiotherapy embolism is attractive to patients because it is an outpatient procedure, is well tolerated, and has little impact on liver function or QOL. The downside is that it is a complicated and costly procedure which is not appropriate for many patients.

Systemic therapeutics in HCC need to be active against multiple targets (vasculature, microenvironment, and tumor) while being tolerable, not hepatotoxic, and not nephrotoxic. Exhibit 2 shows the growth factor pathway targeting agents and immunotherapy options.

Sorafenib (Nexavar®), a multiple pathway TKI, targets the vasculature and tumor cells. It delays progression and prolongs survival by 7.9 to 10.7 months.[9,10] It was FDA approved in 2007 for unresectable HCC and had been the only first-line agent until recent approval of lenvatinib. Pros for using sorafenib include an oral dosage form, titratable dose, high stable disease response rates (~60%), and improved OS in HCV-related HCC (median OS 15 months). Cons are adverse effects, low efficacy in Asian studies, lack of a biomarker for response, and very rare complete responses (which is not sat-

isfying to patients or oncologists). Adverse effects are mostly Grade 1 and 2 and include palmoplantar dysesthesia (Grade 3 in 10 – 15%), diarrhea (46%, Grade 3 in < 5%), anorexia, hypertension (~30%, <15% Grade 3), alopecia (any ~ 25%), and fatigue.

Lenvatinib (Lenvima®) is similar to sorafenib and regorafenib with multiple cellular targets, but also has specific activity against vascular endothelial growth factor receptors (VEGFR) two and three and fibroblast growth factor receptor (FGFR), which the others do not. It was FDA approved in August 2018 for first-line treatment of patients with unresectable HCC and had previously been approved for thyroid cancer. Approval was based on an international, multicenter, randomized, open-label, non-inferiority trial conducted in 954 patients with previously untreated, metastatic or unresectable HCC.[11] This trial demonstrated that lenvatinib was non-inferior, but not statistically superior to sorafenib for OS. Median OS in the lenvatinib arm was 13.6 months compared with 12.3 months in the sorafenib arm. This trial also demonstrated a statistically significant improvement in progression-free survival (PFS) with lenvatinib as compared to sorafenib. Median PFS was 7.3 months in the lenvatinib arm and 3.6 months in the sorafenib arm. The overall response rate was higher for the lenvatinib arm as compared to sorafenib (41% versus 12%). There was a higher patient-reported QOL with lenvatinib compared with sorafenib. Sixty-seven percent of the subjects in this trial were Asian. The adverse effects with this agent are similar to sorafenib, but with a higher rate of hypertension (42%) and lower rate of diarrhea (39%).

Regorafenib (Stivarga®) is second-line therapy after sorafenib or lenvatinib. It was approved by the FDA in April 2017 for patients with HCC previously treated with sorafenib. Median OS is 10.6 months when regorafenib is used in the second-line setting.[12] It is given for three weeks every month with a one-week break. Other TKIs are under investigation for treating unresectable HCC. Cabozantinib is likely to be FDA approved soon in the second-line setting.

Immunotherapy is currently second-line treatment for advanced HCC after a TKI. The rationale for using immunotherapy in HCC is that this cancer is a classical inflammation-induced tumor type and spontaneous immune-induced regression has been observed. Additionally, immunomodulators are rarely metabolized in the liver and occasionally produce dramatic responses, unlike what is seen with TKIs. There is some concern with causing a disease flare when giving them to those with viral hepatitis.

Checkpoint inhibitors, which essentially take the brakes off the immune system allowing it to detect tumor cells, have been studied in HCC treatment and one has been approved so far. Nivolumab received contingent accelerated approval by the FDA in September 2017 as second line for HCC previously treated with sorafenib. This approval was based on a Phase I and II study in patients with well-compensated liver disease who had been heavily pretreated.[13] There was a significant reduction in tumor size in about 25 percent of subjects and PFS was 4.0 months. Median OS has not been reached and is greater than 13.2 months. Responses to nivolumab occur early and appear to be sustained with excellent patient tolerance and a reasonably safe adverse effect profile. PD-L1 expression is not necessary for use of nivolumab in HCC.

Pembrolizumab is under investigation for treating HCC. A single arm, open-label Phase II trial of pembrolizumab in the second-line setting found similar benefits to nivolumab, including a complete response in the subjects.[14] It will likely receive FDA approval for unresectable HCC. Nivolumab, durvalumab and tremelimumab are in trials as first-line therapy in unresectable HCC. Within the next few years, immunotherapy will likely become first-line therapy in advanced HCC.

Conclusion

Current FDA approved treatments for advanced HCC remain limited. Many new therapies are in development that will hopefully continue to improve survival in advanced disease. Combination therapies of local/regional therapy and systemic therapy are likely needed; however, few combinations currently are supported by data. All treatment options must balance potency and safety and tolerability in a patient with two advanced diseases – cirrhosis and liver cancer.

David E. Kaplan, MD, MSc, FACP, FAASLD, AGAF is an Associate Professor of Medicine with the Perelman Center for Advanced Medicine and at the Veteran's Administration Medical Center in Philadelphia, PA.

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Best Practices in the Management of Advanced Non-Small Cell Lung Cancer

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

Summary

The management of non-small cell lung cancer (NSCLC) is rapidly evolving and is becoming very exciting. The issue is that, like much of oncology, the costs related to new therapies are spiraling out of control. The appropriate selection of therapy in this disease is important both from an efficacy and financial point of view.

Key Points

- Treatment of NSLC is rapidly changing.
- First-line treatment for several forms of NSCLC has changed recently.
- Targeted therapy based on genetic mutations, immunotherapy, and chemotherapy are all used in advanced NSCLC.

LUNG CANCER IS NOT JUST ONE DISEASE. It is many different diseases, which impacts treatment selection. Histology, presence of certain cell markers and genetic mutations are used to distinguish the different types of lung cancer. The focus of this article is non-small cell lung cancer (NSCLC), particularly advanced/metastatic disease, which is the area in which most of the new therapies are being used.

Many factors have to be considered when making treatment decisions for untreated advanced NSCLC. Some key factors in decision-making are shown in Exhibit 1. Therapy for advanced NSCLC is summarized in Exhibit 2. Several of the first-line recommendations have changed recently because of new studies being published. Because this field is rapidly changing, clinicians and managed care decision makers are advised to consult the most recent National Comprehensive Cancer Network (NCCN) guidelines and recent literature for the most up-to-date recommendations.[1]

The first factor in determining therapy is whether the disease is squamous or nonsquamous cell because these two types respond differently to therapy. Next is the consideration of targetable genetic mutations because the success with targeted therapy has far exceeded the benefits of chemotherapy and immunotherapy.

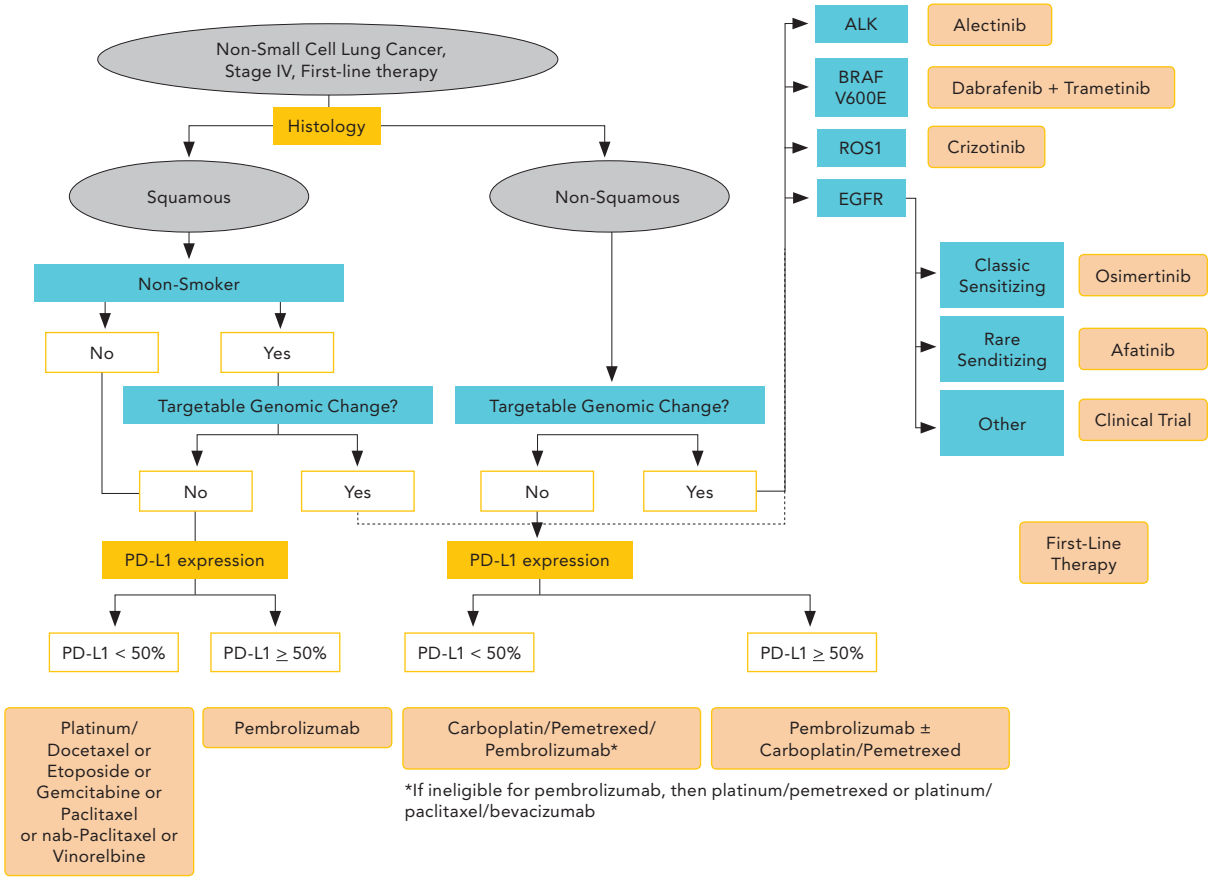
Genomic testing should be performed in all patients with advanced, nonsquamous NSCLC. In patients with squamous NSCLC who are nonsmokers, at minimum, testing should include genomic testing for mutations in EGFR and BRAF, rearrangements in ALK and ROS1 and PD-L1 expression and strong consideration should be given to next-generation sequencing.

Recent trials have led to changes in the recommended first-line therapy for EGFR and ALK mu-

Exhibit 1: Some Key Factors in Decision-Making for Untreated Advanced NSCLC

Disease Characteristics	Patient Medical Characteristics	Symptomatology
• Histology • Extent of disease/Brain Mets • Targetable mutation • PD-L1 expression tumor mutation burden	• Performance Status • Comorbidities • Renal/Hepatic/Hematologic function • Autoimmune Disease • Cardiac Function/History	• Presence/Acuity of symptoms • Hemoptysis • Dyspnea • Neuropathy • GI symptoms
Patient Concerns	**System Concerns**	
• Side effects • Mechanism of delivery • Hospitalization • Impact on lifestyle • Coverage/Cost to patient • Visit schedule	• Drug availability • Coverage/Prior Aouthorization • Cost • Infusion room availability • Risk of ED visits/Hospitalization	

Exhibit 2: First-Line Therapy for Advanced NSCLC



*If ineligible for pembrolizumab, then platinum/pemetrexed or platinum/ paclitaxel/bevacizumab

Exhibit 3: Immunotherapy in Later-Line Therapy of Metastatic NSCLC

Drug	Target	Stage IV, First-Line Monotherapy	Stage IV, First-Line Combination	Stage IV, Later-Line Monotherapy	Stage IV, Later-Line Combination	Stage III Consolidation After Chemorads
Pembrolizumab	PD-1	✔ (PD-L1 ≥ 50%)	✔	✔ (PD-L1 ≥ 1%)	-	-
Nivolumab	PD-1	-	-	✔	-	-
Atezolizumab	PD-L1	-	-	✔	-	-
Durvalumab	PD-L1	-	-	-	-	✔

PD = programmed death
PDFL = programmed death ligand

tations. EGFR mutations L858R and exon 19 del are the classic sensitizing mutations because they are responsive to the initial EGFR inhibitors (gefitinib, erlotinib, afatinib).[2] These initial EGFR inhibitors used to be first-line therapy, but they have been replaced by osimertinib because of improved efficacy and lower rates of adverse effects.[3] Afatinib is still considered first-line therapy for rare sensitizing mutations and is the only EGFR inhibitor with FDA approval for this indication.[4] Treatment of cases with other EGFR mutations (e.g., exon 20 insertions, D761Y, V769M) is primarily in clinical trials because no specific targeted therapies are yet approved.

Crizotinib was the first agent approved for treating NSCLC with rearrangements in ALK and used to be first-line therapy. A second-generation agent, alectinib, has replaced crizotinib because of improved efficacy and lower toxicity.[5,6] It penetrates the central nervous system (CNS) better than crizotinib and is better for treating CNS metastases.

For BRAF V600E mutations, it has been shown that combination therapy with a BRAF inhibitor and a MEK inhibitor is better for shutting down cell growth than BRAF inhibition alone.[7] Thus, the recommended first-line therapy for NSCLC with BRAF V600E mutation is dabrafenib and trametinib.

Crizotinib is the only agent currently approved for targeting ROS1 mutations in NSCLC. Many other mutations and rearrangements are being investigated as targets for therapy. A few of these include MET exon 14, HER2, and KRAS.

Patients with NSCLC with EGFR mutations on targeted therapy who have disease progression should have their disease biopsied to inform second-line decision making. NSCLC can transform into small cell lung cancer or new genetic mutations can develop. Future research needs in the areas of genomic testing and targeted therapies are a better understanding of the mechanisms of resistance and therapies to overcome resistance.

Immunotherapy, which unleashes the immune system to attack tumor cells, is an up-and-coming therapy for many cancers, including NSCLC. Pembrolizumab monotherapy is established as first-line therapy for advanced NSCLC with programmed death ligand one (PD-L1) expression > 50 percent and no targetable mutations. Compared with conventional chemotherapy, pembrolizumab improves progression-free survival (PFS) and overall survival (OS) with fewer serious adverse effects.[8] There is also an established role for immunotherapy in later-line treatment; pembrolizumab, nivolumab, and atezolizumab are approved for use as monotherapy in the second line and beyond setting (Exhibit 3). There is no clear winner among different immunotherapy agents in later-line therapy in terms of efficacy and toxicity. On immunotherapy progression, there is no data to suggest a role for salvage with a different immunotherapy alone. Durvalumab was approved in 2017 for earlier use in treating NSCLC. It is approved for unresectable Stage III NSCLC that has progressed on concurrent platinum-based chemotherapy and radiation. Additional trials are ongoing examining the use of immunotherapy in earlier stages of the disease.

The adverse effects of immunotherapy can be significant and are related to taking the brakes off the immune system. These are very different from those traditionally seen with cancer treatment. Clinicians who care for patients who are receiving immunotherapy need to be aware of the adverse

effects so they can be recognized and managed early. There are safety concerns about using immunotherapy in patients with preexisting autoimmune disease; data are being collected to determine if immunotherapy can be used safely in cases with selected controlled autoimmune disease, such as rheumatoid arthritis. Several areas of need related to immunotherapy include exploring different combinations and sequences; determining a better predictive biomarker; and better toxicity prevention, identification, and management.

For those patients who are not eligible for targeted therapy or immunotherapy, the treatment is combination chemotherapy, which always includes a platinum-based agent, such as carboplatin. First-line treatment for squamous NSCLC is a platinum-based combination. First-line for nonsquamous NSCLC is the combination of carboplatin/pemetrexed with pembrolizumab; for patients with greater than 50 percent PD-L1, pembrolizumab alone is an option.[9] Outcomes from non-head-to-head trials seem to indicate that the outcomes with pembrolizumab alone, compared with triple therapy in those with greater than 50 percent expression, appear to be very similar. If immunotherapy is not an option, either carboplatin/pemetrexed or carboplatin/paclitaxel/bevacizumab are the first-line choices.

Conclusion

Targeted therapy and immunotherapy are treatment options for a large subset of patients with NSCLC. Those not eligible for these agents are treated with combinations of chemotherapy. Discovery of additional genetic mutations that drive NSCLC continues and many more medications will likely be coming to market. Clinicians have more tools for helping patients and are very excited about the possibilities of additional therapies for treating this disease.

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Exploring the Challenges of Severe Asthma: Implementing Personalized Treatment Plans for Improved Patient Outcomes

Charles P. Vega, MD, FAAFP

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

Summary

Managing asthma, especially severe disease, can be challenging. Clinicians can improve patient outcomes by adhering to best practices for asthma management. For those patients with severe disease and an eosinophilic phenotype, there are now several biologics agents which are effective for improving outcomes.

Key Points

- Basic best practices, such as using appropriate medications and checking on inhaler technique demonstration at each visit, are key to achieving asthma control.
- Biologic use in those with eosinophilic phenotype can reduce exacerbations and oral corticosteroid use.
- All the biologics, except dupilumab, are given in a health care setting, which can be burdensome for patients

OVERALL, APPROXIMATELY 8.3 PERCENT of children and adults in the United States (U.S). have asthma.[1] The rates are higher in females compared to males and in African Americans compared to Caucasians and Hispanics. In children, asthma prevalence increased from 3.1 percent in 1980 to 5.5 percent in 1996 and 7.3 percent in 2001 to 8.4 percent in 2010 but was 8.3 percent in 2016.[1] Similar increases have been seen in adults.

Although prevalence has increased, asthma exacerbations have decreased modestly; from 2001 to 2016, both children and adults had fewer asthma attacks.[1] For children, having at least one asthma attack in the previous 12 months declined from 61.7 percent in 2001 to 58.3 percent in 2010 and 53.7 percent in 2015. For adults, asthma attacks declined from 53.8 percent in 2001 to 49.1 percent in 2010 and 44.9 percent in 2015. Asthma attacks occur more often in females than males, occur among those with a family income less than 100 percent of the federal poverty threshold than persons with income between 250 percent and less than 450 percent of the poverty threshold, and occur in those living in the South and West compared to those living in Northeast. Asthma attack prevalence does not differ by race or ethnicity. Although exacerbations have declined, it is important to note that despite national guidelines, good treatment availability, and major pushes for improved asthma care, 45 to 50 percent of those with asthma will have an exacerbation each year.

Asthma results in significant morbidity and mortality; this includes exacerbations as noted previously. In 2015, 1.7 million emergency department (ED) visits occurred with asthma as the primary diagnosis.[1] In 2016, there were 10 deaths per million person-years due to asthma.[1]

Best asthma practices are key to controlling the disease and reducing morbidity and mortality. The first best practice is getting the initial classification of disease severity correct (Exhibit 1).[2] Although mild persistent asthma accounts for 50 to 75 per-

Exhibit 1: Asthma Classification[2]

- **Intermittent**
  - Symptoms less than 2 days/week
- **Mild persistent**
  - Symptoms not daily
  - < 4 nighttime awakenings/month
  - FEV_1 > 80%
- **Moderate persistent**
  - Daily symptoms
  - Awakening at least weekly
  - FEV_1 60% - 80%
- **Severe persistent**
  - Symptoms throughout day
  - Extremely limited function
  - FEV_1 < 60%

FEV_1 = forced expiratory volume in one second

Exhibit 2: Recommended Medication by Asthma Classification[2]

- **Intermittent**
  - Short-acting beta agonist (SABA) only
  - SABA first-line for exercise-induced asthma
- **Mild persistent**
  - Low-dose inhaled corticosteroid (ICS)
- **Moderate persistent**
  - Medium-dose ICS, possibly with long-acting beta agonist (LABA) or montelukast, tiotropium
- **Severe persistent**
  - High-dose ICS w LABA or montelukast, tiotropium.
  - May need oral steroids (and referral)
  - Biologics (selected patients)

cent of cases, it may account for up to 40 percent of exacerbations in urgent care settings.[3] Thus, clinicians and disease management programs should not focus only on those with more severe disease. Also, it is important to note that asthma is a dynamic illness and disease severity classification can change and thus treatment must change. Spirometry for patients over 5 years old to ensure reversibility of disease with a short-acting beta agonist (SABA) and to confirm the diagnosis is vital. It can also be used to monitor the course of the disease over time.

The major treatment goals in asthma are to reduce impairment and reduce exacerbations. Patients should be involved in setting goals. It is important to identify and avoid asthma triggers and allergens. Multifaceted approaches to trigger avoidance are most effective. Clinicians should consider skin or in vitro allergen testing if a patient has persistent asthma.

Asthma education is important in improving outcomes in this disease. A one-time educational intervention for adults who visit an ED for acute asthma has been shown to reduce subsequent asthma admissions to the hospital.[4] Education should be culturally focused and in the patient's native language, if possible.

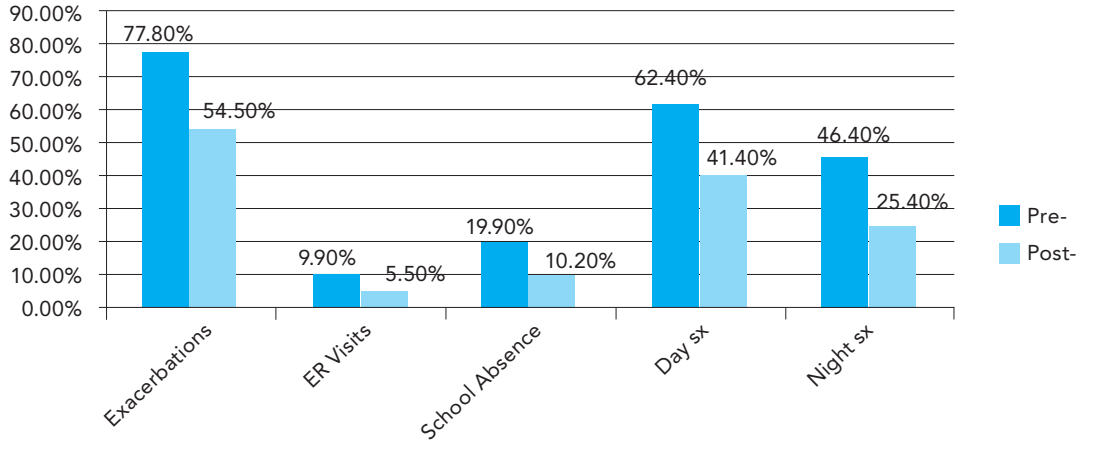
Physical training is another option to improve asthma control. In a review of available studies, physical training produces significant improvements in maximum oxygen uptake, though no effects were observed in other measures of pulmonary function. Physical training is well tolerated among people with asthma and, as such, people with stable asthma should be encouraged to participate in regular exercise training, without fear of symptom exacerbation.[5] Four of five studies evaluating health-related quality of life found a clinically significant benefit for exercise in asthma.

Another best practice is to make sure all patients know how to use their inhaler properly. Improper inhaler use is a common issue in both children and adults. In studies of children and adults with an acute exacerbation, 45 percent had improper metered-dose inhaler (MDI) technique.[6,7] The main reasons for improper use were lack of education and lack of outpatient follow-up after starting the inhaler. Improper MDI use is associated with higher asthma symptom scores and frequent ED visits. If patients do not use their inhalers properly, it is like they were not even prescribed. The website www.use-inhalers.com is noncommercial and provides easy to understand information and videos on inhaler use.

Exhibit 2 shows the recommended medications for each severity classification.[2] It is important to note that inhaled corticosteroids (ICS) have the most relative efficacy at low doses compared to medium or high doses. Increasing the dose only produces a modest bump in efficacy while increasing the risk of adverse effects.

Combination therapy in a single inhaler (corticosteroid and long-acting beta agonist) has been demonstrated to reduce exacerbations requiring oral corticosteroids compared with current best practice strategies (ICS and as needed SABA) and against a fixed high dose of inhaled steroids.[8] The strength of evidence that single inhaler therapy (SiT) reduces hospitalization against these same treatments is weak. There were more discontinuations due to adverse events on SiT compared to current best practice, but no significant differences in serious adverse events. Overall, SiT is an option for asthma control, but it is not a one size fits all solution.

Exhibit 3: Benefits of Community Evidence-based Asthma Care Program[25]



Managing comorbid conditions is another important aspect of asthma control. Common comorbid conditions include gastroesophageal reflux disease (GERD), obesity, obstructive sleep apnea, rhinitis, stress, and depression. Primary care providers should be managing these conditions in conjunction with asthma specialists.

Active follow-up is another best practice. Patients should be seen every two to six weeks until adequate disease control is achieved. Trigger avoidance and inhaler technique should be reviewed at each visit. Education can also be provided at each visit. Medications should be adjusted as necessary. An asthma action plan is important for helping patients to manage their medications and trigger avoidance.

Patients with severe asthma receive a lot of attention from managed care because they account for the majority of exacerbations, ED visits, and hospitalizations. Severe asthma is defined as persistent symptoms despite maximum therapy and systemic corticosteroid requirement for at least half of the past year. This group of patients requires care by an asthma specialist.

Multiple phenotypes of asthma have been identified; examples include early-onset mild allergic asthma, later-onset asthma associated with obesity, and severe non-atopic asthma with frequent exacerbations.[9] Asthma phenotypes have been further refined by including information regarding pathophysiologic mechanisms present in different groups. These groups, called endotypes, include examples such as aspirin-exacerbated respiratory disease and eosinophilic asthma for which there are now biologic therapies.[9] Personalization of asthma therapy using phenotypes and endotypes is going to revolutionize treatment. At present, asthma can be broadly categorized into two endotypes: T helper two (TH2)-high and TH2-low. The TH2-high group typically has an increased eosinophil presence in the sputum, airways, and peripheral circulation while the T2-low group classically exhibits a neutrophilic or a general lack of inflammatory cells in sputum and airways.[10] Those in the TH2-high group typically respond better to ICS.

Biomarkers to guide personalized therapy are being used more often. Eosinophils can be used as a biomarker in asthma treatment. Sputum eosinophils are useful in predicting response to ICS; however, they are not practical in many clinical settings, and the necessary sputum samples are difficult to obtain and interpret. Blood eosinophil levels are easier to use and generally correlate with sputum eosinophils. A level of 400/mm^3 is associated with more exacerbations and use of rescue medications.[11] A Cochrane review concluded that tailoring asthma interventions based on sputum eosinophils is beneficial in reducing the frequency of asthma exacerbations in adults with asthma.[12] Adults with frequent exacerbations and severe asthma may derive the greatest benefit from this additional monitoring test. There is insufficient data available to assess tailoring asthma medications based on sputum eosinophils in children.

Another biomarker is fraction of exhaled nitric oxide (FeNO), which can help to predict exacerbations. In a trial in children with allergic asthma, FeNO measurements did not improve the proportion of symptom-free days, but did result in fewer asthma exacerbations and was associated with an increased leukotriene receptor antagonist use and an

augmentation of the ICS doses.[13] In a trial in adults, a symptom-plus FeNO-driven strategy reduced asthma medication use while sustaining asthma control and quality of life.[14] Using FeNO to manage asthma had the highest probability of cost-effectiveness at a willingness to pay of $50,000/quality-adjusted life year compared to not using FeNO.[14] A Cochrane review of FeNO use in children with asthma found that there were lower rates of exacerbation but no difference in daily symptoms or corticosteroid use.[15] Overall, FeNO monitoring can be a useful tool in those with asthma and frequent exacerbations.

Serum periostin (protein induced by IL-4 and IL-13), genetic testing for IL coding expression, and combinations of biomarkers (i.e., FeNO with urinary bromotyrosine) are also being evaluated for use in asthma. All of these appear helpful in identifying the TH2 subtype of asthma.

Treatment for severe recalcitrant asthma now includes biologics – omalizumab (Xolair®), mepolizumab (Nucala®), reslizumab (Cinqair®), and benralizumab (Fasenra®). All of these biologic agents have high annual acquisitions costs ($15,000 to $32,500 per year) and typically have limits on use imposed by managed care. Clinicians need to make sure the basic steps of asthma care have all been implemented and that the patient is adherent with therapy before moving on to the biologic therapies.

Omalizumab is an injectable anti-IgE antibody indicated for moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS. A systematic review found that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and during steroid tapering phases of clinical trials.[16] Omalizumab was significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their inhaled steroids. The odds ratio for stopping ICS was 2.5. Overall, there was no significant difference in the use of oral steroids and lung function was not necessarily improved by omalizumab treatment. The average reduction in SABA use was 0.39 puffs/day on omalizumab. It is a well-tolerated agent; injection site reactions are the most common adverse effect. There is a low anaphylaxis risk (0.09%), but patients do require observation after each injection.

A British cost analysis of omalizumab found that in adults it costs £83,822 ($134,138) per quality-adjusted life-year (QALY) gained; and £78,009 ($124,835) per QALY gained in children.[17] This analysis found that omalizumab is more economical in cases of recent hospitalization. This analysis concluded that the cost per QALY with omalizumab was above other National Health Service interventions.

Mepolizumab is an interleukin five (IL-5) antagonist monoclonal antibody; IL-5 is an important cytokine for eosinophil activation. It is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype (150 cells/microliter baseline or 300 cells/microliter in last year) and for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). It is given as a 100 mg subcutaneous injection every four weeks at a health care office. This agent reduces risk of exacerbation, improves lung function (forced expiratory volume in one second [FEV_1] by 100 ml), and reduces symptoms.[18] It also has been shown to improve health-related quality of life in those with severe eosinophilic asthma.[19]

Reslizumab is another IL-5 antagonist monoclonal antibody indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype. It is given by intravenous infusion 3 mg/kg once every four weeks in a facility able to handle anaphylactic reactions. It reduces risk of exacerbations.[20]

A systematic review of anti-IL-5 therapies found that the rate of exacerbations decreased by about 50 percent with treatment with these agents. There was no change in the Asthma Control Questionnaire or Asthma Quality of Life Questionnaire scores, but there was a small increase in health-related quality of life and improvement in FEV_1 by 0.08 to 0.11 liters.[21] These agents do have a burden of requiring injection/infusion in a health care setting to allow for monitoring for anaphylaxis. Similar to omalizumab, the major adverse effect with anti-IL-5 therapies is injection site reactions. Anaphylaxis is also possible with this class and requires monitoring post dosing.

Benralizumab binds to the α-subunit of the IL-5 receptor and is indicated as add-on maintenance treatment of severe asthma in those 12 years of age and older with an eosinophilic phenotype. A meta-analysis of five studies with 1,951 patients who required oral corticosteroids found significant improvements in FEV_1, health-related quality of life, the Asthma Control Questionnaire, and exacerbations.[22] This agent leads to a reduction in oral steroid use.[22,23] It is given by subcutaneous injection every four weeks for three doses and then every eight weeks thereafter. Like the other biologics, this is given by a health care provider with 30 minutes of post-dose monitoring.

Dupilumab, originally FDA approved for atopic dermatitis, was recently approved as add-on maintenance treatment in patients with moderate to severe

asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. It binds to the α-subunit of the IL-4 receptor and interrupts signaling of IL-4 and IL-13. It increases FEV_1 about 15 percent and produces similar results regardless of the blood eosinophil count.[24] It also reduces the annualized exacerbation rate compared to placebo. This agent is given subcutaneously every two weeks. This biologic for asthma is unique in that, at least in terms of FDA approved labeling, a patient may self-inject it after training in subcutaneous injection technique.

An important aspect of improving population outcomes in asthma is focusing on how care is delivered. A community-based primary care comprehensive effort to improve asthma outcomes which included an asthma care map, program standards, a management flow chart, and a patient action plan has been shown to reduce risk of exacerbations, symptoms, urgent health service use and productivity loss related to asthma (Exhibit 3).[25]

Conclusion

Basic best clinical practices, such as using appropriate medications and checking on inhaler technique demonstration at each visit, are key to achieving asthma control. Biologics are available primarily for those with eosinophilic phenotype and can reduce exacerbations and oral corticosteroid use. All the biologics, except dupilumab, are given in a health care setting, which can be burdensome for patients.

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Novel Treatment Advances and Approaches in Rheumatoid Arthritis: Personalizing Therapy for Improved Clinical and Economic Outcomes

Jeffrey Curtis, MD, MS, MPH

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

Summary

Numerous strategies are possible to improve clinical and economic outcomes in rheumatoid arthritis (RA) management. This can include selecting the most effective treatment based on clinical trial data, treating to target to achieve remission, and utilizing digital tools.

Key Points

- For patients who cannot or will not take methotrexate, an anti-IL-6R or a JAKi should be preferred over a TNFi.
- Patients who have failed a TNFi should move to agents with other mechanisms of action.
- Baricitinib combined with methotrexate should become the preferred first-line therapy.
- Biosimilars may not be as cost saving as initially anticipated.
- Treatment switching is often under-utilized to attain low disease activity or remission.
- New data sources, digital tools and methods exist to support value-based care in rheumatology.

RHEUMATOID ARTHRITIS (RA) IS A DISEASE that hits people in the prime of life. It is an autoimmune disease which, if not appropriately diagnosed and treated, can be a disabling disease because of joint damage and deformity.

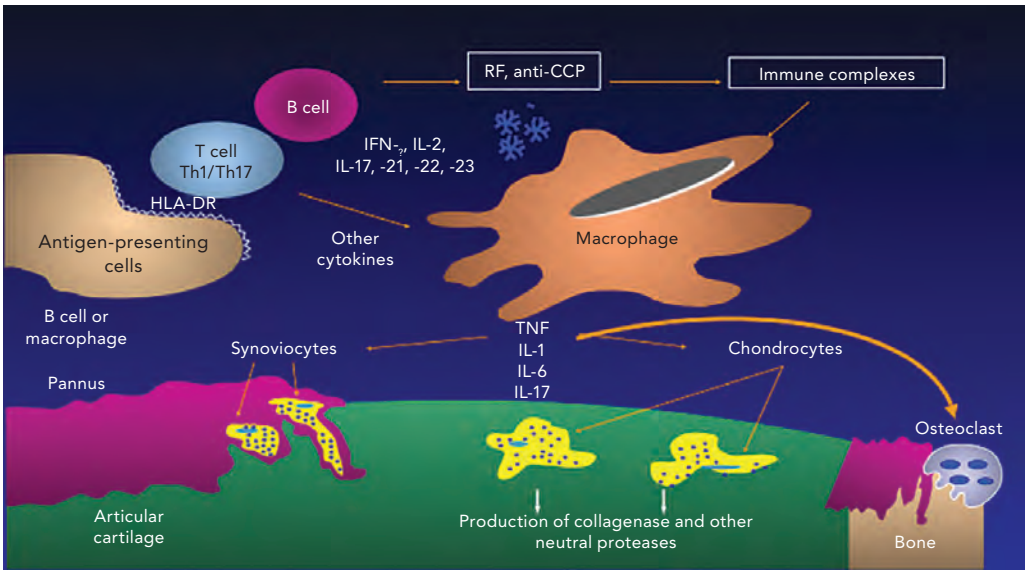
Tumor necrosis factor (TNF-alpha) and various interleukins are central mediators in the pathophysiology of RA and are involved with both inflammation and the joint destructive processes (Exhibit 1).[1] Various agents, which include biologic and targeted synthetic (ts) disease-modifying antirheumatic drugs (tsDMARDs), have been developed that target the cytokines involved in RA (Exhibit 2). The agents to treat RA (and other conditions) are among the top five drug categories by total cost and are the number one specialty category.[2]

The biologics and the tsDMARDs target specific mediators of inflammation compared with older DMARDs like methotrexate or cyclosporine which have widespread immune system effects. Importantly, the biologics work best in combination with methotrexate.[3] Irreversible damage is not changed with biologics or tsDMARDs. Thus, treatment should start in early stage disease when the disease is in the inflammatory stage and joint damage can be prevented.

Janus kinase inhibitors (JAKi) are the newest class of agents that have been approved for RA and other inflammatory autoimmune diseases. Treatment responses with these oral tsDMARDs are similar to what is seen with the injectable biologic DMARDs. Tofacitinib (Xeljanz®) and baricitinib (Olumiant®) are the two approved JAKi.

The other newer class of agents are the anti-interleukin 6 receptor blockers (anti-IL-6R). Sarilumab (Kevzara®) is the most recently approved agent in this class and appears to have comparable efficacy to toclizumab at a lower cost. There are several non-

Exhibit 1: Pathogenesis of RA[1]



HLA-DR = human leukocyte antigen-antigen D related
RF = rheumatoid factor
anti-CCP = anti-cyclic citrullinated peptide antibodies
IFN = interferon
IL = interleukin
TNF = tumor necrosis factor

Exhibit 2: U.S. Marketed Biologics/tsDMARDs

Brand	Launch Year	Mechanism
Enbrel (etanercept)	1998	TNF-α inhibitor
Remicade (infliximab)	1999	TNF-α inhibitor
Humira (adalimumab)	2002	TNF-α inhibitor
Simponi/Simponi Aria (golimumab)	2009 SC 2013 IV	TNF-α inhibitor
Cimzia (certolizumab pegol)	2009	TNF-α inhibitor
Orencia (abatacept)	2005 IV 2011 SC	T-cell co-stimulation modulator
Rituxan (rituximab)	2006	Anti-CD-20 (B cells)
Actemra (tocilizumab)	2009 IV 2013 SC	Anti-IL-6R
Kevzara (sarilumab)	2017	Anti-IL-6R
Xeljanz (tofacitimab)	2012	Pan JAK inhibitor
Olumiant (baricitinib)	2018	JAK 1/2 inhibitor

tsDMARD = targeted synthetic disease modifying antirheumatic drugs
TNF = tumor necrosis factor
IL-6R = interleukin 6 receptor
CD = cluster of differentiation
JAK = janus kinase

Exhibit 3: Non-Evidence Based Myths about RA Therapy that May Result in Poor Policy Decisions

Myth	Resulting Policy Decisions	Knowledge Deficit
All RA biologics and targeted therapies have about the same effectiveness and safety	Implement fail-first and fail-second policies that require use of the cheapest	Recent head-to-head trial data
Biosimilars should be meaningfully cost-saving	Require continued use of TNFi therapy	Frequency of dose escalation for infliximab and adalimumab
Use of inexpensive DMARDs (e.g. MTX) is of minimal importance	Implement adherence and chronic care management programs focused ONLY on biologics/tsDMARDs	Trial and observational data evaluating benefits of concomitant MTX
Most RA patients will require lifelong therapy	Delay approval time to allow first biologic use	Recent RA discontinuation trials
Rheumatologists won't measure RA disease activity, but even if they do, it doesn't matter	Ignore clinician/patient reported outcomes and value of therapy	Evaluate association between quantitative RA evaluation, likelihood to achieve better outcomes (e.g. T2T), downstream costs

evidence-based myths about RA therapy that may result in poor managed care policy decisions (Exhibit 3). The data to refute each of these myths will be discussed.

Until recent studies were published, it was thought that all RA biologics and targeted therapies had about the same effectiveness and safety. Because of the lack of head-to-head studies comparing the various RA treatments, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines have essentially said all the agents are similar in efficacy, and clinicians can choose which to use.[4,5] That means that in the United States (U.S.) whatever agent was cheapest became the first choice of therapy as dictated by managed care. This has typically meant that tumor necrosis factor inhibitors (TNFi) must be used first and in some cases two different TNFi have to fail before moving on to a different mechanism of action.

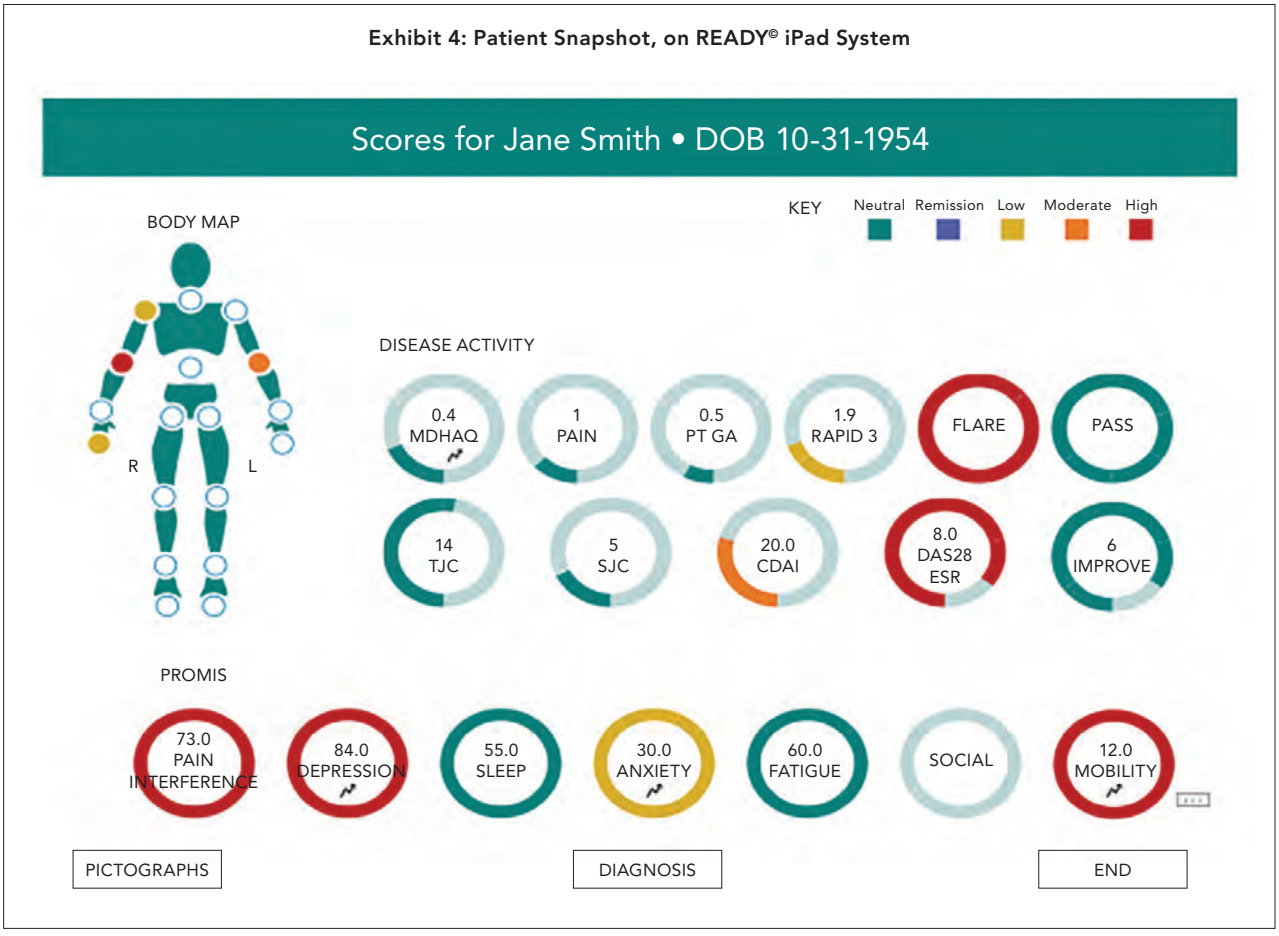
Recent trials have shown that in certain settings agents other than TNFi should be first or second-line. Anti-IL-6R agents are more efficacious than TNFi alone.[6,7] Thus, for patients who cannot or will not take methotrexate, anti-IL-6R agents should be preferred over TNFi because TNFi are most efficacious when given with methotrexate. Tofacitinib and baricitinib are also options for patients who cannot or won't take methotrexate. Trials also show that patients who have failed a TNFi should move to agents with other mechanisms of action rather than be forced to try another TNFi.[8] Baricitinib combined with methotrexate is more efficacious than a TNFi plus methotrexate and should become the preferred first-line therapy for moderate to severe RA.[9] The JAKi are the first-class of agents which are showing superiority over TNFi plus methotrexate.

Biosimilars should be meaningfully cost saving is another possible myth which can lead to managed care requiring that TNFi be used when they may not be the best choice for optimal efficacy. There are now biosimilars marketed in the U.S. for infliximab, etanercept, and adalimumab. The cost savings with biosimilars so far in the U.S. have been 15 to 20 percent which is much less than what has been seen in Europe. Unfortunately, the need for dose escalations with infliximab and adalimumab can negate the cost savings. Ten to 15 percent of patients will have a doubling of their adalimumab dose, and 40 to 60 percent of those receiving infliximab will have the dose or frequency increased. There is limited evidence that dose escalation makes a clinical difference and escalation may offset any cost savings. Policies against dose escalation may be a way to preserve the cost savings of biosimilars.

Implementing adherence and chronic care management programs focused only on biologics or tsDMARD at the expense of methotrexate is shortsighted. Biologic persistence has been shown to be dependent on concomitant methotrexate.[10] This is most likely because the combination is necessary for optimal efficacy. Thus, efforts should be made to make sure patients are receiving methotrexate with a TNFi.

Another myth is that most RA patients will require lifelong therapy, so why not wait to initiate therapy. There are two issues here – when to start therapy and can therapy be discontinued. Structural damage occurs early in RA. In a pre-biologic era,

Exhibit 4: Patient Snapshot, on READY© iPad System



symptomatic relief with conventional DMARDs prior to methotrexate (MTX) still often resulted in structural damage and disability. The ACR and EULAR guidelines advocate treat-to-target in RA.[3,4] Treat-to-target is adjusting treatment based on clinical factors until preset goals are achieved. Disease remission should be the goal. The alternative is to achieve low disease activity. Aggressive treatment with a biologic or tsDMARD should be started as early as three to four months after diagnosis because patients with early disease (< 2 years) are more responsive to treatment than those who have had disease for longer.[11,12] There is a window of opportunity to prevent joint destruction and disability. The treat-to-target approach has been shown to be superior to conventional treatment.[13,14]

Achieving remission in RA has been a difficult concept for clinicians and payers. Clinicians have traditionally allowed patients to have ongoing disease activity and have considered reduced symptoms and improved function good enough. Achieving remission can save costs. Patients who are in remission have lower rates of hospitalization, emergency department visits, mortality, and costs per year.[15]

Once disease remission is obtained, discontinuation of therapy is possible. As in oncology, there can be an induction phase where aggressive therapy is given, which can then be stopped if the patient's disease is put into remission. Two-thirds or more of patients can be taken off a biologic after six to 12 months of disease remission.

Another myth is that rheumatologists will not measure RA disease activity, but even if they do, it does not matter. It is important to measure RA disease activity in order to define that the patient is in remission. Unfortunately, many rheumatologists still just measure disease activity by asking the patient questions and counting joints. Quantitative assessment tools are being used more; however, they are still underused in RA care.[16] Doctors say they measure metrics to improve care and decision-making and the most common reasons why they do not is the lack of time and metric tools are not available in electronic health records.[16]

Disease activity does matter and needs to be measured. One biomarker of disease activity which can be used to identify those patients who are most likely to have damage from their disease and require aggressive treatment is the Vectra Disease Activity (DA) score, which combines measurement

of 12 different cytokines. This score predicts radiographic damage. Combining the Vectra DA score with serologic status (rheumatoid factor or anti-citrullinated protein [anti-CCP] antibody positivity) improves prediction even more.[17] Anti-CCP levels can also be used to predict cost of care; those with high levels are most costly to manage.[18] Thus, biomarkers can be used to predict aggressive disease, the need for biologic and tsDMARD therapy, and future costs of care for various subsets of the RA population.

There are various U.S. data sources to study real-world effectiveness questions in RA. There are multi-center, single center, and specialty databases; electronic medical record registries; and patient registries; and various health care claims databases which can be tapped. An example of data that can be collected and used to manage therapy is the patient-reported outcome data at the University of Alabama. The university has a system to collect patient-reported outcome data electronically from every patient seen in any clinic. Patients complete a tablet-based survey, which adapts based on which condition(s) the patient has. The clinician has a snapshot of how the patient is doing before the visit even starts, which saves time (Exhibit 4). Data from the survey are linkable to electronic medical records and give the health system metrics across various patient populations. For the individual patient, the clinician can trend disease activity over time. Data from this type system can be used to justify the continued use of a biologic or tsDMARD. Some payers are now asking clinicians to demonstrate at least a 20 percent or more improvement with therapy.

Patient-reported outcomes can also be generated between clinician visits. One example is the Arthritis Power application, which can be used to track disease activity between office visits. With the application, patients can track their health with customized assessments, which include the Vector DS score; they can also view results over time to see how symptoms are changing and identify causes of symptom changes, enter and keep track of treatments, and track why they stop taking a medication or particular dose. The data from the application is exportable to electronic medical records. There are also research opportunities for application participants. A future possibility is to link the application to pharmacy data and provide feedback in real time when the patient fails to refill a medication to ask them directly what is going on.

Like efficacy, not all the treatments for RA have the same safety profile. All the agents increase risk for serious and opportunistic infections. The risk is low, but it is still increased. Risk appears to be lower with etanercept and abatacept compared to the other agents. Herpes zoster is a unique risk with the JAKi. The JAKi and anti-IL-6R also increase risk for lipid elevations, liver toxicity, and hematologic abnormalities and thus require more monitoring than TNFi. Fear of adverse effects can be one reason patients stop therapy or never even start it. Clinicians need good tools for presenting balanced information on the risk of RA treatments. One example tool is the Patient Decision Aid for RA Medications (www.RAmedGuide.com). A randomized trial found that this decision support tool, at the time of decision making, resulted in improved objective and subjective knowledge, as well as values clarity, compared to usual care.[19]

Overall, there are several missed opportunities to optimize value in RA care. Clinicians should maximize use of methotrexate (e.g., increase dose, give subcutaneous) and conventional DMARDs (e.g., triple therapy) before biologics. Clinicians and managed care should constrain dose escalation of costly biologics when not supported by evidence. Managed care should eliminate prior authorizations when it makes no sense. A review of prior authorization requests from an academic medical practice found that rheumatology and dermatology specialty medications prescribed for approved indications are seldom denied, and most of the denials are reversed when appealed. [20] These findings suggest that the time spent on prior authorizations, at substantial cost to the practices involved, may be unnecessary, as appropriate treatments are rarely denied.[20] The authors noted that insurers may have other interests in the prior authorization process besides the stated reason of restricting inappropriate or unnecessary prescriptions.

Value-based contracting has come to RA care. In February 2017, Harvard Pilgrim Health Care and Amgen signed an outcomes-based contract for etanercept (Enbrel®) which was billed as the first such contract for RA.[21] A previously developed effectiveness algorithm using data available in pharmacy claims data including patient compliance, switching or adding drugs, dose escalation, and steroid interventions is being used to determine the benefits of etanercept.[22] If patient scores are below a specified level, Harvard Pilgrim will pay less for etanercept because its real-life effectiveness will have been lower. In January 2018, CVS announced Transform Rheumatoid Arthritis Care, a comprehensive solution, powered by the CVS Health integrated pharmacy care model, that helps payors better manage costs and patient care for a costly, complex condition.[23] The outcomes-based

contracting component may include risk-sharing based on expected outcomes, such as continuation of treatment. Value-based contracting will hopefully be expanded beyond these two programs.

Conclusion

Multiple effective therapies for RA exist; however, they are costly. There is growing evidence from trials and observational data to suggest that for some patients there are preferred treatment options. Anti-IL-6R and JAKi therapy offer new options. Treatment switching is often underutilized to attain low disease activity or remission. New data sources, digital tools and methods now exist to support value-based care in rheumatology.

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Perspectives on Treating Psoriatic Arthritis: Exploring Personalized Treatment Strategies

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

Summary

Clinicians are trying to personalize therapy for psoriatic arthritis. At this point, treatment can be somewhat personalized based on symptoms but not yet on the biologic pathways that underlie the disease in the individual patient. Biologic therapies have been developed which target the general biologic pathways of the disease and are effective.

Key Points

- Psoriatic arthritis is a unique inflammatory arthritis with diverse clinical features.
- It occurs in ~ 30 percent of patients with psoriasis and remains underdiagnosed.
- Early diagnosis and effective treatment is critical in order to minimize poor outcomes.
- Comanagement with dermatology and rheumatology can improve patient management.
- Methotrexate alone is not effective for psoriatic arthritis.
- Biologic therapy can benefit all clinical domains and inhibit progressive structural damage.
- A "treat-to-target" and "tight control" strategy has been shown to yield optimal clinical outcomes.

APPROXIMATELY 3.2 PERCENT OF AMERICANS have psoriasis and 10 to 30 percent of them will develop psoriatic arthritis (PsA).[1,2] The typical age of onset for PsA is 30 to 50 years. There is a large geographic variation in prevalence. For example, one case per 100,000 population was found in a Japanese study and 420 cases per 100,000 population were found in an Italian study.[3,4] Psoriasis and PsA are costly to treat. Health care costs related to psoriasis alone are estimated at $11.25 billion annually.

There is a spectrum of clinical manifestations with PsA. Psoriatic arthritis affects the joints as well as surrounding structures, such as the tendon area that inserts onto bone (enthesitis), tenosynovitis of the entire digits (dactylitis), or it can cause nail changes such as pitting or onycholysis. Arthritis mutilans and spondylitis also occur. Patients can have a mild to severe presentation. Patients may exhibit any combination of manifestations, and symptoms vary over time and overlap. In both psoriasis and PsA, disease flares may alternate with periods of remission. The CASPER criteria for classification of PsA are shown in Exhibit 1.[5] It is important to note that not all joint pain in someone with psoriasis is PsA; they must have an inflammatory arthritis that meets the criteria to be diagnosed.

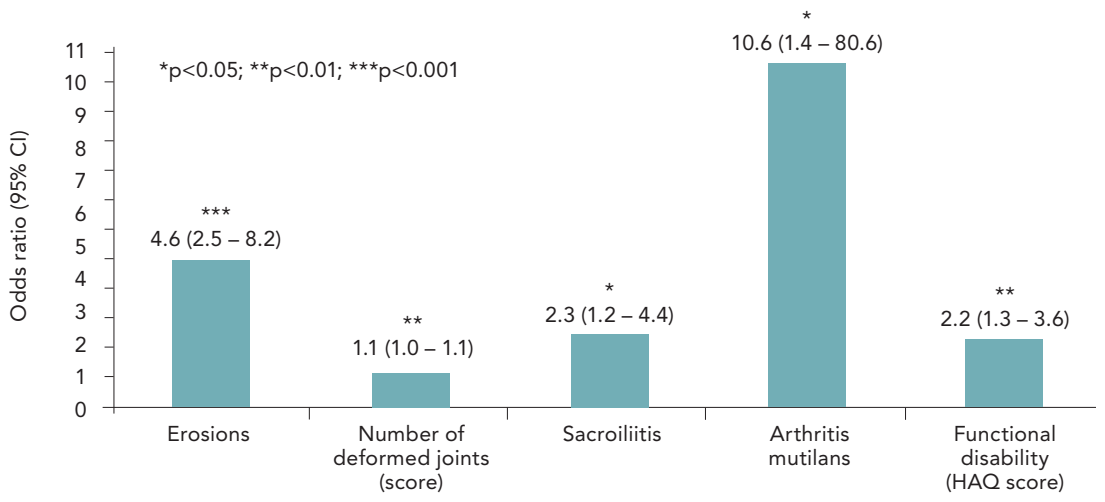
A substantial proportion of patients with psoriasis seen in dermatology centers have undiagnosed PsA.[2] Appropriate and early diagnosis of PsA is important because delayed diagnosis is associated with worse long-term outcomes (Exhibit 2).[6] Improved screening can address the typical delay in diagnosis of PsA (Exhibit 3).[7-11]

Dermatology and rheumatology comanagement is

Exhibit 1: Criteria for the Classification of Psoriatic Arthritis[5]

PsA is diagnosed when ≥3 points below are assigned in the presence of inflammatory articular disease (joint, spine, or entheseal)		
Category	**Description**	**Points**
Current psoriasis, or, personal or family history of psoriasis	Psoriatic skin or scalp disease confirmed by dermatologist or rheumatologist; history of psoriasis from patient, family physician, dermatologist, rheumatologist, or other qualified practitioner; patient-reported history of psoriasis in first- or second-degree relative	2
Psoriatic nail dystrophy on current physical exam	Includes onycholysis, pitting, and hyperkeratosis	1
Negative for rheumatoid factor (RF)	Enzyme-linked immunosorbent assay or nephelometry preferred (no latex) using local laboratory reference range.	1
Current dactylitis or history of dactylitis documented by a rheumatologist	Swelling of entire digit	1
Radiographic evidence of juxtaarticular new bone formation	Ill-defined ossification near joint margins excluding osteophyte formation, on plain x-rays of hand or foot	1

Exhibit 2: Impact of Greater than Six-Month Delay in Diagnosis[6]



Clinical features recorded as percent, unless otherwise stated
HAQ = health assessment questionnaire

important in PsA. Dermatologists should be referring their patients with psoriasis and joint pain to a rheumatologist for evaluation.

Personalization of therapy is slowly coming to PsA management. The clinical presentation of the PsA can be used to select therapy. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommends selecting therapy for PsA based on the involved domains (Exhibit 4).[12]

One of the most commonly used disease-modifying agents in PsA is methotrexate (MTX). It works well for psoriasis; however, in a published randomized double-blind study compared to placebo, it was not effective for PsA.[13] In this trial, there was no statistically significant evidence that six months of MTX treatment was more likely than placebo to improve any rheumatology-related global response index in PsA. There was no evidence that MTX had significant benefits on objective measures of synovitis, including joint counts, ESR and CRP levels.

Exhibit 3: Screening Strategies[7-12]

Questionnaires	Biomarkers
• PEST, PASE, PASQ, TOPAS • High sensitivity and specificity during initial validation. • Clinical performance has not always matched initial validation	• Genetic (eg IL12b SNP), soluble markers (eg CRP) and imaging markers (eg MRI, US enthesitis) may have value. • Validation in large-scale trials is required

CRP = C-reactive protein
PASE = Psoriatic Arthritis Screening and Evaluation tool
PEST = Psoriasis Epidemiology Screening Tool
PASQ = Psoriasis and Arthritis Screening Questionnaire
TOPAS = Toronto PsA Screen
SNP = single nucleotide polymorphism

MTX did significantly improve assessors' and patients' global assessments, suggesting it may have symptom-modifying effects. MTX showed a positive effect on psoriasis skin scores, consistent with its known efficacy in psoriasis. The take away from this study is that the initial use of MTX alone, which is many times mandated by managed care before using a biologic, is not very helpful for PsA and delays the time until effective therapy is instituted.

The first biologics approved for PsA were the tumor necrosis factor inhibitors (TNFi). All the TNFi (infliximab, etanercept, adalimumab, golimumab, certolizumab) appear to have similar efficacy for PsA, as measured by the American College of Rheumatology (ACR) 20, 50, and 70 scores. These agents also produced positive benefits on enthesitis (60-75% improvement), dactylitis (60% improvement), function, quality of life, fatigue, and structural damage. MTX added to TNFi does have benefit in improving response compared to MTX or TNFi alone.[14]

Additional immunologic pathways beyond TNFi have been found to be involved in PsA, and therapies targeting these pathways have been developed. A major pathologic pathway in PsA appears to be issues with the T helper 17 cell, which produces various inflammatory mediators, including interleukin 12, 23, and 17 (IL-12, IL-23, IL-17). Ustekinumab (Stelara®) is an IL12/23 inhibitor; secukinumab (Cosentyx®), ixekizumab (Taltz®), and brodalumab (Siliq®) are IL-17 inhibitors; and tildrakizumab (Ilumya®), guselkumab (Tremfya®), and risankizumab (investigational) are IL-23 inhibitors. Brodalumab, tildrakizumab, and guselkumab are currently only approved for treating psoriasis, but they likely have efficacy for PsA.

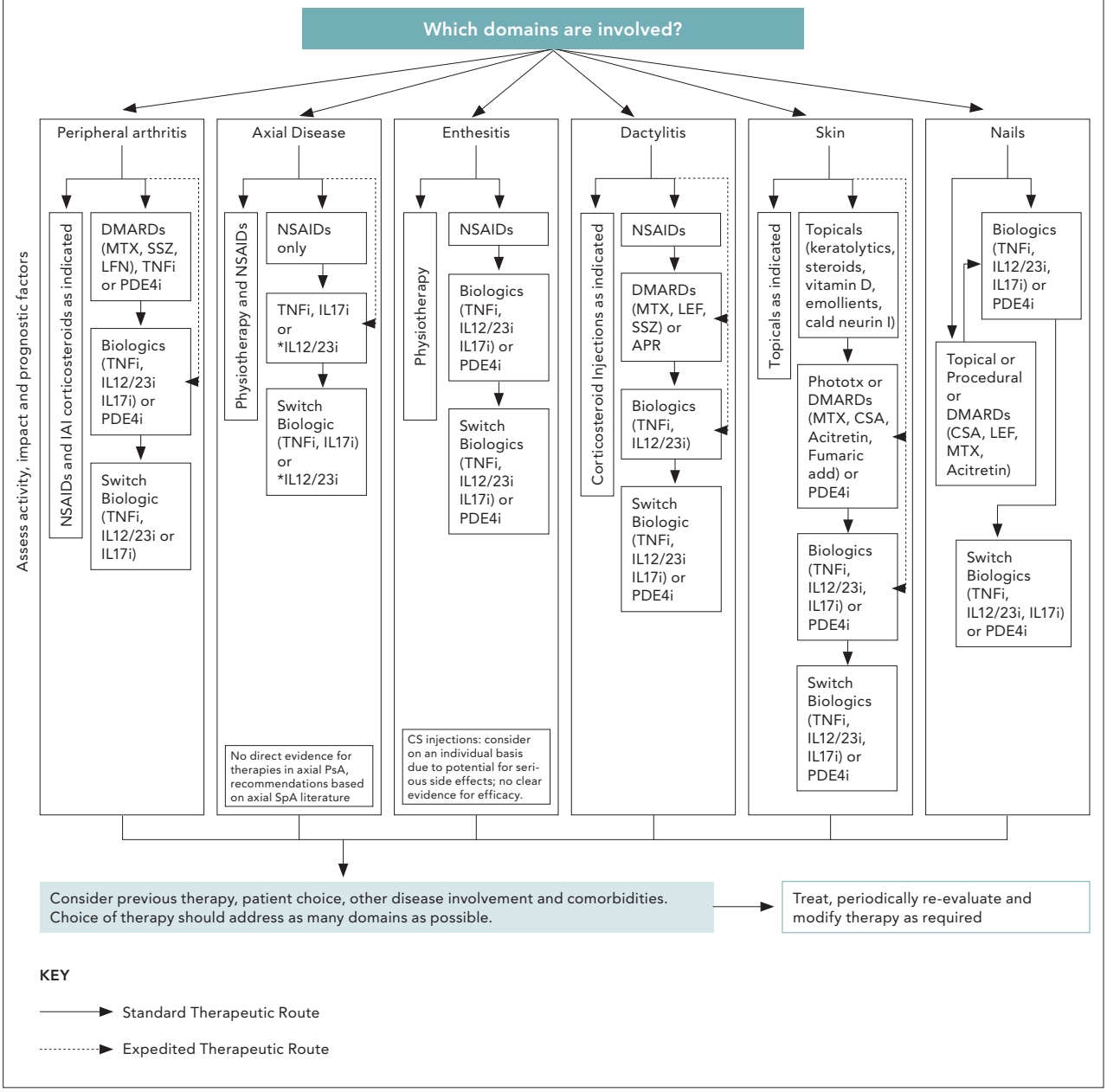
Ustekinumab, secukinumab, ixekizumab, and brodalumab are all more effective than placebo in producing ACR20, ACR50, and ACR70 responses in those with PsA who are TNFi naïve or who have previously been treated with a TNFi.[15] Ustekinumab and secukinumab also produce benefits in enthesitis scores.

There are also agents which inhibit multiple cytokines; apremilast is a phosphodiesterase 4 (PDE4) inhibitor and tofacitinib is a Janus kinase inhibitor. Tofacitinib (Xeljanz®) is the first agent that was FDA approved for PsA, but not for psoriasis. Apremilast (Otezla®) works within the cell to modulate the production of pro-inflammatory and anti-inflammatory mediators. Both tofacitinib and apremilast are oral agents compared to the injected biologic agents, they are well tolerated, and are effective in PsA.[16,17]

At this time, clinicians cannot measure TNFi or any of the various interleukins to identify which cytokines are specifically elevated in a particular patient and thus select the therapy most likely to benefit that individual. Therapy selection for PsA is empiric and may require switching among the various mechanisms of action to find the agent which works for a particular patient.

Although not specifically personalization of therapy, treat-to-target (T2T) and tight control are two strategies for managing PsA which have been adopted from the management of rheumatoid arthritis. A trial of treat-to-target and tight control using MTX and TNFi adjusted based on disease activity found significant improvement of joint outcomes for newly diagnosed patients, with no unexpected serious adverse events.[18] The use of these two strategies was associated with significantly greater improvements in signs and symptoms of disease at week 48, and reduction

Exhibit 4: GRAPPA 2015 Treatment Recommendations[12]



in psoriasis severity was achieved in a higher proportion of patients in the intervention group. The goal of T2T is to achieve minimal disease activity (MDA). A patient is classified as in MDA when they meet five of seven of the following criteria: tender joint count ≤1, swollen joint count ≤1, Psoriasis Area and Severity Index (PASI) ≤1 or body surface area affected by psoriasis ≤3 percent, patient pain on visual analogue scale ≤15, patient global activity score ≤20, health assessment questionnaire (HAQ) score ≤0.5, and tender entheseal points ≤1.[19]

Conclusion

Psoriatic arthritis is a unique inflammatory arthritis with diverse clinical features that occurs in approximately 30 percent of patients with psoriasis and remains underdiagnosed. Early diagnosis and effective treatment are critical to minimize poor outcomes. Comanagement with dermatology and rheumatology can improve patient management. Biologic therapy can benefit all clinical domains and inhibit progressive structural damage. A "treat-to-target" and "tight control" strategy has been shown to yield optimal clinical outcomes.

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Clinical Advances in the Diagnosis, Treatment and Management of COPD

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

Summary

COPD is an expensive, underdiagnosed disease, which significantly impacts patients. Guidelines provide recommendations on selecting the most effective therapy based on severity, symptoms, and exacerbations. Optimizing therapy and improving adherence are all ways to improve outcomes in this chronic disease.

Key Points

- COPD is a preventable and treatable disease, however, it is also underdiagnosed and undertreated.
- Lung inflammation does occur in COPD.
- Airflow limitation is partially reversible in most patients; thus, they benefit from bronchodilators.
- Combination therapy with bronchodilators and antimuscarinics or bronchodilators and inhaled corticosteroids is necessary for most patients.
- Some may require triple therapy.

CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) is a common, preventable, and treatable disease. It is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities and is caused by significant exposure to noxious particles or gases.[1] Chronic inflammation in the lungs, which is not the same as that found in asthma, causes structural changes. Airflow limitation is usually measured by spirometry.

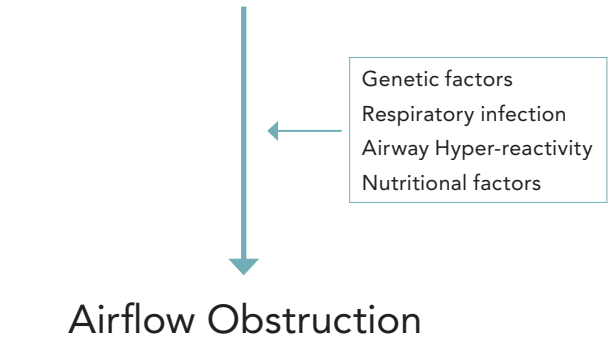
Approximately 15 million Americans have been diagnosed with COPD. [2] About 63 percent of those with COPD remain undiagnosed; importantly, 70 percent of those undiagnosed are under the age of 65.[3,4] Many clinicians only think about COPD as a disease of elderly males; women and those under 65 are the most commonly undiagnosed populations. Diagnosis may not occur until the disease progresses because of lack of serious symptoms and poor recognition of clinical symptoms in the early phase of the disease. Importantly, chronic respiratory symptoms, acute respiratory events, and structural changes in the lungs can exist without significant airflow limitation.

COPD is costly in financial terms. The direct costs have been estimated at $30 billion annually with indirect costs of $20 billion. Exacerbations account for up to 75 percent of the direct costs. Exacerbations are a major driver of costs because they increase health care visits and hospitalizations; there are about 13 million office visits every year due to COPD exacerbations.[5]

Even when patients get diagnosed, they may not receive appropriate care. In one study, 46.6 percent of subjects with a diagnosis of COPD did not receive any COPD-specific medications in the 12 months after the diagnosis.[6] In another study of both commercial and Medicare populations, the majority of those with the disease did not receive any long-term medications for COPD.[7]

COPD is caused by exposure to tobacco smoke,

Exhibit 1: Pathogenesis of COPD



indoor/outdoor air pollution, and occupational pollutants (Exhibit 1). In the United States (U.S), 85 to 90 percent of cases of COPD are caused by tobacco smoking. Risk for development of the disease after exposure to noxious agents is modified by genetic factors, respiratory infection, airway hyper-reactivity, and nutritional factors. Smoking cessation, no matter what the patient's age, is beneficial in slowing lung function decline. An additional factor in the development of COPD is the lung function reserve that a patient starts with. Some people do not achieve predicted maximum lung function and thus start with a lower reserve and are more likely to have symptomatic declines as they age.[8]

Avoiding exacerbations in COPD is important because lung function declines with exacerbations; additionally, the majority of the loss occurs in the earlier stages of COPD.[9] Waiting until the later stages of the disease to focus on exacerbation prevention is too late.

COPD should be considered in any patients with symptoms (persistent shortness of breath, chronic cough, chronic sputum production, or wheezing) who have a history of risk factors (noxious agent exposure, family history, age > 40 years).[1] Spirometry is required to demonstrate airflow limitation and make the diagnosis. A post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.70 confirms presence of persistent airflow limitation.[1] During diagnosis, COPD has to be distinguished from asthma (Exhibit 2). Once diagnosed, COPD can be classified as mild, moderate, severe, or very severe based on spirometry results (Exhibit 3).[1]

Airflow obstruction in COPD is partially reversible. In one study, 65.6 percent of subjects showed a 15 percent or greater increase in FEV_1 after use of a short-acting bronchodilator.[10] Overall, COPD-related lung damage is not reversible; however, some degree of airflow obstruction is reversible.

Exhibit 4 shows some of the progress which has been made in managing this disease. While a great deal of progress has been made, there are still many barriers to optimal management and successful outcomes.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) management guidelines focus on reducing symptoms to improve exercise tolerance and health status and reducing risk of disease progression, exacerbations, and mortality.[1] The four components of COPD management are to assess severity and monitor disease; reduce risk factors; manage stable COPD through patient education, pharmacologic management, and nonpharmacologic treatment; and manage exacerbations. Pharmacologic treatment for COPD should be individualized, matching the patient's therapy to their needs, guided by the severity of symptoms and history of exacerbations, side effects and comorbidities, drug availability and costs, patient response, patient preference, and ability to use a drug-delivery device. Nonpharmacological intervention, such as pulmonary rehabilitation, should also be individualized to maximize personal functional gains. Integrated care, which is perfect for this disease, needs to be individualized to the stage of the person's illness and health literacy.

Assessment of COPD should include the degree of airflow limitation using spirometry; symptoms using a standardized, validated questionnaire; risk of exacerbations; and comorbidities. This assessment will determine the appropriate treatment path. Treatment is selected primarily based on symptoms

Exhibit 2: Differentiating COPD from Asthma

	Asthma	COPD
Onset	Anytime (often childhood or youth)	Later in life
Etiology	Allergic, family history	Smoking, other noxious exposures
Course	Intermittent	Chronic progressive
Clinical Features	Wheeze, episodic dyspnea, cough	Persistent dyspnea, productive cough
Pattern of Symptoms	Variable day to day, more at night/early morning	Less variable, more on exertion
Inflammatory cells and mediators	Eosinophils, mast cells, Th-2 type	Neutrophils, macrophages, Th-1 type
Response to Bronchodilators	Largely reversible	Partially reversible or irreversible
Response to steroids	Substantial	Partial

Exhibit 3: GOLD Grading System[1]

GOLD Grade	Severity	Degree of Airflow Limitation
1	Mild	$FEV_1 \geq 80\%$ predicted
2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
4	Very Severe	$FEV_1 < 30\%$ predicted

and risk of exacerbations. Standardized symptom questionnaires include the Modified Medical Research Council dyspnea scale (mMRC), the COPD Assessment Test (CAT), or the Clinical COPD Questionnaire (CCQ). A history of two or more exacerbations or hospitalization for an exacerbation within the prior year is an indicator of high risk for future exacerbations.

Problems with COPD assessment by clinicians have been shown. A survey of pulmonologists, primary care providers, and patients found an underutilization of questionnaires. Only 6 percent "always" or "most of the time" used symptom assessment tools.[11] There was also underutilization of spirometry, with 35 percent of patients reporting having spirometry at diagnosis and 38 percent reported spirometry within the past year. Additionally, physicians underestimated the rate of exacerbations.[11] Physicians said 35 percent of patients had two or more exacerbations in the past year, whereas 60 percent of patients said they had two or more.[11] Other problems that have been shown with COPD assessment include an emphasis on assessing dyspnea rather than exercise tolerance, lack of distinction between infrequent and frequent exacerbators, comorbidities causing similar symptoms, and poorly performed spirometry being misleading.[12] Patients can have very significant impairment in exercise tolerance, but they have modified their lifestyle to essentially do nothing to avoid symptoms.

The pharmacologic treatment options for COPD include bronchodilators and anti-inflammatory agents. Bronchodilators are either short-acting beta agonists [SABA] or short-acting muscarinic antagonists [SAMA] or long-acting versions of these two classes [LABA, LAMA]. Short- acting agents are used as needed for symptoms, whereas long-acting agents are used for maintenance therapy. LABA/LAMA combination inhalers are available. Anti-inflammatories used in COPD include inhaled corticosteroids (ICS) and phosphodiesterase inhibitors (roflumilast). Because inflammation in COPD

Exhibit 4: Progress and Barriers in COPD

Progress	Barriers
Well defined, Easy to Diagnose	Underdiagnosed, often misdiagnosed
Increased understanding	Heterogeneity and complexity
Good up-to-date guidelines	Lack of application
Increased therapeutic options	Lack of disease modifying therapy
Variety of inhaled devices	Too many inhaled devices
Safe and well tolerated inhaled medications	Poorly tolerated oral medications
Medications borrowed from asthma	Confusion with asthma
Excellent non-pharmacological options	Lack of patient support and access to non-pharmacological options
Lots of Biomarker research	None easily applicable in clinic
Therapeutic progress	Therapeutic nihilism

tends to be more neutrophilic rather than eosinophilic like in asthma, the response to corticosteroids will be less in COPD. Corticosteroids are always used in combination with a LABA in COPD. These are available as combination inhalers.

General therapy for all patients with COPD includes smoking cessation and other risk reductions, weight management, and comorbidities management. Patients with one or fewer exacerbations in the past year and a low level of symptoms (Group A in GOLD guidelines) should receive a short-acting bronchodilator as needed.[1] If symptoms are worse, a daily LAMA is indicated. Those with low exacerbations but more symptoms (Group B) should initially receive a LABA or a LAMA daily. If that is not enough to control symptoms, the combination of LABA and LAMA should be used. If dyspnea is out of proportion to FEV_1 impairment, clinicians should assess for comorbidities, such as heart failure, contributing to symptoms.

Those patients with two or more exacerbations in the past year or an exacerbation that led to hospitalization but lower levels of current symptoms (Group C) should receive a LAMA initially. This group only accounts for about 3 to 5 percent of COPD patients. If there are more exacerbations after starting the initial therapy, a LAMA/LABA or a LAMA/ICS combination should be used. A LAMA/LABA combination is the preferred combination over LAMA/ICS, except in the case of concomitant asthma, which may be driving the exacerbations. Concomitant asthma should be suspected in a patient with a clinical history consistent with asthma in their young adult years.

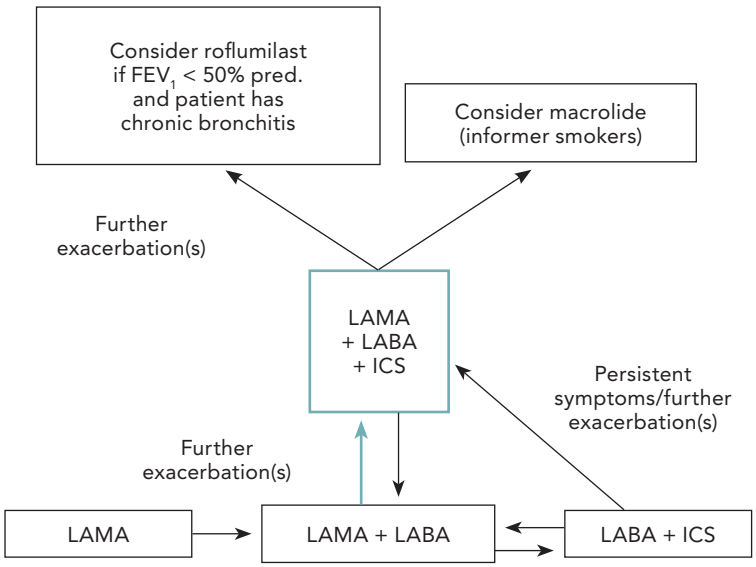
The algorithm for those with frequent exacerbations and a high level of symptoms (Group D) is shown in Exhibit 5. In severe COPD, a LAMA/LABA combination is preferred for preventing exacerbations compared to a LAMA/ICS combination because the ICS component has not been shown to be significantly better than adding LABA.[13,14] Additionally, there is an increased risk of pneumonia with using ICS. Again, concomitant asthma and COPD may require the addition of ICS.

Many clinicians skip the initial step of one agent alone (LABA or LAMA) in Group B, C, and D and go directly to combination therapy because there are many studies showing that the two agents are complementary, without a significant increase in adverse effects. Given that combination inhalers are available, it does not increase patient burden to use combination therapy. It is important to note that all patients should have a SABA as a needed prescription. Poor inhaler technique is a common problem in COPD. Patients need to be taught proper technique, and it should be reviewed at each visit.

Adherence to inhaled medications is poor in COPD. Forty-six percent of patients have been shown to be nonadherent with their LABA and 60 percent with ICS inhalers. Patients tend to be more adherent when they perceive their clinician as a lung disease "expert." Common patient barriers to treatment adherence include inadequate education about COPD and therapy, perceived burden of medication regimens, difficult to use devices, depressed mood, medication-related cost, and adverse effects.

Personalized medicine is slowly coming to COPD management. The use of eosinophils as a biomarker is being evaluated to determine the need for ICS use and to possibly guide use of anti-eosinophil medi-

Exhibit 5: Treatment of Severe COPD[1]



cations. In approximately 20 percent of COPD patients, eosinophils play a role in their disease.[17] The use of a LABA/ICS combination reduces exacerbations in those with higher eosinophil blood counts.[18] Patients with blood eosinophil counts less than 150 or 2 percent are unlikely to benefit from ICS. Those with levels greater than 300 or 4 percent are more likely to benefit. It is not known if ICS would be helpful in those with eosinophil levels between these two cut points. More data are needed before eosinophil level measurement becomes standard in COPD.

Conclusion

COPD is a preventable and treatable disease. Optimal management of this disease would provide better symptom relief, prevent exacerbations, and improve quality of life. COPD is heterogeneous in its development, progression and clinical expression. Better disease characterization should lead to more personalized treatment.

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Implementing Newer Biologic Therapies to Improve Economic and Clinical Outcomes in Patients with Moderate to Severe Atopic Dermatitis

Zelma Chiesa Fuxench, MD, MSCE, FAAD

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

Summary

Atopic dermatitis has a significant impact on the affected patient, especially when moderate to severe. There is a new topical agent for mild disease and biologic agents for moderate to severe disease. The biologic agents are especially exciting for clinicians because they are specifically targeting the pathophysiologic pathways of the disease.

Key Points

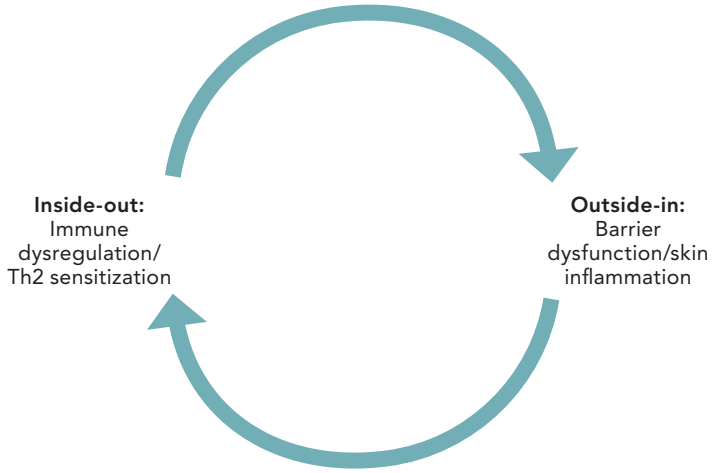
- Moderate to severe AD causes significant impact on quality of life and morbidity.
- Nonadherence with topical therapy is common.
- New agents for mild to moderate and moderate to severe disease are now available.
- Biologics are targeting the underlying pathophysiology of this disease.

ATOPIC DERMATITIS (AD) IS A CHRONIC, pruritic, inflammatory, skin disease characterized by periods of acute disease flare. AD is also called eczema. Studies on prevalence of AD in the United States (U.S.) show different estimates, depending on the source of population studied and definition used. Whereas the prevalence of AD among children can be as high as 20 percent, prevalence of AD in the U.S. adult population has been shown to vary between 3.2 percent and 10.7 percent.[1-3] Many clinicians do not think of AD as an issue in adults; however, 30 percent of all cases of AD are in the adult population. New onset AD can occur in adults, but it is more commonly a continuation from childhood onset.

There are two seemingly competing explanations for the development of AD (Exhibit 1). The inside-out hypothesis states there is immune dysregulation with a skewed T helper cell two (Th2) profile.[4] The outside-in hypothesis states that a skin-barrier defect, caused by filaggrin mutations, leads to increased penetration of allergens/irritants, leading to epicutaneous sensitization, immune activation (Th2), increased production of proinflammatory cytokines IL-4 and IL-13, increased penetration of skin colonizing organisms, and increased risk of skin infections. The barrier defect also results in increased transepidermal water loss, which explains the associated xerosis seen in AD. It really does not matter which pathway is the initiator of the disease; the important issue is that immune dysregulation is what causes it to persist.

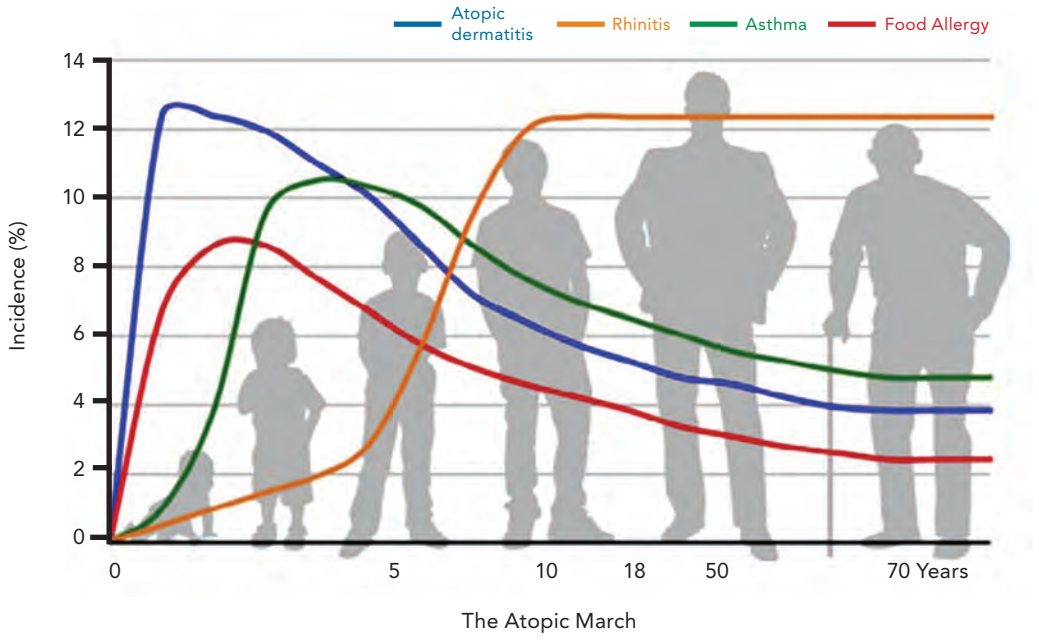
Comorbidities, particularly those related to the Atopic March are common in AD (Exhibit 2). Atopic March, sometimes called Allergic March, refers to the natural history or typical progression of allergic diseases that often begin early in life. These include AD, food allergy, allergic rhinitis (hay fever), and asthma. Immune activation with a predominant Th2 response is thought to initiate the Atopic March. Nasal allergies occur in about 50 percent of those with AD, allergic rhinitis in 15 per-

Exhibit 1: Pathogenesis of Atopic Dermatitis



Th = T helper cell

Exhibit 2: The Atopic March



cent, and asthma in 22 to 30 percent.[3,5] Non-atopic comorbidities are also common and include anxiety (42.5%), depression (37.2%-75%), and attention deficit hyperactivity disorder (13%).[6-9] The underlying mechanism explaining the association between AD and neuropsychiatric disease is not clearly understood. It is thought to be related to the negative impact of AD on health-related quality of life, persistence of chronic itch, and loss of sleep.

Moderate to severe AD can have a major impact on quality of life. In adults with moderate to severe AD, 49 percent have moderate to significant sleep disruption, 82 percent require lifestyle modifications because of their disease, and 55 percent have a decrease in confidence.[10] Fourteen percent of adult patients in the one study believed that their career

Exhibit 3: Economic Burden of Atopic Dermatitis[14,15]

- Adjusted mean annual total per-patient costs ($US)

Type of Insurance	AD	Non-AD
Commercial	$10,461	$7,187
Medicare	$16,914	$13,714
Medi-Cal (medicaid)	$19,462	$10,408

*Outpatient provider visits and prescription costs

	AD N = 620	Psoriasis N = 620	P-value
Mean HCRU (SD)			
Provider visits past six months	6.2 (8.0)	6.3 (9.8)	0.88
ER visits past six months	0.5 (1.1)	0.3 (1.0)	0.02
Mean annual per patient costs (SD)			
Provider visit costs	$14,058 ($18,252)	$14,171 ($21,495)	0.95
Hospitalization costs	$8,177 ($27,040)	$4,244 ($21,435)	0.07
ER visit costs	$1,448 ($3,241)	$750 ($3,008)	0.01
Total direct costs	$23,682 ($37,041)	$19,165 ($34,459)	0.15

progression had been hindered by AD.[11] Lack of sleep from itching secondary to the disease may also have an impact on the development of cardiovascular disease and diabetes.

Studies in adults with AD have shown that patients with this disease have worse quality of life (QOL) scores. In addition to AD impacting a patient's health-related QOL, it can have social, psychological, occupational, and financial impacts through decreased work productivity and increased work absenteeism. AD can impact activities of daily living, such as choice of clothing, shaving, use of makeup, or ability to put on clothes (especially with significant hand involvement).

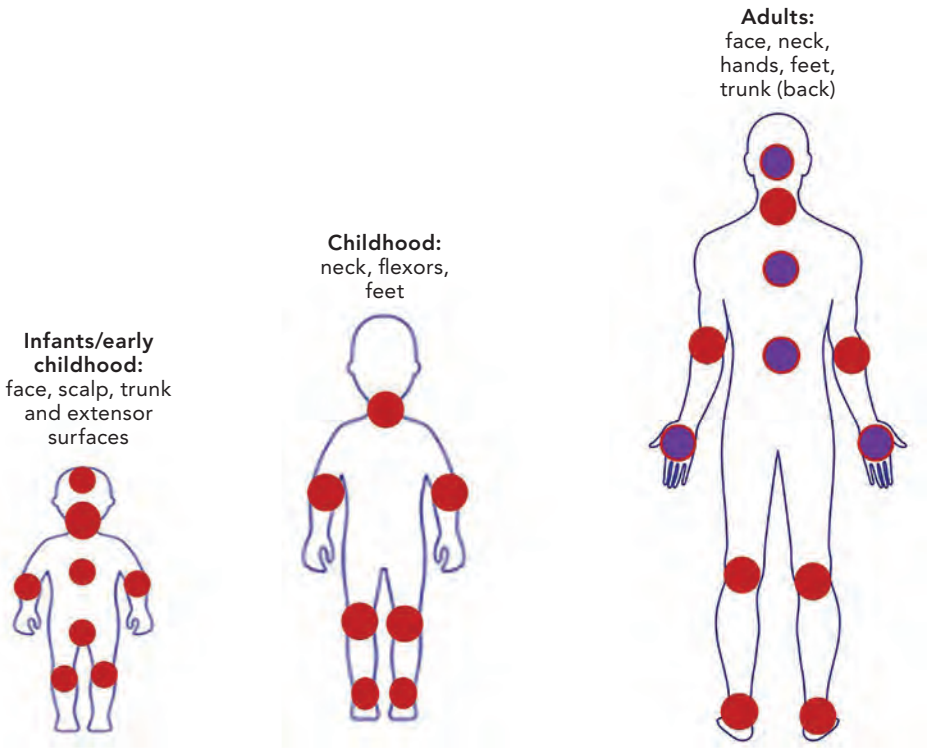
AD also causes a significant economic burden. The estimated annual costs in the U.S. are greater than $5 billion.[12,13] This includes direct costs (health care visits, prescription costs, hospital stays, and transportation) and indirect costs (increased absenteeism, lost productivity, career changes, and impact on QOL). As shown in Exhibit 3, those with AD have higher annual costs than those without the disease and that AD is comparable with or greater than psoriasis in terms of costs and resource utilization.[14,15]

The diagnosis of the disease is made clinically, based on historical features, distribution and morphology of skin lesions, and associated clinical signs. The type and location of skin lesions vary by the age of the patient. (Exhibit 4). Children tend to have a flexural pattern, whereas adults have a non-flexural distribution and atypical morphologic variants. Skin biopsy, patch testing for contact dermatitis, and allergy testing are not usually necessary to make the diagnosis. The United Kingdom working party diagnostic criteria for AD in pediatrics are an itchy skin condition (parental report of scratching or rubbing in a child) and three or more of the following: onset before 2 years of age, history of skin crease involvement, visible flexural dermatitis, history of generally dry skin, and personal or family history of other atopic disease.[16] In adults or children, if the skin is not itchy, it is not AD.

The extent of body surface area (BSA) affected by AD and the impact of symptoms on QOL and daily function are typically used to determine the disease severity. For example, someone with only hand or foot involvement may only have 5 percent of the BSA affected, but this may have major impact on their QOL and on their ability to function. Additionally, qualitative studies have shown there are significant differences in how severe physicians, patients, and caregivers perceive the disease.[17] Patients may have minimal BSA affected, but feel they have severe disease.

Adherence to topical therapy in AD can be poor. Various reasons for nonadherence have been found in studies, but topical corticosteroid phobia is the

Exhibit 4: Clinical Manifestations



most common (~21 – 84% in different studies). Lack of understanding of the disease or treatment, inconvenience of topical treatments, financial burden, and access to care are other reasons for poor adherence.[18] The combination of physician/patient/caregiver dissonance and poor adherence results in poor clinical outcomes in AD.

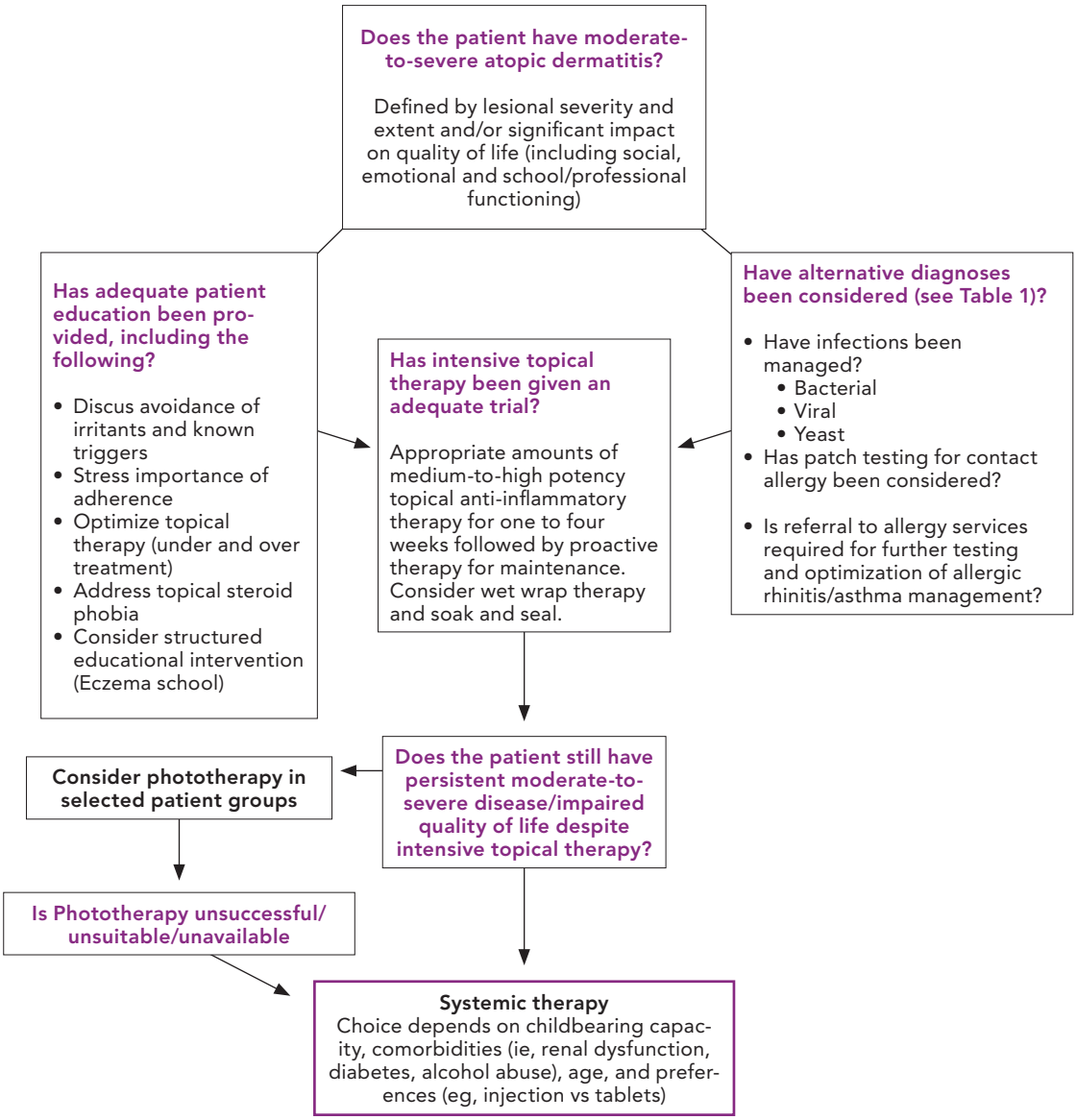
Patient and caregiver education are keys to improving outcomes in AD. Importantly for patient education purposes, there is no cure for this disease. Many patients may think that once their skin is clear that treatment can be stopped. Sometimes this is true in children; however, for most patients, treatment has to be continuous to keep the disease under control. Educational interventions have led to measurable improvements in disease severity and QOL. An AD action plan, similar to an asthma action plan, can be helpful for improving patient and caregiver understanding and medication adherence.[19]

Because AD is a chronic disease characterized by episodic flares, acute flares have to be treated and a long-term management plan has to be in place. Treatment of acute flares should be planned with a long-term perspective and should consider patient preference and adherence to treatment. The overall goal of treatment should be to achieve a state in which symptoms are absent or mild, the rate and duration of acute flares is decreased, and there is no to minimal impact on QOL.

First-line treatments are all topical, including moisturizers, corticosteroids (TCS), calcineurin inhibitors, [tacrolimus (Protopic®)], and phosphodiesterase four (PDE4) inhibitors [crisaborole (Eucrisa®)]. Nonpharmacologic interventions, such as minimizing hot baths and bleach baths, are also first-line. Crisaborole is a relatively new agent for mild to moderate AD. In the trials used for approval, 32 percent of patients achieved a score of 0 or 1 (clear or mostly clear skin) compared with 18 percent to 25 percent in the placebo group.[20] Most patients can be managed with first-line agents.

AD treatment has traditionally been reactive, relying on anti-inflammatory therapies administered to active lesions that are then discontinued once visible skin lesions are cleared. There has been a recent literature discussion on the use of a proactive treatment approach to AD to complement the current reactive approach. A proactive approach is using a combination of predefined, long-term, low-dose, anti-inflammatory treatments applied to previously affected areas of the skin on a regular schedule, in addition to moisturizers on the entire body. The goal with a proactive approach is prevent new flares and achieve longer flare-free intervals. A benefit

Exhibit 5: Management of Moderate to Severe AD[23]



of this approach would be reduced used of high-potency topical corticosteroids to avoid their long-term adverse effects. Tacrolimus and mid-potency topical corticosteroids (e.g., fluticasone propionate) are considered good options for a proactive treatment. Prior studies have demonstrated the clinical and cost-effectiveness of this approach in AD; however, no head-to-head comparisons between currently available treatments (TCI versus TCS) have been done.[21,22] Immunological justification of maintenance treatment is based on the fact that normal-appearing skin in patients with AD shows barrier defects and subclinical inflammation.

More complex disease or disease non-responsive to topical interventions will require phototherapy and/or systemic therapy. Exhibit 5 shows a treatment algorithm for moderate to severe AD.[23] Steps taken before commencing systemic therapy include considering alternate or concomitant diagnoses, avoiding trigger factors, optimizing topical therapy, ensuring adequate patient/caregiver education, treating coexistent infection, assessing the impact on QOL, and considering phototherapy. Phototherapy is effective, but it has some disadvantages, including co-pays for each session, it is time consuming, there are travel costs to get the treatments, and there is lack of availability in many parts of the country. Patients have to be willing and able to commit to photother-

apy. Systemic options for AD include dupilumab, azathioprine, cyclosporine, methotrexate, and mycophenolate. Only dupilumab is FDA approved for treating moderate to severe AD, and it results in the highest efficacy rate (73%) of the systemic agents.[24,25] Cyclosporine is approved in Europe for AD, but not in the U.S. Dupilumab is a human monoclonal antibody against interleukin 4 receptor (IL-4Rα) which blocks activity of IL-4 and IL-13, two of the cytokines involved in AD pathogenesis. The adverse effects of dupilumab are most commonly mild and easy to tolerate, including injection site reactions and conjunctivitis. The other systemic therapies require laboratory monitoring, have contraindications and drug interactions, and can cause much more significant adverse effects than dupilumab.

Dupilumab for AD has a high price tag (~$37,000/year), but the benefits of long-term disease control and improvements in QOL need to be considered. A recent economic study found that it was cost-effective for the treatment of moderate to severe AD in adults compared to standard of care.[26]

Conclusion

Atopic dermatitis is a chronic disease that is challenging to treat and often results in significant impairments in a patient's quality of life. A paradigm shift in the treatment of patients with atopic dermatitis is moving treatment to a proactive approach rather than a reactive approach. Treatment should be selected based on clinical efficacy data, patient safety data, individual patient characteristics, and patient preference.

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Assessing the Value of Biosimilars: The Current and Future Impact on Patient Outcomes

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

Summary

Several biosimilars have already been FDA approved for use in the United States (U.S.) and many more are on the way. Managed care will have a role in educating providers on the use of these agents and how they compare to reference/originator products. There are several barriers which managed care will have to overcome to optimize the use of biosimilars.

Key Points

- More than 40 different analyses/tests are used to show that a biosimilar is similar to a reference biologic.
- Biosimilars may or may not have the same indications as their reference product.
- There are barriers to the use of biosimilars which will need to be overcome.
- Biosimilars are already bringing value to the U.S. health care system.

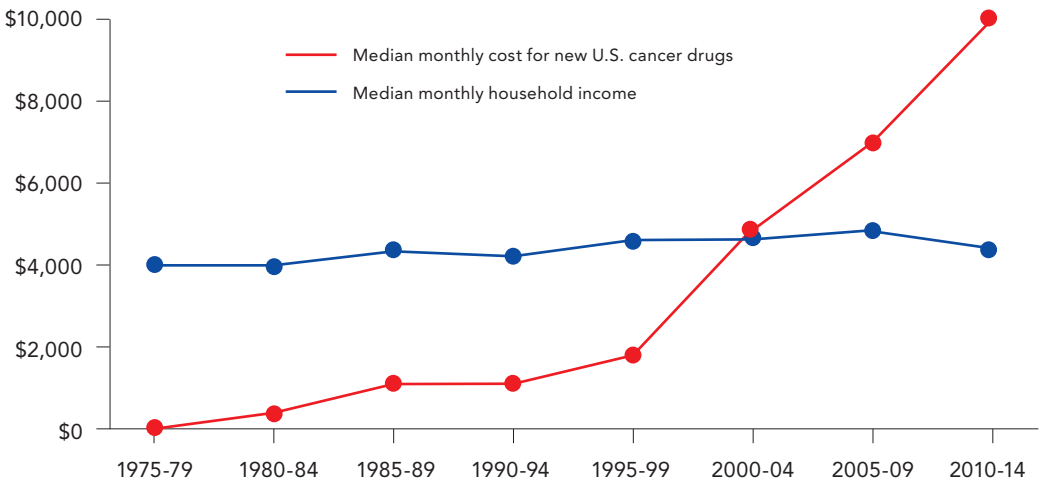
THE FIRST BIOLOGIC, HUMAN INSULIN synthesized via recombinant DNA technology, was introduced in 1982. Biologics are drugs manufactured from living organisms, they are complex, and display minor differences from lot to lot in molecular structure and immunogenicity.

Access to and affordability of biologics remains an issue for many patients. Generally, biologic treatments cost about 22 times more than small-molecule treatments.[1] For example, price increases for pegfilgrastim have driven up the cost of oncology supportive care. The wholesaler acquisition cost (WAC) for pegfilgrastim nearly doubled between 2006 and 2016, whereas the consumer price index for the U.S. only increased 20 percent during this same time period. Increases in cancer drug prices have been a contributor to declining patient affordability (Exhibit 1).[2]

Biosimilars offer patients, providers, and managed care hope for reducing costs of biologics similar to the effect generics have on the cost of brand name pharmaceuticals. The cost benefit of biosimilars will not be as great as what is seen with small-molecule generics.

Biosimilars are products that have been shown to be highly similar to the reference or original biologic product in appropriate comparative, head-to-head quality, non-clinical and clinical studies. These are highly similar to the reference product, notwithstanding minor differences in clinically inactive components. Overall, there are no clinically meaningful differences between a biosimilar and its reference product in terms of safety, purity, and potency. Exhibit 2 shows some of the major differences between small-molecule generics and biosimilars. Intended copies of biological products ("me-too biologics") are copies of already licensed biological products that have not met the regulatory criteria for biosimilars. An example is Dr. Reddy's rituximab (Reditux®) from India, which is not licensed for use in the U.S. Biobetters are biologics that have been structurally and/or functionally altered

Exhibit 1: Cancer Drug Prices Compared with Monthly Household Income[2]



Years	Median monthly cost for new U.S. cancer drugs	Median monthly household income
1975-79	$129	$4,030.90
1980-84	$430	$3,965.40
1985-89	$1,097	$4,336.00
1990-94	$1,199	$4,227.10
1995-99	$1,770	$4,542.10
2000-04	$4,716	$4,656.00
2005-09	$7,000	$4,785.30
2010-14	$10,059	$4,388.80

to achieve an improved or different clinical performance compared with a reference product. These must go through the full FDA development and approval process because they are different products from the reference biologic.

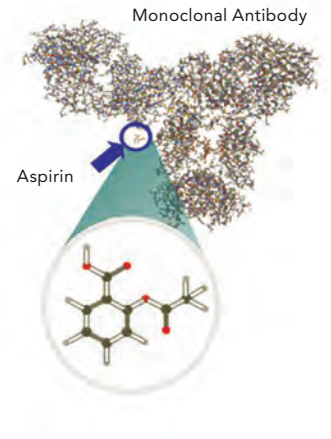
Production variability can make defining a reference biologic product challenging. There are many different sources of variation between a large number of reference products, especially over time. Significant differences in drug products (variability and drift) can arise due to production at different sites and changes to manufacturing processes after initial approval.[3] Manufacturers need to be vigilant for any changes in production and must always assume that they can result in clinically significant issues. FDA approval is required for all changes in the manufacturing process to a biologic. Once a biologic has undergone a manufacturing process change and that change is FDA approved, there is complete extrapolation between all indications, and the changed product is considered interchangeable with prior lots. The patient nor the health care provider is informed of the change because the label on the product does not change. Importantly, both reference biologics and biosimilars are subject to product variability and drift; no two lots of product are exactly the same. For example, infliximab (Rituximab®) has undergone approximately 52 manufacturing changes. Essentially, each biologic becomes a biosimilar to itself over time.

Biosimilars represent a paradigm shift in product development where molecular characterization becomes the most important step in the process and clinical trials are much less important (Exhibit 3).[4] Significant enhancement in analytical and molecular characterization technology over the past two decades allows for highly accurate and detailed comparisons of reference and biosimilar products. Examples include high resolution mass spectrometry; capillary electrophoresis; more sensitive, highly specific pharmacokinetic assays for efficacy and functional aspects; and extensive testing for process

Exhibit 2: Small-Molecule Generics versus Biosimilars

Small-Molecule Generics

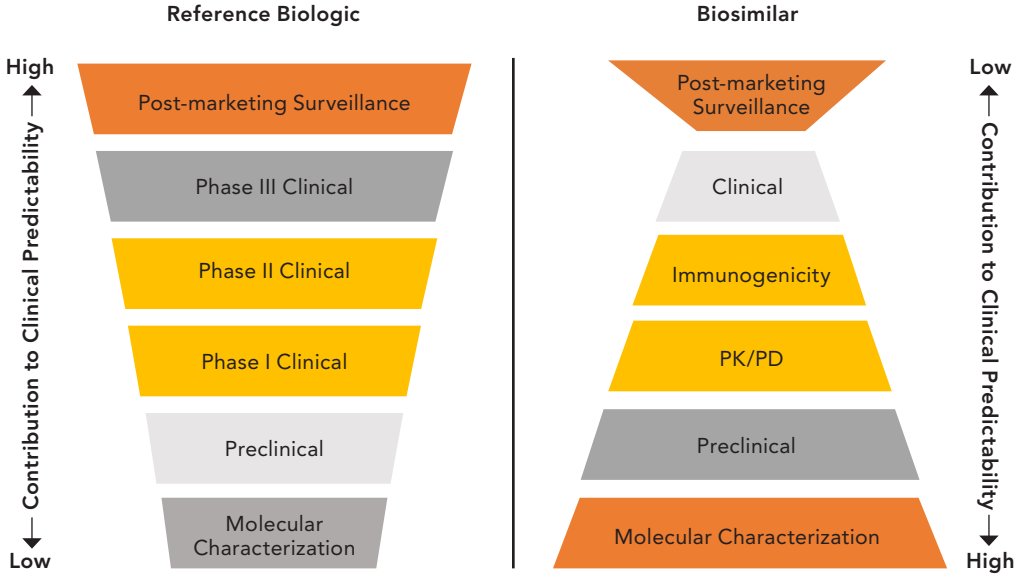
- Precisely defined structure
- Generally produced by chemical synthesis
- Structure can be shown with high precision
- Generic forms demonstrating chemical identity can be validated with preclinical analytic methods



Biosimilars

- Inherent variability based on a complex manufacturing process
- Biosimilars may not be identical to the reference product but must not have clinically meaningful differences
- FDA requires pharmacokinetic, pharmacodynamic and immunogenicity studies
- Need for additional clinical data depends on the need to address residual uncertainty

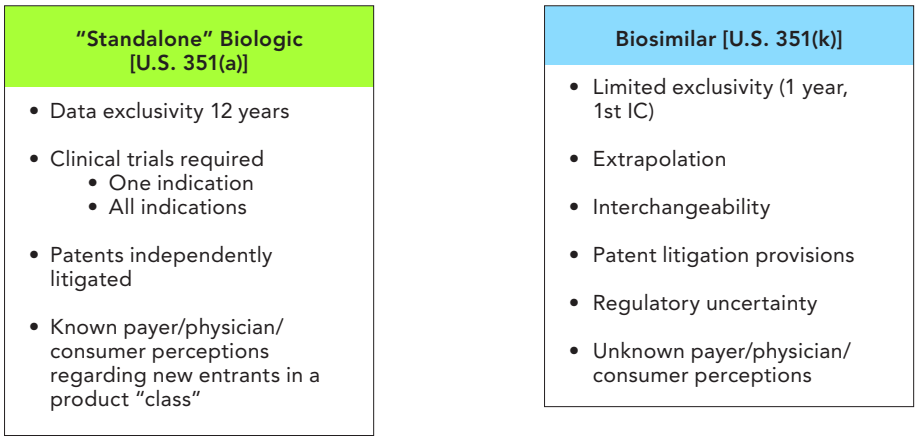
Exhibit 3: Biosimilars Represent a Paradigm Shift in Product Development[4]



and product-related impurity.

The first step in determining if a biosimilar is truly similar to a reference biologic is preclinical assessment. In preclinical assessment, there are four levels of analytical characterization – not similar, similar, highly similar, and highly similar with fingerprint-like similarity.[5] Products characterized as not similar would undergo no further development. Development of similar products would require additional analytical and comparative pharmacokinetic and pharmacodynamic data. For highly similar products, there is high confidence that the two products are very much alike, and the biosimilar is appropriate for targeted clinical studies. With fingerprint-like products, there is even higher confidence in similarity; these products are also appropriate for more targeted clinical studies. Biosimilars submitted to the FDA for approval are supported by 40 or more

Exhibit 4: Approval Pathways for a Biologic



analytical tests showing similarity.

Clinicians tend to be concerned about immunogenicity with biosimilars. All biologics (not just biosimilars) confer a risk of immunogenicity. The risk is related to patient, disease, and product factors. Clinical consequences of immunogenicity are loss of or diminished efficacy and safety and general immune responses (e.g., allergy, anaphylaxis). Case reports of rare, but serious, adverse reactions with biologics have been reported. For example, a manufacturing change to an erythropoietin reference product led to cases of pure red cell aplasia. Changes to the structure of the protein which can occur lot-to-lot and between manufacturers increase variation in immunogenicity; thus, variations in manufacturing must be minimized to limit immunogenicity concerns.[6] Scientific tools for detecting immunogenicity exist, but they are not precise.

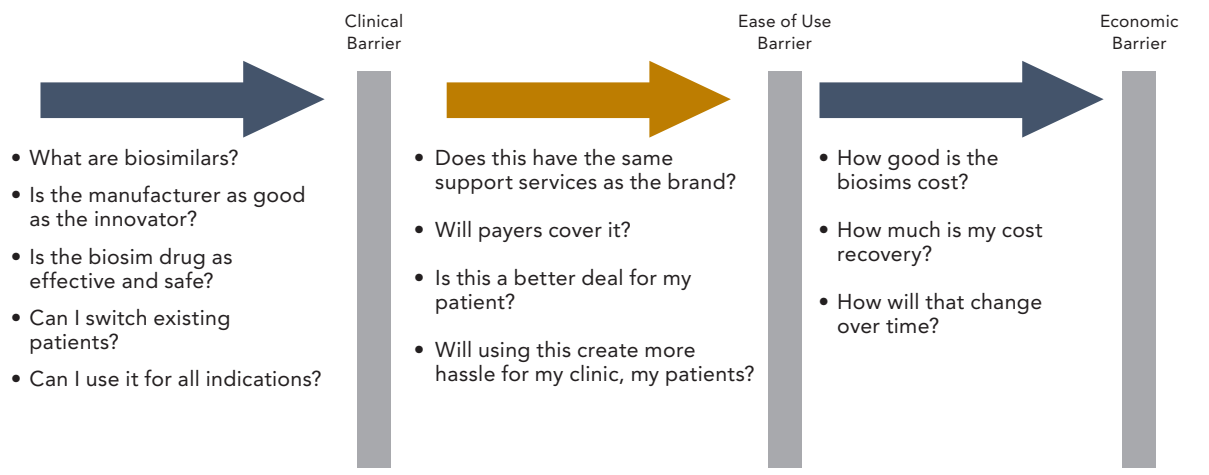
Most biologics are approved under the Public Health Service Act (PHSA), rather than the Food, Drug, and Cosmetics Act. The Drug Price Competition and Patent Term Restoration Act (informally known as the Hatch-Waxman Act), which enabled generic drugs in 1984, does not apply to biosimilars. Prior to the Biologics Price Competition and Innovation Act (BPCI), there was no abbreviated pathway in the PHSA for approving biosimilars. The BPCI Act is a component of the Patient Protection and Affordable Care Act of 2010, which amends the PHSA to define an abbreviated application process for biosimilars. The Biosimilar User Fee Act (BsUFA) allows the FDA to collect fees from the biopharmaceutical industry for timely review of applications.

The approval pathway for biologics is shown in Exhibit 4. The approval pathway selected for each biologic has important implications for commercialization strategy and market access. Sponsors need to weigh the risks/rewards of each pathway for each product.

Traditionally, clinicians have relied on clinical trial data to judge the safety and efficacy of therapeutic agents for a given indication. By definition, approval of a biosimilar for one indication may be based on extrapolation from the biosimilar to the reference biologic. The 351(k) abbreviated process for biosimilars allows extrapolation of the indications for the reference biologic to the biosimilar if there is sufficient scientific evidence per the FDA. Extrapolation across indications for a biosimilar depends on several factors, including a common mechanism of action and receptor/target/interaction, totality of the evidence showing comparability, an acceptable safety profile without increased risks of immunogenicity, and clinical experience with the reference product that can be used to support the use of a biosimilar across indications.[7] For example, rituximab works differently in rheumatoid arthritis and non-Hodgkin's lymphoma. Trials for each indication would be needed to prove efficacy of the biosimilar for each indication. No specific clinical trials with a biosimilar may have been performed in the indications which can be extrapolated. Thus, the paradigm shift in biosimilar development also requires a paradigm shift in the evaluation and use of biosimilars in the clinical setting.

Filgrastim and pegfilgrastim (Neulasta®), granulocyte-colony stimulating factor (G-CSF) agents,

Exhibit 5: Biosimilar Manufacturers will Need to Overcome Several Physician Barriers to Adoption



can be used as example biologics with available biosimilars. Filgrastim (Neupogen®) is the reference product, and there are now two biosimilars - filgrastim-aafi (Nivestym®) and filgrastim-sndz (Zarxio®). There is also a new molecular entity, TBO-filgrastim (Granix®) which the manufacturer chose to pursue the 351(a) path instead of the biosimilar path. A biosimilar pegfilgrastim-jmdb (Fulphila®) was recently FDA approved (June 2018), and several more are under development. The Oncology Drug Advisory Board recommended to the FDA approval of filgrastim-sndz and filgrastim-aafi for all current FDA indications of filgrastim: cancer patients receiving myelosuppressive chemotherapy, patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, cancer patients receiving bone marrow transplant, patients undergoing peripheral blood progenitor cell collection and therapy, and patients with severe chronic idiopathic neutropenia. Because this agent works the same way in all indications, clinical trials with the biosimilars were not required for each indication. One study of switching between a biologic and the biosimilar filgrastim has been published with no evidence of clinically meaningful differences with switching.[8]

Biosimilar manufacturers and managed care will need to overcome several physician barriers to adoption (Exhibit 5). These include clinical barriers related to understanding biosimilars, ease of use, barriers related to payer coverage, office disruption/hassles, pharmaceutical company support such as uninsured patient support; and economic barriers related to product cost.

Education of clinicians about biosimilars and their approval process may also be necessary. In a 2016 survey of dermatologists, gastroenterologists, rheumatologists, nephrologists, hematologist/oncologists and medical oncologists, 60 to 90 percent of specialists could correctly identify specific products as biologics in their area of expertise.[9] Fifty-two percent of respondents in this survey thought it was important for doctors to have data directly evaluating the safety of switching patients from a reference product to a biosimilar.

Biosimilars are already bringing value to the U.S. health care system. The Rand Corporation has estimated there to be a reduction of $54 billion in direct spending on biologic drugs from 2017 to 2026.[10] Express Scripts has estimated a $250 billion projected savings from just 11 biosimilars.[11] Biosimilars are estimated to be about 3 percent of current biologic spending. A large number of branded biologics will be coming off patent between now and 2025. As more biosimilars are introduced into the market, patients will have greater treatment options, greater access to these options and, perhaps due to market dynamics, a greater degree of affordability.

Managed care will have to evaluate the advantages and disadvantage of each biosimilar in deciding whether to add it to formulary or to make it a preferred product. Considerations will include services offered by the manufacturer, the final cost based on drug rebates, which population (commercial versus Medicare/Medicaid) the agent will be used in, and net cost recovery. The value proposition for biosimilars can be difficult because of differentiating

products which are essentially the same.

Conclusion

Biosimilars are now available, and the number will be growing substantially in the coming years. Provider education about biosimilars is going to be important to acceptance and widespread use. Managed care will have to make decisions on which products to have on their formulary. It is hoped that these products will help alleviate some of the financial toxicity of cancer treatment.

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Recent Advances in CFTR Modulator Therapy in the Management of Cystic Fibrosis: Best Practices for Improved Patient Outcomes

Peter J. Mogayzel, Jr., MD, PhD

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

Summary

Treatments targeting the underlying pathophysiology of cystic fibrosis are now available. These treatments are slowing declines in lung function from the disease. Survival is likely to continue to improve and a cure may even be possible.

Key Points

- The survival for CF patients is improving.
- Aggressive, lifelong therapy for pulmonary and nutritional issues is the key to improving the lives of children and adults with CF.
- Targeted therapies affect the basic defect in CFTR to slow the progression of CF lung disease, but they will not reverse damage.
- Adherence with therapy will remain critically important.
- There are many new therapies on the horizon.

CYSTIC FIBROSIS (CF) IS AN AUTOSOMAL recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which was discovered in 1982. The name comes from pathologic examination that found cysts and fibrosis in the pancreas. CF occurs in one in 3,200 live births in Caucasians, and there is a one in 25 carrier rate.

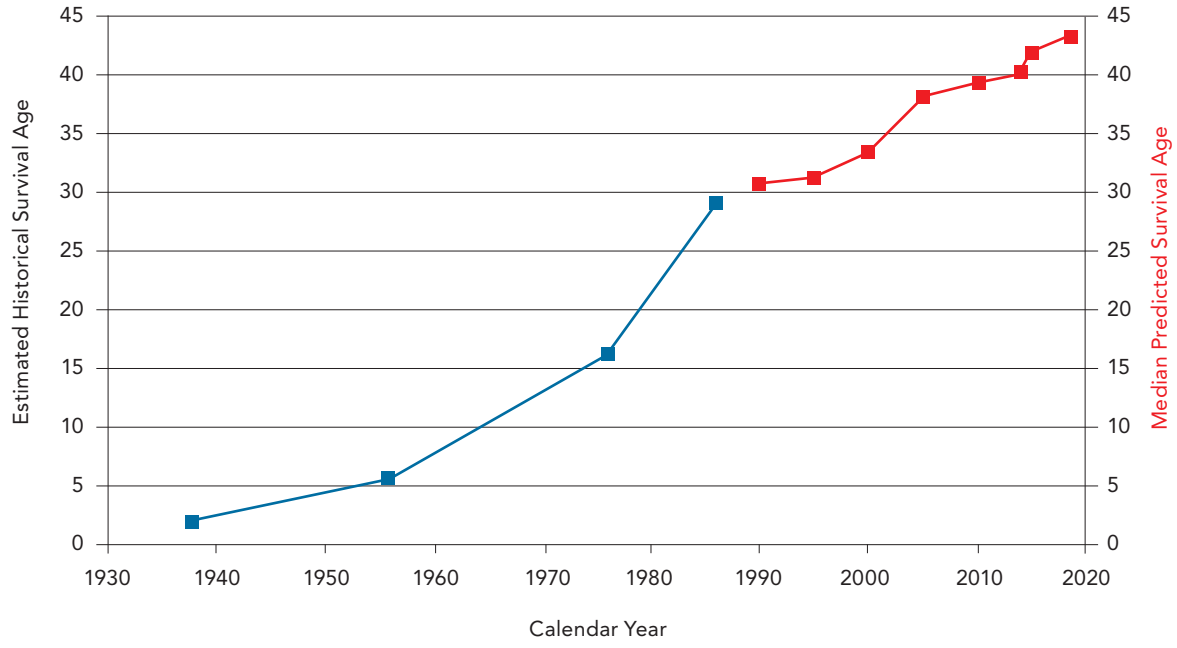
When CF was originally discovered in the 1930s, the average life expectancy was two years. Survival has significantly increased due to improved symptomatic treatment and will likely continue to improve with therapies that target the underlying defects of the disease (Exhibit 1).[1] The percentage of the CF population who are adults has increased from 29.2 percent in 1986 to 52.7 percent in 2016.[2]

The CFTR protein is responsible for transporting sodium and chloride into and out of cells. When the CFTR gene is mutated, a dysfunctional or nonfunctional CFTR protein is produced. The body systems affected by CF are shown in Exhibit 2. Pulmonary disease is the primary issue, but approximately 80 percent of patients with CF have pancreatic insufficiency.

When CFTR works correctly, mucus in the airways covers the cilia, allowing them to move correctly to clear airways. Excessive absorption of salt from the airway lumen of patients with CF carries water with it, dehydrating airway mucous secretions and depleting the volume of liquid on the airway surface. These changes disrupt the mucociliary mechanism, with retained mucus becoming the nidus for chronic infection. Certain bacteria commonly cause pulmonary infections in those with CF, with *staph aureus*, methicillin-resistant *staph aureus*, and *pseudomonas aeruginosa* the major players. The lungs get damaged from repeated infection and inflammation. Pulmonary disease is the primary cause of morbidity and mortality in CF.

Those with CF have a faster rate of lung func-

Exhibit 1: Survival in CF[1]



tion decline than the general population. Slowing the rate of lung function decline is a very important part of CF care. Preventing pulmonary infections is one way to accomplish this goal. Ideally, there would be a therapy that stops pulmonary decline; however, that is not yet a reality. At this time, no therapy reverses any pulmonary damage that already exists. Guidelines are available to help direct therapy for maintaining pulmonary health in CF.[3,4]

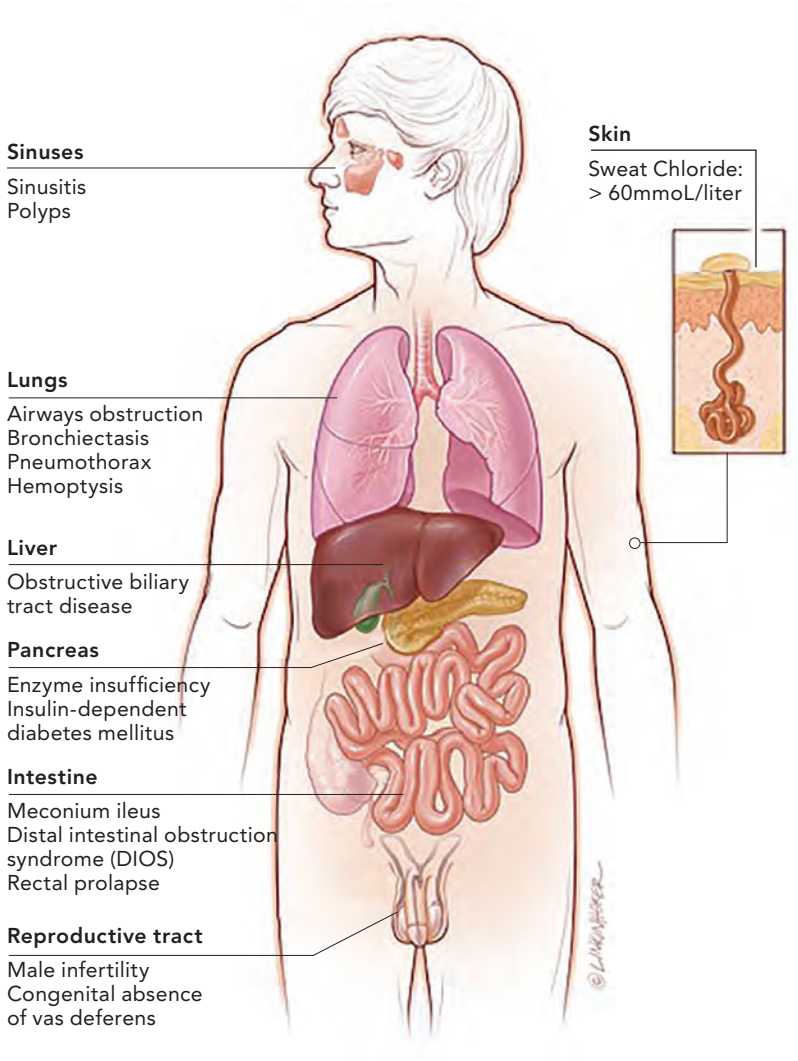
Treatments of CF are divided into symptomatic treatments and molecular defect treatments. Pulmonary therapies for CF are primarily aimed at symptoms and work to clear mucus out of the airways. Options include manual percussion, positive expiratory pressure devices, and high-frequency chest wall oscillation for airway clearance; inhaled mucoactive agents (dornase alfa, hypertonic saline) to thin mucus; and inhaled antibiotics (tobramycin, aztreonam, colsitin) for infections. For a patient with CF to stay healthy, they have to commit to therapies for 30 to 60 minutes every day, at a minimum.

The other aspect of CF therapy is molecular defect therapy. More than 2,000 mutations in CFTR have been described, and these are grouped into six classes (Exhibit 3).[5] Homozygous and heterozygous mutations in this gene can occur. Class I and II defects lead to no CFTR protein on the cell surface and no function of the protein. Class III to VI mutations result in dysfunctional CFTR protein, which has residual function but does not have normal function.

Targeted therapies are now available for the majority of CF patients. Potentiators are used in cases where the CFTR protein is made but needs help to get to the cell surface and correctors are used to modify the function of the CFTR protein channel.

Ivacaftor (Kalydeco®) is a potentiator of CFTR. It initially showed promise in G551D mutated disease, the most common Class III mutation, which occurs in about 3 percent of the CF population. It is now FDA approved for patients age 1 and older who have any gating mutations of CFTR that are responsive to ivacaftor. The manufacturer is pursuing lowering the age of use even further to 1 or 2 months (the typical diagnosed age in the U.S.). In patients with moderate to severe homozygous G551D CF, those who received ivacaftor had a 10 percent increase in lung function, improvement in symptoms scores, improvement in quality of life, reduced exacerbations requiring antibiotics, reduced hospitalizations, and weight gain (3 – 3.5 kg).[6] Similar results have been seen in patients with only one copy of the defective gene and less severe disease and other gating mutations.[7-9] Ivacaftor improves sweat chloride levels to values below CF diagnostic levels.[6] *Pseudomonas* is typically a colonizing organism in CF (i.e., patients can never clear the infection), but those receiving ivacaftor can clear this bacteria.[10] Benefits have been shown out to five years of therapy.[11] This agent is a

Exhibit 2: Body System Affected by CF



preventive – there is a slowing of lung function decline over time and improving or even recovering of pancreatic function.[12-13]

F508del is the most common mutation in CF; 45.8 percent of patients are homozygous for F508del and 40.7 percent are heterozygous.[2] Only 13 percent of CF patients have no copies of this particular mutation. In those with the Class II F508del mutation, correction of the protein being transported to the luminal surface and potentiation of its effect are both needed. Lumacaftor/ivacaftor (Orkambi®) is a combination of a corrector and a potentiator for patients homozygous for F508del. In vitro studies have shown that CFTR function goes from almost zero to about 25 percent when these two agents are given.

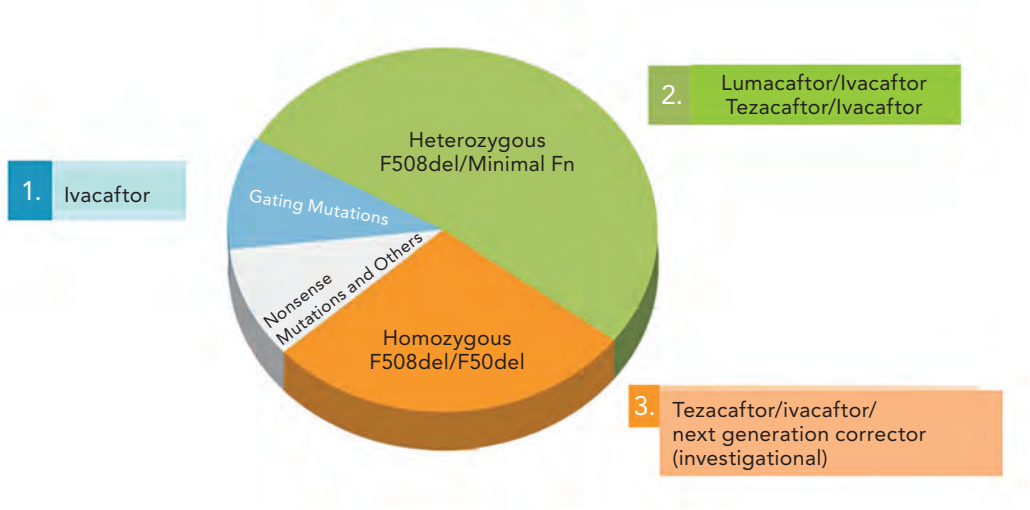
The combination improves FEV_1 modestly (~2%) and increases the time to a pulmonary exacerbation (hospitalization requiring intravenous antibiotics).[14] There is also a significant reduction in exacerbations and a slowing of the rate of lung function decline.[15] Twenty to 30 percent of people experience respiratory side effects with the combination and many cannot tolerate this treatment.

Another combination [tezacaftor/ivacaftor (Symdeko®)] was FDA approved in 2018. It essentially has the same efficacy as lumacaftor/ivacaftor, but it causes fewer adverse effects and has fewer drug interactions.[16] It is FDA approved for the treatment of patients aged 12 years and older who are homozygous for the F508del mutation, or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. The Cystic Fibrosis Founda-

Exhibit 3: CFTR Mutation Classes[5]

Normal	I	II	III	IV	V	VI
CFTR defect	No functional CTFR protein	CTFR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decrease CTFR stability
Type of mutations	Nonsense; frameshift; canonical splice	Missense; aminino acid deletion	Missense; amino acid change	Missense; amino acid change	Splicing defect; missense	Missense; amino acid change
Specific mutation examples	Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

Exhibit 4: Response to CF Targeted Therapy



tion has published practice guidelines for CFTR targeted therapy use.[17]

As shown in Exhibit 4, about 15 percent of patients have gating mutations responsive to ivacaftor and 50 percent are homozygous for F508del. There are no currently approved therapies for those with heterozygous F580del. Triple therapy with two correctors and a potentiator is under study for those with one F580del and a minimal function mutation. There are also no targeted therapies for those with Class I mutations; however, several possibilities are being studied. One approach for those who make no CFTR is to inhale functional RNA. Another is to repair the mutated CFTR with CRISPER, or replace it with gene therapy. These are all in Phase II trials. These approaches, if they work, would be cures for CF.

Conclusion

The survival for CF patients continues to improve. Aggressive, lifelong therapy is the key to improving the lives of children and adults with CF. Targeted therapies altering the basic defect in CFTR are slowing the progression of CF lung disease, but they will not reverse damage that already exists. Adherence with therapy will remain critically important because the underlying problem is not "cured." The future will hopefully bring a cure for CF.

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Value of Personalized Treatment and Sequencing for Castration-Resistant Prostate Cancer

Matthew R. Smith, MD, PhD

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

Summary

Although incurable, metastatic castration-resistant prostate cancer (mCRPC) can be treated with several lines of therapy which all have been shown to increase overall survival. There is also a new agent which can be used for CRPC before it has become metastatic.

Key Points

- Docetaxel, cabazitaxel, sipuleucel-T, abiraterone, enzalutamide, and radium-223 increase overall survival in mCRPC.
- Apalutamide is the first drug approved based on metastasis-free survival and the first drug approved for nonmetastatic castration-resistant prostate cancer (nmCRPC).
- Ongoing studies are addressing questions about the optimal timing, sequencing, and role of combination therapy.
- Poly ADP ribose polymerase (PARP) inhibitors appear active in men with DNA repair defects.

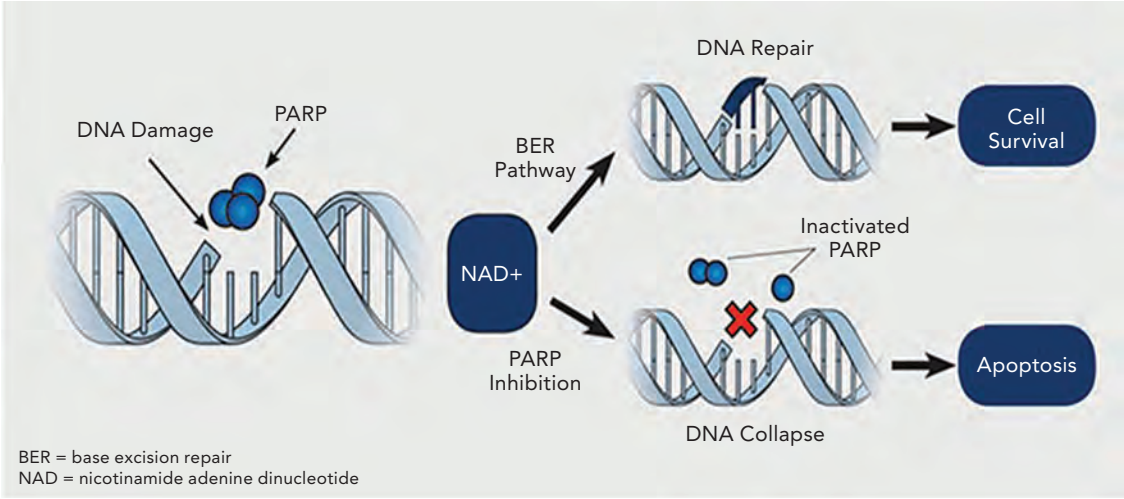
PROSTATE CANCER IS A GLOBAL ISSUE IN men's health. Worldwide, prostate cancer is the second most common cancer in men. There were approximately one million new cases annually accounting for 15 percent of all cancers diagnosed in men.[1] Seventy percent of prostate cancer cases occur in the developed regions of the world. Annually, there are approximately 300,000 deaths worldwide due to this cancer. It is the fifth leading cause of cancer death in men and accounts for about 7 percent of all male deaths.

Skeletal complications are the major cause of prostate cancer morbidity. Bone is the most common site of metastases, but other sites include the lungs and lymph nodes. The majority of men with metastatic prostate cancer have bone-only or bone dominant disease. In contrast to other common solid tumors, prostate cancer forms primarily osteoblastic lesions characterized by excessive formation of disorganized new bone. The clinical manifestations of osteoblastic metastases include pain, fractures, spinal cord compression, and ineffective hematopoiesis or myelophthisis. Prognosis is related to the sites of and the extent of metastases. Survival in metastatic castration-resistant prostate cancer (mCRPC) is best with soft tissue metastases only and worst with bone and soft tissue sites.[2]

Androgen deprivation therapy (ADT) is the mainstay of treatment for metastatic disease. ADT is also used in earlier stages of prostate cancer, where it is used for curative intent. ADT in the United States (U.S.) refers to medical castration (with gonadotropin-releasing hormone antagonists or agonists) and results in initial responses in most men. Bilateral orchiectomies are another form of ADT which are rarely done in the U.S. Unfortunately, nearly all men eventually progress to castration-resistant prostate cancer (CRPC). The average time to ADT failure is 12 months.[2]

Several agents are now approved for treating

Exhibit 1: PARP Mechanism and Inhibition



BER = base excision repair
NAD = nicotinamide adenine dinucleotide

mCRPC. Some of these improve survival (docetaxel, cabazitaxel, sipuleucel-T, abiraterone, enzalutamide, radium-223), whereas others are for palliating symptoms of pain (strontium-89, samarium-153), or reduction of skeletal -related events related to bone metastases (zoledronic acid, denosumab).

Taxane-based chemotherapy (docetaxel and cabazitaxel) improves median overall survival (OS) by approximately three months.[3,4] Docetaxel chemotherapy is the current first-line standard for symptomatic metastatic CRPC. Cabazitaxel (Jevtana®), a novel semi-synthetic taxane, is second-line chemotherapy in metastatic CRPC. In a comparison trial of the two agents, there was no difference in OS nor progression-free survival (PFS) between the two as first-line treatment of mCRPC, so cabazitaxel remains second line.[5]

Abiraterone (Zytiga®) and enzalutamide (Xtandi®) are the two FDA approved ADTs for mCRPC. Abiraterone is an androgen biosynthesis inhibitor which lowers circulating and tumor levels of androgens. It improves OS and PFS in patients who have or have not already had doxetaxel chemotherapy.[6,7] Additionally, it has now been shown to also improve OS and PFS when given with standard ADT in high-risk patients with metastatic disease before their disease has become castration resistant, and it is FDA approved for this indication.[8] Interference with androgen synthesis also interferes with synthesis of other steroids, resulting in hypertension, hypokalemia, and fluid retention, which requires administration of prednisone to prevent.

Enzalutamide is an anti-androgen which blocks the testosterone receptor. This agent does not lower testosterone levels. It has been studied in the pre- and post-chemotherapy settings in mCRPC and improves PFS and OS.[9,10] It is now FDA approved for use in both mCRPC and non-metastatic CRPC (nmCRPC).

There are a few practical considerations in selecting between these two agents. There has not been a head-to-head study of enzalutamide and abiraterone to determine if one is better than the other. The use of abiraterone requires concomitant prednisone twice daily. It may not be a suitable agent for those with diabetes or heart failure. Enzalutamide increases risk of seizures (rarely) and possibly other central nervous system (CNS) adverse effects. It may not be a suitable agent for those with a preexisting seizure disorder or for the rare patient with CNS metastases. The optimal sequence of these agents is unknown. The response rate to abiraterone after enzalutamide and the converse is relatively low, probably because they impact the same pathway. Because of their differing mechanisms of action, the combination of these two agents is under study.

Apalutamide, a next-generation androgen receptor antagonist, is the first oncology drug ever approved based on metastasis-free survival and was the first drug approved for nmCRPC. It is structurally similar to enzalutamide. In the SPARTAN trial, it was shown to improve metastasis-free survival by almost two years.[11] There are three ongoing Phase III clinical studies with apalutamide.

Bone metastases are a major issue in prostate cancer and as noted previously cause most of the complications of this disease (pain, fracture, spinal

cord compression). They are also the major site of disease resistance.

Studies with radium-223 (Xofigo®), a bone-seeking radio-pharmaceutical, changed the thinking about the use of bone-seeking treatment. The other agents used to manage bone disease only reduced pain or prevented skeletal events, but they did not alter the course of prostate cancer. Radium-223, an alpha particle emitter which acts as a calcium mimetic, has been shown to improve median OS in mCRPC (3.6 months) and prolong the time until the first skeletal-related event (5.8 months).[12] It naturally targets new bone growth in and around bone metastases. This agent is being studied in combination with abiraterone and enzalutamide.

The field of prostate cancer treatment has been slow to move toward personalized medicine. Data are now being accumulated on various genetic mutations which increases risk for prostate cancer or are drivers of the disease.

It has been found that DNA repair mutations are disease drivers in some patients. BRCA1 and BRCA2 mutations, which are involved in breast and ovarian cancer, have been shown to increase risk of prostate cancer. These mutations lead to either missing or nonfunctional proteins, which leads to defective DNA repair, transcription, and cell cycle checkpoint regulation. DNA repair aberrations have been found in 19.3 percent of mCRPC tumor biopsies.[13] BRCA1 and BRCA2 are the most often found mutations.[14] Treatment guidelines now recommend germline genetic testing for patients with metastatic prostate cancer and intermediate risk localized disease and for those with family members with the same or related diseases (breast, ovarian).

Poly ADP ribose polymerase (PARP) inhibitors, which are already FDA approved for breast and ovarian cancers with germline BRCA1 and BRCA2 mutations, are being investigated for prostate cancer. In a Phase II study of olaparib, a PARP inhibitor, in all comers with mCRPC, the study found responses in about one-third of subjects.[15] In those with DNA repair mutations, olaparib was effective in improving radiographic disease-free progression (7.2 months) and median OS (6.3 months). Numerous trials of PARP inhibitors in prostate cancer treatment are ongoing to determine efficacy and the appropriate biomarker for treatment selection.

Massachusetts General Hospital is now offering genetic testing and counseling to men with metastatic and/or high-grade prostate cancer. Routine biopsies for tumor genetic analyses for men with treatment-refractory mCRPC are also being done. The hospital is also expanding clinical trials of precision medicine in this disease.

Conclusion

The landscape of treatment for mCRPC has been transformed in recent years. Six therapies are available that increase overall survival in mCRPC. Apalutamide is the first drug approved based on metastasis-free survival and the first drug approved for nmCRPC. Enzalutamide has also been approved for nmCRPC. Ongoing studies are designed to address questions about the optimal timing, sequencing, and role of combination therapy. Emerging evidence suggests that PARP inhibitors are active in men with DNA repair defects. Genetic testing is becoming more common in this disease.

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New Agents and Emerging Strategies in Advanced Breast Cancer: Patient-Centric Navigation in the Age of Personalized Care

Lajos Pusztai, MD, Dphil

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

Summary

A recently approved new class of medications, PARP inhibitors, is bringing new hope to women with BRCA 1 and 2 mutations and metastatic breast cancer. They are increasing progression-free survival while still maintaining good quality of life in this incurable stage of breast cancer. The role of this class of agents is likely to expand to earlier stages of disease and combination regimens.

Key Points

- Five to 10 percent of women with metastatic breast cancer have germline BRCA 1 and 2 mutations.
- PARP inhibition combined with BRCA defects lead to cell death.
- Improvement in progression-free survival and quality of life compared to chemotherapy are the primary benefits of this class of agents.
- BRCA 1/2 mutation testing is important for prevention of breast and ovarian cancer and in treatment of metastatic breast cancer.

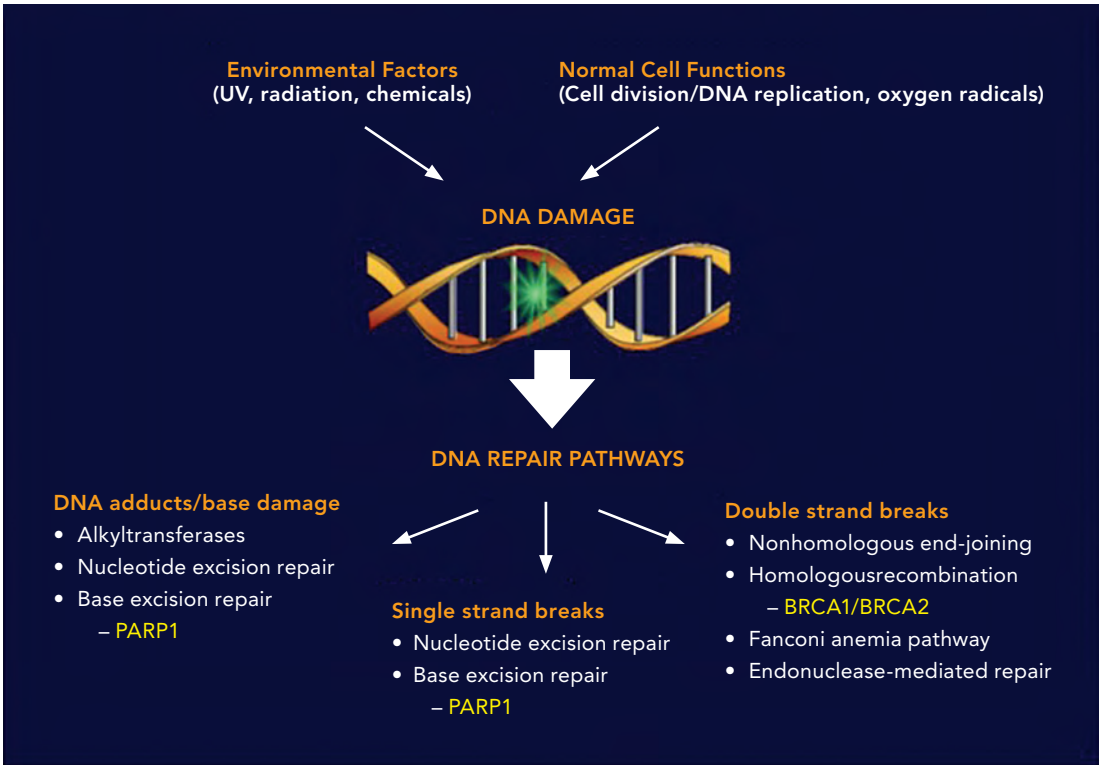
WITH GREATER UNDERSTANDING OF THE underlying mechanism of various types of breast cancer, there are several molecularly targeted therapies, including anti-estrogens for estrogen receptor (ER) positive breast cancer, human epidermal growth factor receptor 2 (HER2)-targeted drugs for HER2 amplified breast cancer, and pembrolizumab for microsatellite unstable cancers which are used based on various biomarkers. The newest therapy is poly adenosine diphosphate ribose polymerase (PARP) inhibition for germline BRCA1 or 2 mutated metastatic breast cancer, which is the focus of this article.

BRCA mutations can be germline or somatic. Germline mutations occur in the germline and are present in all cells of the body. Germline BRCA mutations increase life time risk to develop certain cancers. There is a 50 percent chance to pass on these mutations to a child. Somatic mutations occur in cancer cells, so only the cancer cells carry the mutation. Biological impact on the development of cancer may be different depending on whether the mutation is germline or somatic.

DNA is damaged in our cells all the time by environmental factors and normal cell function, but the cells have mechanisms for repairing this damage (Exhibit 1).[1] There are over 100 different genes that work together to repair DNA damage. PARP1 plays a major role in excising DNA adducts (a segment of DNA bound to a cancer-causing chemical) and repairing single strand DNA breaks. BRCA1 and 2 repair double strand DNA breaks.

PARP can be thought of as a beacon that at-

Exhibit 1: DNA Damage and Subsequent DNA Repair



PARP = poly adenosine diphosphate ribose polymerase
BRCA = breast cancer associated gene

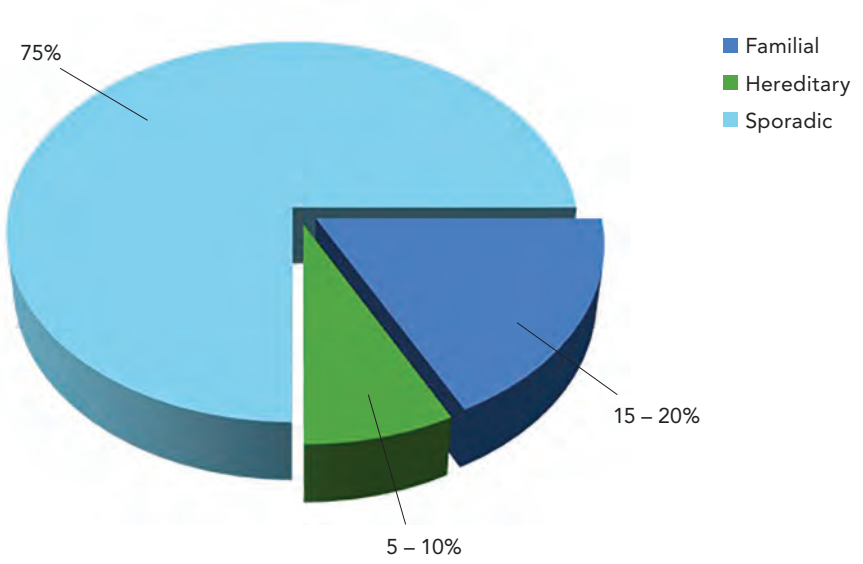
taches to damaged parts of DNA, which activates the rest of the DNA repair machinery. If PARP is blocked, then damage, such as from chemotherapy, is not repaired and it progresses to a double strand break in the DNA at replication. BRCA can repair the double strand break. If someone has defective BRCA1/2, the DNA damage cannot be repaired, and the cell dies. Normal cells that do not replicate their DNA as often as cancer cells, and that lack any mutated BRCA1 or BRCA2 still have homologous repair operating, which allows them to survive the inhibition of PARP. PARP inhibition in someone with BRCA1/2 mutations provides complementary lethality; molecular defects that individually are not lethal become lethal when combined.

Breast cancer cases can be familial, hereditary (identifiable genetic predisposition), or sporadic (Exhibit 2). The majority of breast cancer is of sporadic or unknown origin. With familial breast cancer, where more cases than expected by chance occur in a family, the reasons or particular genes are unknown. Five to 10 percent of breast cancers are hereditary where the problem gene is known. Fifty to 80 percent of these are due to BRCA mutations. In the United States (U.S.), one in 350 women is a BRCA carrier, but the number is one in 40 in the Ashkenazi Jewish population. BRCA carriers have a 60 to 85 percent lifetime risk of developing breast cancer.

Those with BRCA1 mutation have a 30 to 50 percent risk of ovarian cancer compared with a less than 2 percent risk in the general population. BRCA2 mutation leads to a 25 to 35 percent risk. The lifetime risk of prostate cancer in a man with BRCA1/2 mutation is 40 percent (7-15% in the general population). Pancreatic cancer lifetime risk is 2 to 4 percent compared with less than 1 percent in the general population. Male breast cancer occurs in 7 percent of those with BRCA mutation by age 70 (<1% in the general population). DNA repair is vital for all cells in the body; why cancer develops in BRCA carriers in these particular organs and not in others is unknown. There are now two PARP inhibitors FDA approved for treatment of germline BRCA-mutated, HER2-negative metastatic breast cancer (MBC) - olaparib (Lynparza®) and talazoparib (Talzenna®).

In patients with metastatic HER2-negative breast

Exhibit 2: Distribution of Breast Cancer Cases



cancer and a germline BRCA1 or BRCA2 mutation treated with up to two prior chemotherapies for MBC, olaparib improved progression- free survival (PFS) compared to standard chemotherapy (median 7.0 vs. 4.2 months); there was no statistical difference in overall survival (OS), but this was a secondary endpoint for this study.[2] There was a higher objective response rate in the olaparib group compared to standard chemotherapy group (60% vs. 29%). The FDA approved olaparib in early 2018 based on this trial. Anemia and nausea are the two adverse effects which occur most often, however, overall this agent is well tolerated. Mean baseline quality of life (QOL) scores increased during the study in the olaparib arm and decreased in the chemotherapy arm ($p = 0.004$). The median time to a 10 point or greater decrease in QOL score was not reached in the olaparib arm and was 15.3 months in the chemotherapy arm ($p = 0.004$).

Talazoparib was FDA approved in October 2018. A Phase III trial of talazoparib versus physician's choice chemotherapy in germline BRCA-mutated metastatic breast cancer found an improved objective response rate (63% vs 27%), PFS (8.6 months vs 5.6 months), time to deterioration in QOL (24.3 months vs 6.3 months) and overall survival (22.3 months vs 19.5 months, not statistically different).[3] This study was essentially identical to the olaparib study in design and results. Anemia and thrombocytopenia were the two adverse effects of concern with talazoparib.

Compared to chemotherapy, both olaparib and talazoparib significantly improve PFS, overall tumor response rate, and time to deterioration of quality of life, but they do so at the expense of higher rates of anemia with both and thrombocytopenia with talazoparib. One difference between these two oral agents is that olaparib is given twice a day and talazoparib once daily. Remaining unanswered questions about PARP inhibition include do these agents also work in non-mutated germline BRCA or somatic BRCA mutant/BRCA-like metastatic breast cancers, the best partners for combination therapy, and will these agents increase cure rates in early stage germline BRCA mutant breast cancers. Studies addressing some of these questions are ongoing. For example, PARP inhibition is being studied in combination with immunotherapy.

Niraparib and rucaparib are two other PARP inhibitors being studied for breast cancer. Niraparib (Zejula®) is FDA approved for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer after complete or partial response to platinum-based chemotherapy. Rucaparib (Rubraca®) is FDA approved for maintenance therapy in women whose ovarian cancer has recurred and who had a response to a platinum-based chemotherapy. Both are currently in Phase III trials for breast cancer.

The availability of PARP inhibitors has changed the role of germline BRCA1/2. The traditional indication for testing was to identify those at risk of developing a future cancer and risk of cancer in offspring. BRCA1/2 mutation testing is also an option for women and men without current cancer but

with family history indicative of risk. Identification of germline BRCA positive status allows patients to consider effective risk reduction strategies (prophylactic mastectomy and oophorectomy), which can reduce risk of breast cancer by 90 percent and ovarian cancer by a lesser degree. Avoiding a future breast cancer event is likely to be cost effective at the population level with selective National Comprehensive Cancer Network guideline-based testing.

Previously, germline BRCA1/2 testing was not recommended in metastatic breast cancer. Testing is now indicated to identify those who are eligible for PARP inhibitor therapy. The NCCN provides guidelines for BRCA1/2 testing.[4] In the metastatic cancer setting, prevention issues related to BRCA1/2 mutations are mute in the context of a life-limiting, incurable disease. Impact on siblings and offspring of the mutations remain relevant, but testing is preferred at diagnosis rather than at recurrence. Somatic BRCA mutations may be identified through molecular therapeutic target profiling of cancer tissues. If a somatic BRCA mutation is identified, germline testing is required to confirm germline status and eligibility for PARP inhibitor therapy. Metastatic disease tumor profiling with a panel assay followed by germline BRCA testing, if a somatic mutation is identified, may be the most cost-effective testing strategy and is the strategy used at Yale University.

Germline BRCA testing in early stage disease (Stage I – III breast cancer) is appropriate in some patients based on the NCCN guidelines. Among 1,711 patients with early stage breast cancer who met NCCN BRCA testing guidelines, only 53 percent were actually tested.[5] Results are primarily used for counseling regarding prevention options to prevent a contralateral breast cancer or ovarian cancer. Currently, knowing the germline BRCA status does not change the chance of cure from Stage I to III breast cancer. If an ongoing adjuvant olaparib trial (OlympiA) shows that PARP inhibition reduces risk of recurrence, BRCA testing will become more common in early stage disease; however, results from this trial are not expected for many years.

Conclusion

PARP inhibitors are an important new option for 5 to 10 percent of women with metastatic breast cancer. Improvement in progression free survival and quality of life compared to chemotherapy are the primary benefits of this class of agents. Given an effective therapy, women with metastatic breast cancer who meet the NCCN guidelines should have BRCA1/2 mutation testing.

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Personalized Treatment Strategies in the Management of Metastatic Colorectal Cancer (mCRC)

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

Summary

In 2019, biomarkers are being used to select individualized therapy for metastatic colorectal cancer (mCRC). There are both predictive and prognostic biomarkers in use which are used to select immunotherapy and targeted therapy.

Key Points

- RAS mutations are a biomarker for EGFR therapy selection.
- BRAF mutations are prognostic biomarkers.
- Mismatch repair deficiency is a biomarker for immune checkpoint therapy.
- Combining therapies may make nonimmunologic tumors respond to immunotherapy.

COLORECTAL CANCER (CRC) RESULTS IN the third highest cancer incidence rate (~135,000/year) and second highest mortality rate (~49,000/year) in the United States (U.S.). Globally, CRC has the third highest incidence rate and fourth highest mortality rate. Combination chemotherapy regimens and surgery are common treatments for CRC. For metastatic CRC (mCRC), targeted therapies with chemotherapy and immunotherapy are being used to improve outcomes.

The goals of systemic therapy in mCRC are to extend overall survival (OS) and maintain quality of life as long as possible. Tumor response is also a goal, especially if the patient is symptomatic or the tumor is potentially resectable. Selecting systemic therapy requires considering the intensity of therapy, toxicities, patient wishes, and need for aggressive therapy.

Tools for treatment selection are both clinical and molecular. Clinical tools include patient age, performance status, comorbidities, tumor burden, and tumor location. Molecular biomarkers also impact treatment selection. These biomarkers are used to decide what therapy to give for first, second, third line, and beyond treatment.

Targeted therapy with biologics can be used to its full potential by utilizing prognostic and predictive biomarkers. Prognostic biomarkers are those that correlate with clinical outcomes, regardless of therapy, and predictive biomarkers are associated with the likelihood of response to therapy.

The two major tumor growth pathways that are targeted with biologics in mCRC are vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). Bevacizumab, ramucirumab, and aflibercept are anti –VEGF agents and cetuximab and panitumumab block EGFR. All five of these agents added to chemotherapy in mCRC improve progression-free survival (PFS) and median

Exhibit 1: VEGF vs EGFR Antibodies in Advanced CRC

Agent	Strength	Weakness
VEGF antibodies	Delay in tumor progression	Limited single agent activity
	Gain in time	Weak effect on response rate (RR)
	Toxicity profile	
EGFR antibodies	Single agent activity	Gain in time-to-progression moderate
	Consistent increase in RR	Toxicity profile
	Activity independent of line of therapy	
	Predictive marker (RAS mutation)	

OS. Currently, there are no reliable biomarkers for predicting benefit of VEGF therapy. There are biomarkers for EGFR therapy.

RAS mutation status is a predictor for EGFR therapy. Point mutations in RAS genes (HRAS, NRAS, and KRAS) occur in approximately 30 percent of all cancers. KRAS mutations occur in 35 to 40 percent of CRC; the other RAS mutations occur in much smaller percentages of patients. Mutations result in constitutive activation of the RAS-RAF-MAPK signaling pathway, leading to tumor cell proliferation and enhanced cell survival. Numerous studies have shown that patients with mCRC and any RAS mutation do not benefit from EGFR-targeted therapy.[1] The National Comprehensive Cancer Network (NCCN) guidelines recommend testing for all RAS mutations in mCRC.[2]

Whether VEGF or EGFR therapy is a better choice for first-line treatment in KRAS wild- type mCRC has not yet been answered. Two trials conducted in Europe found benefit for EGFR therapy over VEGF and one trial conducted in the U.S. found no difference. [3] Exhibit 1 compares the strengths and weaknesses of VEGF and EGFR therapy in mCRC. Skin adverse effects are a major reason to be cautious with using EGFR therapy in the first line.

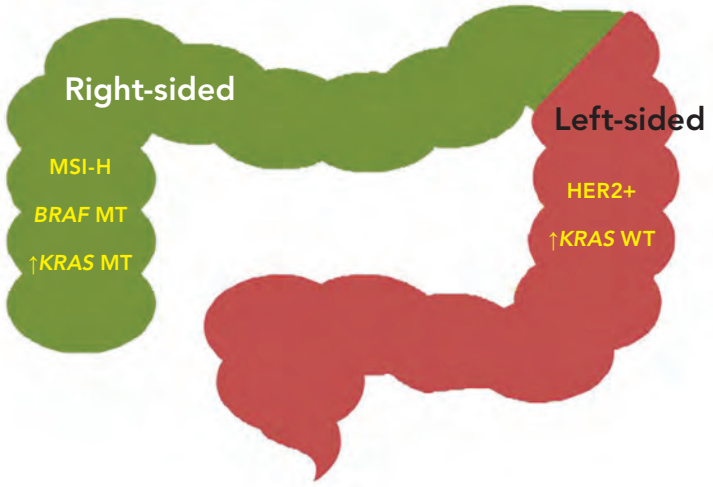
Another biomarker in mCRC is BRAF, a primary effector of KRAS signaling. BRAF mutations occur most frequently in exon 15 (V600E) and are found in 4 to 14 percent of patients with mCRC. BRAF mutations are mutually exclusive with KRAS mutations. The prognosis of patients with the BRAF V600E mutation is poor; thus, BRAF is a prognostic biomarker.[4,5] BRAF mutation testing is now recommended for all patients with mCRC because there is an effective triple combination [vemurafenib (a BRAF targeting agent), cetuximab or panitumumab, and irinotecan], which improves progression-free survival in patients with BRAF V600E mCRC.[2,6]

Another interesting biomarker is the location of the tumor in the colon. Tumors from the right and left side of the colon tend to have differing genetic mutations and prognosis (Exhibit 2). Left-sided primary colorectal cancers have better prognosis than right-sided colon cancers.[7] Right-sided colorectal cancers do not benefit from anti-EGFR therapy, but they do benefit from bevacizumab. Left-sided tumors can benefit from both bevacizumab and anti-EGFR therapy. Exhibit 3 shows a treatment selection algorithm for first-line therapy that includes clinical and molecular characteristics.[8]

A last biomarker to discuss is deficient DNA mismatch repair (dMMR). MMR genes work like genetic "spell checkers" by correcting errors in DNA as cells divide. Because DNA errors are not repaired, tumors with dMMR have a large number of mutations and a high amount of instability due to the mutations (high microsatellite instability, MSI-H). These mutations have the potential to generate neo-antigens which can be recognized by the immune system, allowing the immunotherapy to work. Thus, checkpoint inhibitor therapy has been studied for dMMR mCRC.

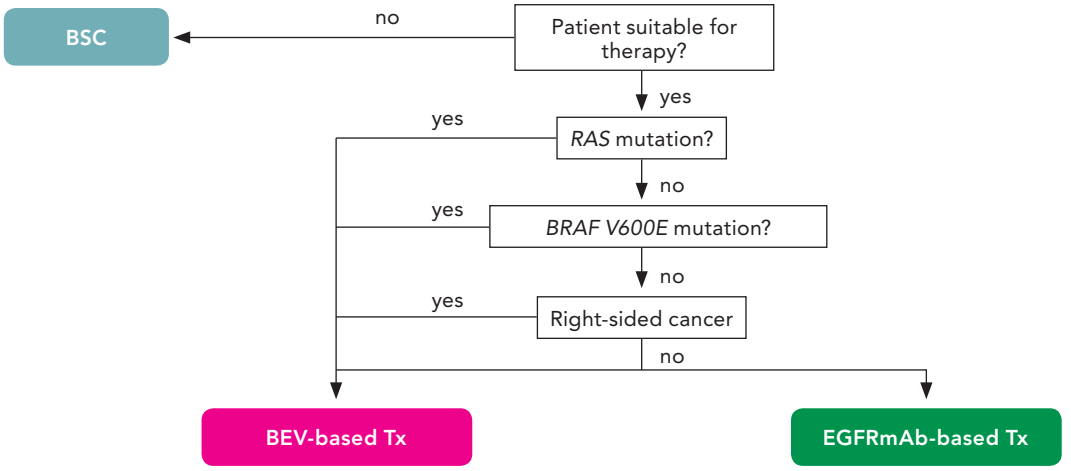
In dMMR mCRC, pembrolizumab (Keytruda®) produced a 40 percent response rate compared to 0 percent in those with proficient MMR. It also improved PFS and median OS.[9] Similar benefits with nivolumab (Opdivo®) alone have been shown.[10] In the nivolumab trial, 80 percent of the patients with dMMR were still alive at 12 months. The combination of two immunotherapy agents (nivolumab and ipilimumab, cytotoxic T-lymphocyte-associat-

Exhibit 2: Primary Tumor Location and Mutation Differences



MSI-H = microsatellite inst
MT = mutant type
WT = wild type
HER2 = human epidermal growth factor two

Exhibit 3: First-line Treatment Selection[8]



ed protein 4 (CTLA4) inhibitor) has been studied in mCRC in those with and dMMR (CheckMate 124). OS has not yet been reached in the combination therapy group; however, 88 percent of the subjects were still alive at 9 months.[11] The problem with combination immunotherapy is toxicity; approximately 26 percent of patients will have Grade III or IV adverse effects compared to 10 to 14 percent of those on a single agent.

Nivolumab, in combination with ipilimumab and pembrolizumab, is FDA approved for mCRC with dMMR/MSI-High. The NCCN guidelines recommend either as an option.[2] Patients who respond to immunotherapy tend to have a very durable response, unlike the response to chemotherapy.

The problem with immunotherapy is that it only benefits about 5 percent of mCRC patients. One area of investigation is how to convert a nonimmunogenic tumor into an immunogenic tumor. One avenue is to combine immunotherapy with MEK inhibition. MEK inhibition alone can result in intratumoral T-cell accumulation and immune

system upregulation. This would synergize with a checkpoint inhibitor to promote durable tumor regression. Cobimetinib, a MEK inhibitor, and atezolizumab, an anti-programmed death one (PD-1) immunotherapy, reduced tumor volume in patients with MSI-stable tumors.[12] The median duration of response was about 14 months, but this combination failed to improve survival when compared to regorafenib in the third-line setting. The search is still continuing for a way to activate "cold" tumors.

Conclusion

Anti-VEGF and anti-EGFR therapies are competing for first-line patients in RAS wild-type mCRC. The best sequence of therapies (anti-VEGF vs anti-EGFR) is still to be established. To determine eligibility for anti-EGFR treatment, testing for all RAS mutations is required. The primary tumor location helps determine the tumor mutations present and the treatment selection. Checkpoint inhibitors are highly active in a select molecular subset. A rational combination of agents may be able to covert a non-immunologic tumor to an immunologic one which will respond to immunotherapy.

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Individualizing Therapy in the Management of Relapsing Multiple Sclerosis: Expert Strategies for Improved Patient Outcomes

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

Summary

Significant changes in managing multiple sclerosis (MS) have occurred in the past two years, and additional therapies are in the development pipeline. Updated management and monitoring guidelines can be used to guide managed care policy decisions. Optimizing outcomes in this disease requires significant focus on therapy selection, adherence, and adverse event prevention.

Key Points

- Numerous disease-modifying agents are available for managing MS.
- Emerging therapies include siponimod, ozanimod, autologous hematopoietic stem cell transplantation, cladribine, high-dose biotin, and altering the gut microbiota.
- Optimizing outcomes in this disease requires selecting the appropriate therapy, managing adherence, monitoring for adverse events, and modifying therapy as needed to achieve no evidence of disease activity (NEDA).
- Updated guidelines for management of MS with disease-modifying therapies and MRI use are available.

MULTIPLE SCLEROSIS (MS) IS A CHRONIC autoimmune demyelinating disease of the central nervous system (CNS), with onset in young and middle adulthood. MS is the second most common cause of disability in young adults. It affects females more often than males (3:1) and is more prevalent in geographic areas further away from the equator. The symptoms include difficulties with ambulation, vision, weakness, sensory loss, balance, bowel and bladder dysfunction, fatigue, and cognitive dysfunction.

MS has a multifactorial etiology of genetic factors and environmental triggers which results in inflammatory and degenerative changes. MS affects both grey and white matter in the CNS, including the optic nerves, periventricular, subcortical white matter, pons, midbrain, and spinal cord. The pathophysiology involves migration of inflammatory cells past the blood brain-barrier into the CNS, resulting in relapses. Eighty-five percent of cases are relapsing-remitting (RRMS); the remainder are secondary-progressive disease (SPMS) and primary-progressive (PPMS).

Exhibit 1 shows the disease-modifying therapies (DMTs) which are currently available for RRMS. The goal of using DMTs is to reduce relapses, reduce disability progression, reduce evidence of CNS damage on MRI, and ultimately achieve no evidence of disease activity (NEDA). The oral thera-

Exhibit 1: Disease-Modifying Therapies

Injectible DMT's					
	Approved	Dosing	MOA	Efficacy	Side-effects
Betaseron (interferon beta-1b)	1993	0.25 mg SC QOD	Induction of anti-inflammatory cytokines and modulates B cell trafficking across the BBB	30% reduction in RR over 2 years	Headache, flu-like symptoms, depression, decrease in wbc, elevation in LFT's and injection site reactions in sc drugs
Avonex (interferon beta-1a)	1996	30 mcg IM Qweek			
Rebif (betaseron beta-1a)	2002	22 or 44 mcg SC TIW			
Extavia (interferon beta-1b)	2009	0.25 mg SC QOD			
Plegridy (pegylated interferon beta-1a)	2014	125 mcg SC Q14 days			
Copaxone (glatiramer acetate)	1997	20 mg SC QD	Synthetic co-polymer that simulates MBP and blocks myelin-damaging T cells	29% reduction in RR over 2 years	Injection site reactions including lipoatrophy, palpitations, chest pain, SOB
	2014	40 mg SC TIW			
Glatopa (glatiramer acetate)	2015	20 mg SC QD			

Oral DMT's					
	Approved	Dosing	MOA	Efficacy	Side-effects
Gilenya (Fingolimod)	2010	0.5 mg po QD	Blocks lymphocytes from exiting lymphatic tissue	54% reduction in RR over 2 years and decreased disability	Bradycardia, macular edema, elevation of LFT's and decreased wbc
Aubagio (teriflunomide)	2012	7 or 14 mg po QD	Inhibits dihydroorotate dehydrogenase resulting in diminished pyrimidine synthesis in proliferating lymphocytes	33% reduction in RR over 2 years	Hair thinning, diarrhea, decreased wbc and elevation of LFT's
Tecfidera (dimethylfumarate)	2013	125 mg po BID x 7 D, then 240 mg po BID	Reduces oxidative stress by activating nrf-2 transcription	45% reduction in RR over 2 years	Flushing, diarrhea, abdominal pain, elevated LFT's and decreased wbc

Intravenous DMTs					
	Approved	Dosing	MOA	Efficacy	Side-effects
Natalizumab (Tysabri)	2006	300 mg IV Q28 days	Inhibits migration of inflammatory lymphocytes across BBB	67% reduction in RR and 42% reduction in disability	Infusion reactions, PML
Alemtuzumab (Lemtrada)	2014	12 mg IV qd x 5 days, then repeat 12 mg IV qd x 3 days in a year	Depletes CD52+ cells and NKC's	50% reduction in RR with efficacy maintained for years after 2 cycles	Autoimmune thyroid disease, ITP, Goodpasture syndrome, infusion reactions, herpes infections
Ocrelizumab (Ocrevus)	2017	300 mg infusions x 2, repeated yearly as 600 mg infusions	Depletes CD20 expressing B cells	47% reduction in RR and 40% reduction in disability progression over 2 years	Infusion reactions

MOA = mechanism of action
RR = relapse rate
SC = subcutaneous
IM = intramuscular
TIW = three times a week
QOD = every other day
QD = every day
BID = twice a day
BBB = blood brain barrier
MBP = myelin basic protein
SOB = shortness of breath
WBC = white blood cells
LFTs = liver function tests
NKCs = natural killer cells
ITP = Immune thrombocytopenic purpura
PML = Progressive multifocal leukoencephalopathy

pies were revolutionary when approved because they are more effective than injectable interferons and are better accepted by patients. Overall, the intravenous DMTs and fingolimod are the most efficacious agents. Therapy with the intravenous agents does lead to some significant adverse events which require ongoing monitoring to identify. It is important to note that one therapy – daclizumab (Zinbryta®) was voluntarily withdrawn from the market in early 2018 by the manufacturer because of concerns of severe liver failure and meningoencephalitis. Additionally, it is important to note that DMT is only for modifying the disease (i.e., reducing disease activity and slowing disease progression); it does not alter the symptoms of the disease, such as fatigue. Symptoms must be managed separately.

Several other therapies are emerging as potential treatments for MS. These include siponimod, ozanimod, autologous hematopoietic stem cell transplantation, cladribine, high-dose biotin, and altering the gut microbiota.

Siponimod is a selective sphingosine 1-phosphate receptor-1 (S1P1) and a sphingosine 1-phosphate receptor-5 (S1P5) modulator. S1P1 receptor binding prevents lymphocytes from entering the CNS and is the same mechanism of action for fingolimod. S1P5 receptor binding on oligodendrocytes and astrocytes modulates damaging cell activity and reduces loss of neurological function. In a randomized, double-blind, placebo-controlled Phase III study in 1,651 SPMS patients, this agent reduced risk of six-month confirmed disability progression by 26 percent, the annualized relapse rate (ARR) by 55.5 percent, reduced brain lesions on MRI by over 80 percent, and slowed the rate of brain volume loss by 23 percent.[1] Adverse events were reported in 89 percent of siponimod patients compared with 15 percent in placebo patients. These included lymphopenia, increased liver function tests (LFTs), bradycardia, bradyarrhythmia, macular edema, hypertension, varicella zoster virus reactivation, and seizures, which is similar to what is seen with fingolimod. Siponimod has been submitted to the FDA for approval, and action is expected by spring of 2019.

Ozanimod is another investigational S1P1 and S1P5 modulator. In a Phase III trial comparing it to interferon, it reduced ARR 0.17 with 1 mg dose and 0.22 with 0.5 mg over two years. It also reduced new/enlarging lesions on MRI by 42 percent for 1 mg and 34 percent for 0.5 mg, gadolinium enhanced lesions by 53 percent for 1 mg and 47 percent for 0.5 mg ($p=0.0030$), and brain volume loss by 27 percent for 1 mg and 25 percent for 0.5 mg.[2] The adverse events were nasopharyngitis, headache, elevated LFTs, flu-like symptoms, hypertension, and urinary tract infections. The manufacturer will likely be submitting this agent to the FDA in early 2019 after their initial submission was rejected in 2018 for insufficient information.

Autologous hematopoietic stem cell transplantation (AHSCT) involves collection of stem cells by filtration of blood, ablation of the immune system with high-dose chemotherapy, and then transplantation of the stem cells back into the body. The goal of AHSCT in MS is to reset the immune system. AHSCT has the potential to maintain a much higher proportion of NEDA in patients at two years (ranging from 78-83%) and at five years (ranging from 60-68%) compared with much lower rates for DMTs (13-46%).[3] Because AHSCT is a costly and toxic procedure to endure and there are still a lot of unanswered questions about it as a treatment for MS, it is still considered experimental.

Cladribine is an oral antineoplastic agent that has been used in the treatment of lymphoproliferative diseases, including hairy cell leukemia. It was approved for treating MS in the European Union and Canada in 2017 and has been submitted to the FDA for treating RRMS. In MS, its effectiveness may be due to its ability to effectively deplete B cells, particularly memory B cells.[4] This agent is given as a half dose over a two-week period during year one and then repeated in year two. Treatment with cladribine significantly reduced relapse rates, the risk of disability progression, and MRI measures of disease activity at 96 weeks compared to placebo.[5] Post-study analysis showed the cladribine group was 4.46 times more likely to have achieved NEDA than the placebo group and was less likely to have new relapses or new MRI lesions.

High-dose biotin has been investigated as a treatment for MS because it is safe, relatively inexpensive, and available through compounding pharmacies. Although high-dose biotin is well tolerated and safe, it does not appear to be especially effective. Small trials have shown mixed results in terms of the ARR and disability, but trials are still ongoing with this agent.[6-8]

Another up-and-coming area is the link between the gut microbiota and MS. The gut bacterial profiles are very different in those with stable and active MS.[9] It is not known yet if the differences in gut microbiota are the cause of MS, a contributor to MS, or a result of the disease. Studies of probiotics being used to alter gut flora will need to be conducted. Biomarkers of dysbiosis in the gut are being studied as markers for risk of a relapse.

Overall, there are several effective DMTs available, and several other treatments are likely to make it to market within the next few years. Successful

Exhibit 2: 2018 AAN Guideline on DMTs for Adults with MS[12]

Starting DMTs:

1. Counsel newly diagnosed patients about specific treatment options at dedicated treatment visit.(B)
2. Incorporate preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common AEs and tolerability in choice of DMT. Engage in ongoing dialogue regarding treatment decisions throughout disease course. (A)
3. Counsel DMTs are to reduce relapses and new MRI lesion activity, not for symptom improvement. (B) Patients must notify clinicians of new or worsening symptoms. (A)
4. Evaluate readiness or reluctance to initiate DMT and counsel on importance. (B)
5. Counsel about comorbid disease, adverse health behaviors and potential interactions with concomitant medications. (B)
6. Evaluate barriers to, and counsel on importance of adherence to DMT. (B)
7. Discuss benefits and risks of, and offer DMT to people with single clinical demyelinating event and two or more brain lesions characteristic of MS. (B)
8. Alternatively, recommend serial imaging at least annually for first five years and close follow-up in people with CIS or relapsing forms of MS not on DMT, no relapses in preceding 2 years and no active new MRI lesion activity. (C)
9. Offer DMT to patients with relapsing MS with recent clinical relapses or MRI activity. (B)
10. Monitor for medication adherence, AEs, tolerability, safety and effectiveness of therapy. Follow-up either annually or according to medication-specific recommendations. (B)
11. Monitor reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT use in women of childbearing potential. (B)
12. Counsel men with MS on reproductive plans regarding treatment implications before initiating teriflunomide or cyclophosphamide. (B)
13. Do not prescribe mitoxantrone unless potential therapeutic effects greatly outweigh risks. (B)
14. Use alemtuzumab, fingolimod or natalizumab in highly active MS. (B)
15. Direct to support programs. Recommend azathioprine or cladribine for relapsing MS if no access to approved DMTs. (C)
16. Initiate natalizumab for patients with positive anti-JCV antibody index > 0.9 only if reasonable benefit compared with risk of PML. (C)
17. Offer ocrelizumab for PPMS unless risks outweigh benefits. (B)

Switching DMTs:

1. Monitor MRI disease activity from clinical onset of disease to detect new lesions. Relapses or new MRI lesions may develop after initiation of DMT and before DMT becomes effective. Discuss switching DMT if DMT use has been long enough to take full effect and adherent to therapy when one or more relapse, two or more new MRI lesions or increased disability over a one-year period. (B)
2. Evaluate degree of disease activity, adherence, adverse effect profiles and mechanism of action of DMTs when switching for breakthrough disease activity. (B)
3. Discuss change to noninjectable or less frequently injected DMT if intolerable discomfort or injection fatigue. (B)
4. Inquire about, and manage, medication AEs and discuss switch if AEs negatively affect adherence. (B)
8. Check for natalizumab antibodies in those with infusion reactions before subsequent infusions, or breakthrough disease with natalizumab use. Switch DMT if persistent natalizumab ab. (B)
9. Counsel those considering natalizumab discontinuation regarding increased risk of MS relapse or MRI disease activity within 6 months of discontinuation. (A) If switching to fingolimod, initiate within 8 to 12 weeks of natalizumab discontinuation (unless pregnant or planning pregnancy.) (B)
10. Counsel women to stop DMT before conception for planned pregnancies, discontinue DMT during pregnancy if accidental exposure occurs, and should not initiate DMT during pregnancy, unless risk of MS activity out weighs risks associated with DMT. (B)

Stopping DMTs:

1. Counsel patient with RRMS and stable on DMT who wants to discontinue, regarding need for ongoing follow-up and periodic reevaluation of decision to discontinue DMT. (B)
2. Assess likelihood of future relapse in SPMS by age, disease duration, relapse history, MRI activity. (B) May advise discontinuation in SPMS without ongoing relapses or gd+ MRI lesions and not ambulatory (EDSS > 7) > 2 years. (C)
3. Review associated risks of continuing vs. stopping DMT's in CIS who have not been diagnosed with MS. (B)

therapy outcomes in MS require that patients be adherent with DMT for many years, even when there is NEDA which can be difficult. Focusing on adherence is one way to improve outcomes in this disease.

Another way to optimize outcomes in MS treatment is to minimize the risks from the various available DMTs with monitoring. One of the most concerning adverse events of therapy with natalizumab is progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by John Cunningham virus (JCV) infection or reactivation. PML can cause severe disability or death. JCV exposure status must be checked before natalizumab is started and monitored during therapy. The incidence of PML is about one in 250 treated patients. A registry of natalizumab-treated patients is being used to iden-

Exhibit 3: CMSC MRI clinical guidelines for diagnosis and follow-up of MS[14]

Baseline studies for CIS or suspected MS:

- Brain MRI with gadolinium at baseline and to establish dissemination in time
- Spinal cord MRI if myelitis, inconclusive brain MRI, or age > 40 with nonspecific brain MRI findings
- Cervical MRI – CIS with or without myelitis
- Orbital MRI if severe optic neuritis with poor recovery

PML surveillance protocol:

- Every 12 months for JCV ab negative on NTZ
- Every 3 months for high index, 6 months for low index for JCV antibody positive and on NTZ > 18 months

Use of gadolinium:

- In CIS – demonstrates dissemination in time
- Follow patients with highly active disease
- With rapid unexpected decline
- Concern regarding alternative diagnosis than MS
- Optional for monitoring subclinical disease which may lead to change in therapy

CIS = clinically isolated syndrome
JCV = John Cunningham Virus
NTZ = natalizumab

tify ways to reduce PML risk. Extending the dosing interval from every four weeks to every five to eight weeks has been shown to lead to a 90 percent reduction in the PML rate.[10] The problem with using an extended interval is that the disease activity of some patients is very sensitive to the dosing interval. PML cases have also been reported with the use of fingolimod, dimethyl fumarate, and ocrelizumab.

All of the DMTs are expensive from an acquisition cost perspective. The cost-effectiveness of DMTs for treatment of RRMS has been examined. In a Markov model predicting RRMS course following initiation of DMT comparing relapses and disease regression with costs of natalizumab, dimethyl fumarate, peginterferon beta-1a, subcutaneous interferon beta-1a fingolimod, and glatiramer acetate over 10 years.[11] Incremental cost-effectiveness ratios were estimated for cost per relapse avoided, relapse-free years gained, progression avoided, and progression-free years gained. Costs ranged from $561,177 for natalizumab to $616,251 for glatiramer. In this analysis, natalizumab, dimethyl fumarate, and peginterferon beta-1a were less costly and more effective compared with subcutaneous interferon beta-1a fingolimod and glatiramer acetate. Alemtuzumab and ocrelizumab were not included in this analysis. The actual impact on a particular plan will vary based on drug pricing and other factors affecting drug cost accrual. There is much interest in developing more cost-effectiveness data on DMT use and using this to steer therapy.

Considering discontinuation of DMT is also an issue with managing both the costs and safety of DMT. Withdrawal of first-line DMT after prolonged treatment in middle-aged MS patients with NEDA appears to be safe; those treated with natalizumab need alternative therapy because severe rebound disease activity typically occurs when natalizumab is stopped. Patients greater than 45 years old and on DMT greater than four years with NEDA have a higher likelihood of remaining relapse-free. Patients greater than 60 years old who discontinue DMT tend to remain off DMT. There may be a higher risk of disability progression in those who discontinue therapy. Whether to stop therapy after a period of NEDA requires a discussion between the neurologist and the patient.

Treatment guidelines for MS from the American Academy of Neurology (AAN) and the European Committee for Treatment and Research in MS (ECTRIMS)/European Association of Neurology (EAN) were recently updated.[12,13] Key recommendations from the AAN guideline on DMT in adults with MS are shown in Exhibit 2.[12] The ECTRIMS/EAN guideline recommends that the entire spectrum of DMTs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive assessment and detection of side effects and capacity to address them promptly. For active RRMS, choosing between the wide range of available drugs from the modestly effective to the highly efficacious will depend on the following factors, in discussion with the patient including patient characteristics and comor-

bidities, disease severity/activity, drug safety profile, and drug accessibility. Patient adherence with both the therapy and the required monitoring is also important in the treatment selection and in achieving the best outcomes.

MRI is used for the diagnosis of MS and monitoring of disease activity and DMT efficacy. The Consortium of Multiple Sclerosis Centers has published an MRI protocol and clinical guidelines for diagnosis and follow-up of MS (Exhibit 3).[14] High quality MRI is considered the gold standard; the open MRI devices are not really acceptable for using in MS. Managed care can use these guidelines in developing coverage policy.

Conclusion

There are many effective DMTs for MS with more to come. Optimizing outcomes in this disease requires selecting appropriate therapy, managing adherence, monitoring for adverse events, and modifying therapy as needed to achieve NEDA. Updated guidelines on DMT and MRI use are available to help guide management of MS.

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† Based on a retrospective, cross-sectional, case-control, claims-based analysis of health care utilization and costs, that included narcolepsy patients ≤18 years of age (N=1427) and control subjects (N=4281).[5]

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