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Implementing New Data and Evolving Standards in Advanced Breast Cancer: Individualizing Treatment for Improved Clinical and Economic Outcomes

Hatem Soliman, MD

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http://www.namcp.org/home/education, and then click the activity title.

Summary

Therapies targeting selected genetic mutations and protein expression are available for treating metastatic breast cancer. Three of these are poly (ADR-ribose) polymerase (PARP) inhibitors, a phosphoinositide 3-kinase (PI3K) inhibitor, and a new anti-HER2 agent, which have all been shown to improve progression-free survival and overall survival in the case of the anti-HER2 agent.

Key Points

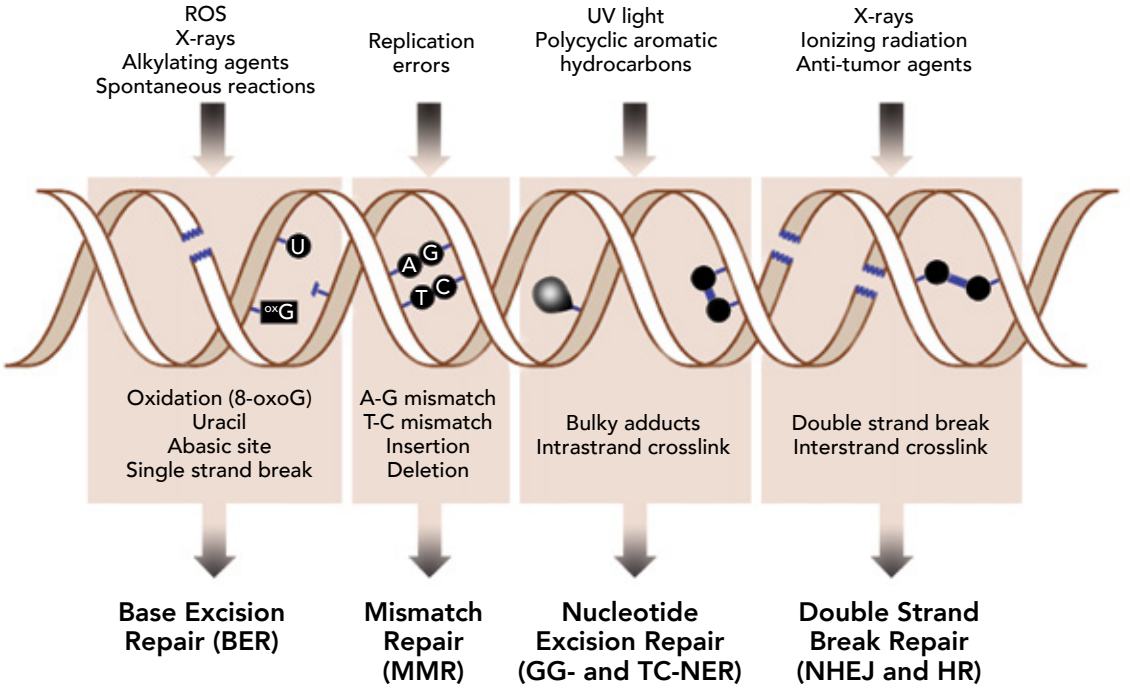
- Olaparib and talazoparib are options for germline BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative breast cancer.
- Germline BRCA testing should be considered in any patient meeting eligibility criteria for on-label olaparib or talazoparib use.
- Alpelisib is the first FDA-approved PIK3CA inhibitor for HR-positive, HER2-negative PIK3CA-mutated metastatic breast cancer.
- Tucatinib is a second-line option for treating HER2-positive disease.

DNA MUTATIONS ARE PRECURSORS TO the development of cancers, including breast cancer. These mutations and damage are routine events (~1 million events per day) and are endogenous (metabolic damage, replication errors) or exogenous (chemicals, ionizing radiation, UV, viruses). A cell must successfully repair DNA damage or it can become old (senescence), die (apoptosis), or immortal (cancer). Luckily, most changes to DNA get fixed by the body's repair system which has built-in redundancy. Repair of these errors is a multistep process that starts with the detection of an abnormality in DNA structure. The abnormal DNA is removed and normal DNA is synthesized. Thus, DNA repair mechanisms maintain genomic stability. Many mechanisms are involved in DNA repair, including base-excision repair, mismatch repair, nucleotide excision repair, single-strand annealing, homologous recombination, and non-homologous end joining (Exhibit 1).

Poly (ADP-ribose) polymerase (PARP) and breast cancer (BRCA) protein are both involved in DNA repair. BRCA is involved in repairing breaks in double-stranded DNA though homologous recombination and PARP is involved in base-excision repair (Exhibit 2). Cells with BRCA gene mutations have nonfunctional homologous recombination but can repair DNA through base-excision repair (non-homologous repair); however, the use of this pathway alone results in genomic instability and increases the risk of developing breast, ovarian, prostate, and pancreatic cancer. BRCA mutations can be germline (present in all cells) or somatic (present only in tumor cells).

PARP inhibitors prevent repair of breaks in single-stranded DNA and induce synthetic lethality in homologous repair-deficient (HRD) cells. In cells with functional homologous recombination, the cell can still repair DNA when PARP inhibition is present. Overall, PARP inhibitors cause synthetic

Exhibit 1: DNA Repair Pathways

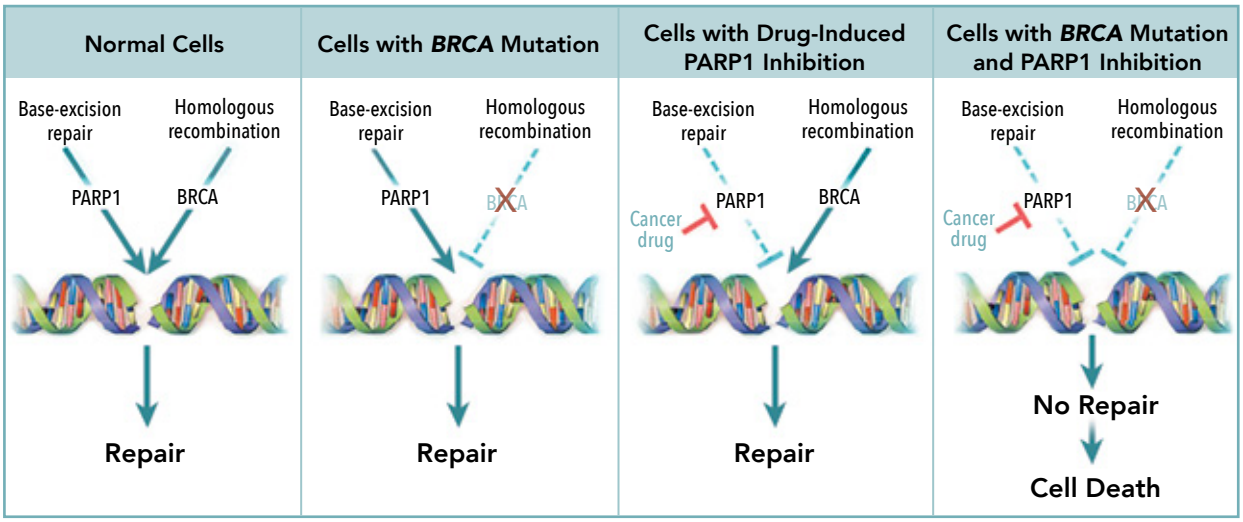


lethality in BRCA-mutated cells and two inhibitors (olaparib and talazoparib) are currently approved for treating germline BRCA-mutated metastatic breast cancer.

The Phase III trial that led to olaparib (Lynparza®) approval in BRCA-mutated breast cancer included subjects who had human epidermal growth factor receptor 2 (HER2) negative, germline BRCA 1/2- mutated metastatic breast cancer treated with no more than two prior lines of chemotherapy. The trial compared olaparib 300mg twice a day to standard of care chemotherapy (capecitabine, eribulin, or vinorelbine). Median progression-free survival (PFS) was significantly longer in the olaparib group than in the standard-therapy group (7.0 months versus 4.2 months; p <0 .001).[1] Overall survival (OS) was not statistically different. The response rate was 59.9 percent in the olaparib group and 28.8 percent in the standard-therapy group. The rate of Grade 3 or higher adverse events was 36.6 percent in the olaparib group and 50.5 percent in the standard-therapy group, and the rate of treatment discontinuation due to toxic events was 4.9 percent and 7.7 percent, respectively. Overall, olaparib monotherapy provided a significant benefit over standard therapy. Median PFS was 2.8 months longer and the risk of disease progression or death was 42 percent lower with olaparib monotherapy than with standard therapy.

Talazoparib (Talzenna®) is the other PARP inhibitor approved for treating germline BRCA-mutated locally advanced or metastatic breast cancer. In the Phase III trial that led to FDA approval, subjects had no more than three prior lines of chemotherapy, but they had to have been treated with taxane and anthracycline. This trial compared talazoparib 1 mg once a day to standard of care chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months versus 5.6 months; $p < 0.001$).[2] The interim median hazard ratio for death was 0.76 ($p = 0.11$). The objective response rate (ORR) was higher in the talazoparib group than in the standard-therapy group (62.6% versus 27.2%; $p < 0.001$). Hematologic Grade 3 and 4 adverse events (primarily anemia) occurred in 55 percent of the patients who received talazoparib and in 38 percent of the patients who received standard therapy. Nonhematologic Grade 3 adverse events occurred in 32 percent and 38 percent of the patients, respectively. Alopecia appears more common with talazoparib compared to olaparib. In this trial, patient-reported outcomes favored talazoparib over chemotherapy; significant

Exhibit 2: PARP Inhibitor Mechanism of Action



overall improvements and significant delays in the time to clinically meaningful deterioration according to both the global health status quality of life and breast symptoms scales were observed. Like olaparib, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to PFS.

PARP inhibitors are being studied in combination with programmed death one (PD-1) checkpoint inhibition immunotherapy. Niraparib, another PARP inhibitor approved for other BRCA-mutated cancers, in combination with pembrolizumab produced good results in patients with metastatic triple- negative breast cancer (TNBC) who had somatic BRCA mutations and PD-ligand one (PD-L1) expression.[3] This trial showed that this combination may be a good choice for treating patients with both HRD and PD-L1 expression. Other trials of PARP inhibitor and immunotherapy are ongoing.

BRCA mutation testing in patients with metastatic breast cancer for treatment selection is not as straight forward as risk-stratified testing for prevention of BRCA-related cancers. In metastatic TNBC approximately 14.6 percent of patients are found to have deleterious mutation, with 11.2 percent having BRCA1/2 mutations.[4] In Stage I to III unselected breast cancer patients, 10.7 percent had deleterious mutation, with 6.5 percent being BRCA 1/2 mutation positive.[5] Positive family history for breast cancer suggestive of BRCA mutation enriches for positivity but will miss a portion of patients who could benefit from PARP inhibitors. Germline testing for BRCA mutation in HER2-negative metastatic breast cancer patients is a reasonable strategy because an effective therapy is available.

Overall, the cost of olaparib and talazoparib ranges from $13,000 to $15,000 per year, which can be cost prohibitive for patients without prescription drug coverage. These agents still have significant toxicity which must be communicated to patients; however, the toxicity is not much more so than standard of care chemotherapy, and these oral agents are much easier for patients to take. For now, PARP inhibitors should be used only in germline BRCA 1/2- mutated breast cancer patients as a line of therapy like chemotherapy. There is a need for more research to identify additional biomarkers for PARP inhibitor benefit to improve the cost/benefit ratio.

Mutations in the PI3K gene are among the most frequent in breast cancer, occurring in 40 percent of estrogen receptor (ER)-positive breast cancer cases. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and protein kinase B (Akt) signaling, cellular transformation and the generation of tumors in in vitro and in vivo models. Alpelisib (Piqray®) is an inhibitor of PI3K with inhibitory activity predominantly against PIK3CA and is the first in class agent approved by the FDA (2019). Many more PI3K inhibitors are under investigation. It is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR) positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. In a cohort of patients with PIK3CA-mutated cancer, PFS was 11.0 months in the alpelisib-fulvestrant group, as compared with 5.7 months in

the placebo-fulvestrant group ($p < 0.001$).[6] The most frequent adverse events of Grade 3 or 4 were hyperglycemia (36.6% in the alpelisib-fulvestrant group versus 0.7% in the placebo-fulvestrant group) and rash (9.9% versus 0.3%). Diarrhea of Grade 3 occurred in 6.7 percent of patients in the alpelisib-fulvestrant group, as compared with 0.3 percent of those in the placebo-fulvestrant group; no diarrhea of Grade 4 was reported. The percentages of patients who discontinued alpelisib and placebo owing to adverse events were 25.0 percent and 4.2 percent, respectively. To improve patient adherence with alpelisib, significant patient education on adverse events and their management is required.

Testing for PI3K mutations can be done with tumor-based (Foundation One CDX) or circulating tumor DNA (ctDNA, Guardant360) tests. Both were predictive of therapy response, but ctDNA may be the better choice. The testing algorithm specifies if ctDNA is negative, the clinician should consider tissue testing. PI3K mutation testing should be considered in HR-positive HER2-negative metastatic breast cancer testing to guide therapy selection.

In about 1 in 5 women with breast cancer, the tumor cells have too much of HER2, a growth-promoting protein, on their surface. Tucatinib (Tukysa®), an oral tyrosine kinase inhibitor with potent selectivity for HER2, was FDA approved in 2020. It is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2 regimens in the metastatic setting. This agent may have an advantage of reduced diarrhea and rash because of its selectivity compared to other less selective HER2 tyrosine kinase inhibitors. PFS at one year was 33.1 percent in the tucatinib/trastuzumab/capecitabine group and 12.3 percent in the placebo/trastuzumab/capecitabine group ($p < 0.001$), and the median duration of PFS was 7.8 months and 5.6 months, respectively.[7] Overall survival (OS) at two years was 44.9 percent in the tucatinib-combination group and 26.6 percent in the placebo-combination group ($p = 0.005$), and the median OS was 21.9 months and 17.4 months, respectively. Among the patients with brain metastases, PFS at one year was 24.9 percent in the tucatinib-combination group and 0 percent in the placebo-combination group ($p < 0.001$), and the median PFS was 7.6 months and 5.4 months, respectively. Common adverse events in the tucatinib group included diarrhea, palmar-plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Diarrhea and elevated aminotransferase levels of Grade 3 or higher were more common in the tucatinib-combination group than in the placebo-combination group. In heavily pretreated patients with HER2-positive metastatic breast cancer, including those with brain metastases, adding tucatinib to trastuzumab and capecitabine resulted in better PFS and OS outcomes than adding placebo. This triple combination is now a National Comprehensive Cancer Network (NCCN) Category 1 recommendation for second-line treatment for those with HER2 positive metastatic breast cancer.[8]

Conclusion

For germline BRCA-mutated HER2-negative breast cancer, olaparib and talazoparib are therapeutic options. Germline testing should be considered in any patient meeting eligibility criteria for on-label PARP inhibitor use. Alpelisib is the first FDA-approved PIK3CA inhibitor for HR-positive, HER2-negative PIK3CA-mutated metastatic breast cancer. Tucatinib will be another tool in treating HER2-positive disease, likely in later line after treatment with pertuzumab and antibody drug combinations.

Hatem Soliman, MD is an Associate Member in the Breast and Immunology Departments and Medical Director of the Clinical Trials Office at Moffitt Cancer Center in Tampa, FL.

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Patient-Focused Treatment Decisions in Advanced Non-Small Cell Lung Cancer (NSCLC): Expert Strategies in an Evolving Treatment Paradigm

Mark A. Socinski, MD

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Summary

Immunotherapy, alone or in combination with chemotherapy, is the treatment of choice for most patients with NSCLC. For the smaller group who have targetable tumor mutations, various targeted therapies are the first-line therapy of choice. Both immunotherapy and targeted therapies have improved outcomes in this disease that is too often only diagnosed once advanced.

Key Points

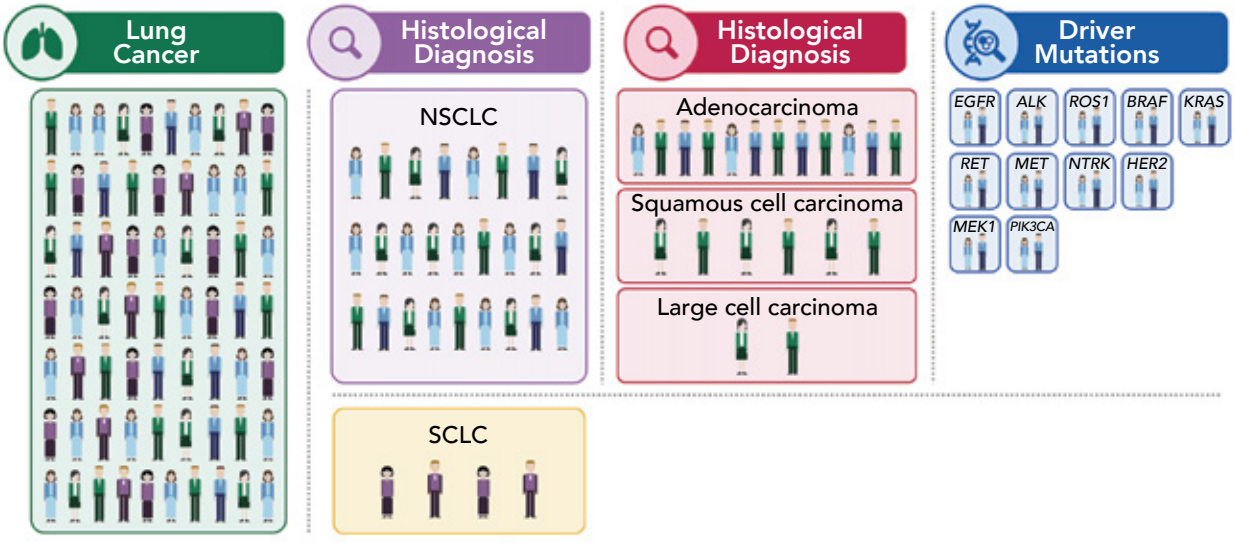
- Histology and selected genetic mutations drive therapeutic choices.
- Targeted therapy is first line for those with selected genetic mutations.
- Platinum-based chemotherapy doublets plus immunotherapy is standard for most patients.
- Anti-angiogenic therapy can enhance the impact of immunotherapy.
- Immunotherapy alone a first-line option in selected patients.

LUNG CANCER IS THE MOST COMMON cause of cancer-related mortality in the United States (U.S.) and accounts for more deaths than breast, prostate, and colorectal cancers combined. The median age at diagnosis is 70 years, and the major risk factor is smoking. Unfortunately, 25,000 to 30,000 never-smoking Americans will develop lung cancer this year. Lung cancer is typically diagnosed at the later stages of the disease because lung cancer screening is not routinely practiced. Histologically and molecularly, lung cancer is a very heterogeneous disease, with non-small cell lung cancer (NSCLC) the most common histological type (Exhibit 1).[1,2]

The current standard of care for diagnosis of lung cancer is a core needle biopsy or fine needle aspiration for procurement of tissue for histologic and genomic testing. NSCLC, particularly adenocarcinoma, is genomically diverse, so comprehensive genomic testing at initial diagnosis is standard of care. Programmed death ligand one (PD-L1) testing for immunotherapy eligibility is standard of care but meaningless until genomic results, which take precedence in treatment selection, are known. Genomic testing is especially important because survival is as much as a year better in those with targetable mutations who receive appropriate targeted therapy compared with those who do not receive targeted therapy for a known mutation, or who have no targetable mutations.[3]

Circulating tumor DNA (ctDNA) detection by liquid biopsy of blood or urine is the next evolution in genomic testing. Cancer-associated genetic alterations can be detected in ctDNA, including point mutations, copy number variations, chromosomal rearrangements, and methylation patterns.[4] Circulating tumor cells can also be used to evaluate medication induced genetic changes which lead to therapy resistance.[5] Exhibit 2 provides

Exhibit 1: Advanced Lung Cancer is a Heterogeneous Disease[1,2]



NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer

a summary of the benefits of ctDNA testing. A large cell-free DNA (cfDNA) study in previously untreated metastatic NSCLC found that a validated comprehensive cfDNA test identifies guideline-recommended biomarkers at a rate at least as high as standard of care tissue genotyping, with high tissue concordance, more rapidly and completely than tissue-based genotyping.[6]

Tissue biopsy remains necessary for diagnosis and staging in lung cancer, but tissue procurement often has its limitations, both biologically and practically. At this time, tissue and plasma-based ctDNA testing should be viewed as complementary. Understanding the strengths and limitations of both are necessary for optimal patient management.

The treatment of advanced or metastatic NSCLC has evolved from chemotherapy in the 1980s and 1990s to targeted therapy aimed at the various genetic mutations which have been identified as disease drivers and the addition of anti-angiogenics to chemotherapy in the 2000s. Checkpoint inhibition immunotherapy was introduced in 2015. Combinations of chemotherapy and anti-angiogenics with checkpoint inhibitors beginning in 2017 are the most recent advances.

If a patient with advanced NSCLC is identified as having a targetable tumor mutation, then targeted therapy is the first-line treatment.[7] Approximately 17 percent of NSCLC cases are found to have an epidermal growth factor receptor (EGFR) mutation. Osimertinib (Tagrisso®) is the tyrosine kinase inhibitor (TKI) of choice for common EGFR mutations (exon 19 and L858R).[7] Afatinib (Gilotrif®) is approved for uncommon mutations (G719X, L816Q, S786I). Importantly, there currently is no approved TKI for exon 20 insertion mutations.

Anaplastic lymphoma kinase (ALK) rearrangements are oncogenic driver mutations for a distinct subset of NSCLC (~5% of cases). Those with ALK rearrangements tend to be younger (median age 52 years), never or light smokers, and with advanced disease at presentation (pleural/pericardial effusion, multiple lesions/sites, and central nervous system metastases). Crizotinib (Xalkori®) was the first targeted agent for this population, but resistance developed quickly. Alectinib (Alecensa®), brigatinib (Alunbrig®), or lorlatinib (Lorbrena®), all second-generation TKIs, are the preferred first-line therapy for patients with newly diagnosed, metastatic ALK-positive NSCLC.[7] Second-generation ALK TKIs are highly effective in improving median progression-free survival (PFS) in the first-line setting. Other less common mutations can also be targeted (Exhibit 3).[7]

If a patient has no oncogenic driver, checkpoint inhibitor immunotherapy, with or without chemotherapy, is the treatment option, depending on the expression of PD-L1. PD-L1 expression testing should be performed on all initial biopsies and results typically take a few days. Ideally, final therapeutic decisions should not be made until full genomic information is available because initial immunotherapy followed by a TKI exposes patients to undue risks. PD-L1 expression of tumor proportion score (TPS) 50 percent or higher is associated with

Exhibit 2: Summary of Benefits of Liquid Biopsy in a Clinical Setting

Tissue	cfDNA
Invasive • Costs • Complications • Delays	Non-Invasive Blood Draw
Qualitative	Quantitative
Limited by sample collection and heterogeneity	Not limited by sample collection and heterogeneity (tumor summary); real-time monitoring
Total Time to Treatment: 3 to 8 weeks	Total Time to Treatment: ≤ 14 days

Exhibit 3: Targeted Therapies for Select Driver-Positive NSCLCs[7]

Driver	First Line	Subsequent
ROS1 fusion	Crizotinib Entrectinib Ceritinib	Lorlatinib Entrectinib
RET fusion	Selpercatinib Pralsetinib Cabozantinib Vandetanib	Selpercatinib Pralsetinib Cabozantinib Vandetanib
NTRK fusion	Larotrectinib Entrectinib	Larotrectinib Entrectinib
BRAF V600E	Dabrafenib + Trametinib	Dabrafenib + Trametinib
MET ex14/amp	Crizotinib Capmatinib	Cabozantinib
HER2 mutation	Ado trastuzumab emtansine (TDM1) Fam-trastuzumab deruxtecan	

favorable outcomes with immunotherapy.

The first immunotherapy approved for advanced NSCLC was pembrolizumab (Keytruda®). In patients who had greater than 50 percent expression of PD-L1 on their tumor, pembrolizumab improved overall survival (OS) and PFS compared to standard platinum doublet chemotherapy.[8] In the long-term follow-up data from this study, the median OS was 30.0 months compared to 14.2 months with chemotherapy. Atezolizumab (Tecentriq®) has also been studied as monotherapy for first-line treatment of NSCLC. In the subgroup of patients with EGFR and ALK wild-type tumors who had the highest expression of PD-L1 (≥ 50%), the median OS was longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months versus 13.1 months; hazard ratio for death, 0.59; $p = 0.01$).[9] Thus, pembrolizumab or atezolizumab is a first-line treatment for those patients without targetable mutations whose tumors express PD-L1 ≥ 50 percent.[7] Either of these agents or nivolumab/ipilimumab can also be combined with platinum-based doublet chemotherapy (chemo-immunotherapy).[7]

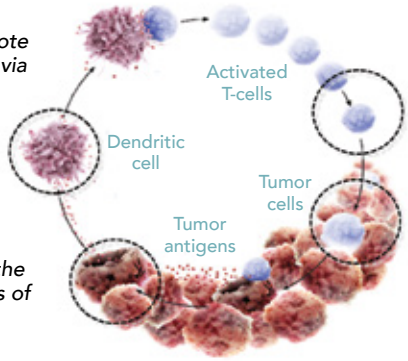
Immunotherapy has also been studied in those with PD-L1 expression of 1 to 49 percent. Pembrolizumab monotherapy is an option in these patients; however, most clinicians prefer using either it, atezolizumab, or nivolumab/ipilimumab in combination with chemotherapy because of 20 to 25 percent better overall response rates compared to immunotherapy alone.

Clinicians should especially consider chemo-immunotherapy in bulky, symptomatic disease. Many clinicians do not recommend immunotherapy alone for patients with < 50 percent PD-L1 expression, but this may be an option in a frailer patient. Treatment-related adverse event incidence is lower with immunotherapy compared with chemotherapy.

Exhibit 4: Rationale for the Combination of Anti-PD-L/L1 Agents + Bevacizumab + Chemotherapy[10-15]

- In addition to its known anti-angiogenic effects, bevacizumab's inhibition of VEGF has immune modulatory effects.

Inhibition of VEGF can promote T-cell priming and activation via dendritic cell maturation



Normalization of the tumor vasculature through VEGF inhibition increases T-cell tumor infiltration

Tumor cell killing by chemotherapy may expose the immune system to high levels of cancer cell antigens

VEGF blockade can establish an immune-permissive tumor microenvironment by decreasing myeloid-derived suppressor cell and regulatory T cell populations

- T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression.

Exhibit 5: Tumor and Immune Biomarkers being Evaluated to Predict Better Outcomes to Immunotherapy[17]

Tumor Antigens

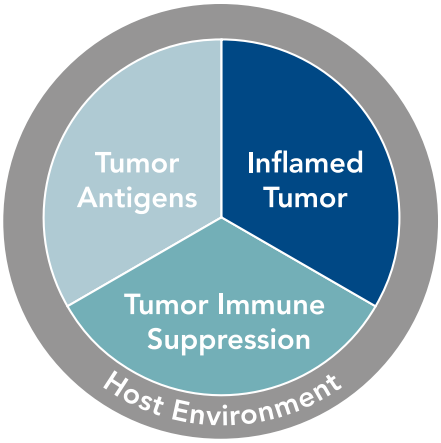
- Biomarkers indicative of hypermutation and neo-antigens may predict response to IO treatment.

Examples:
– TMB, MSI-High, Neo-Antigens

Inflamed Tumor Microenvironment

- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to IO treatment

Examples:
– PD-L1, Inflammatory Signatures



Tumor Immune Suppression

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4 to inform new IO targets and rational combinations

Examples:
– Tregs, MDSCs, IDO, LAG-3

Host Environment

- Biomarkers which characterize the host environment, beyond tumor microenvironment, may predict response to IO treatment

Examples:
– Microbiome, Germline Genetics

IO = immunotherapy; IDO = indoleamine-2,3 dioxygenase; LAG-3 = lymphocyte activation gene-3; MDSCs = myeloid-derived suppressor cells; MSI-High = microsatellite instability high; TMB = tumor mutational burden; Tregs,= regulatory T cells

There is a rationale for combining immunotherapy, chemotherapy, and anti-angiogenics (bevacizumab) in non-squamous NSCLC (Exhibit 4).[10-15] The critical role of angiogenesis in promoting tumor growth and metastasis has been well established scientifically, and consequently blocking this pathway as a therapeutic strategy has demonstrated great clinical success for the treatment of cancer, but it has also been discovered that bevacizumab has effects in reprogramming the tumor milieu from an immunosuppressive to an immune permissive microenvironment in human cancers.[10] Atezolizumab and pembrolizumab have been studied in these triple combinations and are recommended options in the National Comprehensive Cancer Network (NCCN) guidelines.[7] For example, the addition of atezolizumab to bevacizumab plus

chemotherapy significantly improved PFS (8.3 versus 6.8 months) and OS (19.2 versus 14.7 months) among patients with metastatic nonsquamous NSCLC compared to bevacizumab/chemotherapy, regardless of PD-L1 expression and EGFR or ALK genetic alteration status.[16]

Overall, immunotherapy has revolutionized the treatment of advanced NSCLC and is part of the treatment regimen for most patients with NSCLC. Both monotherapy as well as combinations with chemotherapy have changed outcomes. There are subsets of advanced NSCLC patients that may derive great benefit, particularly in combination with bevacizumab. Although PD-L1 is an established (but not perfect) biomarker, other biomarkers are needed to help identify patients at the time of diagnosis who will derive great benefit from immunotherapy. Exhibit 5 illustrates some biomarkers which are under investigation.[17]

Conclusion

Advanced NSCLC is an increasingly complex disease. Histology and selected genetic mutations drive therapeutic choices. Platinum-based doublets, in combination with immunotherapy is standard treatment for most patients with advanced NSCLC. Anti-angiogenic therapy appears to enhance the impact of immunotherapy and may be added to the regimen. Immunotherapy alone is a first-line option in selected patients.

Mark A. Socinski, MD is the Executive Medical Director and Member of the Thoracic Oncology Program at the Florida Hospital Cancer Institute in Orlando, FL.

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New Frontiers in the Treatment and Management of Chronic Lymphocytic Leukemia: Expert Perspectives on Emerging Therapies and MRD

John N. Allan, MD

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

Summary

Treatment of chronic lymphocytic leukemia (CLL) has shifted from chemotherapy or chemoimmunotherapy to oral novel agents. These agents are each having an impact on progression-free survival and when used sequentially, once disease recurs, allow patients to continue to survive.

Key Points

- CLL treatment has shifted away from chemotherapy or chemoimmunotherapy-based approaches.
- Front-line targeted options include Bruton's tyrosine kinase (BTK) inhibitor continuous therapy or venetoclax-based fixed-duration options.
- Phosphoinositide 3- kinase (PI3K) inhibitors are used for treating relapsed/refractory CLL.
- Residual disease monitoring and decision-making are still not recommended in routine practice but have value in prognosticating whether to stop therapy.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a chronic lymphoproliferative disorder of monoclonal B cells. There are approximately 20,000 new cases diagnosed every year in the United States (U.S.) and an estimated 4,060 deaths.[1,2] In 2017, there were an estimated 186,422 people living with CLL in the U.S.[2]

There are now numerous treatment options for CLL, especially chemotherapy-free regimens. The numerous options lead to long in-depth discussions between clinicians and patients about which option to choose. There are fixed duration regimens and regimens that are continued until progression. Each option has adverse events which must be considered. Patients may need some time to discuss the options with their family before making a choice.

Chemotherapy regimens are now used rarely since chemotherapy-free regimens have come along. The chemotherapy-free regimens are oral, are much better tolerated, and produce more durable responses. There is a small subset of patients who may derive long-term survival benefits from chemoimmunotherapy approaches. This subset is a younger patient with low-risk cytogenetics.

FDA-approved novel targeted agents in CLL are mechanistically diverse and include ibrutinib (first-generation Bruton's tyrosine kinase [BTK] inhibitor), acalabrutinib (second- generation BTK inhibitor), obinutuzumab (anti-CD-20 monoclonal antibody), idelalisib (PI3K inhibitor), duvelisib (PI3K inhibitor), and venetoclax (B-cell lymphoma two [BCL-2] inhibitor). The agents now form

Exhibit 1: NCCN Suggested Treatment Regimens[6]

Type	First-Line	Second-Line and Subsequent
CLL with del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab Ibrutinib Venetoclax ± obinutuzumab	Acalabrutinib (category 1) Ibrutinib (category 1) Venetoclax ± rituximab (category 1) Duvelisib Idelalisib + rituximab Venetoclax
CLL without del(17p)/TP53 mutation Frail patient with significant comorbidity or aged ≥ 65 or younger with significant comorbidities (CrCl < 70 mL/min).	Acalabrutinib ± obinutuzumab (category 1) Ibrutinib (category 1) Venetoclax ± obinutuzumab (category 1)	Acalabrutinib (category 1) Ibrutinib (category 1) Venetoclax ± rituximab (category 1) Duvelisib Idelalisib + rituximab
CLL without del(17p)/TP53 mutation Patient aged ≤ 65 without significant comorbidities.	Acalabrutinib ± obinutuzumab (category 1) Ibrutinib (category 1) Venetoclax ± obinutuzumab	Acalabrutinib (category 1) Ibrutinib (category 1) Venetoclax ± rituximab (category 1) Duvelisib Idelalisib + rituximab

the backbone of treating CLL with primarily oral agents; the exception is obinutuzumab.

The BTK inhibitors improve event-free survival and progression-free survival (PFS) in both the frontline and subsequent line therapy.[3-5] These agents are given continuously until disease progression. Ibrutinib was approved by the FDA in 2014 and is a first-line therapy in the National Comprehensive Cancer Network (NCCN) guidelines (Exhibit 1).[6] In the five-year follow-up of continued use of ibrutinib in the frontline setting, the PFS was 70 percent in the ibrutinib group compared to 12 percent for chlorambucil.[3] Acalabrutinib was the second BTK inhibitor to be approved for use in November 2019. It is a highly selective, potent kinase inhibitor that was designed to minimize off-target activity. Depending on the type of CLL and patient factors, it may be given with obinutuzumab (Exhibit 1). Its greater selectivity is expected to reduce major adverse events seen with ibrutinib. Compared to ibrutinib, there are some overlapping toxicities, including mild diarrhea, mild bleeding, and infections. A consideration in choosing a BTK inhibitor is that they are continued until progression. This could be an issue for a 50-year-old patient who might prefer a fixed duration of therapy compared to a 70-year-old who would be on continuous therapy fewer years.

Venetoclax, approved in 2015, is highly active in CLL. It is used in combination with obinutuzumab for first-line therapy and alone or with rituximab (off-label) for second-line and later fixed-duration therapy (typically one year). Tumor lysis syndrome (TLS) is an important, but manageable risk with this agent. TLS is hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia because of rapid destruction of cancer cells. Slow dose increases over a month and good hydration significantly reduce the risk. Other toxicities of note with venetoclax are neutropenia and gastrointestinal disturbances. Venetoclax plus obinutuzumab for one year produces a similar PFS at three years compared to BTK inhibitor continual therapy. Fixed- duration therapy with this combination may be of benefit for a younger patient who does not want to be on long-term therapy, or for an older patient with financial issues. Monitoring must be done frequently, causing some patients to have difficulty complying with the requirements. Optimal duration is another issue – the trials were for one-year (frontline) and two-year

Exhibit 2: Overview of Current CLL MRD Testing Platforms[10]

	Multi-Color Flow Cytometry	RQ-PCR	High Throughput Sequencing
Sensitivity (LOD)	Four-color flow: confirmed 10^{-4} Six-color flow: reported 10^{-5}	Confirmed 10^{-5}	Reported 10^{-6}
Method	Surface antigen detection by different antibody combinations, e.g., CD%/CD19/CD20/cd43/CD79b/CD81	Detention of disease-specific IGHV using patient specific primers.	Detection of disease-specific IGH sequences after amplification of all IGH gene segments using consensus primers
Fresh material required?	Yes, samples must be < 48 hours old	No, but DNA extraction preferably < 48 hour.	
Standardized protocol?	Yes	Yes	Ongoing
Advantages	Directly quantitative Widely available Results quickly available Highly standardized assay	High sensitivity No live leukocytes required	High sensitivity No live leukocytes required Multiple mutations can be detected in one test
Disadvantages	Four-color flow: lower sensitivity Samples must be fresh	Not directly quantitative Requires baseline sample Time and labor intensive Expensive	Not directly quantitative Requires baseline sample Less widely available Expensive

LOD = Lower limit of detection

(relapse) durations; clinicians are still determining the best duration.

The first-line treatment choice between a BTK inhibitor and venetoclax is currently based on a patient's age and comorbidities, disease biology, and status [treatment naïve (TN), relapsed/refractory (R/R)]. In addition, the preference of patients for fixed-duration or continuous therapy, the financial impact of a given choice, and potential adherence issues also must be considered.

Idelalisib and duvelisib are both PI3K inhibitors that are FDA-approved for treating relapsed/refractory CLL. Duvelisib is approved for relapsed/refractory CLL after two or more prior lines of therapy and is used as monotherapy. Idelalisib has the same indication and is used in combination with rituximab. The PI3K inhibitor use is hampered by toxicity (colitis, pneumonitis, diarrhea, infections, hepatotoxicity) and modest effectiveness compared to other classes.[7] They still have a potential role in those with specific comorbidities (atrial fibrillation, renal insufficiency) that contraindicate use of other agents.

Since most patients with CLL will eventually relapse after responding to therapy, clinicians must use multiple lines of therapy. How best to sequence the various agents is still a matter of debate. If a patient's disease progresses on a BTK inhibitor, they could be switched to venetoclax, which is a studied and successful option.[8] Venetoclax appears to be a better option than idelalisib as second-line therapy after a BTK inhibitor and may be better tolerated.[9]

Therapeutic options for CLL patients will likely improve further in the coming years. Additional agents under investigation in the current drug classes include zanubrutinib, vecabrutinib, ARQ-31, umbralisib, MEI-401, and cirmtuzumab. Zanubrutinib (Brukinsa®), a selective BTK inhibitor that is under investigation for CLL, is currently only approved for treating mantle cell lymphoma. It is included in the NCCN guidelines as another recommended regimen for patients with intolerance or contraindication to the other BTK inhibitors.[6] Umbralisib has been submitted to the FDA for approval for marginal zone and follicular

lymphoma and may be better tolerated than the already approved PI3K agents.

In CLL, there is a growing interest in minimal residual disease (MRD) monitoring to assess therapy response and determining duration of therapy. Undetectable MRD (uMRD) is defined as $< 10^{-4}$ detectable leukemic cells in peripheral blood or bone marrow.[6] The standardized and most applied methods to assess MRD in CLL are based on flow cytometry and real-time quantitative polymerase chain reaction (RQ-PCR) (Exhibit 2).[10] High throughput sequencing has some advantages, including a potentially higher sensitivity compared to the standardized methodologies. From a clinical point of view, MRD quantification in CLL has been shown to be an independent prognostic marker of PFS with the novel agents. Thus, beside a durable disease control desirable particularly for older patients and/or for those with comorbidities, an MRD-negative complete remission is becoming a realistic prospect for CLL patients to obtain a long-lasting eradication and possibly cure of the disease. MRD has potential to guide de-escalation of therapy in CLL patients. For example, those with uMRD after three chemoimmunotherapy cycles do just as well as MRD-positive patients after three cycles, but who do not achieve uMRD until six cycles. If using continual BTK inhibitors, MRD does not predict outcome. If using a venetoclax-based therapy, uMRD can identify patients that it appears safe to stop in terms of PFS (i.e., de-escalation). Looking toward the future, several important studies are incorporating MRD into treatment decision-making. Reemergence from MRD negativity is not a recognized indication for retreatment and is a question being evaluated.

Conclusion

CLL treatment has shifted away from chemotherapy and chemoimmunotherapy-based approaches. Frontline targeted options include BTK inhibitor continuous therapy or venetoclax-based fixed-duration options; head-to-head studies of these two approaches are in development. PI3K inhibitors still have a role with umbralisib holding promise to demonstrate improved safety and tolerability which can lead to improved efficacy. MRD monitoring and decision-making are still not recommended in routine practice but have value in prognosticating for patients considering stopping therapy.

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Recent Developments in the Treatment and Management of Psoriatic Arthritis

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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

Psoriatic arthritis occurs in up to 40 percent of people with psoriasis and can have serious debilitating effects on the peripheral joints, spine, tendon insertions, and fingers. There are a growing number of biologic and oral treatments which stop the disease progression, lessen pain, and protect joints by targeting the underlying inflammatory pathology.

Key Points

- It is important to start treatment early to limit the joint damage.
- Communication is key to achieving goals and promoting good outcomes.
- Therapy should be monitored and adjusted often.
- Options include traditional oral medications, anti-TNF inhibitors, and multiple newer agents, which target IL-12/23, IL-23, IL-17, JAK, T-cell co-stimulation, and phosphodiesterase4 (PDE4) inhibitors.
- Methotrexate may not be disease modifying in psoriatic arthritis.

PSORIATIC ARTHRITIS (PsA) OCCURS IN 0.05 to 0.25 percent of the United States (U.S.) population; it occurs in 6 to 40 percent of those with psoriasis.[1] Psoriatic skin lesions generally appear about 10 years before arthritis symptoms. The cumulative incidence following psoriasis diagnosis is 1.7 percent at five years, 3.1 percent at 10 years, and 5.1 percent at 20 years.[2] The amount of skin affected by psoriasis has no bearing on whether a patient will develop PsA or how bad the PsA will be. This arthritis primarily affects the peripheral joints, spine, tendon insertions, and fingers. The mean age at diagnosis is 43 years, with equal occurrence in males and females. It is frequently underdiagnosed in patients with psoriasis by dermatologists. About 15 percent of those with psoriasis followed by dermatologists have undiagnosed PsA.[3]

PsA, like psoriasis, is a heritable polygenic disease.[4] Heritability of PsA is three to five times higher than that of psoriasis; both are associated with Class I major histocompatibility complex alleles.[5] In PsA, human leukocyte antigen (HLA)-B38 and HLA-B39 are associated with peripheral arthritis, whereas HLA-B27 is associated with spinal involvement.[6] Association studies have identified shared risk alleles in patients with psoriasis and in those with PsA, including interleukin (IL)-12A, IL-12B, IL-23R, and genes regulating nuclear factor kappa B.

In genetically predisposed patients, an environmental trigger such as infection or mechanical stress initiates a chronic inflammatory process primarily involving the joints and skin, resulting in the production of IL-23, which is a central cytokine in the pathogenesis of PsA and psoriasis.[7] Enthesitis, which is inflammation at the site where ligaments, tendons, and joint capsules attach to the bone, is the prominent pathologic lesion in PsA, in contrast to synovitis in rheumatoid arthritis (RA). IL-23 secretion leads to the production of IL-17, IL-22, and tumor necrosis factor (TNF)-alpha, which promotes inflammation, bone loss with erosions, and osteoproliferation.[7] The newer therapies for PsA target IL-23 and IL-17, rather than nonspecific inhibition of the immune system like the traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate.

Exhibit 1: Psoriatic Arthritis Treatment Options

Anti–TNF-α	Not Disease-Modifying	Newer Therapies
• Etanercept	• NSAIDs	• Ustekinumab (IL-12/23)
• Adalimumab	• Corticosteroid injections	• Secukinumab (IL-17A)
• Infliximab	• Corticosteroids (oral)	• Abatacept (CTLA4-Ig)
• Golimumab		• Apremilast (PDE4)
• Certolizumab	**Nonpharmacologic Measures**	• Ixekizumab (IL-17)
	• PT and OT	• Tofacitinib (JAK3)
Traditional DMARDs	• Obesity control	• Guselkumab (IL-23)
• Methotrexate	• Depression treatment	**Under Investigation**
• Leflunomide	• Cardiovascular risk factor modification	• Brodalumab (IL-17R)*
• Sulfasalazine	• Smoking cessation	• Risankizumab (IL-23)*
• Cyclosporine	• Microbiome modification	• Tildrakizumab (IL-23)*

CTLA4 = cytotoxic T lymphocyte associated (molecule)-4; Ig = immunoglobulin; JAK = janus kinase; PDE = phosphodiesterase; PT = physical therapy; OT = occupational therapy.
*Currently FDA-approved for treating moderate to severe plaque psoriasis. Under study for psoriatic arthritis

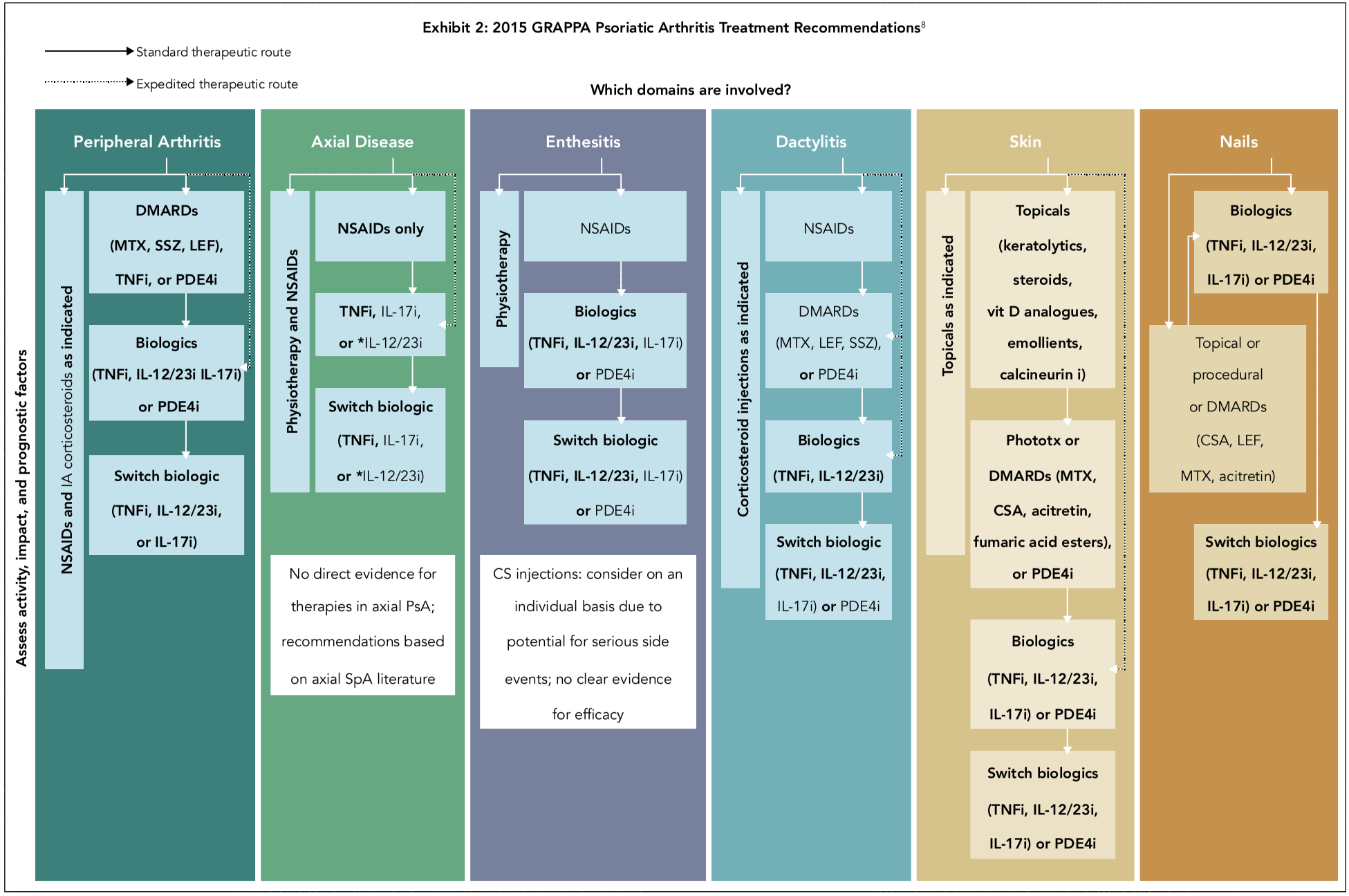
Exhibit 1 shows the multitude of treatment options for PsA. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2015 treatment recommendations are shown in Exhibit 2.[8] These guidelines provide a more tailored treatment selection based on the primary involved area of the body and provide expedited therapeutic routes. It is important to note that guselkumab, an IL-23 targeted agent, has been FDA-approved since this guideline was published.

The American College of Rheumatology (ACR) and the National Psoriasis Foundation updated their guidelines in 2018.[9] These guidelines are somewhat controversial because they rely on low to moderate grade evidence and recommend TNF inhibitors or traditional oral DMARDs as first-line therapy. For treatment-naïve patients with active PsA, the use of a TNF inhibitor biologic or traditional oral DMARD is recommended over an IL-17 inhibitor or an IL-12/23 inhibitor biologic.[9] An IL-17 or IL-12/23 inhibitor may be used instead of TNF inhibitors in patients with severe PsA or contraindications to TNF inhibitors and may be used instead of oral DMARDs in patients with severe PsA. An IL-17 inhibitor is recommended over an IL12/23i biologic. The IL-12/23 inhibitors may be used in patients who have concomitant inflammatory bowel disease, or who desire less frequent drug administration. Guselkumab is also not included in these guidelines. The guidelines do point out that because they rely on very low to moderate evidence there needs to be active discussion between the physician and patient on a treatment choice.

Traditional DMARDs include methotrexate, leflunomide, sulfasalazine, and cyclosporine. While these agents have been shown to be disease modifying in RA, they have not been shown to be disease modifying in PsA. The advantages of these agents are long years of experience with them, they are helpful in some cases, they are inexpensive, and they prevent antibody generation with biologic therapy. A placebo-controlled trial in active PsA found no evidence for methotrexate improving synovitis.[10] A cohort analysis showed that patients on methotrexate for up to four years had significantly higher radiographic progression than those on TNF inhibitors.[11] A small study using high-resolution micro computerized tomographic imaging showed that neither therapy stops progression of bone apposition in metacarpophalangeal joints, which suggests that MTX is not disease modifying in PsA.[12] In addition to lack of disease modifying benefit, there is a lack of high-quality data to support the use of traditional DMARDs, and they are typically dosed suboptimally in real-world practice.

The TNF inhibitors all appear to have similar efficacy in treating PsA. They produce a 58 percent ACR20 (20% improvement in composite of symptoms and disease scores) compared to 8 to 14 percent placebo response rate.[14] For RA, the

Exhibit 2: 2015 GRAPPA Psoriatic Arthritis Treatment Recommendations[8]



*Open-label data available
Text not bolded identifies conditional recommendations for drugs that do not currently have regulatory approvals or for which recommendations are based on abstract data only.
CS = corticosteroid; CSA = cyclosporin A; DMARD = disease-modifying antirheumatic drug; i = inhibitor; IA = intra-articular; GRAPPA = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; IL-12/23 i= interleukin-12/23 inhibitor; IL-17i = interleukin-17 inhibitor; LEF = leflunomide; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; PDE4i = phosphodiesterase-4 inhibitor; phototx = phototherapy; SSZ = sulfasalazine; TNFi = tumor necrosis factor inhibitor; vit = vitamin.

Exhibit 3: Challenges in Translating Clinical Trial Evidence[28-30]

Overload of information

Limited ability and motivation to sustain attention and deliberation.

- Health literacy and numeracy
- Age and general health impair cognition
- Poverty and health literacy influence risk perception
- Value of information to an individual patient (salience)

Need to simplify complex concepts and risk propositions to patient's level.

Support deliberation over time to reduce going for the default.

- Decision aids
- Include support persons
- Follow-up office visits, phone coaching

combination of a TNF inhibitor and methotrexate appears to be better than either alone. In PsA, at least one trial found that the addition of methotrexate did not provide any substantial benefit.[13]

Ustekinumab, an IL-23 and IL-12 inhibitor, improves PsA with 43 percent of subjects achieving ACR20 and achieving a 55 percent Psoriasis Area and Severity Index (PASI) 75 (75% skin clearing).[15,16] Guselkumab was recently FDA-approved for PsA, in addition to psoriasis. In biologic-naïve patients with active PsA, significantly greater proportions of patients in the guselkumab every four-weeks group (64%) and every eight-weeks group (64%) than in the placebo group (33%) achieved an ACR20 response at week 24 (both $p < 0{\cdot}0001$).[17] In another placebo controlled trial, 58 percent of the guselkumab group and 18 percent of the placebo group achieved an ACR20 response at week 24 ($p < 0{\cdot}0001$).[18] Two other IL-23 specific agents, risankizumab and tildrakizumab, are currently FDA-approved for treating moderate to severe psoriasis and are under study for PsA.

IL-17 has also been shown to be another important mediator in PsA. Secukinumab, an IL-17 inhibitor results in a 50 percent ACR20 rate compared with 15 percent with placebo and 54 percent versus 12 percent for PASI 75.[19,20] Ixekizumab, another IL-17 inhibitor, has been compared to placebo and adalimumab in one trial in biologic-naïve patients with PsA. Higher PASI 75, PASI 90, and PASI 100 rates and higher ACR20 rates were shown with ixekizumab compared to adalimumab, but the study was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab, so no statistics were done comparing the rates.[21] Brodalumab, a third IL-17 inhibitor, is approved for treating moderate to severe psoriasis but not yet approved for PsA.

Abatacept (Orencia®), a selective T-cell co-stimulation modulator, is FDA-approved for PsA, RA, and polyarticular juvenile RA (pJIA). It inhibits T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28. Activated T lymphocytes are implicated in the pathogenesis of PsA, RA, and pJIA and are found in the synovium of these patients. Abatacept significantly increased ACR20 response versus placebo at week 24 (39.4% versus 22.3%; $p < 0.001$).[22]

Often patients prefer oral therapy over injectable biologics. Apremilast and tofacitinib are both oral agents that are FDA-approved for treating PsA and psoriasis. Apremilast decreases inflammatory cytokines, including TNF, IL-12, IL-17, IL-22, and IL-23. In the PsA trials, 37 percent of patients achieved ACR20, and 21 percent a PASI 75 compared to 18 percent and 7 percent of placebo-treated patients.[23-25] Tofacitinib, a Janus kinase (JAK) inhibitor, also reduces various inflammatory cytokines. In the PsA trials with this agent, 54 percent of TNF inhibitor- naïve patients and 48 percent of TNF inhibitor inadequate responders achieved ACR20 compared to 30 percent of placebo-treated patients.[26] Forty-two percent of tofacitinib treated who were TNF inhibitor-naïve and 32 percent of TNF inhibitor non-responders achieved PASI 75 compared to 14 percent of the placebo group. Although no comparative statistics were done, tofacitinib treatment produced higher PASI 75 and ACR20 responses than adalimumab.[27]

No matter what therapy is chosen, shared decision-making is important to patient buy-in and adherence. Shared decision-making is a collaborative process in which patients and clinicians make treatment decisions together by integrating evidence and patient preferences. A good decision is one that is informed, consistent with patient values, and acted upon. The informed piece is a set of medically reasonable options and their respective benefits and risks presented to the patient. Exhibit 3 outlines some of the challenges in translating clinical trial evidence to patients.[28-30] Patient values need to be elicited and incorporated into therapeutic decisions. Patient goals, including the things they want to

maximize such as physical activity and those they want to minimize such as costs or adverse events, are important to set.

Patient and provider communication is also important for maintaining patient motivation and engagement in care. Trust on the part of the patient to communicate what is really happening in his or her life can help the clinician understand/explore reasons for declines in adherence and set up realistic expectations. Providers should take a health literate approach to prescribing and educating patients.

Conclusion

Patient goals are important. These goals may be to improve quality of life, function, and social participation; control symptoms and inflammation (enthesitis, dactylitis, joints); and prevent joint damage. It is important to start treatment early for psoriatic arthritis to limit the joint damage. Communication is key to achieving goals and promoting good outcomes. Therapy should be monitored and adjusted, as often as every eight to 12 weeks may be necessary. Options include traditional oral DMARDs which may not be disease modifying, TNF inhibitors, and multiple newer agents which target IL-12/23, IL-23, IL-17, JAK, T-cell co-stimulation, and PDE4.

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New Treatment Paradigms in the Management of Metastatic Bladder Cancer: A Closer Look at Emerging Therapies Following Immunotherapy Failure

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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

Advanced or metastatic bladder cancer is a difficult to treat stage of disease for which survival is not optimal. Several new therapies, including five immunotherapies, have been approved since 2016 which are improving tumor responses and overall survival.

Key Points

- There are numerous treatment options now available for advanced or metastatic bladder cancer beyond chemotherapy.
- Several chemotherapy/immunotherapy combinations, immunotherapy/immunotherapy combinations, and immunotherapy/antibody drug combinations are on the horizon.

BETWEEN 1997 AND 2016, CHEMOTHERAPY was the primary treatment of advanced or metastatic bladder cancer. Response rates were tumor regression in 50 to 55 percent of patients and an additional 33 percent with stable disease. Gemcitabine and cisplatin were the primary combination and are still used in many patients. The median progression-free survival (PFS) with this combination is 7.5 months and overall survival (OS) is 14 months.[1]

In 2016, the immunotherapy revolution began with the approval of checkpoint inhibitors targeting programmed death one (PD-1) or programmed death ligand one (PD-L1). Atezolizumab (Tecentriq®) was approved by the FDA for bladder cancer that year, followed by nivolumab (Opdivo®), durvalumab (Imfinzi®), avelumab (Bavencio®), and pembrolizumab (Keytruda®) in 2017 for the treatment of platinum-refractory bladder cancer. Exhibit 1 shows data from the Phase III trials in this setting.[2-6]

Pembrolizumab and atezolizumab are also both approved as first-line therapy in those who are cisplatin ineligible. Data from the trials with these two agents are shown in Exhibit 2.[7,8] PD-L1 testing is required by the FDA-approved package labeling for use in frontline metastatic bladder cancer cisplatin-ineligible patients. The FDA-approved diagnostic assay for atezolizumab is Ventana SP142 and a positive test is expression in ≥ 5 percent of tumor-infiltrating immune cells. The FDA-approved diagnostic assay for pembrolizumab is Dako 22C3. This test measures expression in immune and tumor cells as a percentage of total tumor cells, with a combined score ≥ 10 as a positive result.

The National Comprehensive Cancer Network (NCCN) treatment guidelines recommend avelumab maintenance after completion of first-line platinum-based chemotherapy if there was no disease progression during therapy.[9] This is based on a Phase III trial showing improved survival with avelumab maintenance compared to best supportive care (control). OS at one year was 71.3 percent in the avelumab group and 58.4 percent in the control group (median OS, 21.4 months versus 14.3 months; $p = 0.001$).[10] Avelumab also significantly prolonged OS in the PD-L1-positive population; OS at one

Exhibit 1: Immune Checkpoint Inhibitors in Platinum-Refractory Setting[2-6]

	Pembrolizumab	Durvalumab	Nivolumab	Avelumab	Atezolizumab
Dosing	200 mg Q 3 weeks	10 mg/kg Q 2 weeks	3 mg/kg Q 2 weeks	10 mg/kg Q 2 weeks	1,200 mg Q 3 weeks
ORR	21%	18%	20%	17%	13%
OS (months)	10.3	18.2	8.7	6.5	11.1
PFS (months)	2.1	1.5	2.0	1.5	2.1
12-month Survival	44%	55%	43%	47%	39%
Grade 3 / 4 TRAE	15%	7%	18%	8%	16%

Exhibit 2: Immune Checkpoint Inhibitors in Front Line Setting (Cisplatin Ineligible)[7,8]

	Pembrolizumab	Atezolizumab
Dosing	200 mg Q 3 weeks	1,200 mg Q 3 weeks
ORR	29%	23%
CR	7%	9%
OS (months)	11.5	15.9
PFS (months)	2.0	2.7
Landmark Survival	48% (12 months)	57% (12 months)

year was 79.1 percent in the avelumab group and 60.4 percent in the control group ($p < 0.001$). The median PFS was 3.7 months in the avelumab group and 2.0 months in the control group in the overall population and 5.7 months and 2.1 months, respectively, in the PD-L1-positive population. The incidence of adverse events of Grade 3 or higher was 47.4 percent and 25.2 percent, respectively.

Another evolution in treating bladder cancer is identification of potential genetic mutations targets; one targeted therapy has been FDA approved (erdafitinib [Balversa™]). The fibroblast growth factor receptor 3 (FGFR3) plays a critical role in driving oncogenesis of a subset of patients with bladder cancer. Aberrant FGFR3 alterations have been described in 15 to 20 percent of muscle-invasive bladder cancer and up to 60 percent of non-muscle-invasive bladder cancer.[11] The FGFR3 alterations appear to be associated with lower sensitivity to immune interventions. In an open-label, Phase II study in patients who had locally advanced and unresectable or metastatic bladder cancer with prespecified FGFR alterations, the confirmed response to erdafitinib therapy, an oral FGFR2/3 kinase inhibitor, was 40 percent (3% with a complete response and 37% with a partial response).[12] Among the 22 patients who had undergone previous immunotherapy, the confirmed response rate was 59 percent. The median duration of PFS was 5.5 months, and the median duration of OS was 13.8 months. Treatment-related adverse events of Grade 3 or higher, which were managed mainly by dose adjustments, were reported in 46 percent of the patients; 13 percent of the patients discontinued treatment because of adverse events. There were no treatment-related deaths. This agent is FDA approved for those with advanced or metastatic disease, susceptible FGFR3 or FGFR2 genetic alterations, and disease progression during or after at least one course of chemotherapy, or within 12 months after neoadjuvant or adjuvant chemotherapy. Importantly, this agent can cause central serous retinopathy/retinal pigment epithelial detachment. Patients receiving it need monthly ophthalmological examinations during the first four months of treatment, every three months afterward, and at any time for visual symptoms.

Antibody drug combinations are also changing the treatment of bladder cancer. The antibody allows the conjugate molecule to attach to and enter tumor cells where the drug is released and kills the cell. Enfortumab vedotin (Padcev™) is a Nectin-

Exhibit 3: Current Treatment Paradigms for Advanced/Metastatic Bladder Cancer[9]

- **CISPLATIN ELIGIBLE**
  - gemcitabine/cisplatin followed by avelumab maintenance
- **CISPLATIN INELIGIBLE**
  - immunotherapy (pembrolizumab or atezolizumab) if PD-L1+
  - gemcitabine/carboplatin followed by avelumab maintenance
- **CHEMOTHERAPY UNFIT**
  - immunotherapy (pembrolizumab or atezolizumab)
- **PLATINUM REFRACTORY**
  - 5 immunotherapy options (pembrolizumab preferred)
  - Erdafitinib (aberrant FGFR3)
  - Enfortumab vedotin

4-directed antibody and microtubule inhibitor conjugate that was FDA approved in 2019 based on tumor response rates. Nectin-4 expression is nearly ubiquitous on bladder cancer cells. This agent is indicated for the treatment of adult patients with locally advanced or metastatic bladder cancer who have previously received a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. In the Phase II single-arm trial that lead to FDA approval, the objective response rate was 44 percent, including 12 percent complete responses.[13] Similar responses were observed in prespecified subgroups, such as those patients with liver metastases and those with no response to prior anti-PD-1/L1 therapy. Median duration of response was 7.6 months (range, 0.95 to 11.30 plus months). The most common treatment-related adverse events were fatigue (50%), any peripheral neuropathy (50%), alopecia (49%), any rash (48%), decreased appetite (44%), and dysgeusia (40%). No single treatment-related adverse events Grade 3 or greater occurred in 10 percent or more of patients. Exhibit 3 shows the current treatment paradigm for metastatic bladder cancer.[9] The preferred treatment options depending on the patient's concomitant conditions, general health, and prior treatments.

Frontline chemotherapy combined with immunotherapy (chemoimmunotherapy) is likely to be the next iteration of first-line therapy for metastatic bladder cancer. The combination of enfortumab vedotin and pembrolizumab has been studied for first-line therapy; there was a 70 percent response rate in a Phase Ib study, but the final results from this trial have not yet been published.[14] Chemoimmunotherapy has also been investigated in the IMvigor130 trial which compared atezolizumab, atezolizumab/cisplatin or carboplatin/gemcitabine, and chemotherapy alone. Addition of atezolizumab to platinum-based chemotherapy as first-line treatment prolonged PFS in patients with metastatic disease. At the time of the final PFS analysis and interim OS analysis (May 31, 2019), median PFS in the intention-to-treat population was 8.2 months in the chemoimmunotherapy group, and 6.3 months in the chemotherapy group (one-sided $p = 0.007$).[15] Median OS was 16.0 months in the chemoimmunotherapy group, 15.7 months in the immunotherapy group, and 13.4 months in the chemotherapy group. Adverse events that led to withdrawal of any agent occurred in 34 percent of the chemoimmunotherapy group, 6 percent of the immunotherapy group, and 34 percent of the chemotherapy group. The Phase III KEYNOTE-361 trial evaluating pembrolizumab in combination with chemotherapy for the first-line treatment of patients with advanced or metastatic bladder cancer did not meet its pre-specified dual primary endpoints of OS or PFS, compared with standard of care chemotherapy, according to a company press release.[16] Though in the final analysis of the study there was an improvement in OS and PFS for patients treated with the anti-PD-1 therapy in combination with chemotherapy, the results did not meet statistical significance per the pre-specified statistical plan; final results from this trial have not yet been published.

Combinations of two different immunotherapies are also under investigation. There is rationale for combining anti-PD1 or PD-L1 with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies because they target different parts of the immune system, but combination immunotherapies further unleash the immune system, which can lead to much higher rates of immune-related adverse events than when one immunotherapy is given. The combination of nivolumab and ipilimumab is under investigation and is showing promising results, including improved OS.[17] The combination of durvalumab and tremelimumab is also in ongoing trials.

Bempegaldesleukin (NKTR-214) is an investigational immunotherapy. It is a PEGylated interleukin-2 (IL-2) acting as a CD122-preferential IL-2 pathway agonist designed to activate and proliferate CD8+ T cells and natural killer (NK) cells.[18] In August 2019, the FDA granted breakthrough therapy designation to it in combination with nivolumab for the treatment of advanced melanoma. It is in early phase trials in combination with nivolumab and pembrolizumab for bladder cancer.

Conclusion

Dramatic changes in the treatment of bladder cancer have already been seen. There is one targeted therapy, numerous immunotherapies, proven chemotherapy regimens, and a new antibody drug combination. The landscape is likely to change further with chemotherapy/immunotherapy combinations, immunotherapy/immunotherapy combinations, and immunotherapy/antibody drug combinations being incorporated into the treatment paradigm.

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Navigating an Increasingly Complex Treatment Landscape in the Management of Acute Myeloid Leukemia: Improving Clinical and Economic 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

Management of acute myeloid leukemia (AML) has changed dramatically in recent years with the introduction of targeted agents for specific genetic mutations and better tolerated chemotherapy formulations. The therapies, which are given orally, have led to a paradigm shift in treating this disease, primarily on an outpatient basis.

Key Points

- New therapies for AML are improving outcomes and shifting care toward the outpatient setting, especially for older adults.
- Unique toxicity profiles for the new therapies, along with high acuity of AML patients, will require resources and excellent communication for optimal management in the community.
- There is an opportunity for AML cost reduction if the new therapies are successful.

ACUTE MYELOID LEUKEMIA (AML) IS unchecked proliferation of hematopoietic stem cells from the myeloid lineage. Unless treated, this leads to marrow failure and patient death. AML can be de novo or secondary (due to prior myelodysplastic syndrome [MDS], myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents). Age is the major risk factor, with prior chemotherapy for other cancers, ionizing radiation, and industrial solvents accounting for less than 10 percent of the annual incidence in the United States (U.S.). The median age of AML onset is approximately 70 years; however, it affects all age groups.

AML is driven by many different genetic mutations. In adult de novo AML, mutations are found in one of nine categories of genes, including transcription-factor fusions (18% of cases), nucleophosmin (NPM1, 27%), tumor-suppression (16%), DNA-methylation (44%), signaling (59%), chromatin-modifying (30%), myeloid transcription-factor (22%), cohesin-complex (13%), and spliceosome-complex (14%).[1] The genetic mutations which are present have prognostic implications. For example, FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD high) is a driver mutation that presents with a high leukemic burden, confers a poor prognosis, and has a significant negative impact on the management of patients with AML.[2]

The treatment of AML has undergone a revolution in the past few years with the FDA approval of nine new therapies since 2017 (Exhibit 1). Several of these agents are targeted at specific genetic mutations and are given orally. Over-expression of FLT3 is common in AML, with 25 percent of cases having internal tandem duplication (FLT3-ITD) and 5 percent having point mutations in tyrosine kinase domains (FLT3-TKD).[2,3] Midostaurin (Rydapt®), an oral multitargeted kinase inhibitor, is added for FLT3 mutation-positive disease during induction and consolidation (days 8 to 21 of each cycle). Midostaurin improves four-year overall survival (OS), reduces the risk of death by 23 percent, and improves OS after stem cell transplant (SCT, for first complete response).[4] Gilteritinib (Xospata®)

Exhibit 1: New Therapies Approved for AML 2017 to 2020

Year Approved	Drug	Class/Mechanism	Primary Indication
2017	Midostaurin (Rydapt®)	FTL3 inhibitor	FLT3+, new AML
2017	Gemtuzumab Ozogamicin (Mylotarg®)	CD33 antibody-drug conjugate	CD33+, new AML
2017	Daunorubicin-cytarabine liposome (Vyxeos®)	Cytotoxic chemotherapy	New secondary AML
2017	Enasidenib (Idhifa®)	IDH2 inhibitor	IDH2+ relapsed/refractory AML
2018	Venetoclax (Venclexta®)	BCL2 inhibitor	New, elderly AML (combined with azacitidine, decitabine, or cytarabine)
2018	Gilteritinib (Xospata®)	FLT3 inhibitor	FLT3+ relapsed/refractory AML
2018	Glasdegib (Daurismo™)	SMO inhibitor	New, elderly AML (combined with cytarabine)
2019	Ivosidenib (Tibsovo®)	IDH1 inhibitor	IDH1+ new or relapsed/refractory AML
2020	Azacitidine (Onureg®)	Nucleoside metabolic inhibitor	New AML, unable to tolerate intensive therapy

is another oral FLT3 inhibitor indicated for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation. It is a highly potent, selective FLT3/AXL inhibitor with activity in vitro against FLT3-ITD and FLT3-D8354-6. In a Phase III trial of this agent, the median OS in the gilteritinib group was significantly longer than that in the chemotherapy group (9.3 months versus 5.6 months, $p < 0.001$).[5] The median event-free survival (EFS) was 2.8 months in the gilteritinib group and 0.7 months in the chemotherapy group. The percentage of patients who had complete remission (CR) with full or partial hematologic recovery was 34.0 percent in the gilteritinib group and 15.3 percent in the chemotherapy group.

In some people with AML, the leukemia cells have a mutation in the isocitrate dehydrogenase (IDH1 or IDH2) gene, an enzyme of the citric acid cycle. Mutant IDH produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation. IDH inhibitors can block the production of 2-HG and seem to work by helping the leukemia cells differentiate into more normal cells. Ivosidenib (Tibsovo®) is an IDH1 inhibitor used to treat IDH1 mutation-positive AML, either as the first treatment in the older or unfit patient, or for relapsed/refractory disease. Enasidenib (Idhifa®) is an IDH2 inhibitor approved for IDH2-positive relapsed/refractory AML. Both are oral agents and have efficacy in AML.[6,7]

AML cells can also have mutations in a cell signaling pathway called hedgehog. The hedgehog pathway is crucial for the development of the embryo and fetus and is important in stem cell maintenance, among other critical functions. Dysregulation of components of the pathway results in the development, maintenance, and expansion of leukemic stem cells. Glasdegib (Daurismo®) targets a protein in this pathway (SMO) and can be used with chemotherapy in people with newly diagnosed AML who are 75 years or older, or who are not healthy enough to tolerate aggressive chemotherapy. In this group, it has been shown to help people live longer.[8,9]

B-cell lymphoma two (BCL-2) overexpression in AML allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins. Venetoclax (Venclexta®) binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis. It is used in combination with chemotherapy (decitabine, azacitidine, low-dose cytarabine) in those with newly diagnosed or relapsed/refractory AML, who are 75 years or older, or who are not healthy enough to tolerate aggressive chemotherapy.[10] In trials of venetoclax in combination with single-agent chemotherapy for those with newly diagnosed disease, more than 60 percent of patients achieved CR and CR with incomplete hematologic recovery (CRi).[11,12] Key issues surrounding venetoclax use are relatively short reported follow-up data to

Exhibit 2: Toxicity Issues

Drug	Important Toxicities
Midostaurin	Nausea and vomiting Prolonged QTc
Gilteritinib	Nausea and vomiting Prolonged QTc Differentiation Syndrome
Enasidenib and Ivosidenib	Differentiation syndrome Prolonged QTc Nausea and vomiting
Daunorubicin-cytarabine liposome	Prolonged myelosuppression
Venetoclax	Severe myelosuppression
Glasdegib	Dysgeusia Edema Rash

Exhibit 3: Costs of New Drugs Are High

Drug	Average Wholesale Price
Midostaurin	$170.24 per 25 mg tablet
Gilteritinib	$300.00 per 40 mg tablet
Enasidenib	$1,029.79 per 100 mg tablet
Ivosidenib	$522.30 per 250 mg tablet
Glasdegib	$338.50 per 25 mg tablet
Venetoclax	$111.51 per 100 mg tablet
Daunorubicin-cytarabine liposome	$9,579.00 per 44 to 100 mg vial
Azacitidine (oral)	$1,492 per 200 mg tablet

date and under-representation of secondary AML patients in the trials. There is also limited efficacy in p53 mutant AML.

An oral form of azacitidine (Onureg®), which was originally FDA approved for intravenous or subcutaneous administration in 2004, was approved in September of 2020. It is a nucleoside metabolic inhibitor indicated for maintenance treatment of adult patients with AML who achieved first CR or CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy. In this setting, it increased median OS (24.7 months versus 14.8 months for placebo).[13] The oral formulation has a different indication form and dosing; thus, it cannot be substituted for the intravenous/subcutaneous formulation.

As noted previously, secondary AML (s-AML) can develop after an antecedent myeloid malignancy and after leukemogenic therapy. A liposomal co-formulation of cytarabine and daunorubicin (Vyxeos®, previously called CPX-351) is one of the advances in chemotherapy for AML and is indicated for secondary AML. It was designed to achieve synergistic leukemia cell killing in vitro with a 5:1 molar ratio of cytarabine:daunorubicin. The liposomes are selectively taken up by bone marrow leukemia cells in xenograft models. In older adults with newly diagnosed s-AML, this combination significantly improved median OS versus standard of care cytarabine plus daunorubicin chemotherapy (9.56 versus 5.95 months, one-sided $p = 0.003$).[14] The overall remission rate was also significantly higher with the liposomal combination versus standard chemotherapy (47.7% versus 33.3%; two-sided $p = 0.016$). Improved outcomes were observed across age-groups and AML subtypes.

In terms of adverse events with the newer therapies for AML, the common issues with cancer treatment remain; neutropenia and other severe cytopenia, infections, and nausea/vomiting can be an issue. With oral therapies, nausea/vomiting can be an unexpected issue for patients. Other major toxicities are shown in Exhibit 2. Differentiation syndrome is a serious and potentially lethal adverse event from IDH inhibitors and sometimes with other medications for AML. It occurs in 10 to 15 percent of patients; high blast counts and high LDH levels are the primary risk factors. The most frequent manifestations are dyspnea, fever, pulmonary infiltrates, and hypoxia. Onset appears to correspond to medication-induced myeloid cell differentiation and maturation and it may occur later in therapy rather than initially. It is treated by holding the medication and giving corticosteroids.

The old way of treating AML was in-hospital intensive chemotherapy and stem cell transplants

and then retreatment at the time of relapse in a never-ending cycle. The development of oral agents that are taken at home has driven a paradigm shift in treating AML. Patients now can get in-hospital or clinic-based treatment, home-based oral treatment only, or a combination. Patients receiving only oral therapy may still require hospitalization for adverse events, but hopefully at a lower rate than with traditional chemotherapy. There are several challenges in this shift to primarily outpatient care. Distance from a primary treating center can be a barrier to at home treatment. Transportation costs and the need for frequent follow-up visits can be costly for patients. Community-based oncologists are not as familiar with less frequent cancers like AML and may need education on the appropriate use, adverse event management, and follow-up of the oral agents. Community resource strains (e.g., blood products), communication with tertiary specialists, and accessibility of medical records between centers can also cause problems.

One of the major challenges of the newer therapies is the cost (Exhibit 3). The cost of these agents adds to the already burdensome costs of AML treatment for the predominately elderly patient population. Before the development of several of the new medications, the total medical cost per patient per month was $27,756 for the first year after diagnosis and $12,953 in the second year.[15] Based on an estimate of 17,000 cases annually of AML in the U.S. in those over 60 and an average 10-month life expectancy for these patients, it costs an estimated $4.2 billion to care for older AML patients. Data are needed to determine whether the newer therapies, although very expensive, could be cost saving through reduced use of hospital-based resources. One budget impact analysis found that the use of daunorubicin-cytarabine liposome for induction treatment for patients with s-AML, instead of the standard regimen, may have a limited economic impact on the budget of commercial health plans and may result in cost offsets, particularly in patients who respond to therapy.[16]

Conclusion

Multiple new therapies for AML are improving outcomes and shifting care toward the outpatient setting, especially for older adults. Unique toxicity profiles for many new drugs, along with high acuity of AML patients, will require resources and excellent communication for optimal management in the community. There is an opportunity for AML cost reduction if the new therapies are successful. Future research should focus on patient financial burden of new oral AML drugs and the effects they have on outcomes.

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New Advances in Treatment of Inflammatory Bowel Disease: Expert Strategies for Optimal Management

Stephen B. Hanauer, MD

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

Summary

Biologics for treating inflammatory bowel disease have been available for more than 20 years. During those same 20 years much has been learned about targeting the underlying inflammatory process, rather than just managing symptoms to improve long-term outcomes. Early intervention with biologics, treat-to-target control of inflammation, and tight long-term control are all important to altering the long-term outcomes of this disease.

Key Points

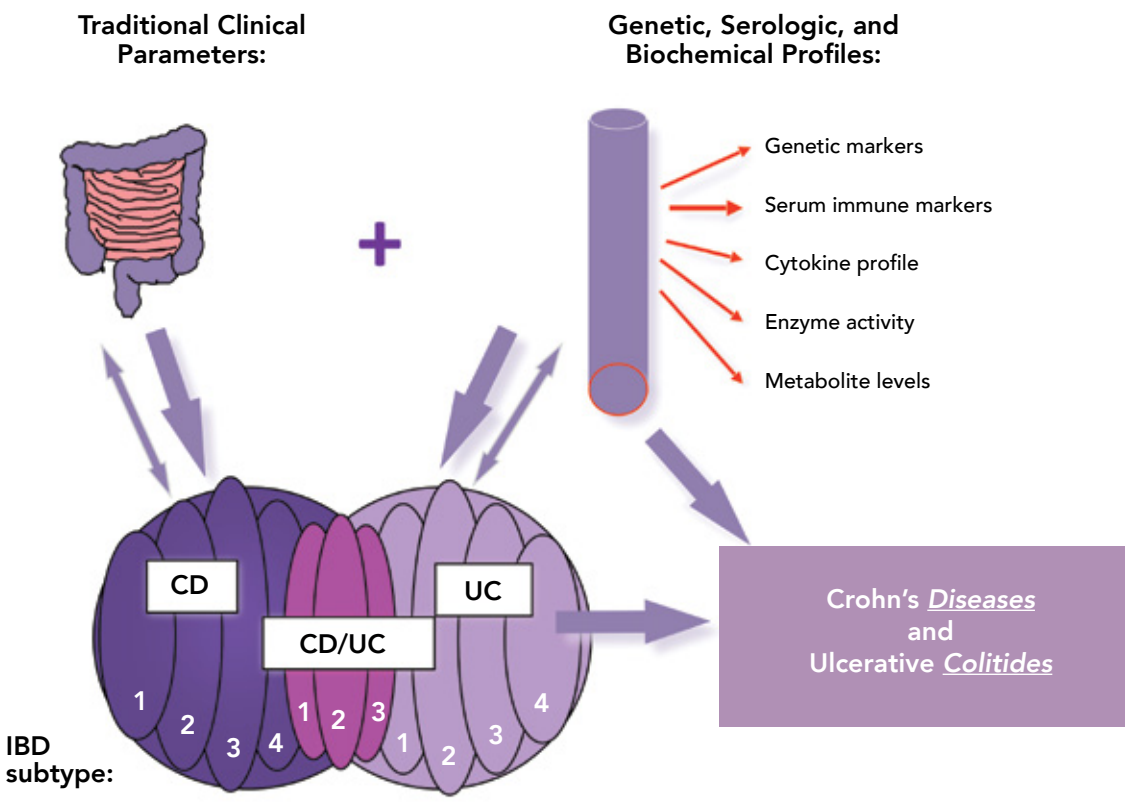
- IBD is a chronic, heterogenous immune-mediated inflammatory disorder.
- Early, multi-disciplinary interventions to induce and maintain mucosal remissions are critical to prevent disease progression and long-term complications.
- Treat-to-target strategies are evolving to modify long-term disease modification.
- Shared decision-making is often compromised by third party interventions based on pricing, rather than on outcomes.

INFLAMMATORY BOWEL DISEASE (IBD) is an autoimmune disease that is thought to occur because of interaction between host factors, environmental factors, and inappropriate immune response.[1] Approximately 15 percent of patients with IBD have known predisposing genetic mutations; many other mutations are likely yet to be discovered. Environmental factors include diet, antibiotics, medicines that cause mucosal disruption (nonsteroidal anti-inflammatories), pathogens, and stressors (stress, smoking). Most of these environmental factors lead to a disrupted microbiome in the gastrointestinal (GI) tract. Patients with active inflammation in the GI tract have a reduced diversity in their gut; it is not yet known whether the reduced diversity leads to IBD or inflammation causes reduced diversity. Overall, IBD is a summation of events culminating in intestinal inflammation.

The pathophysiology of IBD is like other autoimmune diseases (i.e., rheumatoid arthritis, psoriatic arthritis, psoriasis) in the components of the immune system which are dysregulated and the overlap of effective treatments. Whereas rheumatoid arthritis and psoriatic arthritis primarily affect joints and psoriasis affects the skin, IBD primarily affects the gastrointestinal tract.

Traditionally, IBD has been divided into Crohn's disease (CD) and ulcerative colitis (UC) based on clinical patterns of disease on colonoscopy. UC is diffuse superficial inflammation of the colon, and CD is focal areas of deep inflammation interspersed with normal tissue throughout the GI tract. UC can lead to chronic changes in the colon lining, which can lead to colon cancer. The deep inflammation of CD through the layers of the intestines leads to the complications of fistula, stricture, bowel obstruction, abscesses, and colon cancer. It is now known that there are many different subtypes of IBD (Exhibit 1); about 10 percent of patients have features of both UC and CD (indeterminate colitis).

Exhibit 1: Inflammatory Bowel Diseases



IBD is a chronic and progressive disease in which the symptoms do not reflect the actual inflammatory burden of the disease.[2] The common symptoms of UC are diarrhea and rectal bleeding, while the symptoms of CD are diarrhea and abdominal pain. Patients can have few symptoms, yet they may show significant inflammation on examination of the GI tract. The FDA now requires both improvement of symptoms and documentation of improved inflammation within the bowel to approve medications for IBD.

Treat-to-target (T2T) improves long-term outcomes. It is important to start therapy soon after diagnosis, treat-to-target, and get the most out of initial therapy to bring the disease under control (Exhibit 2).[3] A higher percentage of patients will achieve remission if treated early in the disease compared to later in the disease. A recent meta-analysis found that early use of biologics (first two years after diagnosis) in CD was associated with statistically higher rates of clinical remission, lower relapse rates, and higher mucosal healing rates

Exhibit 2: The Three Pillars of IBD Care[3]

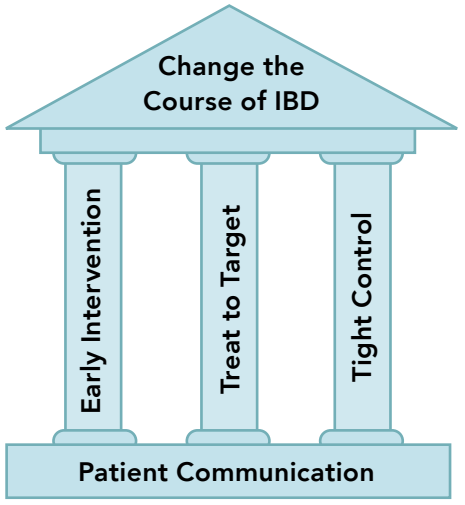
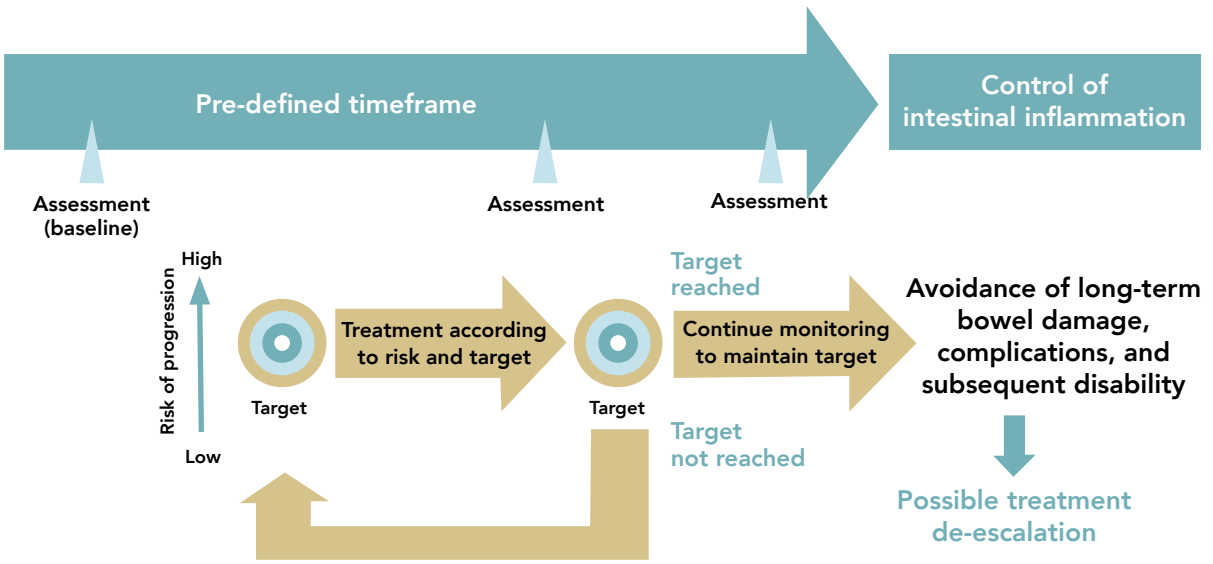


Exhibit 3: Treat-to-Target Concept in IBD[5]



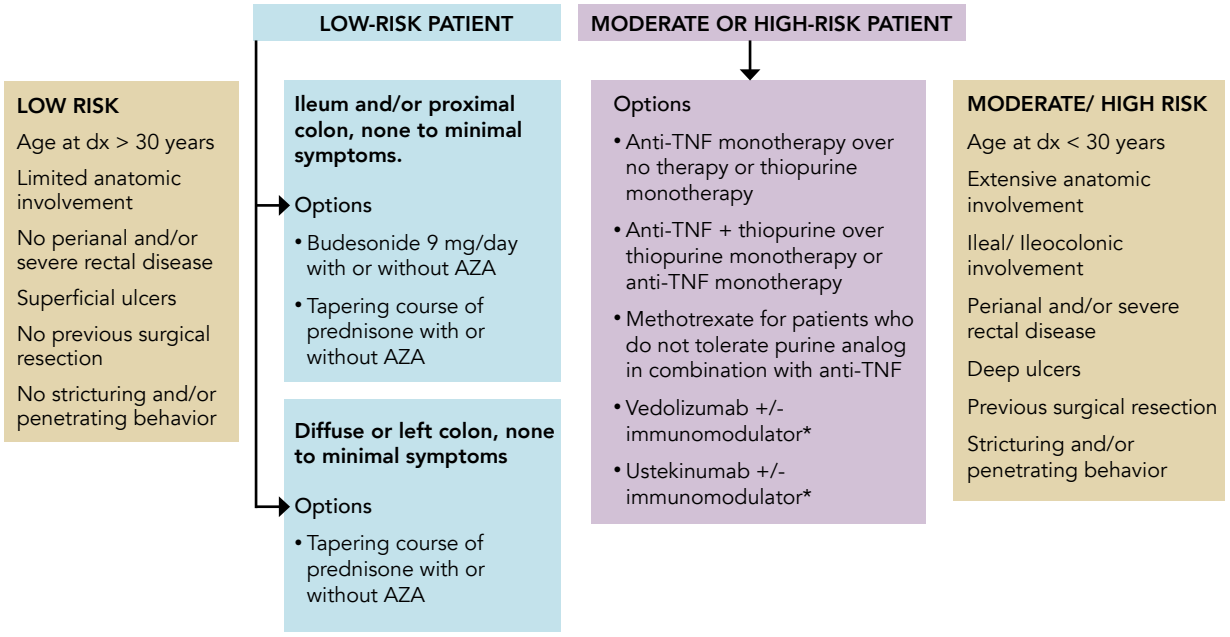
compared with late or conventional management in not only prospective clinical trials but also in real-world settings.[4] Early deep remissions also reduce risk of disease progression. Once a patient loses response to the first treatment, there is a 50 percent lower response to a second agent. Maintaining tight control is also important to reducing consequences of the disease.

Like many other autoimmune diseases (multiple sclerosis, rheumatoid arthritis, psoriatic arthritis), a T2T approach should be used when managing IBD (Exhibit 3).[5] Desired outcomes of the T2T approach in early disease are complete absence of symptoms, no disease progression, no complications or disability, and no quality of life impact (QOL). Outcomes in later disease are stabilization of non-inflammatory symptoms, no progression of damage or disability, and improved QOL. Because IBD is really several heterogeneous diseases, each aspect of the T2T strategy may need to be tailored to the individual patient. As already noted, outcomes in late-stage disease will differ from those achievable in early disease. The choice of the treatment target may also vary, given that a stringent target may not be achievable in some patient types. For example, symptomatic remission may not be achievable in late-stage disease, and mucosal healing may also be harder to achieve in longstanding disease where there is considerable accumulated bowel damage. Individual patient-reported outcome goals should also be considered, and the frequency of outcome assessments tailored to the patient's symptoms (for example, a minimum every three months until symptom resolution and at least every six to 12 months after resolution). Treatment choices will also be tailored to the patient's prognosis and disease type, and to the risk of treatment toxicity. The frequency and choice of monitoring assessments may also vary by patient.

Proactive therapeutic drug monitoring (TDM) for certain medications (thiopurines, infliximab) is also part of tight control. In a retrospective trial comparing two TDM approaches (reactive after loss of response and proactive while in clinical remission) found that proactive measurement of infliximab levels therapy was associated with reduced treatment failure, reduced IBD-related surgery and hospitalization, fewer antibodies to infliximab, and fewer serious infusion reactions.[6]

In choosing treatment, both disease activity and severity are taken into consideration; both are used to assess risk of colectomy and other complications in determining how aggressive initial therapy is needed.[7] Disease activity reflects cross-sectional assessment of biologic inflammatory impact on symptoms, signs, endoscopy, histology, and biomarkers. Disease severity includes longitudinal (disease course) and historical factors that provide a more complete picture of the prognosis and overall burden of disease. The domains to determine if patient has mild, moderate, or severe disease are impact on the patient (symptoms, QOL, disability),

Exhibit 4: Initial Treatment of Crohn's Disease[14]



*Approved since last update of guidelines

Dx = diagnosis; AZA = azathioprine

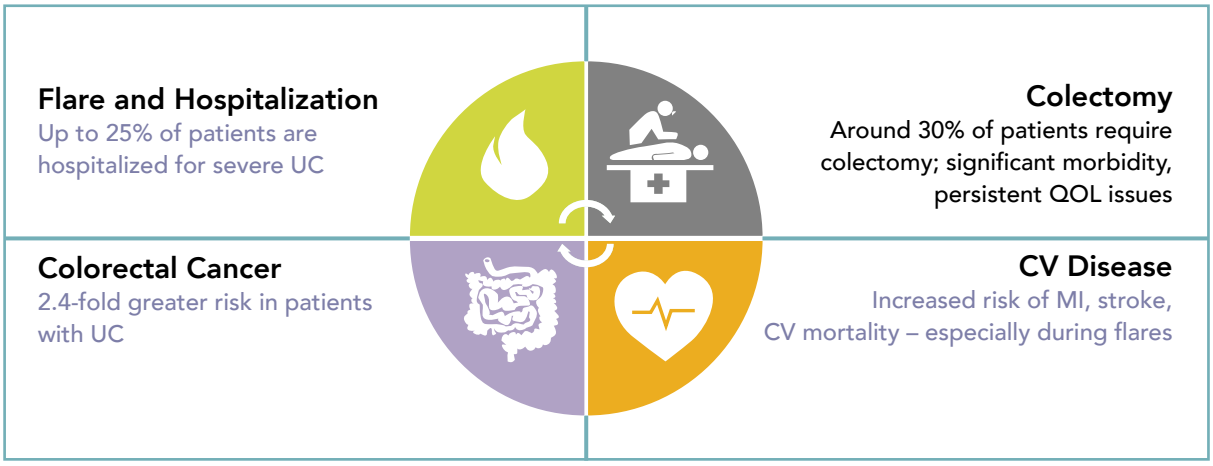
inflammatory burden (C-reactive protein (CRP), extent of GI lesions, other serum markers of inflammation), and disease course (bowel damage, intestinal resection, perianal disease, number of disease flares). Patients at high risk for progression and colectomy are those who initially present with extensive disease, deep ulcers in the GI tract, age < 40 years, high CRP and erythrocyte sedimentation rate (ESR), steroid-requiring disease, history of hospitalization, *Clostridioides difficile* infection, and cytomegalovirus infection. A patient at high-risk on initial diagnosis would be classified as having moderate to severe disease.

The anti-tumor necrosis (TNF) therapies have been available for treating IBD the longest (~20 years) and are effective for treatment of CD and UC. From the use of these agents for many years, much has been learned about treating IBD, including that all monoclonal antibodies are immunogenic (i.e., induce anti-drug antibodies which can lead to loss of efficacy). High-dose induction and regular maintenance therapy along with concomitant immunomodulators (azathioprine, methotrexate) reduce immunogenicity. Additionally, combination therapy of anti-TNF and immunomodulators is more efficacious than monotherapy with either alone. Another lesson learned is that loss of response may be due to immunogenicity, insufficient serum levels, or loss of mechanism. Lastly, the risks of monoclonal antibodies include infections and a small risk of neoplasia, especially when combined with mercaptopurines. It is important to recognize that the highest risk of infections or deaths in IBD patients is the use of corticosteroids; thus, the use of steroids should be minimized as much as possible.

Treatment recommendations have evolved with better clinical understanding of the disease and availability of effective medications. In the past, moderate UC had been treated with steroids for induction. It is now known that those initially treated with steroids will not respond to thiopurines and biologics for maintenance therapy. In addition to risk of colectomy and death, steroids carry a much greater risk for adverse events than the biologics and have a risk for causing steroid-dependent disease. Avoiding the use of corticosteroids from the beginning should be the goal of treating IBD, but this contrasts with the policies of third-party payers who require failure of certain therapies including steroids before the use of biologics irrespective of disease severity.

A pyramid approach to IBD is no longer recommended for moderate to severe UC. The American Gastroenterology Association (AGA)

Exhibit 5: Inadequate Treatment Leads to Serious Consequences[18-22]



CVD = cardiovascular disease; MI = myocardial infarction

suggests early use of biologic agents with or without immunomodulator therapy or tofacitinib, rather than gradual step up after failure of 5-aminosalicylates for those with moderate to severe disease.[8] Anti-TNF therapy (infliximab, adalimumab, golimumab), vedolizumab (Entyvio®, integrin inhibitor), tofacitinib (Xeljanz®, Janus kinase inhibitor), or ustekinumab (Stelara®, IL-12/23 inhibitor) are all possible therapies for induction of remission in biologic-naïve patients with moderate to severe UC. In adult outpatients with moderate to severe UC, the AGA suggests combining anti-TNF agents or vedolizumab with thiopurines or methotrexate, rather than biologic or thiopurine monotherapy.[8] Combination therapy has shown higher rates of steroid-free remission and mucosal healing.[9,10]

Tofacitinib is indicated for the treatment of adult patients with moderately to severely active UC, who have had an inadequate response, or who are intolerant to a TNF inhibitor. A black box warning was added in 2019 about increased all-cause mortality and increased arterial and venous thrombosis and pulmonary embolism risk with tofacitinib 10 mg twice daily. This warning was based on findings in a study of rheumatoid patients who were over 50 years of age and had one or more cardiovascular risk factor. This is very different population from the typical newly diagnosed UC patient. No increased risk of thrombosis or cardiovascular disease was shown in the studies of tofacitinib in UC. Clinicians are now limiting use of tofacitinib to those who have failed a TNF inhibitor. The induction dose is 10 mg twice daily. Once the induction phase is done, the dose of tofacitinib should be lowered to 5 mg twice daily, which does not appear to have the same risks.

Comparative efficacy of the available agents in inducing clinical remission and mucosal healing in UC is primarily based on historical data and not head-to-head trials. For clinical remission, infliximab or vedolizumab is more effective than tofacitinib, which is more effective than adalimumab or golimumab.[11,12] For mucosal healing, infliximab (59%) is better than vedolizumab (56%), which is better than tofacitinib (47%), golimumab (43%), and adalimumab (41%). Significant differences have not been seen with these various agents for maintenance therapy. One game changer study (Varsity) was published in 2019. This trial compared vedolizumab and adalimumab in moderate to severe UC and found significant mucosal healing benefits of vedolizumab for TNF-naïve (43.1% versus 29.5%) patients.[13] The difference between the two agents in TNF exposed or failure (26.6% versus 21.0) patients was not statistically different. The AGA does recommend tofacitinib or vedolizumab for induction of remission in anti-TNF experienced patients with moderate to severe UC, is recommended.[8] After successful induction, the same agent will be also used as the maintenance agent (except for steroids).

The AGA recommendations for initial treatment of CD are shown in Exhibit 4.[14] Again recommended therapy is based on disease severity and risk of complications. The FDA-approved labeling states biologics should be used in patients with moderate to severe disease who have failed conventional therapy, even though conventional therapy is no longer

Exhibit 6: Proposed IBD Care Bill of Rights

1. Patients should have informed providers who make the diagnosis quickly.
2. Patients should have access to expert care and second opinions.
3. Patients and providers should understand the goals of management and have a systematic thoughtful approach to relapse or loss of response.
4. There must be adequate support for an engaged and collaborative multidisciplinary team.
5. There must be appropriate education of available treatment options and shared decision-making between patients and their primary IBD providers.
6. The care of IBD must be affordable for the individual and for our society.
7. Patients and providers must have access to needed therapies in a timely manner.
8. There must be an appropriate, transparent and expedited appeals process for decisions by payers.
9. Patients should have appropriate accommodation for their condition at school, at work and in public spaces.

recommended by the AGA guidelines as initial treatment for moderate to severe CD. Following the FDA-approved indications only limits the long-term benefits of biologics in CD because patients are treated too late – after fistula and stricture formation.[15] It appears that the first two years of disease are when the most aggressive therapy would provide the most benefit. Patients with early-stage CD are often seen in a community setting, but they probably should be referred to an IBD specialist and multidisciplinary care.

For both CD and UC, patient- and therapy-related factors can also drive treatment decisions. Comorbidities, previous experience with medications, extraintestinal manifestations (joints, skin, eyes, and biliary tract), and patient preference for mode of administration are some important patient-related factors. Therapy factors may include desire for rapid induction of remission, early non-clinical signs of response (e.g., inflammatory biomarker normalization), durability of remission (dose optimization +/- TDM), favorable safety profile, time on the market, immunogenicity (need for combo), and impact on extraintestinal manifestations. There is a paucity of head-to-head trials that inform clinicians on the appropriate, efficacious, and safe treatment regimens for IBD.

Many third-party payers have protocols/policies based on FDA approvals and FDA-dosing, which limit access to biologics and tofacitinib. Plans dictate therapies that must be failed, such as immunomodulators prior to anti-TNF and one or more anti-TNFs prior to vedolizumab or ustekinumab, which goes against the knowledge that the first therapy chosen in moderate to severe IBD is the most effective and that the optimal time to intervene in the disease is within the first two years of diagnosis. A review of 50 of the top 125 insurance plans in the United States (U.S.) found that most of the policies reviewed failed to adhere to the current AGA pathway.[16]

When a recommended therapy is denied by a third-party payer, patients try several options including time intensive insurance appeals with the help of providers; switch to a possibly less effective medication; utilize a patient assistance program; pay out-of-pocket; purchase foreign medication; or use alternative therapies. One survey found 25.4 percent of patients reported delays in medical care and 55.3 percent were denied coverage by an insurance company.[17] Most importantly, inadequate treatment leads to serious consequences (Exhibit 5), which can be more costly than the originally denied medication.[18-22] An IBD bill of patient rights has been proposed (Exhibit 6).

Lastly, Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) is an international, pediatric, and adult database to monitor and report on outcomes of COVID-19 occurring in IBD patients (covidibd.org). Clinicians can report cases to this database. The website also has a risk calculator for the risk of hospitalization, intensive care unit (ICU) admission, mechanical ventilation, or death in IBD patients with COVID-19. Based on data reported to this group, the risk of developing COVID-19 in those with IBD is like the general

population, but IBD patients are still considered high-risk. Risk factors include age (older > younger), male gender, and smoking. Thus far, medications do not seem to increase risk. The International Organization for IBD Recommendations (ioibd.org) suggest continuing ongoing therapy for IBD unless infected.[23] This guidance recommends immunosuppressants/modulators and biologics should be withheld if a patient becomes infected, even though the long half-lives of these agents lead to a prolonged immune effect, and tapering of steroids should be attempted, even though steroids are utilized in treating severe Covid-19 related pneumonitis. Therapies should be resumed seven to 14 days after symptom resolution.

Conclusion

IBD is a chronic, heterogenous immune-mediated inflammatory disorder. Early, multi-disciplinary interventions to induce and maintain mucosal remissions are critical to prevent disease progression and long-term complications. Treat-to-target strategies are evolving to modify long-term disease modification. Shared decision-making is often compromised by third- party interventions based on pricing rather than on outcomes. Combination therapies are likely to evolve like other immune-mediated diseases. Despite chronic disease and immunosuppressive medications, patients with IBD appear to have similar outcomes related to COVID-19 as the general population, with age and comorbidities as contributors to hospitalizations and deaths (in contrast to medical therapies).

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Best Practices in the Management of Heart Failure: What Managed Care Needs to Know About an Evolving Treatment Paradigm

Michael Miller, MD, FACC, FAHA, FASPC, FNLA

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

Summary

Heart failure continues to be a major, costly issue. Two important outcomes to managed care related to this disease are hospitalizations and readmissions. Several interventions including newer therapies, cardiac rehabilitation, and medication adherence improvements can help improve these important outcomes.

Key Points

- Biomarkers (including BNP) should be used for diagnosis/prognosis.
- Comorbid conditions that may be contributing to decompensation and hospitalizations need to be optimally managed.
- Newer therapies (sacubitril/valsartan, ivabradine) reduce mortality and hospitalization and should be considered in appropriate patients.
- Cardiac rehabilitation programs and medication adherence measures reduce hospitalization.

HEART FAILURE (HF) LEADS TO A significant clinical and economic burden in the United States (U.S.). The prevalence is 6.5 million in U.S. adults.[1] The lifetime risk of HF is one in five after age 40 and the five-year mortality rate is 50% after age 80. The total direct medical costs were estimated to be $30.7 billion in 2012 and are projected to increase to $69.7 billion by 2030. Hospitalizations drive a significant portion of the costs with over four million hospitalizations annually.[2] There is a high readmission rate after initial hospitalization for HF - 20% within one month and 50% within six months.[3] Seventeen percent of patients are readmitted two or more times. Medicare incurs the majority of the economic burden of HF. HF-related mortality decreased significantly from 2006 to 2009, but it did not change meaningfully between 2009 and 2014.[2] Given the substantial health care costs, the mortality burden of HF, and the aging U.S. population, continued improvements in HF prevention, management, and surveillance are important.

Goals in managing HF to reduce costs are to prevent patients from requiring hospitalizations and, if hospitalized, preventing readmissions. Clinical practice guidelines are available for managing HF and can provide guidance on therapies which have been shown to improve morbidity and mortality and reduce hospitalizations. The American College of Cardiology, the American Heart Association, and the Heart Failure Society of America (ACC/AHA/HFSA) did a focused update of their management guidelines in 2017.[3] One aspect that was updated was the use of biomarkers in the initial and serial evaluation of HF. The guidelines recommended measurement of natriuretic peptide biomarkers to support a diagnosis or exclusion of HF in patients presenting with dyspnea.[4] Measurement of B-type natriuretic peptide (BNP) or N-terminal (NT)-pro hormone BNP (NT-proBNP) is also useful for establishing prognosis and disease severity in chronic HF. Lastly, measurement of baseline levels of natriuretic peptide biomarkers on admission to the hospital is useful to establish a prognosis in acutely decompensated HF.

Identification and management of comorbidities which may be contributing to the HF is very

Exhibit 1: Diagnostic Testing in the Initial Evaluation of HF[5]

Tests	Purpose
CBC, BMP,LFTs, magnesium, calcium	Evaluate the patient's suitability for particular therapies, detect reversible/treatable causes of HF.
Lipid profile	Evaluate for comorbidities.
TSH	Rule out hypo- and hyperthyroidism.
HbA1c	Evaluate for comorbidities.
BNP, NT-proBNP	Assist in diagnosis of HF.
EKG	Evaluate rate, rhythm, QRS morphology, QRS duration.
CXR	Evaluate for comorbidities, evidence of HF.
Echocardiogram	Determine Efm, evaluate for valvular and other structural heart disease.
Noninvasive imaging to detect ischemia e.g., stress testing, etc.)	Detect underlying myocardial ischemia.
Additional tests for select patient populations	**Purpose**
Ferritin, TIBC, transferrin saturation	Rule out hemochromatosis, anemia.
HIV	Evaluate suitability for particular therapies, detect reversible/treatable causes of HF.
ANA, Lyme serology	Evaluate for underlying diagnosis.
Cardiac MRI	Evaluate for myocardial infiltration (e.g., amyloid) or scar tissue from a previous cardiac event.

ANA = antinuclear antibodies; BMP = basic metabolic profile; BNP = B-type natriuretic peptide; CBC = complete blood count; CXR = chest x-ray; EFm = ejection factor measurement; EKG = electrocardiogram; HF = heart failure; HIV = human immunodeficiency virus; LFTs = liver function tests; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TIBC = total iron binding capacity; TSH = thyroid stimulating hormone.

important. Uncontrolled hypertension, diabetes mellitus, chronic kidney disease, and atrial fibrillation can all contribute to HF decompensation and hospitalization. Treatment of each of these underlying conditions needs to be optimized to limit their impact. The recommended diagnostic tests for HF can identify many of these (Exhibit 1).[5] Some of the comorbidities have specific recommendations based on updated information in the revised guidelines. For patients with anemia who have New York Heart Association (NYHA) class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is < 20%), intravenous iron replacement might be reasonable to improve functional status and quality of life. In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality because newer data show an absence of therapeutic benefit. A new section on hypertension was added to the revised guidelines. In patients at increased risk for HF (stage A HF), the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg. Patients with heart failure with reduced ejection fraction (HFrEF) and hypertension should be prescribed guideline-directed medical therapy (GDMT) titrated to attain systolic blood

Exhibit 2: Comorbid Sleep Disorders[4]

COR	LOE	Recommendations	Comment and/or Rationale
IIa	C-LD	In patients with NYHA class II–IV HF and suspicion of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable.	**NEW:** Recommendation reflects clinical necessity to distinguish obstructive versus central sleep apnea.
IIb	B-R	In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.	**NEW:** New data demonstrate the limited scope of benefit expected from CPAP for obstructive sleep apnea.
III: HARM	B-R	In patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm.	**NEW:** New data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnea.

COR = Class of Recommendation; LOE = Level of Evidence; C-LD = limited data; B-R = moderate randomized data;
NYHA = New York Heart Association; CPAP = continuous positive airway pressure; HFrEF = heart failure with reduced ejection fraction

pressure less than 130 mm Hg. Patients with heart failure with preserved ejection fraction (HFpEF) and persistent hypertension after management of volume overload should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg. The recommendations for comorbid sleep disorders are shown in Exhibit 2.[4]

Once diagnosed, therapy appropriate to the level of disease (Exhibit 3) and tailored to the patient should be initiated.[6] The cornerstone of medical treatment for HFrEF has been the combination of an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) with a beta-blocker. All three of these medication classes and mineralocorticoid receptor antagonists (MRA, spironolactone and eplerenone) have been shown to reduce mortality.

The newer combination of valsartan (ARB) and sacubitril (neprilysin inhibitor) [Entresto®] appears to reduce mortality better than either an ACE-I or an ARB alone (20% reduction) in those with HFrEF. Valsartan/sacubitril costs approximately $5460 annually compared to the much less expensive, generic ACE-I or ARBs. The guidelines recommend switching to this combination in patients with NYHA class II to III HFrEF who have adequate blood pressure on ACE-I or ARB and have no contraindications to either component to further reduce morbidity and mortality.[4]

Ivabradine (Corlanor®) can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.[4] In the SHIFT trial comparing ivabradine to placebo, there was an 18% reduction in composite of cardiovascular death or hospitalization for HF and a 26% reduction in hospitalization for HF with ivabradine therapy.[7] The rationale for adding this agent is to further reduce HF hospitalizations.

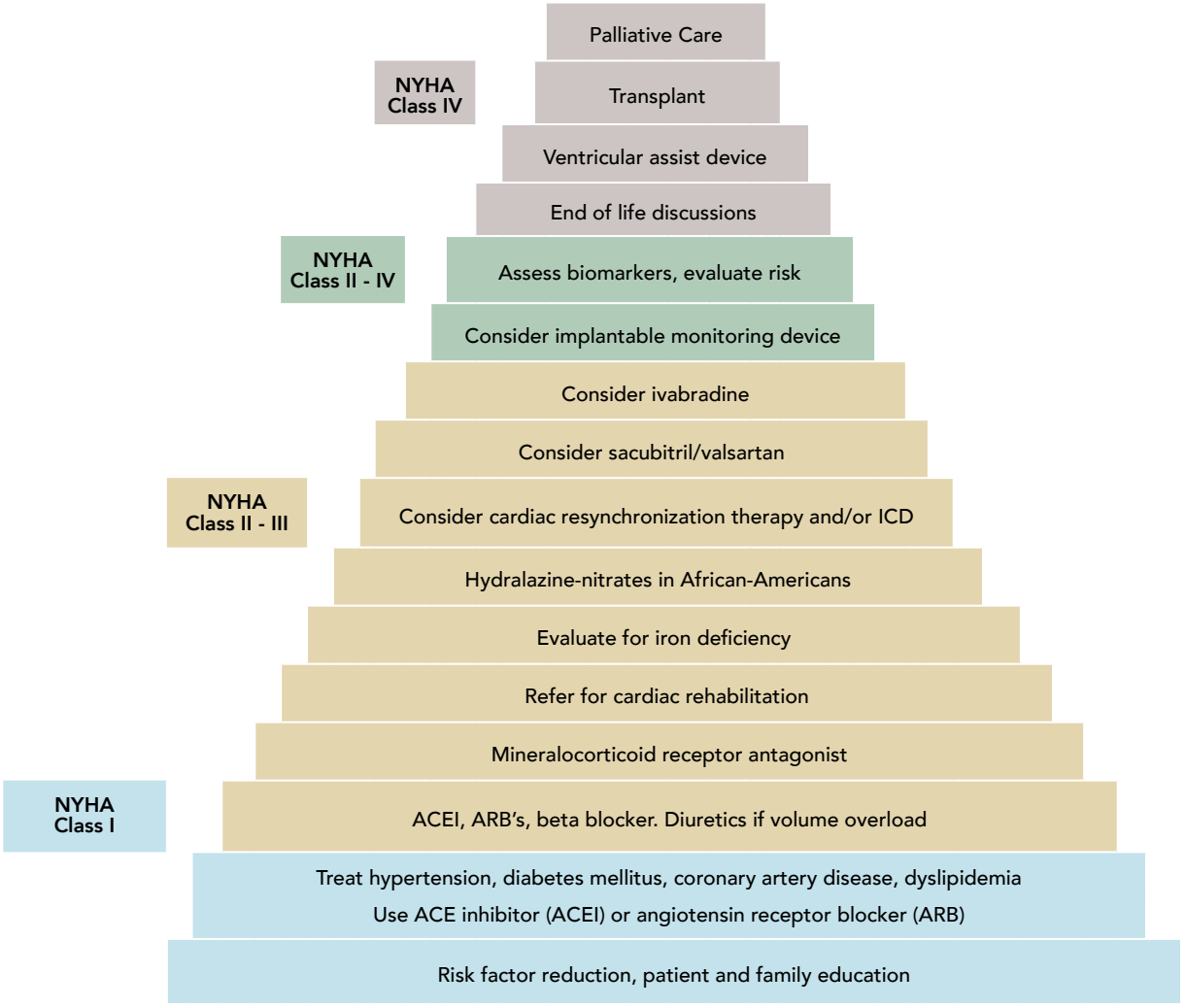
Exercise-based cardiac rehabilitation (CR) programs are another treatment option. Low to moderate quality evidence shows that CR probably reduces the risk of all-cause hospital admissions and may reduce HF-specific hospital admissions in the short term (up to 12 months).[8] CR may confer a clinically important improvement in health-related quality of life, although these benefits are uncertain because the evidence is of low quality.

Poor adherence to medications is a common problem among HF patients, which leads to increased HF exacerbations, reduced physical function, and higher risk for hospital admission and death. Overall, medication adherence interventions were found to significantly reduce mortality risk among HF patients (relative risk, 0.89; 95% CI, 0.81, 0.99), and decrease the odds for hospital readmission (odds ratio, 0.79; 95% CI, 0.71, 0.89).[9] Daily weight measurement may be more useful than monitoring medication taken to prevent hospital readmission. Medication adherence should be addressed in regular follow-up visits with HF patients, and interventions to improve adherence should be a key part of HF self-care programs.

Conclusion

Heart failure continues to pose a high economic burden in the U.S. Best practice in HF management includes using biomarkers (BNP) for diagnosis/prognosis and optimally managing comorbid conditions. Newer therapies (sacubitril/valsartan, ivabradine) reduce mortality and hospitalization and should be considered in appropriate patients. Cardiac

Exhibit 3: Approach to the Heart Failure Patient[6]



rehabilitation programs and medication adherence measures reduce hospitalization. These should both be covered by and endorsed by managed care.

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Informed Decision-Making in the Treatment and Management of Multiple Sclerosis: Optimizing Therapeutic Switching and Sequencing 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

There are now numerous disease-modifying treatments which effectively treat multiple sclerosis. The optimal choice of therapy for a given patient requires shared decision-making between the clinician and patient which considers many patient, disease, medication, and access factors. Those patients with risk for progression and disability need more aggressive therapy.

Key Points

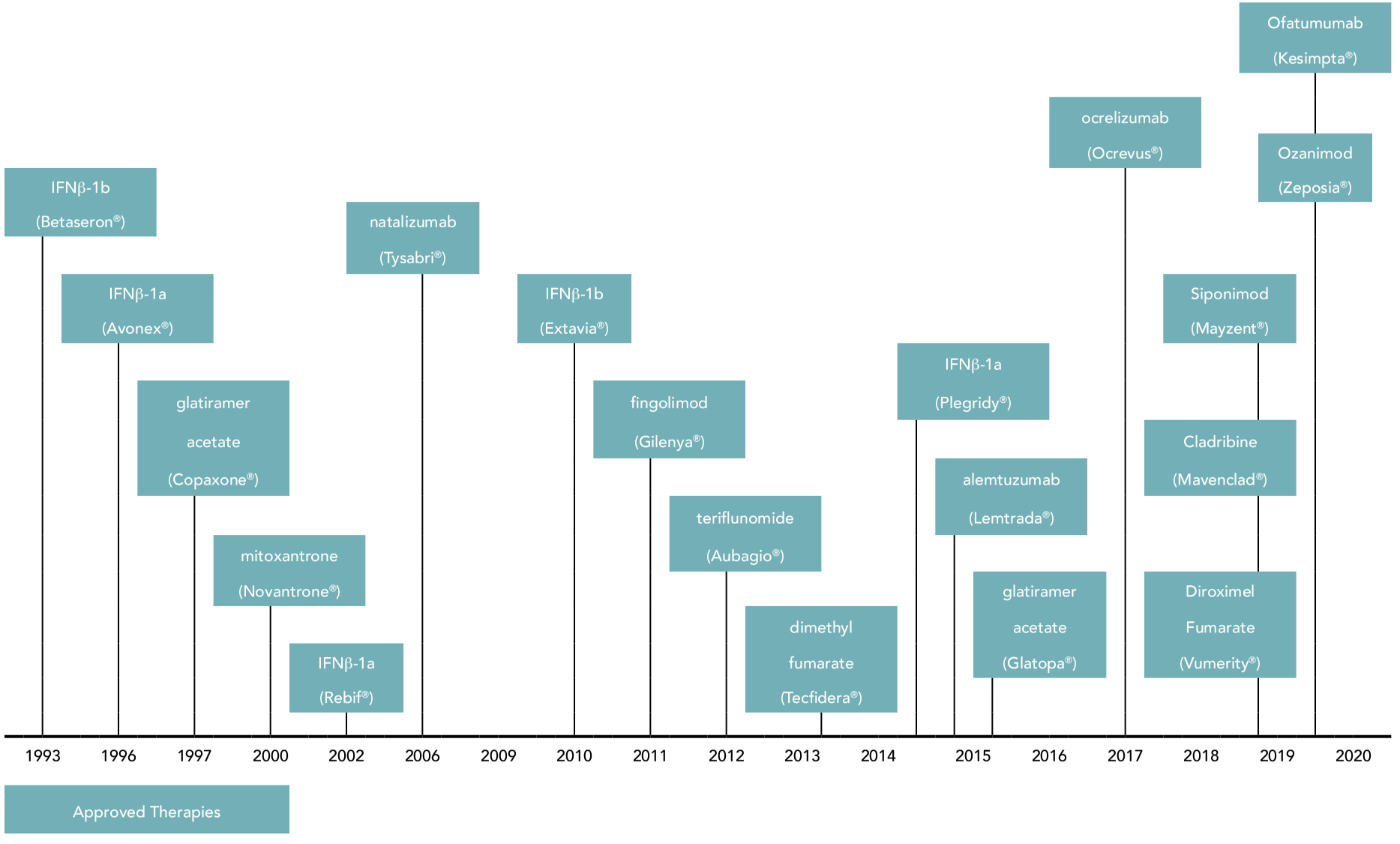
- Disease, medication, patient, and access factors affect therapy selection.
- Modifiable risk factors for disease activity and progression also must be addressed.
- Patient adherence to the therapeutic regimen and follow-up is important.
- Patients need to buy into the choice of therapy and understand the risk versus benefit of that choice.
- Monitor patients closely and make adjustments based on tolerability and efficacy.

MULTIPLE SCLEROSIS (MS) IS A LIFELONG, complex, heterogeneous, chronic autoimmune demyelinating disorder of the central nervous system (CNS) characterized by the accumulation of inflammatory cells and cytokines at the sites of demyelination and plaque formation. It causes issues with motor, sensory, balance and coordination, cognition, vision, and speech function. Physical fatigue, mental fatigue, chronic pain, and incontinence also occur. MS is broadly categorized into three major subtypes: relapsing–remitting MS (RRMS); progressive MS, both primary (PPMS) and secondary (SPMS), and clinically isolated syndromes (CIS).

In MS, autoreactive lymphocytes [T helper (Th)1, Th2, Th9, Th17, Th22 cells, CD4+, CD8+ T cells and B cells] cross the blood-brain barrier (BBB) and enter the CNS where various inflammatory cytokines (Interleukin [IL] -2, IL-6, IL-9, IL-12, IL-17, IL-22, IL-23, IL-27, interferon [IFN]-gamma, tumor necrosis factor [TNF]-alpha) are released. The inflammatory storm leads to axonal damage, gliosis, disruption of the blood–brain barrier (BBB), and demyelination within the brain and spinal cord.

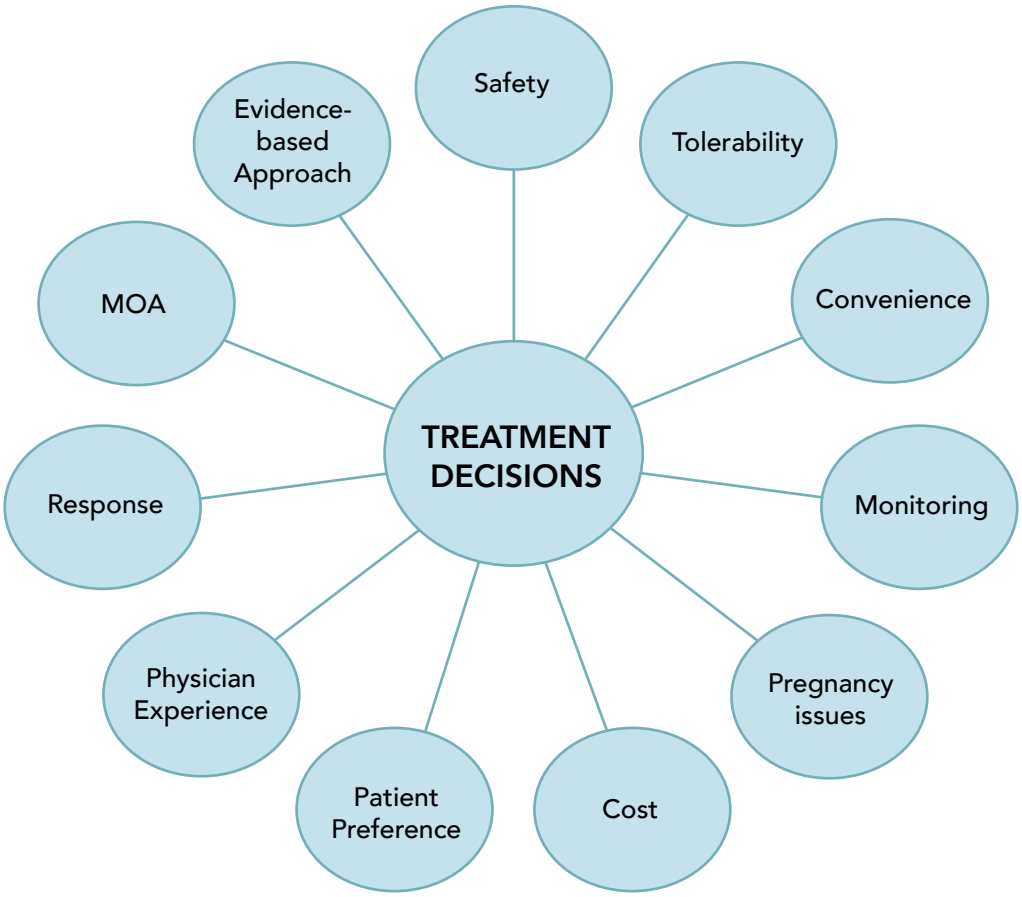
Current MS therapeutic approaches include wellness and health maintenance, treatment of acute clinical attack/relapses, symptomatic therapy, and disease-modifying therapy (DMT). There is increasing evidence that wellness and health maintenance improve CNS reserve, function, and repair and can be considered DMT. Components of wellness and health maintenance involve maintaining high-normal vitamin D levels, maintaining vitamin B12 levels greater than 400 pg/mL, regular aerobic

Exhibit 1: FDA-Approved MS Disease-Modifying Therapies



IFNβ = interferon beta

Exhibit 2: Making Treatment Decisions



exercise, weight loss if appropriate, no smoking, limiting alcohol and salt, consuming a healthy diet, having regular mental and social stimulation, practicing good sleep hygiene, and developing stress management techniques. It is also important that patients control their blood pressure, lipids, and glucose values to reduce cardiovascular and cerebrovascular risk.

General principles of MS treatment with DMT are to begin treatment as soon as possible after diagnosis and to consider disease activity and prognostic profile in selecting therapy. Treatment should ideally start at the CIS stage. If both disease activity and prognostic profile are worrisome, the most aggressive therapy possible is indicated. Other principles are to follow patients closely and switch therapies if there is a poor response.

The current therapeutic landscape includes numerous DMTs, including some generics with 10 different mechanisms of action (Exhibit 1). All are FDA approved for relapsing forms of MS, one approved for PPMS, and two approved for SPMS. These agents are injectables, orals, and monoclonal antibodies, plus the chemotherapy agent mitoxantrone, which is now rarely, if ever, used.

Two new agents were FDA approved in 2020 and are reviewed here. Ofatumumab is a recombinant anti-CD20 antibody given subcutaneously once a month after three weekly loading doses. It was originally approved by the FDA in 2009 for chronic lymphocytic leukemia that is refractory to fludarabine and alemtuzumab. It has the same mechanism of action as ocrelizumab (Ocrevus®) and reduces B lymphocytes. The efficacy of ofatumumab was demonstrated in two randomized, double-blind, double-dummy, active comparator (teriflunomide) controlled clinical trials of identical design, in patients with relapsing forms of MS. Both studies enrolled patients with at least one relapse in the previous year, two relapses in the previous two years, or the presence of a T1 gadolinium-enhancing (GdE) lesion in the previous year. Patients were

Exhibit 3: Prognostic Factors

	Good	Poor
Race	Caucasian	Black
Age at onset	Young (< 35 years of age)	Older (> 35 years of age)
Gender	Female	Male
Smoker	No	Yes
Subtype	Relapsing	Progressive
First attack	Optic neuritis, sensory, unifocal	Motor, cerebellar, sphincter, multifocal
Recovery	Complete	Incomplete
Attack rate	Low	High (≥ 2 in one year)
Disability at five years	No	Yes
MRI lesions	Cerebral	Brainstem, cord
Lesion load	Low	High (≥ 2 in one year)
Enhancement	Absent	Present

also required to have an expanded disability status scale (EDSS) score from 0 to 5.5. In both studies, ofatumumab significantly lowered the annual relapse rate (ARR) compared to teriflunomide (0.11 vs 0.22, 0.10 vs 0.25).[1] It also significantly reduced the risk of three-month confirmed disability progression, the number of T1 GdE lesions, and the rate of new or enlarging T2 lesions in both studies compared to teriflunomide. The most common adverse reactions (incidence greater than 10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions. There are no published data comparing ofatumumab to ocrelizumab.

Ozanimod (Zeposia®) is an oral sphingosine 1-phosphate receptor modulator, like siponimod (Mayzent®) and fingolimod (Gilenya®), indicated for the treatment of relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary-progressive disease in adults. It blocks the capacity of lymphocytes to exit lymph nodes, reducing the number of lymphocytes in peripheral blood. Ozanimod has been compared to interferon beta-1a in two trials. In a 24-month, Phase III, double-blind, double-dummy study in participants with relapsing multiple sclerosis, ozanimod was well tolerated and associated with a significantly lower rate of clinical relapses than intramuscular interferon beta-1a (0.17 vs 0.28).[2] The incidence of treatment-emergent adverse events was higher in the interferon beta-1a group (83%) than in the ozanimod 1.0 mg group (74.7%). More participants in the interferon beta-1a group had treatment-emergent adverse events leading to treatment discontinuation than in the ozanimod groups. Incidences of infections and serious treatment-emergent adverse events were similar across treatment groups. No cases of ozanimod-related symptomatic reduction in heart rate and no second-degree or third-degree cases of atrioventricular block were reported. Similar efficacy results were shown in a 12-month trial with the same design (ARR 0.18 vs 0.35).[3] The most common adverse effects (incidence ≥ 4%) are upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension. Ozanimod has not been directly compared to siponimod or fingolimod.

In selecting DMT, the clinician has to consider the benefits and risks of each therapy (Exhibit 2). Prognosis is also important (Exhibit 3). Disease factors to consider are frequency and severity of relapses, duration since MS onset, lesion burden on MRI, lesion location, residual neurologic deficits, and the EDSS score.[4-7]

Access factors include formulary restrictions and out-of-pocket costs. Patient factors include patient preference on potency, safety and administration

Exhibit 4: AAN Guidelines for Initiating DMT Therapy[4]

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

DMT = disease-modifying therapy;
CIS = clinically isolated syndrome;
AE = adverse event

route (IV, SQ, oral); risk tolerability; monitoring requirements; age; plans for future pregnancy; comorbidities; impairment impacting monitoring or adherence; and ethnicity. The best medication for a given patient is one that suppresses disease activity, is tolerable, causes no adverse effects, is accessible, and allows him/her to continue a high quality of life.

Shared decision-making is very important in selecting therapy. When patients engage in shared decision-making, they learn about their health and understand their health conditions, recognize that a decision needs to be made and are informed about the options, understand the pros and cons of different options, and have the information and tools needed to evaluate their options. They are also better prepared to talk with their health care provider, collaborate with their health care team to make a decision right for them, and they are more likely to follow through on their decision (adherence).

Patients with increased risk of worsening disability might be expected to benefit from more aggressive initial therapy. Multiple relapses with short inter-relapse intervals, relapses with incomplete recovery, residual motor or cerebellar disability, older age at presentation, higher lesion burden on MRI, brainstem and spinal cord lesions, and African-American ethnicity are all risk factors for disability.[4,8-11]

Exhibit 4 summarizes the American Academy of Neurology (AAN) guidelines on starting DMT.[7] It is important to note that the AAN guidelines have not been updated since the approval of siponimod, ozanimod, and ofatumumab, which are also options in patients with highly active MS.

Once a therapy is selected, clinicians, working with the patient, should define treatment goals and expectations develop and a monitoring plan. It is important for clinicians to set reasonable expectations (decreased relapses, disability, MRI activity) of therapy with the patient and for them to understand that there is no cure for MS; however they also need to understand that therapy can control the disease and limit long-term damage. Patients need to be taught how to recognize any clinical changes suggestive of relapse and the importance of being in contact with their care team as soon as possible at the time of occurrence. An assessment of the clinical changes and treatment adherence can verify disease breakthrough activity.

The monitoring plan should include efficacy, treatment adherence, and adverse effect monitoring. Clinical symptoms for relapse or worsening can be assessed at each visit. Avoidance of relapses is important because relapses on treatment decrease time to progressive MS, and relapses in progressive MS increase disability progression.[12] Adherence should also be assessed at each visit. Documentation of adherence is a precondition for confirming breakthrough and prevents unnecessary medication intensification. In addition to symptoms and EDSS, medication efficacy is measured by MRI.

The Consortium of MS Centers, an international group of neurologists, radiologists, and imaging scientists with an expertise in MS from North America and Europe, publish recommendations on the use of MRI in MS, which can be used by managed care as a basis for approval of these scans.[13] A brain MRI with gadolinium is recommended for the diagnosis of MS, and a spinal cord MRI is recommended if the brain MRI is non-diagnostic,

or if the presenting symptoms are referable to the spinal cord. Follow-up brain MRI is recommended to demonstrate dissemination in time for diagnosis, to detect clinically silent disease activity while on treatment, as safety monitoring including progressive multifocal leukoencephalopathy (PML) surveillance while on treatment, to evaluate unexpected clinical worsening, to reassess the original diagnosis, as a new baseline MRI before starting or modifying therapy, and every six months to two years for patients with relapsing MS. The recommended interval for those with stable relapsing MS and unchanged DMT has changed from every six to 12 months and can even be extended beyond two years. A long-term study of interferon and glatiramer combination therapy found that activity on MRI at three years did not predict risk of worsening over up to seven years of follow-up.[14]

Treat-to-target in MS is a concept borrowed from rheumatoid arthritis and other disease. The target in MS is no evidence of disease activity (NEDA), and the complete absence of detectable disease activity while on DMT. This means no new MRI lesion activity, no clinical relapses, and no disability worsening. NEDA rates are increasingly reported in clinical trials and can be utilized in practice.

Expansion of DMT options with various potencies now present questions of what is the best treatment strategy – escalation or induction.[6,15-17] Currently, an escalation treatment paradigm is the norm where initial therapy is started with monitoring for evidence of breakthrough disease and switching to an alternate class agent if breakthrough occurs. Initial therapy may involve first-generation or newer higher-potency agent. An induction treatment paradigm involves giving the highest potency agents or a bone marrow transplant to achieve rapid disease control and possibly reset the immune system. For example, alemtuzumab (Lemtrada®) might produce a durable response through a permanent rebalancing of the immune system.[15] Subsequent maintenance therapy could be given with an agent with a better safety profile for possible maintenance of the immune reset by prolonged immune-modulating effects. Therapy after induction may only be needed periodically for recurrent inflammation. Trials are ongoing to examine the induction approach.

The complexity of the MS therapeutic landscape dictates a multidisciplinary team to deliver comprehensive care. Multiple medical, physical, social, and psychologic issues can be addressed by various team members. A comprehensive care team may be able to identify breakthrough disease early. This type of care also leads to empowerment for patients, families, and the care team and improves communication, adherence to treatment, continuity of care, and patient quality of life.

Numerous agents are under investigation for MS treatment. High-dose biotin, a co-enzyme for carboxylases in the Krebs cycle believed to improve cellular energy production, improved EDSS in 12.6 percent of 154 patients with progressive MS in a 12-month study.[18] Clemastine, an antihistamine shown to stimulate oligodendrocyte precursor differentiation in vitro, improved latency of visual evoked potential (VEP) in patients with chronic optic neuropathy.[19] Opicinumab, a monoclonal antibody that blocks an inhibitor of myelination and axonal regeneration (anti-LINGO-1), produced improvement on VEP latency versus placebo in acute optic neuritis, but the SYNERGY study failed to show confirmed disability improvement on a composite endpoint.[20,21] Ibudilast, which inhibits macrophage inhibitory factor, decreased the rate of brain atrophy in primary-progressive MS.[22]

Conclusion

Clinicians need to consider disease, medication, access, and patient factors in selecting therapy. Modifiable risk factors for disease activity and progression also must be addressed. Stressing adherence to the therapeutic regimen and close follow-up are also important. Clinicians need to monitor patients closely and make adjustments based on tolerability and efficacy.

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Navigating Recent Advances in the Treatment of Advanced Renal Cell Carcinoma (RCC)

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Summary

The past decade of research in renal cell carcinoma (RCC) has resulted in numerous new treatments. The paradigm for treating metastatic disease has changed significantly recently based on new studies and FDA approvals. Combination therapy is becoming the norm for first-line therapy in metastatic disease.

Key Points

- Clear cell histology is the most common form of RCC.
- First-line treatment of metastatic disease is selected based on surgical resectability, tumor histology (clear cell or non-clear cell), and in the case of clear cell histology, risk profile.
- Combination therapy with antiangiogenic oral medications and checkpoint immunotherapy has been shown to improve overall survival and progression-free survival over antiangiogenic therapy alone.

THE AMERICAN CANCER SOCIETY estimates there will be 76,080 new cases of renal cell carcinoma (RCC) and approximately 13,780 people will die from this disease in the United States (U.S.) in 2021.[1] Most people with this cancer are older, with an average age of 64 at diagnosis; it is very uncommon in people younger than age 45. RCC affects more men than women. The overall five-year survival rate for RCC is 75.2 percent.[2]

Treatment of RCC depends on the stage at diagnosis.[3] Unlike many other cancers, the majority of RCC cases are diagnosed when the disease is still localized to the kidney (56%), and only 16 percent of cases are metastatic at diagnosis.[2] RCC can often be cured by surgical resection if it is diagnosed and treated when still localized to the kidney and to the immediately surrounding tissue.[4]

The major advances in treatment have occurred in the management of advanced RCC (Stage IV, metastatic). Advanced disease can be treated surgically with cytoreductive nephrectomy or systemically with immune checkpoint inhibitors and antiangiogenic and other tyrosine kinase targeted therapies (axitinib, cabozantinib, pazopanib, sunitinib). First-line treatment is selected based on surgical resectability, tumor histology (clear cell or non-clear cell), and in the case of clear cell histology, risk profile. Clear cell is the most common type of RCC. Exhibit 1 shows the two risk models used by the National Comprehensive Cancer Network (NCCN) guidelines to direct treatment for metastatic disease.[5,6] Those with low or favorable risk have the best survival compared to those with intermediate or poor risk. In a population-based study, using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, two-year overall survival (OS) in those with favorable risk was 75 percent, with intermediate risk 53 percent, and with poor risk 7 percent.[7]

For clear cell histology, checkpoint immunotherapy is part of several of the preferred regimens (Exhibit 2).[3] There are only two preferred therapies for non-clear cell histology – enrollment in a clinical trial or sunitinib. Combination therapy with immunotherapy and a tyrosine kinase inhibitor (TKI) is becoming the most common choice in first-line

Exhibit 1: Risk Models to Direct Treatment[5,6]

Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model	
Prognostic Factors	Prognostic Risk Groups
Interval from diagnosis to treatment of less than 1 year	Low-risk: No prognostic factors
Karnofsky performance status less than 80%	Intermediate-risk: 1 to 2 factors
Serum LDH greater than 1.5 times ULN	Poor-risk: 3 or more factors
Corrected serum calcium greater than ULN	
Serum hemoglobin less than LLN	
International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria	
Prognostic Factors	Prognostic Risk Groups
Less than 1 year from diagnosis to systemic therapy	Favorable-risk: No prognostic factors
Performance status less than 80% (Karnofsky)	Intermediate-risk: 1 to 2 factors
Hemoglobin < LLN	Poor-risk: 3 to 6 factors
Calcium > ULN	
Neutrophil > ULN	
Platelets > ULN	

LDH = lactate dehydrogenase; ULN = upper limit of normal; LLN = lower limit of normal

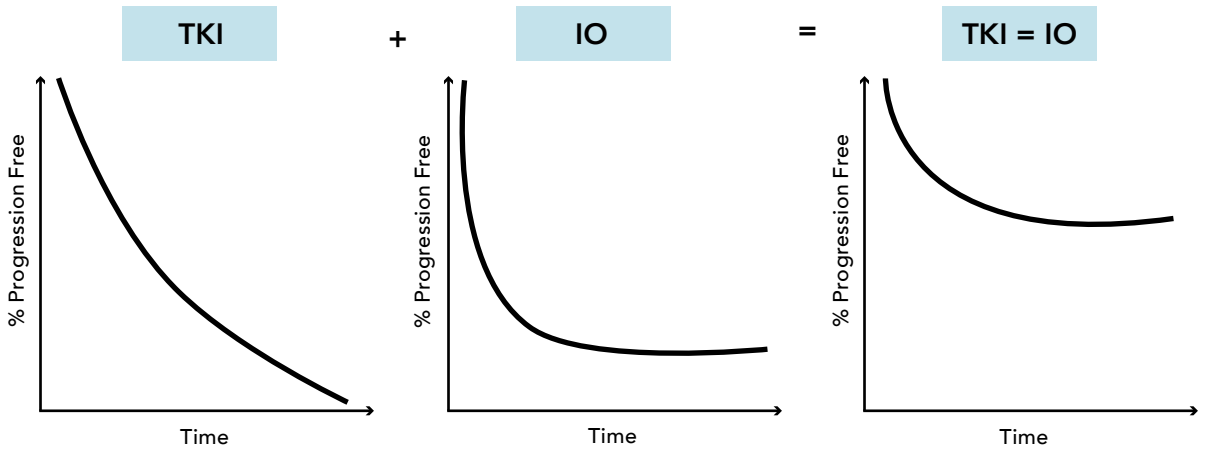
therapy for advanced clear cell RCC with the hope of increasing those who remain progression free (Exhibit 3).

The combination of pembrolizumab, anti-programmed death one (PD-1) immunotherapy, and axitinib, a selective second-generation TKI which inhibits vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, were compared to sunitinib in the Keynote-426 trial in previously untreated advanced clear cell RCC.[8] After a median follow-up of 12.8 months, the estimated percentage of patients who were alive at 12 months was 89.9 percent in the pembrolizumab-axitinib group and 78.3 percent in the sunitinib group ($p < 0.0001$). Median progression-free survival (PFS) was 15.1 months in the pembrolizumab-axitinib group and 11.1 months in the sunitinib group ($p < 0.001$). The benefit of pembrolizumab plus axitinib was observed across the IMDC risk groups (i.e., favorable, intermediate, and poor risk) and regardless of programmed death

Exhibit 2: NCCN First-Line Therapy for Clear Cell Histology RCC[3]

Risk	Preferred Regimens
Favorable	Axitinib + pembrolizumab
	Cabozantinib + nivolumab
	Pazopanib
	Sunitinib
Poor/Intermediate	Axitinib + pembrolizumab (category 1)
	Ipilimumab + nivolumab (category 1)
	Cabozantinib + nivolumab
	Cabozantinib
See guidelines for other recommended regimens and agents useful in certain circumstances	

Exhibit 3: Objective of Combination Therapy



TKI = tyrosine kinase inhibitor; IO = immunotherapy

ligand 1(PD-L1) expression. Grade 3 or higher adverse events of any cause occurred in 75.8 percent of patients in the pembrolizumab-axitinib group and in 70.6 percent in the sunitinib group.

Cabozantinib plus nivolumab is another preferred combination of VEGF-TKI and checkpoint immunotherapy. The CheckMate 9ER trial, comparing this combination to sunitinib in the first- line setting, found that the combination improved PFS (16.6 months versus 8.3 months, $p < 0.0001$) and OS at interim analysis ($p < 0.001$).[9] Response rates also significantly favored the combination (56% versus 27%). These benefits appeared to be irrespective of IMDC prognostic subgroups and PD-L1 biomarker status. Quality-of-life data favored the cabozantinib and nivolumab combination. Other combinations, including ipilimumab/nivolumab and axitinib/avelumab and single-agent VEGF-TKI, are also possible options.[3]

Numerous other combinations and additional new VEGF-TKI are under study. Cabozantinib in combination with atezolizumab and tivozanib in combination with nivolumab are examples that are being studied. Tivozanib has been submitted to the FDA for approval for refractory or relapsed RCC. Also under investigation is chimeric antigen receptor (CAR) T-cell therapy. This is a promising new way to get T cells to fight cancer by changing them in the lab so they can find and destroy cancer cells. In RCC, CAR-T-cell therapy is directed at various markers expressed on the tumor cell.[10]

An interesting area of investigation is the impact of the body's microbiome on the efficacy of immunotherapy. Research is showing that primary resistance to immune checkpoint inhibitors in RCC and non-small cell lung cancer can be attributed to abnormal gut microbiome composition.[11] Investigators are currently trying to determine which components of the gut microbiome predict responses and if altering the microbiome improves responses. For example, *clostridium butyricum* (CBM 588), a probiotic, is being studied in combination with nivolumab/ipilimumab in advanced RCC (ClinicalTrials.gov Identifier: NCT03829111).

Conclusion

Progress is being made in improving survival in advanced RCC. Combination therapy targeted at angiogenesis and activating the immune system has become first-line therapy for clear cell histology, metastatic RCC.

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Novel Treatment Approaches in Moderate to Severe Rheumatoid Arthritis: Expert Perspectives on an Evolving Treatment Paradigm

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Summary

Undertreated rheumatoid arthritis (RA) can be a devastating disease. There are now numerous disease-modifying therapies targeting various components of the underlying immune pathophysiology which can put the disease into remission and prevent disease-related disability.

Key Points

- Clinicians need to follow guideline-recommended care and treat-to-target (remission).
- Early treatment of RA is important to prevent joint damage.
- Treatment decision-making needs to be personalized.
- Switching to another class of therapy after TNF inhibitor failure is a better option than cycling TNF inhibitors.
- Adherence interventions are important in achieving good outcomes.

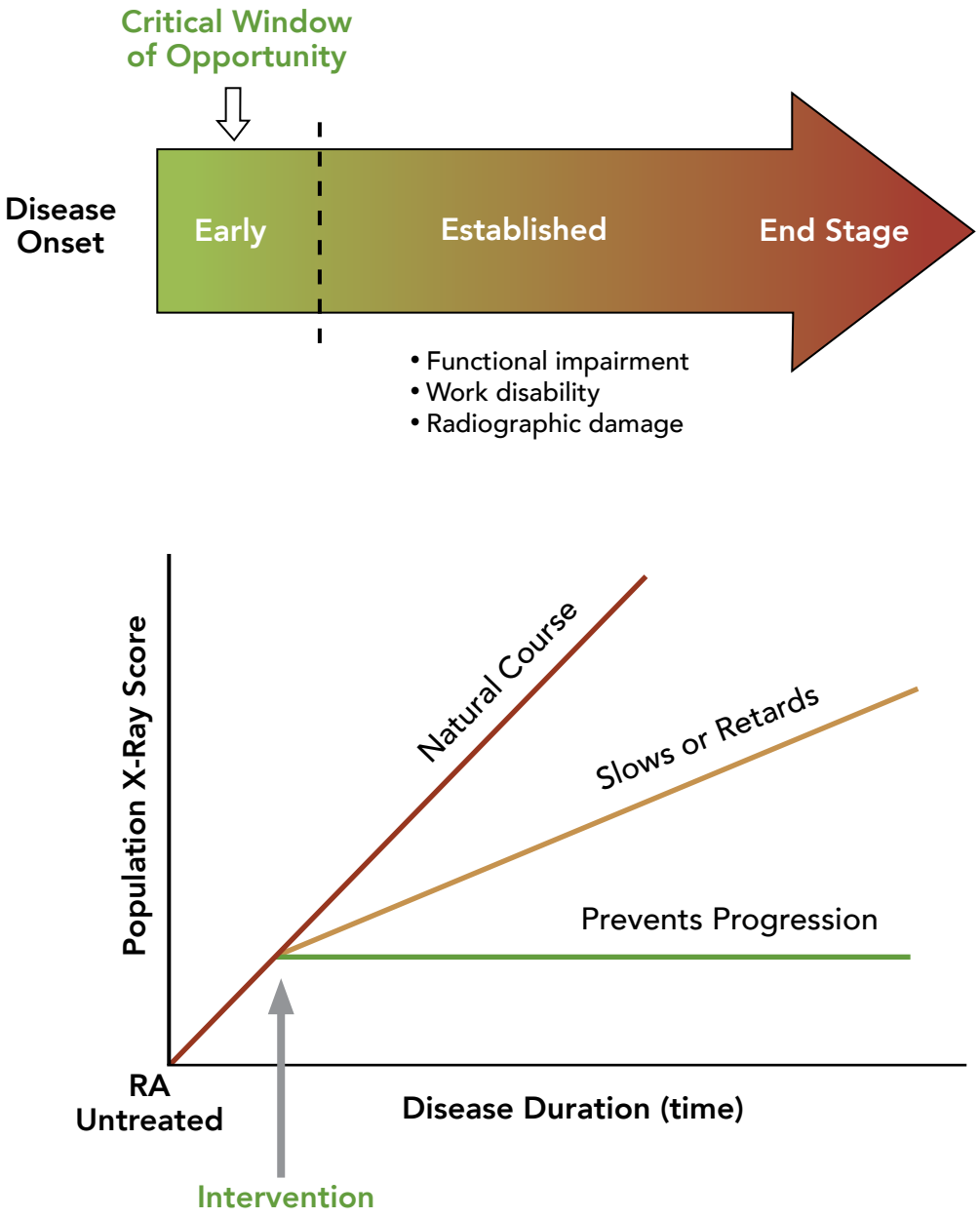
RHEUMATOID ARTHRITIS (RA) AFFECTS about 1.3 million Americans.[1] Women are two to three times more likely to get RA than men. Because RA is a systemic autoimmune inflammatory disease, there is a high incidence of comorbidities and extra-articular manifestations; underlying inflammation leads to cardiovascular disease, interstitial lung disease, and depression. If left untreated, 20 to 30 percent of RA patients become work-disabled within three years of disease onset.[2] The disease causes a significant health-related quality of life burden, which can be improved by effective treatment.[3]

RA is also a costly disease for the health care system. It is estimated that RA costs $39 billion in direct and indirect medical costs annually.[4,5] RA patients with fatigue and/or stiffness incur increased health care resource utilization and medical costs compared to those without these symptoms.[6]

Fifty to 70 percent of patients with RA have radiographic damage within the first two years after onset of symptoms.[7] Thus, there is a critical window of opportunity during the early phase of disease to intervene to prevent joint damage (Exhibit 1).[8] Timely diagnosis of RA and quick initiation of disease-modifying treatment is essential to maximizing outcomes in this disease.

Improving early diagnosis is an issue which needs to be addressed. The use of certain biomarkers may be helpful. Anti-citrullinated protein antibodies (ACPAs) are one biomarker which has been shown to increase several years before symptoms develop and may be used in the future to identify those at risk for clinical RA[9]. Certain citrullinated antigens bind to specific human leukocyte antigen alleles, leading to formation of ACPAs. The joint synovium affected by RA contains many citrullinated proteins: fibrin,

Exhibit 1: Therapeutic Window of Opportunity in Early RA[8]



vimentin, alpha-enolase, and Type II collagen. ACPAs are highly specific for RA and have become one of the prime biomarkers for the diagnosis of RA and prediction of erosive disease.[10-12] In addition, the biology of autoimmunity to citrullination may be critical to the pathogenesis of RA.

Once diagnosed, the American College of Rheumatology (ACR) recommends a treat-to-target (T2T) strategy in all patients, regardless of disease activity level.[13] Exhibit 2 outlines the components of a T2T approach.[13,14] The goal of treatment should be remission, which is an absence of signs and symptoms of significant inflammatory disease activity. For patients in the later stages of the disease, a goal of low disease activity may be acceptable and the only attainable option.

Exhibit 3 shows the FDA-approved targeted disease-modifying therapies for RA and some of those under investigation. It should be noted that filgotinib, an investigational Janus kinase (JAK) inhibitor, was rejected by the FDA in August of 2020 because of concerns with sperm concentrations.

Exhibit 4 shows the treatment algorithm from the ACR guidelines.[13] In spite of their up-front costs, the addition of biologics to other treatment modalities has been shown to be cost effective when used in appropriate patient populations.[15,16] The ACR position on patient access to biologics is that early use of biologics in rheumatic conditions reduces costs by preventing work absences, improving work performance, and avoiding long-term disability.[17] Although the ACR recognizes that biologic costs are a factor in health care delivery, it believes that restricting access to biologics not only adversely affects patients' health, but impacts important public health outcomes as well.

Many managed care plans require either failure of traditional disease-modifying antirheumatic drugs (DMARDs) or tumor necrosis factor (TNF) inhibitors before moving on to other biologics. Approximately 90 percent of biologic-naïve RA patients receive a TNF inhibitor as their first biologic treatment, even though several alternative mechanism of action (MOA) therapies are approved as first-line options.[18] Restrictive policies may defeat the goal of aggressive treatment early in the disease process and significantly prolong the time until disease remission. Most biologic-naïve RA patients fail to reach treatment targets on their first biologic therapy; in pivotal trials, between 25 and 42 percent of TNF inhibitor-treated patients achieved ACR50 (50% reduction in composite symptom and rating scores).[19] After three months of therapy, patients may remain on anti-TNF therapy even if they fail to achieve the treatment target, mainly due to formulary structures. Patients may have to endure a second and even a third ineffective TNF inhibitor (TNF inhibitor cycling) before changing the MOA. All TNF inhibitors target the same molecular and inflammatory pathways; thus, it is not surprising that most patients who are primary non-responders to their initial TNF inhibitor fail to achieve their treatment targets when cycled through alternative TNF inhibitors. Avoiding cycling would prevent disease progression and improve quality of life for RA patients who are primary non-responders to TNF inhibitors.

Switching to a therapy with a different MOA after TNF inhibitor failure improves clinical outcomes for patients with RA and is more efficient in terms of health care costs and medication adherence than TNF inhibitor cycling.[20] This is supported by the ACR guidelines, which recommend other agents FDA-approved for first-line therapy as an alternative to TNF inhibitors or as a second-line therapy after one TNF inhibitor has been tried, instead of switching to a second TNF inhibitor.[13] Sarilumab, tocilizumab, tofacitinib, baricitinib, rituximab, abatacept, and upadacitinib have been shown to be effective after TNF inhibitor failure or an inadequate response.

Numerous disease, patient, and treatment-related factors must be considered when individualizing RA treatment (Exhibit 5).[21-23] The effect of comorbidities on the patient and any medication selected have to be considered. Hypertension, depression, and hyperlipidemia are the three most common comorbidities in those with RA.[24,25] Some disease factors which predict poor outcomes include moderate to high disease activity after traditional DMARD therapy, high acute phase reactant levels, high swollen joint counts, presence of rheumatoid factor and/or ACPA, especially at high levels, presence of erosions, and failure of two or more traditional DMARDs.[26] Patients whose disease factors suggest moderate to severe disease activity and poor outcomes should receive the most aggressive therapy.

Exhibit 2: Treat-to-Target Ensures Optimal Long-Term Outcomes[13,14]

Treat to desired goal: REMISSION

- Remission: absence of signs and symptoms of significant inflammatory disease activity.
- For long-standing disease, goal may be: **Low disease activity**

Measure disease activity

- High/moderate disease activity: **Monthly**
- Remission/low disease activity: **Every six months**

Use disease activity measures

- Combining joint assessment, patient-reported outcomes, and labs

Adjust therapy

At least every **three months** until target is reached

Personalize treatment strategy

Consider **all factors**, including comorbidities, structural changes, functional impairment

Exhibit 3: Approved and Emerging Targeted Therapies for RA

Status	Therapy	Target	Route	Dose Frequency
	Injectable Biologics			
Approved	Rituximab	CD-20	IV	Q6M (2 doses)
	Abatacept	CD80/CD86	SC/IV	QW/Q4W
	Adalimumab	TNF-α	SC	Q2W
	Certolizumab	TNF-α	SC	Q2W/Q4W
	Etanercept	TNF-α	SC	QW
	Golimumab	TNF-α	SC/IV	Q4W/Q8W
	Infliximab	TNF-α	IV	Q8W
	Anakinra	IL-1R	SC	QD
	Sarilumab	IL-6R	SC	Q2W
	Tocilizumab	IL-6R	SC/IV	QW/Q4W
	Oral JAK Inhibitors			
	Tofacitinib	JAK 1/3	Oral	BID/QD
	Baricitinib	JAK 1/2	Oral	QD
	Upadacitinib	JAK 1	Oral	QD
Phase III (complete or ongoing)	Filgotinib	JAK 1	Oral	QD
	Peficitinib	JAL 1/3	Oral	QD
	Olokizumab	IL-6R	SC	Q2W/Q4W

R = receptor; IV = intravenous; Q2W = every 2 weeks; QD = daily; BID = twice a day; Q6M = every 6 months

Even when the right medication is selected for the right patient, there can be barriers to optimal outcomes. Exhibit 6 outlines some of the treatment access barriers.[28] Adherence with therapy is also a barrier. RA patients offered medication therapy management programs show significantly higher injectable RA medication adherence and improved patient-reported outcomes.[27]

Conclusion

Uncontrolled RA contributes to costly joint damage and comorbidities, including cardiovascular issues. Treatment decision-making in RA management is complex given the evolving treatment armamentarium with new and emerging therapies with novel mechanisms, marked heterogeneity of RA disease, and numerous patient-specific factors. Thus, treatment decision-making needs to be personalized. To make informed decisions to improve RA outcomes, clinicians need to follow guideline-recommended care. Because early treatment is associated with better outcomes, early treatment targeted at the underlying pathology of RA should be initiated. T2T in early RA is more cost effective than symptomatic treatment. Clinicians need a way to identify which patients would benefit from which mechanism of action to prevent unnecessary costs associated with therapeutic failure. Early identification of patients at risk for non-adherence and medication therapy management interventions improves patient outcomes.

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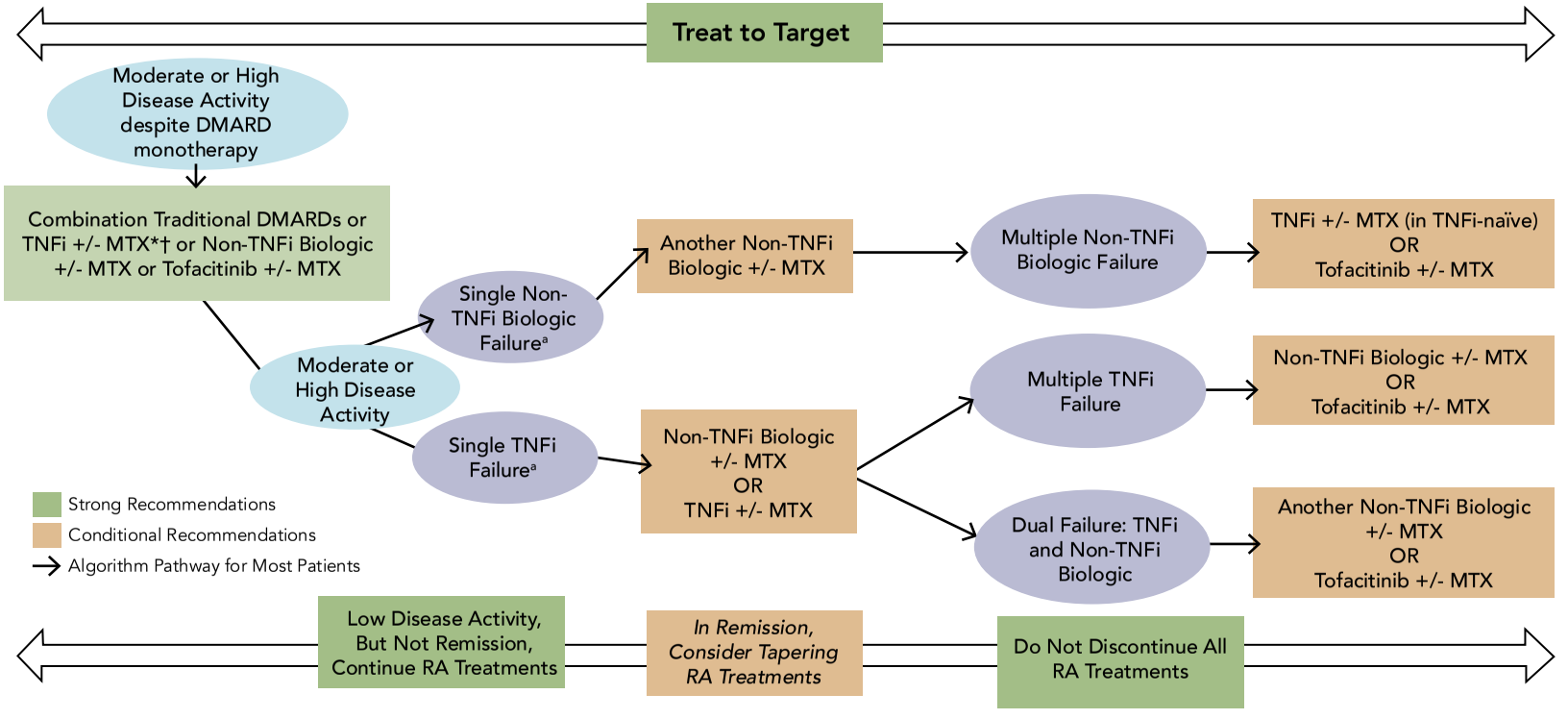
Exhibit 4: ACR Treatment Strategy[13]



[a]Failure defined as patients with moderate or high disease activity despite biologic DMARD therapy.

Exhibit 5: Individualizing RA Treatment is Central to RA Care[21-23]

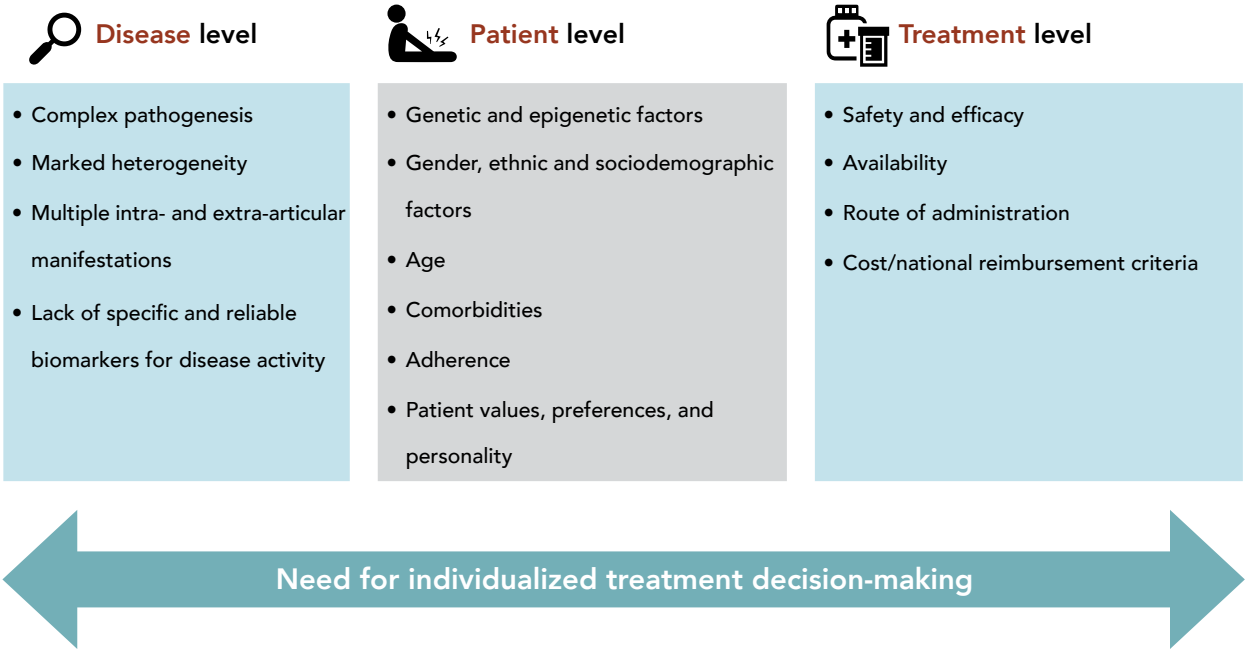


Exhibit 6: Treatment Access Barriers for People with Rheumatic Diseases[28]

Health Systems Coverage and Management	Performance and Organization of Health Care Services	Interaction Between Patients and Health Professionals	Access to Therapies
• Insufficient supply and coverage • Delay in authorization, pricing, and reimbursement system • Unequal eligibility rules for treatments	• Delay in timely access to diagnosis and treatment • Lack of care pathways and standards of care • Lack of integration of electronic information	• Patients and health professionals have insufficient time together • Cultural differences and power imbalance between patients and health professionals • Insufficient access to other health professionals (nurses, etc.)	• High direct costs • Insufficient patient involvement in the development of new therapies

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Recent Evidence on the Management of Narcolepsy: Improving Outcomes through Expert Treatment Strategies

Michael Thorpy, MD

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http://www.namcp.org/home/education, and then click the activity title.

Summary

Narcolepsy is not just being sleepy during the day; it causes a significant patient burden and impacts a patient's quality of life. There are several medications which can improve daytime sleepiness and cataplexy, which occur because of dysregulated sleep and lack of orexin.

Key Points

- Delayed diagnosis is common and results in delayed treatment, increased burden of the disease, and detrimental effects on health care resource use, employment, and quality of life.
- Oxybate is the most effective medication in narcolepsy.
- Pitolisant is approved for excessive daytime sleepiness, but it also improves cataplexy.
- Alternative treatments to these two agents are solriamfetol, armodafinil, and norepinephrine reuptake inhibitors.
- Future treatments will target orexin systems.

NARCOLEPSY IS A NEUROLOGIC DISORDER characterized by excessive daytime sleepiness (EDS), rapid eye movement (REM)-related phenomena, and disturbed nocturnal sleep.[1,2] Patients can have continual background sleepiness, voluntary sleep episodes (naps), involuntary sleep episodes (sleep attacks), and wakeful sleepiness (automatic behavior, microsleeps). The REM-related phenomena include cataplexy (sudden loss of voluntary muscle tone), which occurs in about 60% of those with narcolepsy, hypnagogic hallucinations in 67%, and sleep paralysis in 64%. Nightmares and unpleasant frequent dreams are also REM-related phenomena. The diagnostic criteria for narcolepsy with cataplexy (type 1) and without cataplexy (type 2) are shown in Exhibit 1.[3] Overall, narcolepsy is a 24-hour disorder where sleep intrudes into wakefulness and wakefulness intrudes into sleep.

The diagnosis of narcolepsy is often delayed by eight to 15 years after symptom onset. It may be more delayed in female patients. The median age at onset is 16 and diagnosis is 33. Delays are related to mildness of initial symptoms, gradual onset of symptoms, lack of recognition of the condition by the patient or clinician, misdiagnosis, and comorbidities with sleep related symptoms. Narcolepsy can be misdiagnosed as attention deficit hyperactivity disorder (ADHD), depression, obstructive sleep apnea (OSA), or insomnia. OSA, along with depression, obesity, and anxiety, is a common comorbidity of narcolepsy.[4]

Lack of awareness of the symptoms of narcolepsy, especially cataplexy, contributes to delays in diagnosis. In a survey, only 7 percent of primary care physicians in the United States (U.S.) could identify all five main narcolepsy symptoms.[5] In the same survey, only 63 percent of sleep specialists

Exhibit 1: Narcolepsy Diagnosis Criteria ICSD-3[3]

Narcolepsy Type 1 (narcolepsy with cataplexy)

- Chronic EDS (daily for at least 3 months)

  and

- Presence of 1 or both of the following:
  - **Cataplexy** + mean sleep latency ≤ 8 minutes and ≥ 2 SOREMPs on MSLT*
  - **Low CSF hypocretin-1** level (either ≤ 110 pg/mL or < 1/3 of mean values)

Narcolepsy Type 2 (narcolepsy without cataplexy)

- Chronic EDS (daily—at least 3 months)
- Mean sleep latency ≤ 8 minutes and ≥ 2 SOREMPs on MSLT*
- **Cataplexy absent**
- CSF hypocretin-1 concentration not measured or CSF hypocretin-1 level is > 110 pg/mL or > 1/3 mean values.

*A SOREMP on the preceding night's polysomnogram may substitute for 1 of the SOREMPs on MSLT
EDS = excessive daytime sleepiness; MSLT = multiple sleep latency test; PSG = polysomnography; CSF = cerebrospinal fluid; ICSD-3 = International Classification of Sleep Disorders, 3rd ed.; SOREMP = sleep-onset REM period

identified excessive daytime sleepiness (EDS) and cataplexy as 2 primary narcolepsy symptoms and less than 25 percent could identify all five symptoms of narcolepsy.[5] Cataplexy can be difficult for physicians to recognize, as well as challenging for patients to describe. Cataplexy should be explored on more than one occasion because many patients fail to recall the symptom when first asked, and the symptom has great variability.

Narcolepsy is associated with a high level of medical resource utilization, and contributes to substantial productivity burdens.[6] The pattern and extent of health care utilization among narcolepsy with cataplexy are the same as those without identified cataplexy and vastly different from matched controls. There are school- and work-related burdens such as poor grades, job loss, and forced retirement. Patients may also limit social activities and driving for fear of falling asleep.

Overall, delayed diagnosis results in delayed treatment, increased burden of the disease, and detrimental effects on health care resource use, employment, and quality of life. There is definitely a need to promote a greater awareness of narcolepsy and facilitate early diagnosis and implementation of effective treatment. Ways to lessen the burden of this disease on patients, their families, and society are needed.

Narcolepsy may have several causes. Although the cause of narcolepsy is not completely understood, current research suggests that narcolepsy may be caused by a lack of orexin in the brain.[2] Studies have shown that the majority of patients with narcolepsy with cataplexy have undetectable levels (<40 pg/ml) of hypocretin-1 in their cerebrospinal fluid (CSF).[7] Other experiments have shown that cases of human narcolepsy are associated with a complete loss of hypocretin-containing neurons in the perifornical area of the posterior hypothalamus.[8] Orexin levels are usually normal in people who have narcolepsy without cataplexy. Although the reason for orexin-producing cell loss is unknown, it appears to be linked to an auto-immune attack on the brain cells because of a combination of genetic and environmental factors. Most cases of narcolepsy are sporadic. However, clusters in families sometimes occur—up to 10 percent of individuals diagnosed with narcolepsy with cataplexy report having a close relative with similar symptoms. Narcolepsy rarely results from traumatic brain injury or brain tumors.

The goals of treatment are to reduce EDS; control REM-associated features; improve disturbed nocturnal sleep; improve cognition, psychosocial and school/work functioning; and improve safety of the patient and public.[9] Medications approved for EDS in narcolepsy include modafinil (Provigil®,

Exhibit 2: Treatment Algorithm

- Trial of oxybate in all type 1 and type 2 patients if acceptable to patient and no contraindications.
  - If not fully effective for EDS then add solriamfetol.
  - If not fully effective for cataplexy then add pitolisant.
- If unable to take oxybate, trial of pitolisant.
  - If not fully effective for EDS then add solriamfetol.
  - If not fully effective for cataplexy then add venlafaxine.
- If oxybate and pitolisant are contraindicated or unacceptable, then use solriamfetol.
  - After stabilizing on solriamfetol, if cataplexy is present, add venlafaxine

generic); armodafinil (Nuvigil®, generic); sodium oxybate (Xyrem®); calcium, magnesium, potassium, and sodium oxybates (Xywav®); solriamfetol (Sunosi®); and pitolisant (Wakix®). Solriamfetol and pitolisant were both approved by the FDA in 2019 and multi-salt oxybate (Xywav®) in 2020. Amphetamine derivatives are also occasionally used, but there are concerns about tolerance, abuse, misuse, and adverse effects.

It is thought that cataplexy is the muscle paralysis that normally occurs during REM sleep intruding into waking hours. Cataplexy can be treated with oxybate, pitolisant, and various antidepressants which are inhibitors of the REM generator in brain, but only oxybate is FDA approved for managing cataplexy.

Modafinil and armodafinil, the R-isomer of modafinil, have lower potency than amphetamine, fewer peripheral side effects, and lower addictive potential than amphetamines. Because of abuse potential, they are Schedule IV controlled substances. Their mechanism of action is dopamine transmitter inhibition. Armodafinil has a longer half-life, which may make it more effective than modafinil and makes it more convenient with once-a-day dosing. These two agents have no effect on cataplexy. Post-marketing surveys have shown that modafinil increases the risk of fetal malformations, and animal data shows potential harm from armodafinil; therefore, neither should be used during pregnancy because alternatives are available. These stimulants lead to a significantly increased rate of psychosis, psychiatric hospitalizations, tachyarrhythmias, polysubstance abuse, anorexia and weight loss.[10,11]

Both sodium oxybate and multi-salt oxybate are salts of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Oxybate is thought to act via GABA B or specific GHB receptors. It reduces dopamine release at night, and it likely causes secondary dopamine increase during the day. Oxybate is indicated for the treatment of EDS and cataplexy in patients with narcolepsy who are seven years and older. Oxybate improves nocturnal sleep; increases slow wave sleep; reduces arousals and awakenings; can eliminate cataplexy; reduces vivid dreams, nightmares and hallucinations; improves overall cognitive functioning; and reduces sleep paralysis. It is the only medication that can treat all symptoms of narcolepsy.[12] Overall, oxybate is the most effective drug for the treatment of cataplexy and the first-line drug for the treatment of narcolepsy.

Because of the risks of CNS depression, abuse, and misuse, oxybate, a Schedule III controlled substance, is available only through a restricted distribution program called the XYREM and XYWAV REMS Program, using a central pharmacy that is specially certified. Prescribers and patients must enroll in the program. Besides the prescribing restrictions and abuse potential, bi-nightly dosing is necessary for most patients. Half of the prescribed dose is given at bedtime, and the other half 2.5 to 4 hours later (which requires the patient to set an alarm to get up and take the dose). The initial starting dose is 4.5 grams, which can be increased to 9 grams. Some patients only require 1 nightly dose, and others may need 3 total doses per night. At 6 to 9 grams daily, sodium oxybate treatment contributes 1100 to 1640 mg to daily sodium intake, which can be an issue for those with sodium-sensitive diseases and makes it very difficult to adhere to general sodium restriction recommendations. The oral solution multi-salt oxybate has 92% less sodium than sodium oxybate. Both are manufactured by same company, which is encouraging transition to the multi-salt formulation.

Oxybate is contraindicated in combination with

Exhibit 3: Agents Under Investigation for Narcolepsy

New Forms of Sodium Oxybate
• Once a night formulation
Modafinil Augmentation
• Modafinil/Flecainide (THN102)
GABA-A antagonists
• Clarithromycin
• Flumazenil
• Pentetrazol (BTD-001)
Norepinephrine Reuptake Inhibitors (NERIs)
• Reboxetine
Histamine 3 receptor inverse agonists
• SUVN-3031
Orexin Agonists
• TAK-925/944
• Mazindol

sedative hypnotics or alcohol in those with succinic semialdehyde dehydrogenase deficiency, and in untreated obstructive sleep apnea. It should be used with caution in those with depression and especially with suicidal ideation. The most common adverse effects are nausea, dizziness, vomiting, somnolence, enuresis, and tremor. It also has a black box warning that CNS depression from this agent can result in seizure, respiratory depression, decreased consciousness, coma, and death.

Solriamfetol is approved for EDS from narcolepsy and OSA. It is a norepinephrine–dopamine reuptake inhibitor (NDRI) and is derived from phenylalanine. The dose is 75 or 150 mg taken once daily, and it is a Schedule IV controlled substance. It significantly improves the Maintenance of Wakefulness Test (MWT) and the Epworth Sleepiness Scale (ESS) score versus placebo (all $p < 0.0001$).[13] At week 12, higher percentages of patients treated with solriamfetol 150 mg (78.2%) reported Patient Global Impression of Change (PGI-C) improvement relative to placebo (39.7%; both $p < 0.0001$). There is no effect on cataplexy. The most common adverse effects are headache, nausea, decreased appetite, insomnia, irritability, and anxiety. It should be avoided in unstable cardiovascular disease because it can increase blood pressure and heart rate. This agent has efficacy for at least 9 hours during the day and no evidence of dependence or withdrawal has been seen. It is also considered safe during pregnancy.

Pitolisant, a histamine three (H3) receptor antagonist/inverse agonist, increases histamine synthesis and release. Histaminergic neurons in the posterior hypothalamus, stimulated by orexin neurons, control waking, feeding, learning, and memory (H1 through H4). H3 is an autoreceptor and presynaptic heteroreceptor. H3 suppresses histamine neuronal firing and inhibits synthesis and release of histamine. H3 also inhibits the release of acetylcholine, noradrenaline, and dopamine. Dosing starts with 8.9 mg once a day and can be increased to 35.6mg daily with weekly dose changes. The most common adverse effects are headache, insomnia, nausea, and anxiety. Pitolisant reduced EDS comparable to modafinil and better than placebo, improved attention, decreased cataplexy frequency (40-76%), and increased MWT sleep latency by 80 percent.[14,15] It reduced partial cataplexy episodes 65 percent and total cataplexy episodes 76%.[15] The FDA only approved this agent for EDS, even though it has shown benefits on cataplexy and is approved in Europe for this indication. Importantly, this agent is not a controlled substance, unlike all the other agents for EDS. This agent can increase the QTc interval, and its use should be avoided in patients taking other drugs that prolong the QTc interval, or who have risk factors for prolonged QTc interval. An alternative non-hormonal contraceptive method is recommended during therapy and for at least 21 days after discontinuation of treatment.

Antidepressants that inhibit norepinephrine reuptake in the brain inhibit cataplexy.[16] Venlafaxine and atomoxetine are the most effective. Antidepressants are not effective for other REM phenomena or sleepiness and can disturb nocturnal sleep. They also can cause sexual side effects. Reboxetine, a norepinephrine reuptake inhibitor (NERI) which is approved in other countries as an antidepressant, is under investigation in the U.S. for cataplexy. An issue with these is rebound in the case where the patient suddenly stops the medications.

In selecting therapy for narcolepsy, oxybate is first line for both type 1 and type 2 because of the ability to treat all the symptoms of narcolepsy (Exhibit 2). Second-line therapy for EDS and cataplexy is pitolisant, because it is not FDA approved for cataplexy, but it is effective. Second-line therapies for EDS are modafinil/armodafinil and solriamfetol. Solriamfetol appears to be better

tolerated and has less risk of psychiatric issues than modafinil/armodafinil. Second line for cataplexy is venlafaxine or atomoxetine. Methylphenidate and amphetamines should be for third-line use because of their adverse effects and abuse issues.

Numerous other agents are under investigation for treating narcolepsy (Exhibit 3). FT218 is an investigational controlled-release formulation of sodium oxybate intended for once-nightly dosing, which would make this agent much easier for patients to adhere with. The next revolution in treating narcolepsy is likely to be the targeting of orexin. Options for orexin supplementation include direct replacement, gene therapy and orexin cell transplantation to restart production in the brain, and orexin agonists.[17] Oral orexin agonists are in Phase 2 trials in the U.S. and are showing promise.

Conclusion

Oxybate is the most effective medication in narcolepsy. Pitolisant is approved for EDS, but it improves cataplexy. Alternative treatments to these two agents are solriamfetol, armodafinil, and norepinephrine reuptake inhibitors. Future treatments will target orexin.

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