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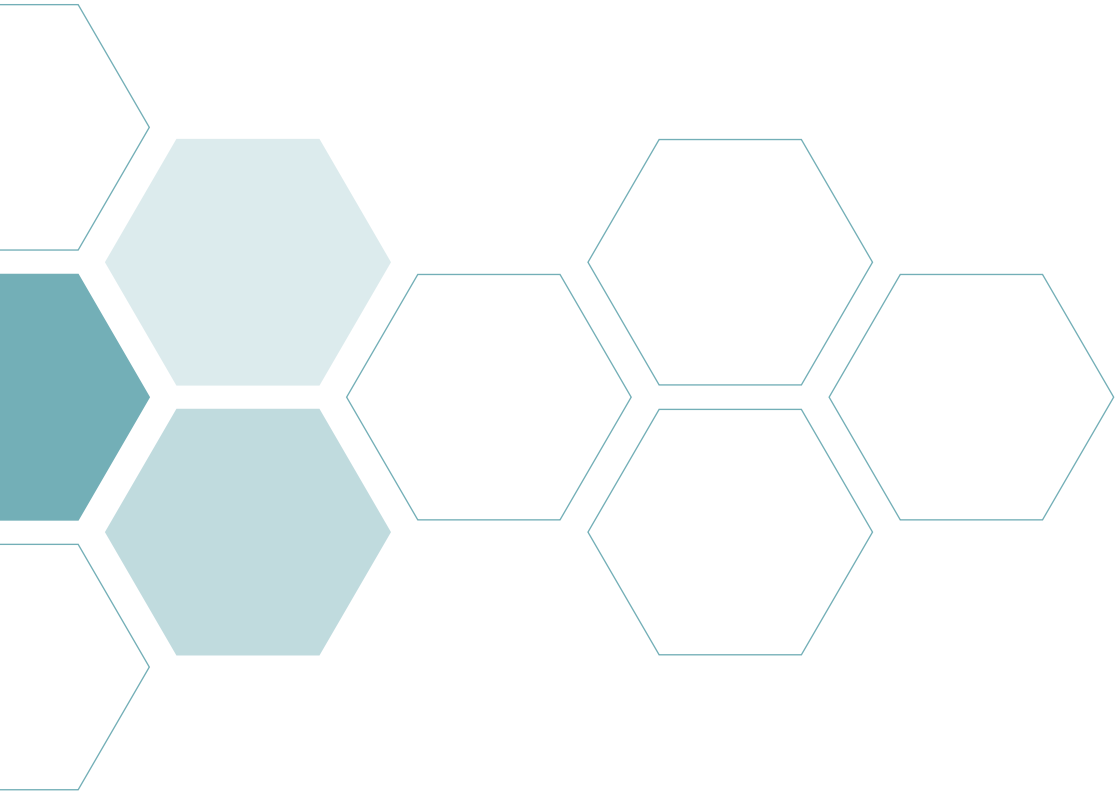

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Slowing Disease Progression in Amyotrophic Lateral Sclerosis: Managed Care Strategies for Improved Clinical and Economic Outcomes

Hiroshi Mitsumoto, MD, DSc

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

Summary

Amyotrophic lateral sclerosis (ALS) remains an incurable and devastating disease. Two disease-modifying agents are available to improve quality of life and slow disease progression. Uncovering the cause and finding reliable biomarkers for diagnosis and other indications is vital.

Key Points

- Early diagnosis and treatment are essential.
- Disease-modifying therapies, nutritional interventions, respiratory care interventions, aggressive symptomatic management, and multi-disciplinary care are keys to improving quality of life and prolonging survival.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a rare incurable progressive neurodegenerative disorder affecting upper and lower motor neurons and bulbar neurons. ALS and other neurodegenerative disorders are similar in that they affect similar patient populations and have an unknown cause and no cure. With ALS, there is a highly predictable prognosis in about half of the patients. ALS leads to the inability to move, speak, eat, and eventually breathe. Some neurologic functions, including cognition, extraocular movements, bowel and bladder function, and sensation, are typically not affected in ALS patients. Greater than 95 percent of patients will maintain normal cognition.

Median five-year survival with ALS is 25 percent, and 10-year survival is from eight to 16 percent.[1] The incidence of ALS is one to three per 100,000, and prevalence is 4.8 per 100,000. Approximately 30,000 Americans have ALS with cases in males slightly predominate (3:2 ratio).[2] Approximately 10 percent of cases are genetically based [familial ALS (fALS)] with the rest considered sporadic (sALS).[1]

ALS has a major impact on patients and caregivers. Because of the widespread effects of the disease, ALS causes the highest disability on the Sickness Impact Profile, a measure of health-related quality of life (HRQOL), of any disease. The receipt of a fatal diagnosis is devastating leading to tremendous emotional distress and anxiety. Patients have difficulty transitioning from being the main financial supporter of the family to a dependent family member. The pace of disease progression can outpace learning and coping. For example, a patient starts out with a foot drop and learns to use a brace to manage. Just when they have mastered the brace, the syndrome has progressed and a walker is needed, and they then rapidly progress to requiring a wheelchair. Families and caregivers have high physical and psychological burdens, anxiety, depression, distress, and low quality of life (QOL). Eventually, the home becomes a "mini-hospital."

In addition to the QOL impact, ALS causes significant financial burden. Medical costs are substantial and increase rapidly as disability worsens.[3] The annual total cost per patient has been

estimated to be $69,475.[4] Costs associated with ALS are greater than that of other neurological diseases. The total disease-duration costs have been estimated at $1,433,992 with 85 percent paid by insurance, 9 percent paid by families, and 6 percent paid by charities.[4] The highest healthcare costs are for in-home caregivers ($669,150), ventilation ($212,430), and hospital care ($114,558). The national economic burden of ALS in the United States (U.S.) is estimated at $279,000,000 to $472,000,000 annually.

At the beginning, ALS may involve degeneration and death of only upper motor neurons (UMN) or lower motor neurons (LMN), but it eventually progresses to involve both. Similar to many other degenerative diseases, there is a very long preclinical process with ALS.[5] Motor neurons are already markedly depleted when weakness is detected and even when muscle strength is normal.[6] A patient may have normal muscle strength and a 30 percent to 50 percent neuronal loss. When weakness is detected, 80 percent of neurons can be depleted. Thus, early diagnosis is important if there is any hope of slowing the disease progression.

Most experts consider ALS a syndrome because there are many different presentations. In addition to familial and sporadic cases, there are several types of onset including spinal (classical ALS), bulbar (speech and swallowing), and respiratory. There are also variants, including unilateral (Mills' syndrome) and mononeuritis/monomeric. Disease progression is very different among patients with some having very rapid progression and others having a much slower disease process. It is likely that various genes are involved, which leads to the different presentations.

It is unknown what exactly starts the process of UMN and LMN loss. Most investigators and clinicians agree that several factors including oxidative injury linked to free radical formation, inflammation, excitotoxicity, neurotrophic factor impairment, apoptosis, mitochondrial dysfunction, protein aggregates, autophagy, derangements in cytoskeletal protein and glutamate metabolism, defects in axonal transport, and RNA metabolism are involved in the pathogenic process of ALS. It appears that the process is triggered in a genetically susceptible person who encounters risk factors such as excessive physical activity or environmental exposure.

Early diagnosis of ALS is critical and essential. Earlier in the disease motor neurons are still alive and functioning and therapies are still effective, but it can be difficult to make an early diagnosis. Fasciculations and muscle cramps often precede motor function symptoms. New diagnostic criteria for ALS have been proposed from a consensus conference sponsored by the International Federation of Clinical Neurophysiology, the World Federation of Neurology, the ALS Association, and the Motor Neuron Disease Association (Exhibit 1).[7]

Exhibit 1: Proposed Diagnostic Criteria[7]

- Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function,

and

- Presence of upper[a] and lower[b] motor neuron dysfunction in at least one body region[c], (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) or lower motor neuron dysfunction in at least two body regions,

and

- Investigations[d] excluding other disease processes

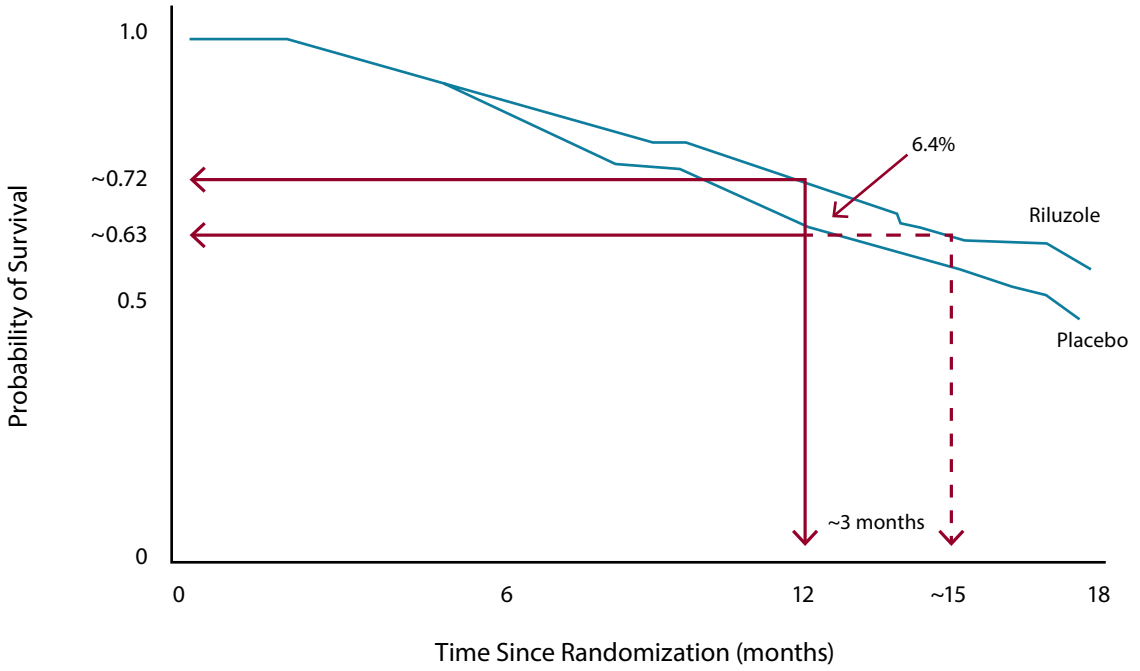
[a]Upper motor neuron dysfunction implies at least one of the following: Increased deep tendon reflexes, including the presence of a reflex in a clinically weak and wasted muscle, or spread to adjacent muscles; presence of pathological reflexes, including Hoffman sign, Babinski sign, crossed adductor reflex, or snout reflex; Increase in velocity-dependent tone (spasticity); slowed, poorly coordinated voluntary movement, not attributable to weakness of lower motor neuron origin or Parkinsonian features.

[b]Lower motor neuron dysfunction in a given muscle requires either; clinical examination evidence of muscle weakness, and muscle wasting or EMG abnormalities that must include both evidence of chronic neurogenic change, defined by large motor unit potentials of increased duration and/or increased amplitude, with polyphasia and motor unit instability regarded as supportive but not obligatory evidence and evidence of ongoing denervation including fibrillation potentials or positive sharp waves, or fasciculation potentials.

[c]Body regions are defined as bulbar, cervical, thoracic and lumbosacral. To be classified as an involved region with respect to lower motor neuron involvement, there must be abnormalities in two limb muscles innervated by different roots and nerves, or one bulbar muscle, or one thoracic muscle either by clinical examination or by EMG.

[d]The appropriate investigations depend on the clinical presentation, and may include nerve conduction studies and needle EMG, MRI, or other imaging, fluid studies of blood or CSF, or other modalities as clinically necessary.

Exhibit 2: Riluzole Benefit on Survival from Clinical Trial[8,9]



These criteria include the use of electromyography (EMG) to identify fasciculation which can be an early marker of ALS. Biomarkers for diagnosis, disease-progression prediction, and medication effectiveness are the holy grail in ALS management. Neurofilament, oxidative stress markers, creatinine, and C reactive protein are some which are being investigated but none are yet available for routine clinical use.

Riluzole (Rilutek®, Tiglutik®) and edaravone (Radicava®) are the two FDA-approved disease-modifying treatments approved for ALS treatment. For both drugs, the mechanism of action in relation to ALS remains unknown. It appears to be a neuroprotective effect via inhibition of glutamatergic neurotransmission and anti-excitotoxic effect for riluzole and reduced oxidative stress through scavenging of free radicals for edaravone.

Riluzole prolongs median tracheostomy-free survival by about three months compared to placebo in patients younger than 75 years of age with definite or probable ALS who have had the disease for less than five years and who have a forced vital capacity (FVC) of greater than 60 percent (Exhibit 2).[8,9] FVC is the most commonly used measure of respiratory muscle function for prediction of ALS survival and disease progression. Real-world data has shown improvements in median survival times of more than 19 months.[10] The American Academy of Neurology (AAN) ALS practice parameter states that riluzole should be offered to slow disease progression in patients with ALS (Level A evidence).[11] It is more effective in the initial stages of the disease which is another reason that early diagnosis is important. About 70 to 80 percent of patients are currently taking riluzole. The major disadvantages of this agent are high drug costs (~$9,600 annually for generic), limited Medicare coverage, low cost-effectiveness, and potential for liver toxicity.

Edaravone (Radicava®), which is an intravenous antioxidant, was approved by the FDA in 2017 to slow the functional decline in patients with ALS. The first trial in patients within three years of symptom onset showed no benefit over placebo, but a post-hoc analysis suggested that a subset of patients with a more rapid rate of progression benefitted from treatment with edaravone.[12] A second trial included 137 people who showed some degree of impairment in each of the ALS Functional Rating Scale-Revised (ALSFRS-R) domains, had an FVC ≥ 80 percent of expected value, were within two years of symptom onset, and had a further decline of -1 to -4 ALSFRS-R points during a 12-week observation period. For this subset of patients, edaravone slowed the rate

of disease progression, as measured by a decrease in ALSFRS-R score, by 33 percent at six months compared to the rate of disease progression for patients in the placebo group.[13] The disadvantages of edaravone are the need for intravenous infusion and the cost (~$148,000 per year). Edaravone has not yet been included in the AAN practice guidelines.

Real-world use of edaravone was examined in a study using Veterans Health Administration data.[14] Of 369 patients who received edaravone between FDA-approval in 2017 and September 2019, 59.9 percent of edaravone patients had discontinued treatment and of those, 49.5 percent (108 of 218) received only one to three treatment cycles. Approximately 30 percent (110 patients) died. In a matched evaluation, significantly more acute all-cause hospitalization events occurred with edaravone (35.4% versus 22.0% for those receiving riluzole only); 72.6 percent of the edaravone cohort received edaravone with riluzole. Among chronic users, edaravone patients (70.8% edaravone with riluzole) had an increased hazard ratio of ALS-associated hospitalization (2.51; 95% CI, 1.18 to 8.16). The death rate was lower with edaravone, but the difference was not statistically significant. Because this was a retrospective data analysis, caution must be use in interpreting the results.

Because the care of patients with ALS is complex, it is best accomplished in a multidisciplinary clinic which has been shown to prolong survival by eight to 10 months and improve QOL.[15-17] Additional advantages of multidisciplinary care include effective symptomatic treatment, sensitive discussions regarding diagnosis with patients, virtual problem solving by multiple experts, minimized patient travel time visiting different professionals or therapists, highly specialized healthcare professionals, and clinical research and trials that can be effectively performed. There are more than 100 ALS Centers in the U.S., but some areas of the country lack these clinics. The major disadvantages of multidisciplinary care are the high costs and a tiring experience for both patients and providers. The AAN-practice parameters recommend patients with ALS should be considered for referral to a specialized multidisciplinary ALS clinic to optimize healthcare delivery (Level B), prolong survival (Level B), and enhance QOL (Level C).[18]

Symptomatic management in ALS is especially important in maintaining QOL. Clinicians need to identify symptoms the patient is bothered by and aggressively manage those. These can be psychological, musculoskeletal (cramps), gastrointestinal, pulmonary, emotional (pseudobulbar affect), and others (fatigue, insomnia, drooling, etc.). The easiest and safest symptomatic medications should be tried first before using those with potentially more adverse events and that are more difficult to manage. There may be non-pharmacological options such as physical therapy or robotic assistive devices to assist with these.

Two important interventions in ALS are PEG tubes for maintaining nutrition and non-invasive ventilation (NIV). In patients with ALS with impaired oral food intake, enteral nutrition via PEG should be considered to stabilize body weight and for prolonging survival.[11] To optimize safety of the procedure, PEG placement for dysphagia in ALS may be considered when forced vital capacity (FVC) is close to 50 percent of predicted. FVC of less than 50 percent predicted increases the risk of anesthesia. NIV should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and to slow the rate of FVC decline.[11] It also improves QOL, sleep quality, and comfort in those with respiratory insufficiency. Patients can continue to function with this type of ventilation; however, with continued respiratory function decline, tracheostomy and invasive ventilation have to be considered.

An emerging therapy for ALS is a combination of sodium phenylbutyrate and taurursodiol which is thought to mitigate endoplasmic reticulum stress and mitochondrial dysfunction. A multicenter, randomized, double-blind trial in 137 subjects with definite ALS with onset of symptoms within the previous 18 months compared sodium phenylbutyrate-taurursodiol (3 g of sodium phenylbutyrate and 1 g of taurursodiol, administered once a day for 3 weeks and then twice a day) to placebo. The combination resulted in slower functional decline than placebo as measured by the ALSFRS-R score over a period of 24 weeks (0.42 points per month difference; $p = 0.03$).[19] In an open-label extension trial of the randomized trial, median overall survival was 25.0 months among participants originally randomized to the combination and 18.5 months among those originally randomized to placebo (hazard ratio, 0.56; 95% confidence interval, 0.34 to 0.92; $p = .023$).[20] Gastrointestinal issues are the primary adverse events. This combination was submitted to the FDA for approval in March 2021.

Ultra-high doses of methylcobalamin are also being evaluated. In a trial in 373 patients with ALS (duration ≤ 36 months) which compared placebo, 25 mg and 50 mg of methylcobalamin daily, the primary endpoints of the time interval to primary events (death or full ventilation support) and changes in the ALSFRS-R score from baseline to week 182 showed no significant differences with either of the three interventions.[21] However, post-hoc analyses of

methylcobalamin-treated patients diagnosed and entered early (≤ 12-months' duration) showed longer time intervals to the primary event ($p < 0.025$) and less decreases in the ALSFRS-R score ($p < 0.025$) than the placebo group.

Antisense oligonucleotides (ASO) are under investigation for superoxide dismutase 1 (SOD1) mutated ALS. Tofersen is an ASO given by intrathecal administration that mediates the degradation of messenger RNA to reduce SOD1 protein synthesis. In a Phase I – II trial in 50 patients, cerebrospinal fluid SOD1 concentrations decreased at the highest concentration of tofersen administered intrathecally over a period of 12 weeks.[22] In the Phase III study, the primary endpoint as measured by the ALSFRS-R change did not reach statistical significance; however, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed.[23] The manufacturer is continuing to explore this agent.

Conclusion

Enormous progress in the care and management of ALS has been made. Early diagnosis and initiation of disease-modifying treatment is especially important. Once diagnosed, a combination of disease-modifying therapies, aggressive symptomatic treatment, and nutritional and respiratory care in a multidisciplinary clinic improve overall QOL and prolong survival in patients with ALS. Maximum efforts continue to be made to find biomarkers and the cause of ALS.

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References

1. Oskarsson B, Gendron TF, Staff NP. Amyotrophic lateral sclerosis: An update for 2018. *Mayo Clin Proc*. 2018;93(11):1617-28.
2. Mehta P, Kaye W, Bryan L, et al. Prevalence of amyotrophic lateral sclerosis — United States, 2012–2013. *MMWR Surveill Summ*. 2016;65(No. SS-8):1-12.
3. Meng L, Bian A, Jordan S, et al. Profile of medical care costs in patients with amyotrophic lateral sclerosis in the Medicare program and under commercial insurance. *Amyotroph Lateral Scler Frontotemporal Degener*. 2018;19 (1-2):134-42.
4. Gladman M, Zinman L. The economic impact of amyotrophic lateral sclerosis: A systematic review. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15(3): 439-50.
5. Eisen A, Kiernan M, Mitsumoto H, Swash M. Amyotrophic lateral sclerosis: a long preclinical period? *J Neurol Neurosurg Psychiatry*. 2014;85(11):1232-8.
6. Sobue G, Sahashi K, Takahashi A, et al. Degenerating compartment and functioning compartment of motor neurons in ALS: possible process of motor neuron loss. *Neurology*. 1983;33(5):654-7.
7. Shefner JM, Al-Chalabi A, Baker MR, et al. A proposal for new diagnostic criteria for ALS. *Clin Neurophysiol*. 2020;131(8):1975-8.
8. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med*. 1994;330(9):585-91.
9. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet*. 1996; 347(9013):1425-31.
10. Hinchcliffe M, Smith A. Riluzole: Real-world evidence supports significant extension of median survival times in patients with amyotrophic lateral sclerosis. *Degener Neurol Neuromuscul Dis*. 2017;7:61-70.
11. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. 2009;73(15):1218-26.
12. Abe K, Itoyama Y, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014;15(7-8):610-7.
13. Writing Group on Behalf of The Edaravone ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: A randomized, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(7):505-12.
14. Vu M, Tortorice K, Zacher J, et al. Assessment of use and safety of edaravone for amyotrophic lateral sclerosis in the Veterans Affairs Health Care System. *JAMA Netw Open*. 2020;3(10):e2014645.
15. Chiò A, Bottacchi E, Buffa C, et al. Positive effects of tertiary centers for amyotrophic lateral sclerosis on outcome and use of hospital facilities. *J Neurol Neurosurg Psychiatry*. 2006;77(8):948-50.
16. Traynor BJ, Alexander M, Corr B, et al. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: A population-based study, 1996-2000. *J Neurol Neurosurg Psychiatry*. 2003;74(9):1258-61.
17. Van den Berg JP, Kalmijn S, et al. Multidisciplinary ALS care improves quality of life in patients with ALS. *Neurology*. 2005;65(8):1264-7.
18. Miller RG, Jackson CE, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2009;73;1227-33.
19. Paganoni S, Macklin EA, Hendrix S, et al. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. *N Engl J Med*. 2020; 383(10):919-30.
20. Paganoni S, Hendrix S, Dickson SP, et al. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. *Muscle Nerve*. 2021;63(1):31-9.
21. Kaji R, Imai T, Iwasaki Y, et al. Ultra-high-dose methylcobalamin in amyotrophic lateral sclerosis: a long-term Phase II/III randomized controlled study. *J Neurol Neurosurg Psychiatry*. 2019;90(4):451-457.
22. Miller T, Cudkowicz M, Shaw PJ, et al. Phase I – II trial of antisense oligonucleotide tofersen for SOD1 ALS. *N Engl J Med*. 2020;383(2):109-19.
23. Biogen announces topline results from the tofersen Phase III study and its open-label extension in SOD1-ALS. October 21, 2021. Available at investors.biogen.com. Accessed 1/1/2022.

Novel Treatment Advances and Approaches in the Management of HER2-Positive Advanced Breast Cancer: Expert Strategies on the Role of New and Emerging Therapies

Mark D. Pegram, 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

The treatment of metastatic breast cancer with human epidermal growth factor two (HER2) overexpression continues to change with additional data development. A triple regimen is now first-line therapy, and a newer antibody/chemotherapy conjugate has replaced an older agent. These patients cannot yet be cured, but they can be palliated with multiple line therapy.

Key Points

- First-line therapy is the triple combination of pertuzumab, trastuzumab, and docetaxel.
- Fam-trastuzumab deruxtecan has replaced ado-trastuzumab emtansine as second-line therapy.
- There are many options for subsequent lines of therapy.

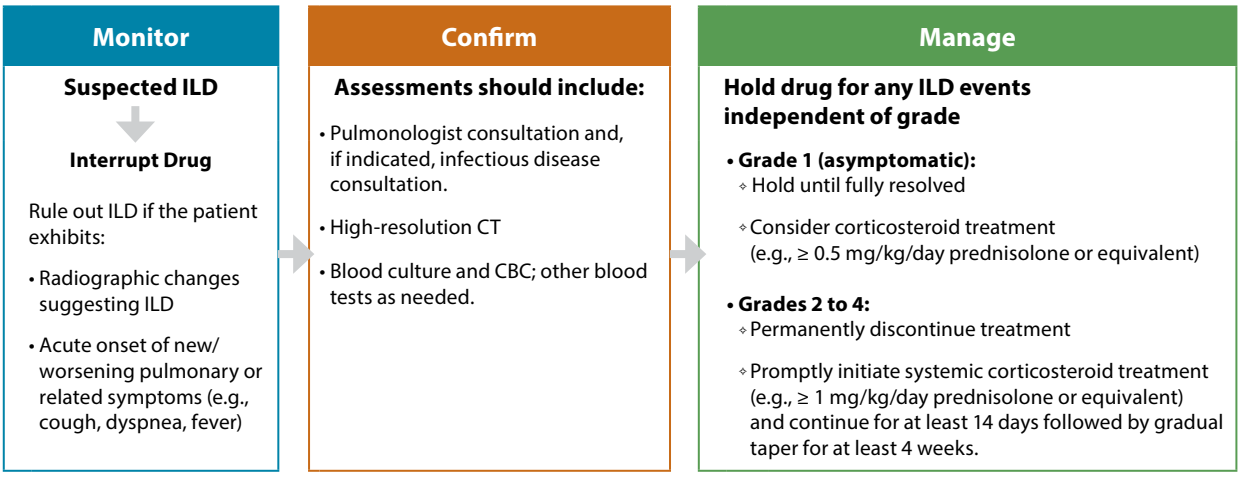
IN THE UNITED STATES (U.S.) IN 2021, approximately 65,000 women were diagnosed with metastatic breast cancer (mBC) and 43,600 women died from breast cancer.[1] For all types of mBC, the five-year survival is 28 percent.[2] Median overall survival (OS) for mBC is four years with hormone receptor (HR) positive/human epidermal growth factor receptor two (HER2) negative, five years for HER2 positive (HER2+), and two years for triple-negative breast cancer (TNBC).

HER2 is overexpressed and/or amplified in approximately 20 percent of breast cancers, conferring an aggressive tumor behavior but also an opportunity for targeted therapies.[3] HER2+ mBC continues to result in poor outcomes despite the availability of targeted therapies. Most HER2+ mBC patients will progress within one year of first-line trastuzumab-based therapy and will require a subsequent line of therapy. HER2 targeting therapies include trastuzumab (Herceptin®, Ontruzant® [biosimilar]), pertuzumab (Perjeta®), ado-trastuzumab emtansine (Kadcyla®, also known as T-DM1), fam-trastuzumab deruxtecan (Enhertu®), lapatinib (Tykerb®), neratinib (Nerlynx®), tucatinib (Tukysa®), and margetuximab (Margenza®). Trastuzumab, pertuzumab, and margetuximab are all monoclonal antibodies that bind to HER2 receptor. Lapatinib, neratinib, and tucatinib are oral tyrosine kinase inhibitors which target the intracellular portion of the HER2 receptor. Ado-trastuzumab emtansine and fam-trastuzumab deruxtecan are antibody chemotherapy conjugates that lead the chemotherapy component into the tumor cell via HER2 receptor binding.

Trastuzumab was the first targeted therapy for this type of breast cancer and in combination with chemotherapy has changed the natural history of HER2+ mBC. Patients with HER2+ MBC treated with trastuzumab now have comparable outcomes with HER2-negative mBC.[4] Median OS for HER2+ MBC increased from 39 months in 2008 to 5.25 years in 2018 and continues to increase.[4, 5]

Because patients still progressed on trastuzumab, pertuzumab, a novel recombinant humanized antibody directed against extracellular domain II of HER2 protein that is required for the heterodimerization of HER2 with other HER receptors, was developed. The synergistic combination of trastuzumab and pertuzumab with chemotherapy is the standard of care first-line therapy for HER2+ mBC because of major OS

Exhibit 1: Management of Interstitial Lung Disease with Trastuzumab Deruxtecan[9]



benefits (> 16 months) compared to trastuzumab/chemotherapy.[6]

Fam-trastuzumab deruxtecan has replaced ado-trastuzumab emtansine as the preferred second-line therapy.[7] Fam-trastuzumab deruxtecan is the most active single-agent HER2-targeted therapeutic and has a high chemotherapy to antibody ratio, an ability to kill neighboring non-HER2+ tumor cells, and activity in "HER2-low" tumors. In a planned interim analysis, it significantly improved progression-free survival (PFS) over ado-trastuzumab emtansine in patients previously treated with trastuzumab/chemotherapy (DESTINY-Breast03 trial, NCT03529110).[8] There was a strong trend toward improved OS; however, the OS data are still immature. This agent does cause typical chemotherapy adverse events, including nausea, vomiting, diarrhea, alopecia, and cytopenias. Importantly, this agent can cause interstitial lung disease (ILD) which has led to some deaths. Exhibit 1 presents information on how to manage ILD.[9]

Tucatinib, neratinib, and margetuximab are the three newest HER2 targeting therapies which are all FDA-approved for third-line or later use in combination with chemotherapy and sometimes other HER2 targeted therapies. Tucatinib is an oral HER2-selective tyrosine kinase inhibitor. It, in combination with trastuzumab and capecitabine, is a good option for second- or third-line therapy in those with HER2+ mBC and have central nervous system metastases based on PFS and OS data from the HER2Climb study.[10]

Neratinib has activity against HER2 kinase domain mutants (which are usually HER2-negative). It can cause severe diarrhea requiring high-dose loperamide-based prophylaxis. Permanent discontinuation due to any adverse reaction was reported in 14 percent. It is FDA-approved in combination with capecitabine following two or more prior anti-HER2-based regimens in the metastatic setting.

Margetuximab is an Fc-engineered chimeric antibody with enhanced immune effect or function and has the same specificity/affinity to HER2 as trastuzumab with similar ability to disrupt signaling. Margetuximab improved PFS compared with trastuzumab in patients with pretreated HER2-positive metastatic breast cancer in the open-label Phase III SOPHIA clinical trial. In a planned exploratory analysis, the PFS benefit observed with margetuximab was enhanced in CD16A-158F carriers. Median PFS was 6.7 months longer in those with CD16A-158F.[11] Fc-gamma polymorphisms like CD16A-158F influence immune responses, and margetuximab's Fc portion is engineered to have enhanced affinity for binding to both the low affinity F and high-affinity V alleles for the activating Fc-gamma CD16A receptor, as well as decreased affinity for the inhibitory Fc-gamma receptor CD32B.[12] Treatment with this agent results in a similar low drug discontinuation rate to Trastuzumab, but there is an increased incidence of infusion-related reactions (13.3% all grade versus 3.4% for trastuzumab).

The National Comprehensive Cancer Network (NCCN) guidelines recommend the combination of docetaxel/trastuzumab/pertuzumab as first-line therapy for those with HER2+ mBC.[7] This triple regimen would not be used in a patient who received either pertuzumab or trastuzumab in earlier stage disease treatment. The selected therapy is continued until disease progression. Most patients will be candidates for multiple lines of therapy to palliate

Exhibit 2: Systemic Therapy Regimens for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease[7]

HER2-Positive			
Setting	Regimen	NCCN Category of Preference	NCCN Category of Evidence
First-line	Pertuzumab + trastuzumab + docetaxel	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel	Preferred Regimen	2A
Second-line	Fam-trastuzumab deruxtecan-nxki	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)	Other Recommended Regimen	2A
Third-line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine	Other Recommended Regimen	1
	Trastuzumab + docetaxel or vinorelbine	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel + carboplatin	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib	Other Recommended Regimen	2A
	Trastuzumab + lapatinib (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents Neratinib + capecitabine	Other Recommended Regimen	2A
	Neratinib + capecitabine	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A

mBC as long as they are interested in continuing to pursue therapy and have adequate performance status and overall health (Exhibit 2).[7]

Conclusion

The discovery of HER2-targeted therapy has transformed the treatment of HER2+ mBC with significant improvements in survival, but there is still work to be done. Double HER2 therapy (trastuzumab/pertuzumab) combined with chemotherapy is the first-line regimen. The second-line regimen is now fam-trastuzumab deruxtecan, but a tucatinib-containing regimen is an option in the case of brain metastases. There are numerous third-line options; however, there is little data on the best sequence of these options.

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin.* 2021;71(1):7-33.
2. American Cancer Society. Survival Rates for Breast Cancer. Available at cancer.org. Accessed 1/28/2022.
3. Martínez-Sáez O, Prat A. Current, and future management of HER2-positive metastatic breast cancer. *JCO Oncology Practice.* 2021;17(10):594-604.
4. Dawood S, Broglio K, Buzdar AU, et al. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol.* 2010;28(1):92-8.
5. Kaczmarek E, Saint-Martin C, Pierga JY, et al. Long-term survival in HER2-positive metastatic breast cancer treated with first-line trastuzumab: results from the French real-life curie database. *Breast Cancer Res Treat.* 2019;178(3):505-12.
6. Swain SM, Miles D, Kim SB, et al; CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): End-of-study results from a double-blind, randomized, placebo-controlled, Phase III study. *Lancet Oncol.* 2020;21(4):519-30.
7. National Comprehensive Cancer Network. NCCN Clinical Guidelines in Oncology. Breast Cancer. Version 2.2022. Available at nccn.org. Accessed 1/28/2022.
8. Enhertu significantly improved progression-free survival in DESTINY-Breast03 head-to-head trial vs trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer. News release. AstraZeneca. August 9, 2021. Accessed 1/28/2022.
9. Fam-trastuzumab deruxtecan-nxki (Enhertu®) package insert. Daiichi Sankyo, Inc.1/2021.
10. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med.* 2020;382(7):597-609.
11. Rugo HS, Im SA, Cardoso F, et al; SOPHIA Study Group. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: A Phase III randomized clinical trial. *JAMA Oncol.* 2021;7(4):573-84.
12. Kuznar W, Margetuximab Superior to Trastuzumab on PFS in HER2-Positive Metastatic Breast Cancer Carriers of CD16A-F Allele. Available at onclive.com/view/margetuximab-superior-to-trastuzumab-on-pfs-in-her2positive-metastatic-breast-cancer-carriers-of-cd16af-allele. Accessed 1/28/2022.

Evolving Considerations in the Treatment and Management of Chronic Lymphocytic Leukemia

Farrukh T. Awan, 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

Chronic lymphocytic leukemia (CLL) affects primarily older people and may not require treatment for a while after diagnosis. Targeted therapies which change B-cell signaling are now the preferred first-line treatment. These therapies have replaced chemoimmunotherapy which should now be used rarely.

Key Points

- Oral Bruton's tyrosine kinase (BTK) inhibitors are first-line choices for treatment.
- Venetoclax in combination with obinutuzumab is a time-limited option for first-line treatment.
- Chemoimmunotherapy should be used in few or no patients.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL), a chronic lymphoproliferative disorder of monoclonal B cells, impacts a substantial number of patients worldwide, and predominantly affects older patients. With an estimated 21,250 new cases in the United States (U.S.) in 2021, CLL represents 22 to 30 percent of all leukemias worldwide and is the most common leukemia in Western countries.[1,2] The median age at diagnosis is 72 years and over 90 percent of patients are over 55 years of age at diagnosis.[3] Men are twice more likely to develop CLL than women.[4] Up to 80 percent of patients are asymptomatic at disease diagnosis. A CLL diagnosis is often based on results from blood tests ordered for routine care or unrelated condition.

Survival of CLL cells is dependent on ongoing B-cell receptor signaling, which is aberrantly and constitutively activated in CLL.[5] With newer treatments, CLL therapy can be targeted to turning off B-cell signaling in several ways rather than killing random cells with chemotherapy. Overall survival (OS) has significantly improved over the years with better identification of patients who have higher-risk disease and may require earlier and more aggressive treatment. Various chromosomal abnormalities in the CLL cells found on fluorescence in situ hybridization (FISH) are prognostic for OS. This includes Deletion 13q (Del13q), Del (11q), Trisomy 12, and Del (17p).[6] Other prognostic factors include tumor protein 53 (TP53) and immunoglobulin heavy chain variable region (IGHV) mutation. For example, patients with unmutated IGHV have a poor prognosis that is independent of the stage of disease.[7] Data from the real-world informCLL® registry show that in community-treated CLL patients, many of these prognostic factors are not measured, especially TP53 and IGHV mutational status.[8] Only 30 percent of cases had FISH testing. In addition to issues with prognostic marker testing, data from informCLL® indicate a 'knowledge gap' in terms of selection of therapies. Sixty-one percent of patients in this registry who received chemoimmunotherapy (CIT) received bendamustine and rituximab which has been shown to be inferior to all other options. To improve care and OS, all patients should be cared for by a CLL specialist rather than a general oncologist.

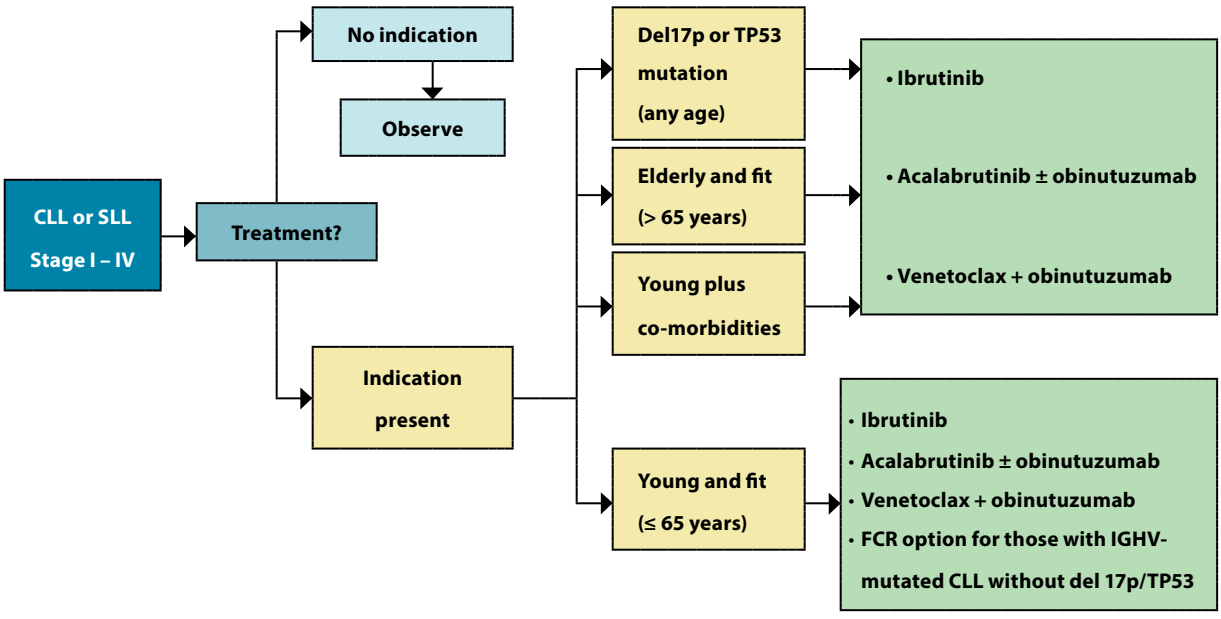
Not everyone with CLL needs immediate treatment. Treatment initiation is based on stage, the presence of active disease, and disease-related symptoms (Exhibit 1).[9,10] Treatment can be delayed, as prompt treatment does not improve survival, but the concept of having cancer and not treating

Exhibit 1: Indicators for Treatment[9,10]

Binet Stage C or Rai Stage III or IV* or any other Binet/Rai Stage with Active Disease	Disease-related Symptoms
Active disease is defined as having ≥1 of the following: • Bulky disease (spleen > 6 cm beneath costal margin, lymph nodes > 10 cm) • Anemia (Hgb < 11 g/dL) • Thrombocytopenia (platelet count <100,000 cells/mm) • Autoimmune complications • Lymphocyte doubling time ≤6 months	NIGHT SWEATS FATIGUE WEIGHT LOSS SYMPTOMATIC OR FUNCTIONAL EXTRANODAL INVOLVEMENT

*Anemia or thrombocytopenia from non-CLL cause should be excluded.
CLL = chronic lymphocytic leukemia; Hgb = hemoglobin.

Exhibit 2: Summary of Front-Line Therapy[7]



SLL = small lymphocytic lymphoma ; FCR = fludarabine, cyclophosphamide, and rituximab;
IGHV = immunoglobulin heavy chain variable

it can be difficult for patients to understand. Treatment options incorporate the following agents, with some administered as combinations: Bruton tyrosine kinase (BTK) inhibitors (e.g., ibrutinib, acalabrutinib), the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax, anti-CD20 monoclonal antibodies (e.g., rituximab, obinutuzumab), purine analogs (e.g., fludarabine, pentostatin), and alkylating agents (e.g., chlorambucil, cyclophosphamide, bendamustine). First-line CLL treatment has shifted away from chemoimmunotherapy (CIT) based approaches to oral targeted therapy because of survival advantages and fewer short- and long-term adverse events. The National Comprehensive Cancer Network (NCCN) publishes treatment guidelines and Exhibit 2 summarizes first-line therapies from

Exhibit 3: Which Therapy is the Best Initial Therapy?[15,16,18,19]

Targeted Therapies	Four-year PFS Outcomes
Ibrutinib (Phase I)	92% at 4 years (7 years = 83%)
Acalabrutinib (Phase I)	96% at 4 years
Venetoclax + obinutuzumab (Phase III)	74% at 4 years
Ibrutinib (Resonate-2, Phase III)	70% at 5 years
Acalabrutinib (Elevate-TN, Phase III)	87.3% at 2 years
Acalabrutinib + obinutuzumab (Elevate-TN)	92.7% at 2 years

these guidelines.[7]

The primary CIT regimen has been fludarabine, cyclophosphamide, and rituximab (FCR) which has shown to be superior to bendamustine/rituximab which is still frequently used in the community. FCR is an option for a small select group of patients – those younger than 65 years and fit with IGHV-mutated CLL without del 17p/TP53 mutation. This regimen has been shown to produce a very high 13-year progression-free survival (PFS) of 53.9 percent in this patient group.[11]

Oral targeted therapies do not cure CLL, but they can control it for many years. Ibrutinib (Imbruvica®) is the most commonly used first-line therapy of CLL. It improves OS over chemotherapy and CIT in both older and younger patients.[12-14] Ibrutinib benefit is consistent in patients no matter what prognostic risk factors are present. Ibrutinib treated patients are also more likely to stay on therapy over time.[8] The adverse events (hypertension, atrial fibrillation, infections, bleeding) are primarily a problem during the first year of therapy. The longer the patient stays on ibrutinib the better the tolerance. Infections are the only problematic longer-term adverse events.

Other options for first-line therapy are acalabrutinib with or without obinutuzumab and venetoclax plus obinutuzumab. Acalabrutinib is a second-generation BTK inhibitor which causes fewer adverse events than ibrutinib and has similar efficacy. The combination of acalabrutinib and obinutuzumab is more effective than acalabrutinib alone in terms of PFS, but survival data have not yet been published.[15] Obinutuzumab is an intravenous agent given over several hours for four doses during the first month and then monthly for a total of six cycles. Regimens that include obinutuzumab are less patient friendly than all oral regimens. Venetoclax plus obinutuzumab is a time-limited option for patients with financial issues, or who prefer not to be on long-term therapy, and has similar efficacy to the other options.[16]

The combination of ibrutinib and venetoclax has been studied but is not yet an approved or recommended regimen. In a combination trial, untreated CLL patients' age < 70 years received three cycles of ibrutinib and then 12 cycles of combined ibrutinib plus venetoclax and those who achieved confirmed undetectable measurable residual disease (uMRD) were then randomized to placebo or ibrutinib alone for one year. The one-year disease-free survival (DFS) rate was 95 percent in the placebo group and 100 percent in the ibrutinib group.[17] This suggests the potential for fixed-duration treatment with this all-oral, once-daily, chemotherapy-free regimen in first-line CLL. The measurement of uMRD is technically difficult and the appropriate tests are not available in all settings. The possibility of ending therapy with uMRD achievement and the use of additional combinations is the future of CLL treatment.

How clinicians choose an initial therapy in treatment naïve CLL depends on many factors. There is no one ideal therapy for all patients. Considerations include patient preference, comorbid conditions, toxicity considerations, and available resources. Efficacy and long-term disease control with each option can be considered. Exhibit 3 compares PFS from different trials but no one agent can yet be said to be better because head-to-head trials have not been published.[15, 16, 18, 19] The bottom line is that no matter which option is chosen, the survival outcomes are good.

Relapse is common with CLL. The treatment options at relapse will depend on prior treatment and various patient factors, including cardiac comorbid conditions, anticoagulation requirements,

renal failure, autoimmune disorders, and patient preference. All of the options for first-line treatment are possible plus a few oral targeting agents only indicated for relapsed/refractory CLL. Idelalisib is a selective PI3-K delta inhibitor which produces an overall response rate of 72 percent and a 39 percent partial response in this setting when used alone.[20] It can also be combined with rituximab. Duvelisib is a dual PI3-K gamma + delta inhibitor. Delta inhibition blocks the survival and proliferation of malignant B cells. Gamma inhibition disrupts the recruitment and differentiation within the tumor microenvironment that support malignant B cells. It improves PFS in the relapsed/refractory setting compared to ofatumumab.[21] Overall, multiple agents are available for the management of patients with relapsed CLL. Sequencing and patient factors are important in selecting therapy. Patient education and input is essential in deciding the course of action.

Conclusion

CLL, the most common form of leukemia in older adults, is treated based on the presence of progressive disease. Oral BTK inhibitors have now established long-term efficacy and safety against CIT approaches in younger and older populations and are first-line choices for treatment. The other first-line option includes venetoclax in combination with obinutuzumab. Chemoimmunotherapy should be used in very few patients, if any, due to inferior outcomes.

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References

1. Union for International Cancer Control. who.int/selection_medicines/committees/expert/20/applications/CLL.pdf. Accessed 1/17/2022.
2. American Cancer Society. Key Statistics for Chronic Lymphocytic Leukemia. Available at cancer.org/cancer/chronic-lymphocytic-leukemia/about/key-statistics.html. Accessed 1/17/2022.
3. Eichhorst B, Robak T, Montserrat E, et al; ESMO Guidelines Committee. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol*. 2015;26 Suppl 5:v78-84.
4. Scarfò L, Ferreri AJ, Ghia P. Chronic lymphocytic leukemia. *Crit Rev Oncol Hematol*. 2016;104:169-82.
5. Awan FT, Byrd JC. New strategies in chronic lymphocytic leukemia: shifting treatment paradigms. *Clin Cancer Res*. 2014;20(23):5869-74.
6. Bazargan A, Tam CS, Keating MJ. Predicting survival in chronic lymphocytic leukemia. *Expert Rev Anticancer Ther*. 2012;12(3):393-403.
7. National Comprehensive Cancer Network. NCCN Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2022. Available at nccn.org. Accessed 1/17/2022.
8. Mato AR, Barrientos JC, Sharman JP, et al. Real-World Prognostic Biomarker Testing, Treatment Patterns and Dosing Among 1461 Patients (pts) with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) from the informCLL Prospective Observational Registry. 62nd ASH Annual Meeting and Exposition. Poster presentation 547. December 2020.
9. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukemia. *Nat Rev Dis Primers*. 2017;3:16096.
10. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-60.
11. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-9.
12. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26):2517-28.
13. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353-63.
14. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432-43.
15. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukemia (ELEVATE TN): A randomized, controlled, Phase III trial. *Lancet*. 2020;395(10232):1278-91.
16. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-36.
17. Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: Primary analysis results from the minimal residual disease cohort of the randomized Phase II CAPTIVATE Study. *J Clin Oncol*. 2021;39(34):3853-65.
18. Byrd JC, Woyach JA, Furman RR, et al. Acalabrutinib in treatment-naive chronic lymphocytic leukemia. *Blood*. 2021;137(24):3327-38.
19. Burger JA, Barr PM, Robak T, et al. Long-term efficacy, and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the Phase III RESONATE-2 study. *Leukemia*. 2020;34(3):787-98.
20. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;23(22):3390-7.
21. Flinn IW, Hillmen P, Montillo M, et al. The Phase III DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446-55.

Navigating an Increasingly Complex Treatment Landscape in the Management of Non-Small Cell Lung Cancer

H. Jack West, 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 options for advanced non-small cell lung cancer have exploded over the last several years. For some patients, targeted therapy is the first-line option. For those without targetable mutations and a biomarker of immunotherapy response, immunotherapy is the first-line option.

Key Points

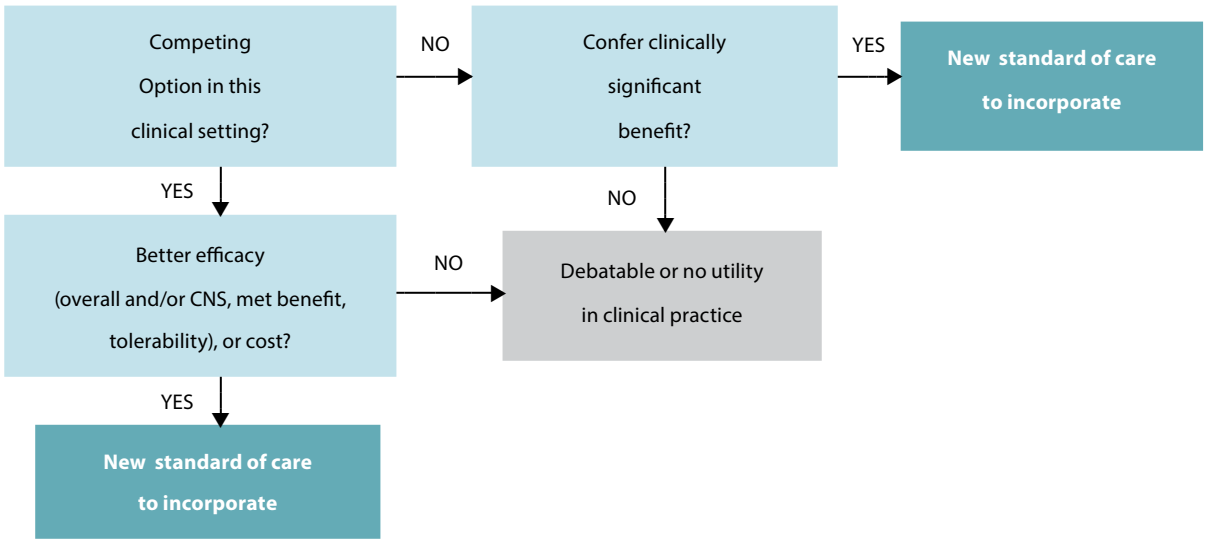
- Clinicians and managed care need to evaluate the benefits of new therapies relative to currently available options.
- Next-generation sequencing should be done at the initial workup for advanced NSCLC.
- If a targetable mutation is present, targeted therapy should be used first-line.
- For those without targeted mutation and PD-L1 expression, immunotherapy is the first-line option.

AS WITH MANY OTHER CANCERS, THE available treatments for non-small cell lung cancer (NSCLC) have been expanding dramatically. Unfortunately, new is not always improved. Some of the newer agents do not yet have compelling data to prove they should be used instead of older therapies. Just because an agent has FDA approval does not necessarily mean it should be used. In order to determine if a particular new therapy should replace older therapies, the new option needs to either be first in setting or offer one or more clear significant incremental benefits over our current standard of care (SOC), (Exhibit 1).

Numerous clinically relevant genetic mutations have been identified as drivers of NSCLC and have a targeted therapy available.[1] The most recent National Comprehensive Cancer Network (NCCN) guidelines include 10 different mutations which have at least one targeted therapy available.[2] An example of a therapy which is replacing prior therapies as SOC because of demonstrated benefit is selpercatinib for RET rearrangement positive advanced NSCLC.[3] Appropriate targeted therapy should be used first-line if a genetic mutation is present over immunotherapy because of better response rates and tolerance.[2]

Because there are so many known genetic mutations in NSCLC, it is no longer efficient to only test for individual mutations. Next-generation sequencing (NGS) can identify relevant mutations with a single test. NGS is recommended in the initial workup of advanced NSCLC to ensure the most appropriate initial therapy is selected and to help patients with rare mutations seek out clinical trials.[2] The guidelines recommend testing before therapy starts, but turnaround time (typically > 3 weeks) and availability of biopsied tissue are practical challenges. Liquid biopsies can help in some patients. Many of the mutations are rare findings. An individual practitioner may see one ROS1-positive case every five years or one NTRK gene fusion over their entire career. It is only feasible to test for these rare mutations as a broad strategy. NGS reports often do a poor job highlighting what is critical, emerging, and an aspirational finding, which can lead to misinterpretation.

Exhibit 1: Determining Benefits of New Therapies



CNS = central nervous system; met = metastases

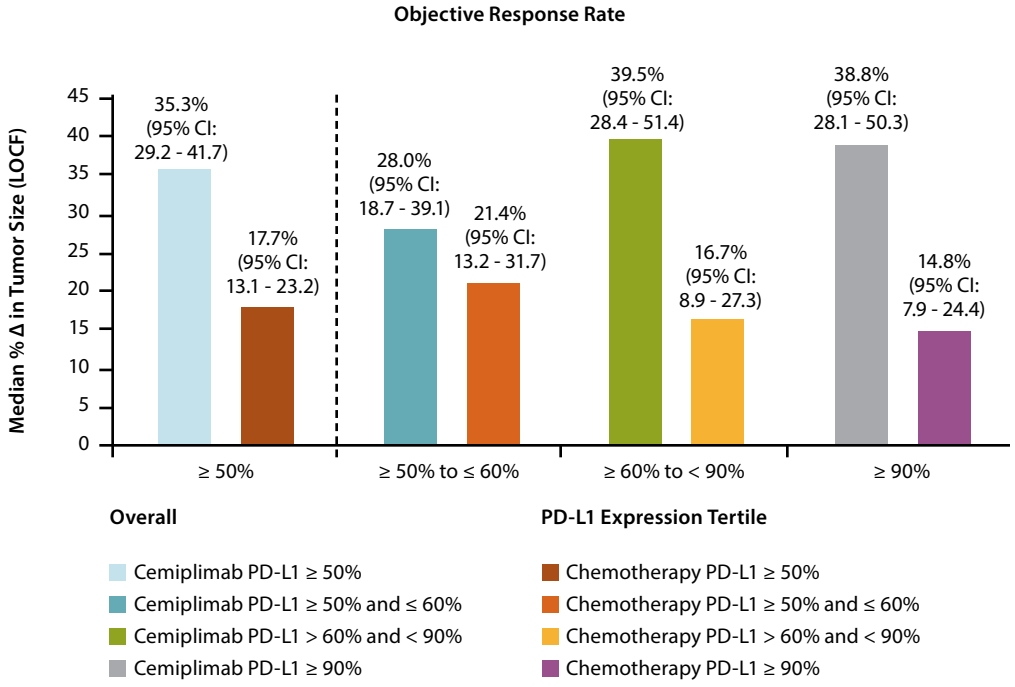
Exhibit 2: Preferred First-Line Therapy for Advanced NSCLC with PD-L1 Expression, No Actionable Mutations, and Performance Status 0-2[2]

PD-L1 1% to 49%	PD-L1 ≥ 50%
Adenocarcinoma, large cell, or NOS	*Adenocarcinoma, large cell, or NOS*
• Carboplatin or cisplatin + pemetrexed + pembrolizumab	• Pembrolizumab
Squamous cell	• Carboplatin or cisplatin + pemetrexed + pembrolizumab
• Carboplatin + paclitaxel + pembrolizumab	• Atezolizumab
	• Cemiplimab
	Squamous cell
	• Pembrolizumab
	• Carboplatin + paclitaxel + pembrolizumab
	• Atezolizumab
	• Cemiplimab

PD-L1 = programmed death ligand one; NOS = not otherwise specified
Note: All are Category 1 recommendations. Only preferred recommendations are included.

Many patients will not have a targetable mutation. For these patients, a blockade of programmed cell death-1 (PD-1) and its ligand (PD-L1) with checkpoint immunotherapy has transformed the first-line treatment of advanced NSCLC without targeted mutations. A recent Cochrane review found that single-agent immunotherapy in people with NSCLC and PD-L1 ≥ 50 percent leads to a higher overall survival (OS) rate and may lead to a higher progression-free survival (PFS) and overall response rate (ORR) when compared to platinum-based chemotherapy. It may also lead to a lower rate of adverse events

Exhibit 3: PD-L1 Expression Correlates with Response Rate to Cemiplimab[7]



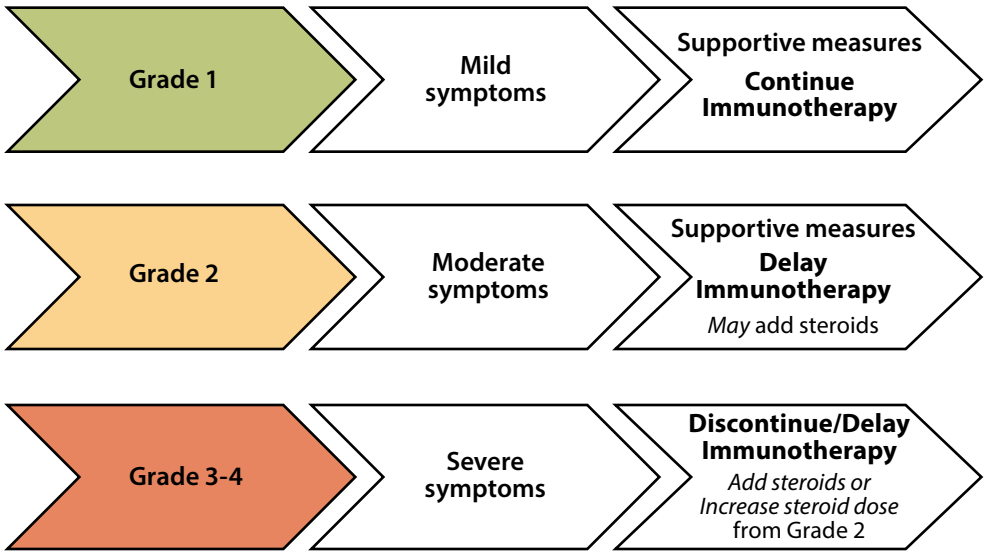
and higher health-related quality of life (HRQOL).[4] The NCCN guidelines have immunotherapy as the Category 1 preferred treatment option for first-line treatment of advanced NSCLC positive for PD-L1 expression and negative for actionable mutations in patients with performance status of 0 to 2 (Exhibit 2).[2] Pembrolizumab (Keytruda®) with and without chemotherapy, atezolizumab (Tecentriq®), and cemiplimab (Libtayo®) are the three recommended agents.

Cemiplimab is the most recently approved checkpoint inhibitor for advanced NSCLC (February 2021). The FDA-approved indication is for the first-line treatment of patients with NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations, and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or metastatic.[5] This agent also has indications for cutaneous squamous cell carcinoma and basal cell carcinoma.

The NSCLC indication was based on results from a multicenter, open-label, global, Phase III, randomized, controlled trial (EMPOWER-Lung 1).[6] In the PD-L1 50 percent or greater population, which consisted of 563 patients, median OS was not reached with cemiplimab (n = 283) versus 14.2 months with chemotherapy (n = 280; hazard ratio [HR] 0.57; p = 0·0002). Median PFS was 8.2 months with cemiplimab versus 5.7 months with chemotherapy (HR 0.54; $p < 0.0001$). Significant improvements in OS and PFS were also observed with cemiplimab in the intention-to-treat population despite a high crossover rate (74%). In this trial, PD-L1 expression correlated with response rate to cemiplimab (Exhibit 3).[7] Grade 3 and 4 treatment-emergent adverse events occurred in 98 (28%) of 355 patients treated with cemiplimab and 135 (39%) of 342 patients treated with chemotherapy.

A cost-effectiveness analysis from the perspective of United States (U.S.) payers comparing cemiplimab or chemotherapy as first-line treatment of advanced NSCLC with a PD-L1 level of at least 50 percent found cemiplimab cost-effective at the willingness-to-pay threshold of $150,000 per quality-adjusted life years (QALYs).[8] Treatment of advanced NSCLC with cemiplimab added 0.546 QALYs (1.492 LYs) and resulted in an incremental cost of $22,069.804 compared with chemotherapy, which was associated with an incremental cost-effectiveness ratio of $40,390.412 per QALYs gained. The results of one-way sensitivity analysis found that the cost of cemiplimab was the most sensitive factor. The probabilistic sensitivity analysis showed that the probability of cemiplimab being cost-effective was 100 percent.

Exhibit 4: Basic Management Approach for Immune-Related Adverse Events[17,18]



Another cost analysis from the U.S. payer perspective found comparable results.[9] Survival data and transition probabilities from the EMPOWER-Lung I trial were used in a Markov model, with three mutually exclusive health states, to compare the expected health outcomes and cost of cemiplimab with chemotherapy. Treatment of NSCLC with cemiplimab yielded an extra 1.07 QALYs at an additional cost of $98,211 compared with chemotherapy, associated with an incremental cost-effectiveness ratio of $91,891/QALYs and an incremental net health benefit of 0.087 QALYs at a willingness to pay threshold of $100 000/QALYs. The probabilistic sensitivity analysis indicated that cemiplimab provided an 83.2 percent probability of being cost-effective. No cost-effectiveness analyses comparing the three checkpoint immunotherapies were identified.

The NCCN guidelines do not include any preference among the three preferred Category 1 checkpoint inhibitors.[2] At the time of this writing, cemiplimab is not yet incorporated in the discussion section of the guidelines of which an update is in progress. The three agents have not been directly studied against each other; therefore, absolute benefit of one over the other cannot be determined at this time. A network meta-analysis compared cemiplimab and pembrolizumab using data from separate trials (EMPOWER-Lung I, KEYNOTE-024, and KEYNOTE-042).[6, 10-14] For first-line treatment of advanced NSCLC with PD-L1 ≥ 50 percent, cemiplimab was associated with significantly greater PFS and overall response rate (ORR), and comparable OS compared to pembrolizumab.[10] Grade 3 to 5 adverse events, immune-related adverse events (irAEs) and all-cause discontinuation due to adverse events were comparable for the two agents. At two years, numerically more patients receiving cemiplimab were alive (59% versus 49%) and significantly more were alive without progression (37% versus 18%). This analysis did not include the atezolizumab first-line trial (IMPower110) because a different PD-L1 assay was used.[15] Longer-term (5 year) survival data are available for pembrolizumab but are not yet available for atezolizumab nor cemiplimab in the first-line advanced NSCLC setting.[14] In the absence of head-to-head trials or NCCN recommendations preferring one agent over another, many clinicians have continued to use pembrolizumab because it has been available longer, they are familiar with its use, it has longer term data, and it can be used in those with any level of PD-L1 expression. A significantly lower cost, if that existed, might be a driver for selecting atezolizumab and cemiplimab.

No matter what immunotherapy is selected, clinicians have to monitor for and manage irAEs which are very different from the typical adverse events seen with chemotherapy. Checkpoint immunotherapy takes the breaks off the immune system and thus the typical adverse events are related to an overactive immune system trying to

attack itself and includes hepatitis, colitis, nephritis, pneumonitis, and endocrinopathies. High-risk patients receiving checkpoint immunotherapy should be regularly monitored for treatment-related complications by specialized multidisciplinary teams, ideally using a personalized surveillance strategy.[16] The American Society of Clinical Oncology and NCCN have published specific management guidelines for irAEs. Exhibit 4 provides a basic outline of management based on severity from these guidelines.[17,18]

Conclusion

Clinicians and managed care need to evaluate the benefits of new therapies relative to currently available options in determining whether to adopt and pay for the new therapies. Next-generation sequencing should be done at the initial workup for advanced NSCLC, ideally before therapy starts, to identify the optimal therapy. If a targetable mutation is present, targeted therapy should be used first-line. For those without targeted mutation and PD-L1 expression, immunotherapy is the first-line option. Immunotherapy toxicities are an ongoing concern and should be managed by multidisciplinary teams.

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References

1. Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Transl Lung Cancer Res.* 2015;4(1):36-54.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. Version 1.2022. Available at nccn.org.
3. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. *N Engl J Med*. 2020;383(9):813-24.
4. Ferrara R, Imbimbo M, Malouf R, et al. Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer. *Cochrane Database Syst Rev.* 2021;4(4):CD013257.
5. Cemiplimab-rwlc (Libtayo®) injection, for intravenous use package insert. Regeneron Pharmaceuticals, Inc. 2/2021.
6. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: A multicenter, open-label, global, Phase III, randomized, controlled trial. *Lancet*. 2021;397(10274):592-604.
7. Kilickap S, Sezer A, Gümüş M, et al. EMPOWER-Lung 1: Clinical benefits of first-line (1L) cemiplimab monotherapy by PD-L1 expression levels in patients with advanced NSCLC. Presented at: 22nd World Conference on Lung Cancer of the International Association for the Study of Lung Cancer; January 28-31, 2021. Abstract OA01.03.
8. Wang L, Peng Y, Zeng X, et al. Cost-effectiveness analysis of cemiplimab versus chemotherapy as first-line treatment in advanced NSCLC with PD-L1 expression levels of at least 50. *Adv Ther.* 2021;38(8):4354-65.
9. Zhang M, Liu X, Wen F, Wu Q, Zhou K, Bai L, Li Q. First-line cemiplimab versus standard chemotherapy in advanced non-small cell lung cancer patients with at least 50% programmed cell death receptor ligand-1 positivity: Analysis of cost-effectiveness. *Clin Oncol (R Coll Radiol).* 2021:S0936-6555(21)00374-5.
10. Freemantle N, Xu Y, Florence Wilson F, et al. Network meta-analysis (NMA) of immuno-oncology (IO) monotherapy as first-line (1L) treatments (txs) for advanced non-small cell lung cancer (NSCLC) with PD-L1 expression ≥50%. *J Clin Oncol*. 2021;39:15-suppl, e21091.
11. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37(7):537-46.
12. Reck M, Rodríguez-Abreu D, Robinson AG, et al; KEYNOTE-024 investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):182333.
13. Mok TSK, Wu YL, Kudaba I, et al. KEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomized, open-label, controlled, Phase III trial. *Lancet*. 2019;393(10183):1819-30.
14. Garon EB, Hellmann MD, Rizvi NA, et al. Five-year overall survival for patients with advanced non-small-cell lung cancer treated with pembrolizumab: Results from the Phase I KEYNOTE-001 study. *J Clin Oncol*. 2019;37(28):2518-27.
15. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383(14):1328-39.
16. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management, and surveillance. *Nat Rev Clin Oncol*. 2019;16(9):563-80.
17. Thompson JA, Schneider BJ, Brahmer J, et al. Management of Immunotherapy-Related Toxicities. Version 1.2019. *J Natl Compr Canc Netw.* 2019;17(3):255-89.
18. Brahmer JR, Lacchetti C, Schneider BJ, et al; National Comprehensive Cancer Network. management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714-68.

New Horizons in the Treatment and Management of Chronic Inflammatory Demyelinating Polyneuropathy: Expert Perspectives on Immunoglobulin Therapy

Chafic Karam, 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

Chronic inflammatory demyelinating polyneuropathy (CIDP). Treatments to modulate the immune system can be effective in reducing symptoms and improving muscle strength. Many patients will need to have maintenance therapy to maintain function.

Key Points

- Corticosteroids, plasma exchange, and immunoglobulin are the treatment options.
- Subcutaneous immunoglobulin is an option for maintenance therapy that is preferred by patients and may lower costs when self-administered at home.

CHRONIC INFLAMMATORY DEMYELINating polyneuropathy (CIDP) is a rare immune-mediated neurological disease that leads to progressive weakness and impaired sensory function in the legs and arms.[1] The primary symptoms are weakness, imbalance, dead asleep feeling, and tingling in the limbs. Its course is progressive, developing over about eight weeks, and sometimes relapsing. There is segmental demyelination in multiple motor nerves or nerve roots on nerve conduction studies and increased cerebrospinal fluid protein levels. Nerve biopsy can show inflammation, demyelination, and remyelination. The exact cause of CIDP is unknown, but there are strong indications that CIDP is an autoimmune disorder.[1]

Classical CIDP has proximal and distal symmetrical limb weakness, loss of deep tendon reflexes, and loss of large fiber sensation. CIDP variants include multifocal, distal CIDP, pure motor, pure sensory, and focal. The initial diagnosis of CIDP is based on signs and symptoms, but the diagnosis can be confirmed by electrodiagnostic testing and nerve biopsy, if necessary.[2] Electrodiagnostic testing is recommended for all patients with suspected CIDP. It has to be distinguished from many different diseases and syndromes which have similar symptoms, including multifocal motor neuropathy and distal acquired demyelinating syndrome. An accurate diagnosis is important because treatment varies.

Treatment focuses on suppressing the immune system with intravenous or subcutaneous immunoglobulin (IVIG, SCIG), corticosteroids, and plasmapheresis. In refractory cases, rituximab, cyclophosphamide, and other less studied immunosuppressant medications are used. Refractory cases require consideration of an incorrect diagnosis before pursuing alternative therapies. Considerations that drive the selection of initial therapy include disease severity, comorbid disorders, venous access, potential adverse events, and cost. The goals of therapy are to improve muscle strength and prevent permanent disability due to demyelination and secondary axonal loss. The earlier treatment is initiated the more likely patients are to regain function.

Response to treatment can be measured with objective measures such as the Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, the Inflammatory Rasch-built Overall Disability Scale (I-RODS), the Medical Research Council (MRC) sum score (muscle

Exhibit 1: Comparing SCIG and IVIG[8]

	IVIG	SCIG
INFUSION PRACTICALITIES		
Induction/Loading dose	2 g/kg bw (20 mL/kg) divided over 2 to 5 consecutive days.	N/A–SCIG not approved for induction therapy.
Maintenance dose	1 g/kg bw (10 mL/Kg) in 1 to 2 infusions over consecutive days.	0.2 to 0.4 g/kg bw (1 to 2 mL/kg) in 1 to 2 infusions.
Infusion duration	Three to five hours.	1 to 1½ hours.
Infusion frequency	Typically, 3 to 4 weeks.	Typically, weekly.
Infusion rate	0.3 mL/kg per hour for initial infusion, increasing up to ≤ 4.8 mL/kg per hour as tolerated.	≤ 20 mL/site per hour for initial infusion, increasing up to ≤ 50 mL/site per hour, as tolerated. (≤ sites simultaneously, typically 2 to 4 sites used)
Onset of action	One to two weeks	Four weeks
Setting	Home, hospital, or infusion clinic	Home, school, work (or other convenient location)
HCP required	Yes	Typically, no
TYPICAL SAFETY PROFILE		
Systemic AEs	Yes	Less frequent
Local AEs	Rarely	Yes
Premedication	Yes	Rarely
Venous access	Yes	No
IG levels	Trough and peaks	Stable–approaching steady state
Wear-off effects	Can occur between doses	Rarely, due to more frequent infusion

BW = body weight; HCP = healthcare provider.

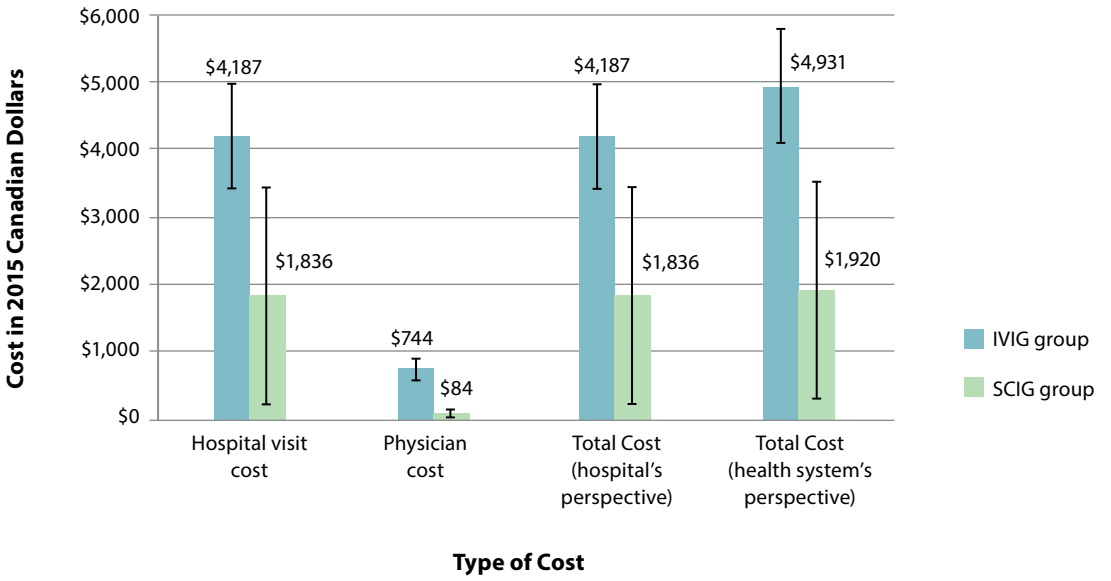
strength), and grip strength. The MRC measures strength of upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsal flexors. Most neurologists will be checking each of these muscle areas at each visit. Accuracy of grip strength measurement is dependent on patient effort and ability. There is a high correlation between overall clinical status and grip strength, and it can be used as a home-based measure to assess efficacy of IVIG/SCIG.[3]

There are several unmet needs for CIDP. It can be difficult to diagnose and distinguish from other neuropathic disease. There are currently no established biomarkers for diagnosis nor treatment efficacy. There is no curative treatment, and it is a chronic problem in most patients. Drug-free remission can happen in 10 to 30 percent of patients; however, the balance of patients require chronic maintenance therapy. Lastly, adverse events with current treatments can be significant.

Corticosteroids are effective, can lead to remission, are oral and easy to prescribe, and are the least costly in terms of acquisition price. Adverse events are frequent and can be serious. These include mood issues, moon face, weight gain, swelling, hypertension, diabetes, osteoporosis, increased risk of infections, skin changes, and cataracts. Because CIDP is a chronic disorder, adverse events are an issue, especially in those who require higher doses for extended periods of time.

Plasma exchange is also effective and has a quick onset of action. It is an intensive and invasive procedure which requires an intravenous port. Additionally, it is expensive, the vascular access can

Exhibit 2: Cost Comparison of IVIG and SCIG[9]



IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin
Note: The error bars represent the standard deviation for each variable and group.

get infected and thrombosed, and blood pressure issues and rash can occur during the procedure. The procedure requires a visit to a specialized center which may not be available for many patients and is time consuming for the patient.

Immunoglobulins are the most commonly used treatment for CIDP. IVIG is effective in improving disability scores and measures of nerve transmission and muscle strength (ICAT, MRC, grip strength, electrophysiologic testing), has a quick onset of action, and can be used for both induction and maintenance.[4,5] It is better tolerated than corticosteroids. Unfortunately, it is expensive, requires venous access, and causes adverse events, including headaches, nausea, rash, and blood clots.

Subcutaneous immunoglobulin infusion was developed as a more convenient alternative to IVIG. In addition to being effective, SCIG causes fewer adverse events compared to IVIG, results in better steady state IG levels, is more convenient for patients, and does not need venous access.[6,7] The primary adverse events of SCIG are local skin reactions. SCIG infusions take much less time than IVIG (1 to 1½ hours versus 3 to 5 hours). Patients typically can take over self-administration after four or fewer training sessions.[6] Additionally, in one trial, 53 percent of patients preferred SCIG over their previous IVIG treatment, compared with 18 percent who preferred IVIG.[6] A disadvantage of SCIG is that it is not FDA-approved for induction therapy, and the patient has to be transitioned to SCIG after induction with IVIG. It is also more expensive in terms of acquisition cost than IVIG, and self-administration requires a significant learning curve. Exhibit 1 compares SCIG and IVIG.[8] Overall, SCIG addresses many of the issues encountered by those unable, or unwilling, to tolerate the treatment burden of long-term IVIG.

Home-based SCIG has been compared to hospital-based IVIG in an economic analysis from a hospital and health system perspective. This analysis showed cost savings associated with home-based SCIG therapy compared with hospital-based IVIG therapy (Exhibit 2).[9] The savings included reduced nursing time.

Other costs have to be considered in selecting therapy in CIDP. Quality of life, days of work missed, missed time with friends and family, long-term adverse events, short-term adverse events, co-pays, and need for caregiver involvement should all be considered. Clinicians should employ shared decision-making when choosing treatment for patients with CIDP in the initial management and maintenance settings. Exhibit 3 shows some patients who might be most appropriate for each route of IG administration.[8]

Exhibit 3: Selecting Patients for a Particular Route of Administration[8]

PATIENTS WHO MAY BE MORE SUITABLE FOR IVIg
Patients lacking skill, confidence or drive to learn self-administration, including limitations in some elderly patients.
Patients whose compliance for self-administration is in question.
Patients with poor dexterity and lacking a reliable support network.
Patients preferring an clinic setting and/or treatment administered by an HCP.
Patients preferring more infrequent infusions.
Patients with excessive bruising and subcutaneous bleeding tendency.
PATIENTS WHO MAY BE MORE SUITABLE FOR SCIg
Patients with poor venous access or those where a port is being considered.
Patients experiencing intolerable side events with IVIG infusions.
Patients experiencing treatment-related fluctuations between IVIG infusions.
Patients wanting more autonomy, freedom, or flexibility with their infusion location/schedule.
Patients preferring shorter, more frequent infusions.
Patients with comorbidities putting them at higher risk for severe adverse events.

Conclusion

CIDP is a rare chronic condition which has a major impact on patients and which is hard to diagnose. Treatments that are effective include corticosteroids, plasma exchange, and immunoglobulins. Immunoglobulins are the most frequently used, and subcutaneous self-administered products are a preferred option for many patients.

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References

1. National Organization for Rare Disorders. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Available at rarediseases.org/rare-diseases/chronic-inflammatory-demyelinating-polyneuropathy/. Accessed 1/10/2022.
2. Van den Bergh PY, Hadden RD, Bouche P, et al; European Federation of Neurological Societies; Peripheral Nerve Society. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. *Eur J Neurol.* 2010;17(3):356-63.
3. Doneddu PE, Hadden RDM. Daily grip strength response to intravenous immunoglobulin in chronic immune neuropathies. *Muscle Nerve.* 2020;62(1):103-10.
4. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomized placebo-controlled trial. *Lancet Neurol.* 2008 ;7(2):136-44.
5. Léger JM, De Bleecker JL, Sommer C, et al. Efficacy and safety of Privigen® in patients with chronic inflammatory demyelinating polyneuropathy: results of a prospective, single-arm, open-label Phase III study (the PRIMA study). *J Peripher Nerv Syst*. 2013;18(2):130-40.
6. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomized, double-blind, placebo-controlled, Phase III trial. *Lancet Neurol.* 2018;17(1):35-46.
7. Markvardsen LH, Sindrup SH, Christiansen I, et al. Subcutaneous immunoglobulin as first-line therapy in treatment-naive patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study. *Eur J Neurol.* 2017;24(2):412-18.
8. Beydoun SR, Sharma KR, Bassam BA, et al. Individualizing therapy in CIDP: A mini-review comparing the pharmacokinetics of IG With SCIG and IVIG. *Front Neurol.* 2021;12:638816.
9. Fu LW, Song C, Isaranuwatchai W, Betschel S. Home-based subcutaneous immunoglobulin therapy vs hospital-based intravenous immunoglobulin therapy: A prospective economic analysis. *Ann Allergy Asthma Immunol.* 2018;120(2):195-199.

Exploring the Latest Guidelines and Evidence of IBD Management: An Update in Diagnosis and Treatment

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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

Inflammatory bowel disease (IBD) is a group of chronic inflammatory diseases of the gastrointestinal tract. Early identification and treatment are important to avoid long-term damage from chronic inflammation. There are multiple available treatments now for moderate to severe IBD, which when used appropriately over time, should reduce the rate of complications.

Key Points

- Specific treatment targets should be set for IBD treatment.
- Several self-injectable and infusion biologic agents are available for treating moderate to severe Crohn's disease and ulcerative colitis.
- Tofacitinib and ozanimod are oral agents for induction and remission of moderate to severe ulcerative colitis.

INFLAMMATORY BOWEL DISEASE (IBD) represents a group of disorders of unknown cause that result in chronic intestinal inflammation, typically with a relapsing and remitting course. Crohn's disease (CD) and ulcerative colitis (UC) are the best known IBDs. About 10 to 15 percent of patients with IBD have indeterminate colitis which has overlapping symptoms, histology and pathology of CD and UC. Other forms of IBD include microscopic colitis (collagenous and lymphocytic), infectious colitis, ischemic colitis, radiation colitis, and drug-induced colitis.

There are approximately 1.6 million cases in the United States (U.S.) of UC and CD, with males and females equally affected.[1] The rates of CD and UC are highest in industrialized countries. The typical age of onset is between 15 and 35 years of age although IBD can develop at any age with a second peak, in some studies, at age 50 to 80 years. UC and CD are chronic, lifelong diseases without medical cure.

The cause is a disordered immune response to gut contents in genetically predisposed individuals. Development requires the interaction of genetic susceptibility, immune dysregulation, and environmental triggers. Environmental triggers include infection, nonsteroidal anti-inflammatory drugs, smoking, diet, and early exposure to antibiotics.

Family history is a strong risk factor for developing IBD with first-degree relatives having a 3 to 20-fold increased risk (CD > UC). In monozygotic twins, concordance is 44 to 58 percent for CD and 6 to 18 percent for UC. The lifetime risk of developing IBD in first-degree relatives is 8.9 percent for offspring and 8.8 percent for siblings. Seventy-five to 80 percent of families with multiple IDB affected patients are concordant for disease type. Multiple genes, which increase or decrease (protective) risk for IBD, have been identified.

The diagnosis of IBD is made utilizing clinical, laboratory, endoscopic, radiologic, and histologic data. Gastrointestinal (GI) specific complaints include diarrhea, abdominal pain, rectal bleeding, and weight loss. Extraintestinal manifestations of IBD are found in 10 percent of patients at presentation and up to 30 percent of patients over time. These include joint (colitic arthritis, sacroiliitis, ankylosing spondylitis), skin (erythema nodosum, pyoderma

Exhibit 1: Crohn's Disease versus Ulcerative Colitis

CROHN'S DISEASE	ULCERATIVE COLITIS
Inflammatory disease of any segment of the digestive tract.	Inflammatory disease of large intestine and rectum.
Most often in ileum and/or ascending colon.	Usually confined to inner lining of colon and rectum.
Transmural inflammation	Inflammation of mucosal lining
Rectal sparing	Invariably begins in the rectum
"Skip" lesions	Spreads to upper colon in a contiguous fashion.

gangrenosum), ocular (episcleritis, iritis, uveitis), and hepatobiliary (primary sclerosing cholangitis, autoimmune hepatitis) manifestations. Diagnosis of CD can be more difficult than UC.

UC is a diffuse, superficial mucosal disease with rectal involvement. Forty-five percent of patients have only the distal colon involved at diagnosis, 36 percent will have left side of colon disease, and 18 percent will have the entire colon involved. Complications of UC include anemia, bowel perforation, colorectal carcinoma, hemorrhage, toxic megacolon, and malnutrition. CD manifests as patchy, transmural, and segmental inflammation of the GI tract usually affecting the small bowel and colon and may spare the rectum. Fissures and fistulas are more common with CD. In addition to fissures and fistulas, other complications of CD include anemia, bowel stenosis/perforation, perianal disease, calcium oxalate stones, B12 malabsorption, colorectal carcinoma, and malnutrition. Exhibit 1 compares the two IBDs.

Early diagnosis of UC and CD is important. Early disease is defined when major inflammation occurs and this provides a window of opportunity for intervention before structural damage is done (Exhibit 2).[2] Targeting the underlying immune process early in the disease can be disease-modifying which would prevent strictures and the need for surgery.

Treatment paradigms are shifting, based on advances in understanding the inflammatory activity in IBD. Treatment is now based on objective markers of inflammation rather than symptoms alone. Symptoms are insensitive and nonspecific for bowel inflammation. The objective markers are serologic [C-reactive protein (CRP) reduction], endoscopic (mucosal healing), and radiographic

Exhibit 2: Natural History of Crohn's Disease

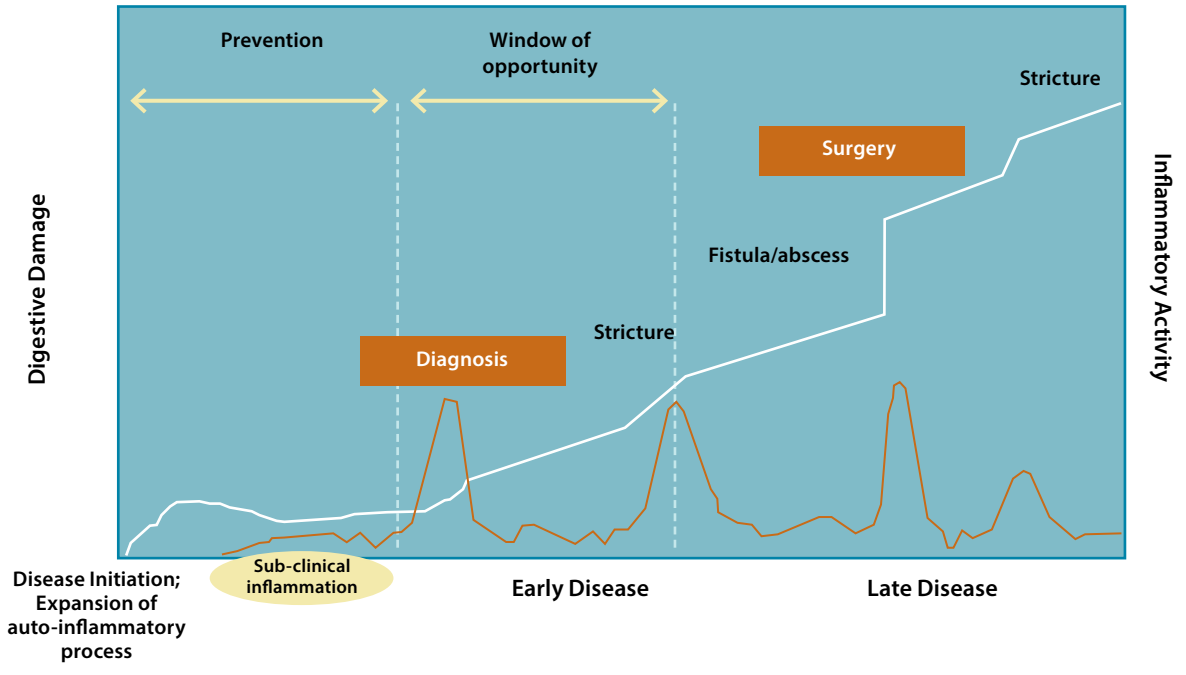
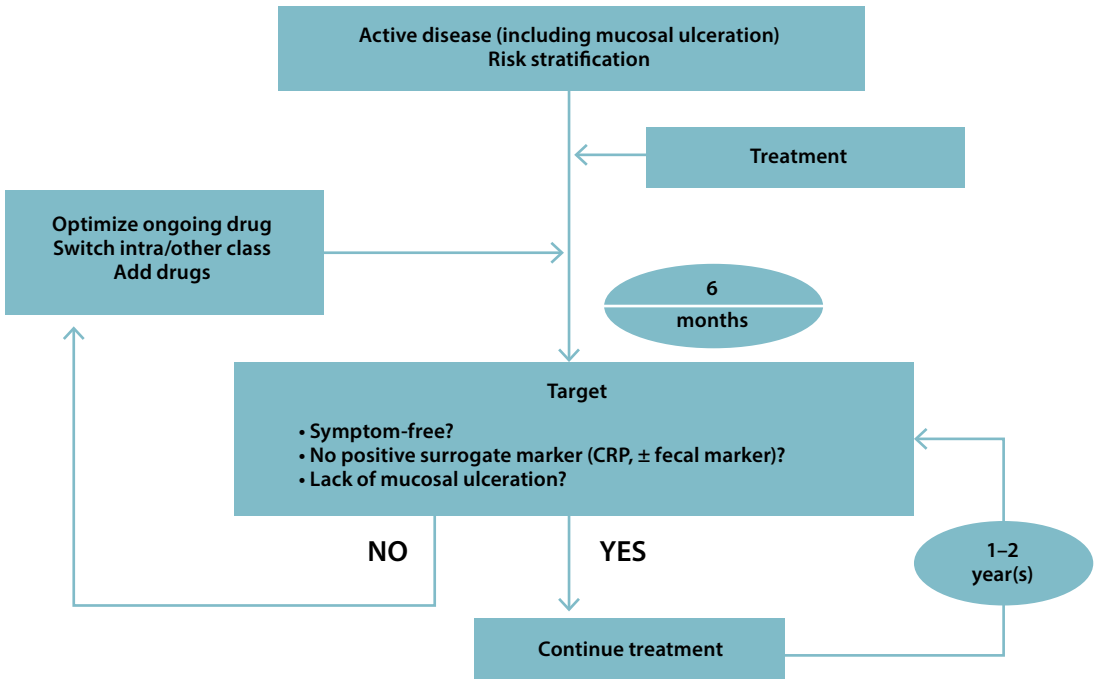


Exhibit 3: Treat-to-Target Algorithm



(computed tomography enterography improvement). The concept of treat-to-target (T2T), which uses clearly defined and objective markers to prevent progressive bowel damage and complications, is now being used in IBD management and is endorsed by the American College of Gastroenterology guidelines.[3,4] T2T has been shown to produce higher rates of deep remission [Crohn's disease activity index < 150, no steroids for ≥8 weeks, no fistula, Crohn's disease endoscopic index of severity (CDEIS) < 4, and no deep ulcers] and biologic remission (fecal calprotectin < 250 μg/g, CRP < 5 mg/L, and CDEIS < 4) in CD compared to routine clinical management.[5] An example algorithm for T2T is shown in Exhibit 3.[6]

Overall goals of IBD treatment include induced remission, maintained remission, maintained quality of life, and to prevent complications, hospitalizations, and surgery. Disease location and severity may help dictate treatment modalities. Mild to moderate disease is managed with oral and topical mesalamine and corticosteroids. Corticosteroids have been used to treat IBD since the 1950s. They should only be used for induction in CD and UC as 60 to 80 percent of patients will attain remission over a one-to-three-month course. Corticosteroids cause the overall highest rate of adverse events of any of the classes used for IBD. With all the other therapies that are now available for IBD, they should not be used for maintenance therapy.

Azathioprine and 6-mercaptopurine are both immunomodulators which are effective maintenance agents in moderate to severe IBD, but they have a slow response (8 to 16 weeks). They are used as adjunct therapy with certain biologics to reduce development of anti-drug antibodies. Unfortunately, these agents are not tolerated by 15 to 20 percent of patients and cause malaise, nausea, pancreatitis, myelosuppression and, most importantly, lymphoma. Methotrexate, another immunomodulator, has demonstrated benefit in CD patients for induction and maintenance. It is also used as an adjunct with certain biologics to reduce development of anti-drug antibodies. Like the other two, it is not tolerated by 15 to 20 percent of patients and causes hepatic fibrosis, interstitial pneumonitis, nausea, and teratogenicity.

Therapy for moderate to severe IBD has become complicated with five different classes of biologic or small molecule agents now approved:

- anti-tumor necrosis factor (TNF) monoclonal antibodies [infliximab and infliximab biosimilars, adalimumab, certolizumab (CD only), golimumab (UC only)].

Exhibit 4: Comparing Classes

Class	Pros	Cons
Anti-TNF	• Targeted therapy • 60 to 90% initial response; ~ 50% continued response • Several choices available for CD and/or UC • Biosimilars available now for infliximab and in 2023 for adalimumab • Effective when used with immunomodulators	• Tuberculosis/opportunistic infection warnings • Need for viral hepatitis testing • Conflicting data on long-term cancer risk
Anti-Integrins	• Selective effect on gut-homing cells • Favorable safety profile to date • Equivalent efficacy to other MOAs • No PML cases in otherwise healthy patients with IBD	• Slower time to response • Effect on non-gut manifestations?
Anti-IL-12/23	• Limited immune modulation (IL-12/23) • Efficacy in anti-TNF failures • Low rates of immunogenicity	• Systemic immunosuppression but less than anti-TNFs
JAK inhibitor	• Oral agent • Induction and maintenance efficacy • Small molecule so no immunogenicity	• Systemic immunosuppression • Zoster (1.5% to 5%) • Off-target effects; blood counts, HDL/LDL • Black box warning for VTE • Lab monitoring
S1P1 Modulator	• Oral agent • Small molecule so no immunogenicity	• Contraindications - Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, sino-atrial block unless functioning pacemaker, severe untreated sleep apnea, with monoamine oxidase (MAO) inhibitor.

- anti-integrin monoclonal antibodies [vedolizumab, natalizumab (CD only)].
- anti-interleukin 12/23 monoclonal antibody (ustekinumab).
- Janus Kinase (JAK) inhibitor [tofacitinib (UC only)]
- sphingosine 1 phosphate receptor subtype one (S1P1) modulator [ozanimod (UC only)].

All are effective treatments but have pros and cons (Exhibit 4). Two additional IL-23 monoclonal antibodies, 2 JAK inhibitors, and another S1P1 modulator are likely to be approved by the FDA in the next two years which will complicate treatment choice even further.

Vedolizumab (Entyvio®) is an improvement over natalizumab (Tysabri®). Because vedolizumab only targets the gut, it is believed to be safer than natalizumab. It is also FDA-approved for both UC and CD whereas the other agent is only approved for CD in addition to multiple sclerosis. Tofacitinib and ozanimod are potential improvements over the injectable and infusion agents because they are the first targeted oral agents for IBD.

Tofacitinib (Xeljanz®) is FDA approved for UC and numerous rheumatic conditions. In patients with moderately to severely active UC, tofacitinib was more effective as induction and maintenance therapy than placebo. In the OCTAVE Induction

1 trial, remission at eight weeks occurred in 18.5 percent of the patients in the tofacitinib group versus 8.2 percent in the placebo group ($p = 0.007$); in the OCTAVE Induction 2 trial, remission occurred in 16.6 percent versus 3.6 percent ($p < 0.001$).[7] In the OCTAVE Sustain trial, remission at 52 weeks occurred in 34.3 percent of the patients in the 5mg tofacitinib group and 40.6 percent in the 10mg tofacitinib group versus 11.1 percent in the placebo group ($p < 0.001$ for both comparisons with placebo).[7]

Ozanimod is FDA-approved for UC and multiple sclerosis. It is effective as induction and maintenance therapy for UC. The incidence of clinical remission was significantly higher among patients who received ozanimod than among those who received placebo during both induction (18.4% versus 6.0%, $p < 0.001$) and maintenance (37.0% versus 18.5%, $p < 0.001$).[8] The incidence of clinical response was also significantly higher with ozanimod than with placebo during induction (47.8% versus 25.9%, $p < 0.001$) and maintenance (60.0% versus 41.0%, $p < 0.001$).

Selecting treatment requires provider/patient decision-making, weighing the risks and benefits of the various treatment options, patient factors, and costs. Agents from each biologic/small molecule class should be available on managed care formularies. High-risk patients should be considered for prompt treatment with a biologic or small molecule. Markers of high-risk for complications include complex fistula, deep ulcerations on endoscopy, youthful age, steroid-dependence/resistance, high-risk anatomy (upper GI involvement, extensive disease, perianal disease), severe disease activity (weight loss, low albumin and/or hemoglobin), and high serological burden [anti-saccharomyces cerevisiae antibodies (ASCA), anti-flagellin antibodies.

Surgical intervention is required in about two-thirds of CD patients and as many as one-third of UC patients. Indications for surgery include perforation, uncontrollable hemorrhage, intractable or fulminant disease, suspicion or identification of cancer, growth retardation in children, systemic complications of the disease or medication, and certain CD complications (anorectal disease/fistula, intra-abdominal abscess, and intestinal obstruction due to stricture). Surgeries in CD include stricturoplasty, resection of small intestinal segment, partial or complete colectomy, and proctocolectomy. CD cannot be cured with surgery. In UC, proctocolectomy (removal of the colon and rectum) with ileostomy or an ileoanal pouch is used. UC is "cured" once the colon is removed.

A team approach within an IBD specialty group can be helpful in managing those with moderate to severe disease. Team members can include physicians and physician extenders, colorectal surgeons, nurses including stoma nurses, medical assistants, and pharmacists. There needs to be access to radiology, mental health, nutrition, and other specialties.

Conclusion

IBD is caused by chronic inflammation in the gut which can result in serious complications including colon cancer. Clinicians should set treatment goals to target not only symptom relief but more importantly disease remission based on markers of inflammation and examination of the GI tract. Numerous biologic and small molecule agents targeted at the underlying inflammatory process are now available.

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References

1. Talley NJ, Abreu AT, Achkar J-P, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol*. 2011;106:S2–S25.
2. Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory bowel diseases. *Gastroenterology*. 2017;152(2):351-61.e5.
3. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018; 113(4):481-517.
4. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol*. 2019;114(3):384-413.
5. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): A multicenter, randomized, controlled Phase III trial. *Lancet*. 2017;390(10114):2779-89.
6. Bouguen G, Levesque BG, Feagan BG, et al. Treat to target: A proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol*. 2015;13(6):1042-50.e2.
7. Sandborn WJ, Su C, Sands BE, et al; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18): 1723-36.
8. Sandborn WJ, Feagan BG, D'Haens G, et al; True North Study Group. Ozanimod as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2021;385(14):1280-91.

A Closer Look at the Latest Advances in the Treatment and Management of Ankylosing Spondylitis

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Summary

Axial spondyloarthritis, which includes ankylosing spondylitis, is a potentially disabling inflammatory arthritis of the spine which usually presents as chronic back pain. It is underrecognized, and there is usually a significant delay in diagnosis. Treatment options have improved recently with the approval of a new class of medication.

Key Points

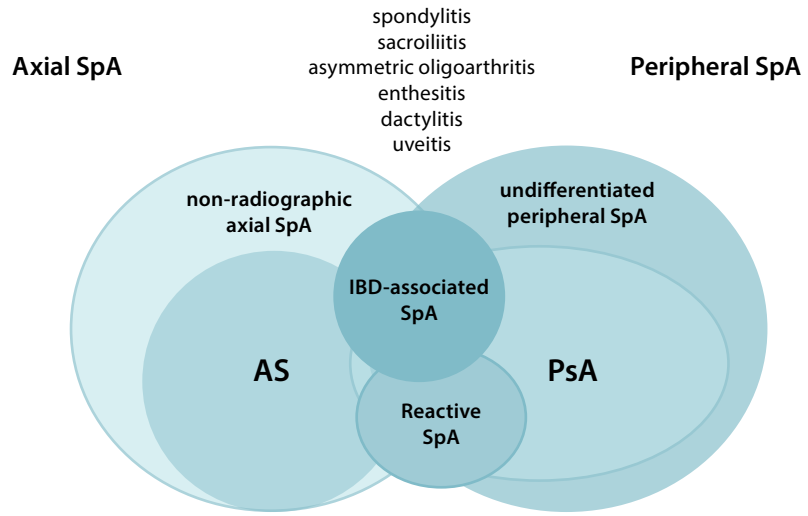
- It is important to identify and treat affected patients to reduce patient burden and potential for spinal deformity.
- Non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy are first-line treatment.
- Tumor necrosis factor inhibitors are second-line treatment.
- Inhibitors of IL-17A are third-line treatment.
- Tofacitinib is now approved and is an alternative to the other therapies.

SPONDYLOARTHRITIS (SpA) IS A FAMILY OF diseases with overlapping disease manifestations including spondylitis and sacroiliitis giving rise to inflammatory back pain, peripheral arthritis, (which is often an asymmetric oligoarthritis of the lower extremities), dactylitis, enthesitis, and uveitis (Exhibit 1). Features of inflammatory back pain include insidious onset before age 45 years, association with morning stiffness (> 30 minutes), improvement with exercise but not rest, alternating buttock pain, and good response to treatment with NSAIDs. Ankylosing spondylitis (AS) is the prototype of axial SpA (axSpA) and psoriatic arthritis (PsA) is the prototype of peripheral SpA. However, patients with axial disease may have peripheral disease and subsets of patients with PsA may have axial involvements, and the phenotype in individual patients may change over time. Axial spondyloarthritis is the focus of this article.

Axial spondyloarthritis can be divided into AS and non-radiographic axial spondyloarthritis (nr-axSpA). The diagnosis of radiographic AS requires both symptoms of inflammatory back pain and reduced spine mobility along with evidence of sacroiliitis on x-ray of the sacroiliac joint (Exhibit 2).[1] Non-radiographic axial spondyloarthritis involves inflammatory back pain and other clinical axSpA features, but without x-ray disease evidence.[1] An MRI of the sacroiliac joint can be used to confirm inflammation of this joint and the diagnosis of non-radiographic disease.

Radiographic AS occurs more often in men than in women (5:2) and 80 to 90 percent of patients are human leukocyte antigen B27 positive (HLA-B27+). Non-radiographic axSpA occurs in both men and women at the same rate; 60 percent are HLA-B27+, and it causes less functional impairment. Progression from non-radiographic to radiographic disease occurs in about 20 percent of patients over a 10-year period.[2] Risk factors for progression are male gender, HLA-B27+, high inflammatory activity, and smoking. Those who are HLA-B27 negative are older at disease onset.[3] Diagnostic delays are common with axSpA, as it takes a median of six years from

Exhibit 1: Spondyloarthritis Subtypes



SpA = spondyloarthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; IBD = inflammatory bowel disease

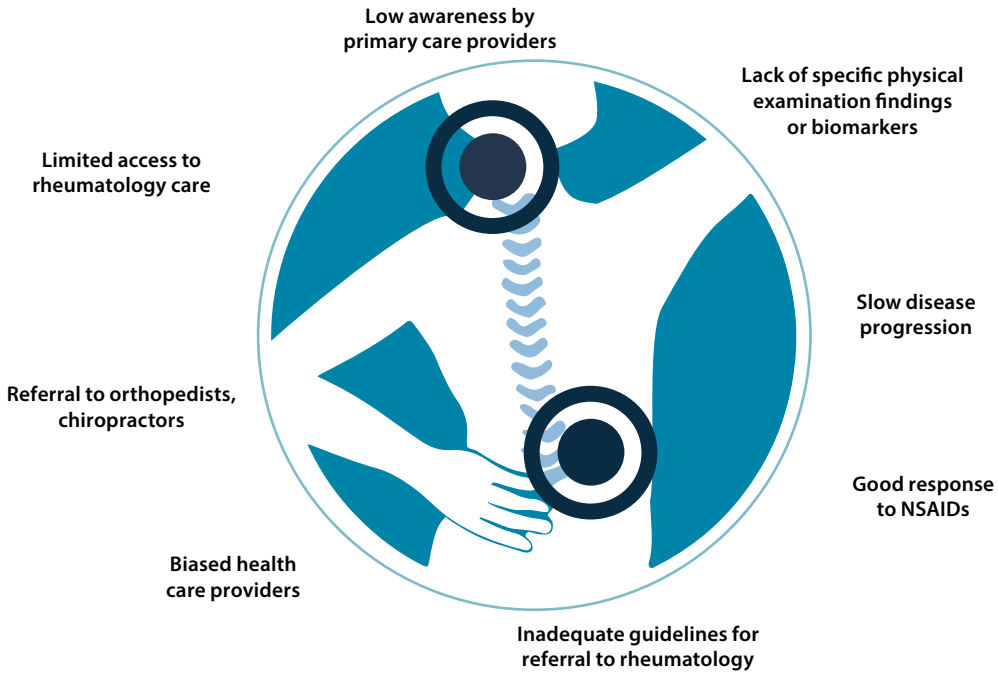
Exhibit 2: Classification Criteria for Axial SpA[1]

Patients with back pain ≥ 3 months and age at onset < 45 years		
Sacroiliitis on imaging plus ≥1 SpA feature	**or**	HLA-B27 plus ≥ 2 other SpA features
Sacroiliitis on imaging • active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA OR • definite radiographic sacroiliitis		• inflammatory back pain • arthritis • enthesis (heel) • uveitis • dactylitis • psoriasis • Crohn's disease/ulcerative colitis • good response to NSAIDs • family history for SpA • HLA-B27 • elevated CRP

symptom onset to diagnosis.[4,5] Diagnostic delays occur more frequently in patients who are female, young at symptom onset, HLA-B27 negative, or have psoriasis.[3,5]

There are numerous reasons why axSPA is underrecognized (Exhibit 3).[6] The effective identification of those individuals who are likely to have axSpA among patients with chronic back pain in primary care and their subsequent referral to a rheumatologist for establishing a correct diagnosis is important because effective treatments are available. Candidate referral parameters that can easily be

Exhibit 3: Reasons for Diagnostic Delay in axSpA/AS[6]



applied to patients with chronic back pain and age at onset ≤ 45 years (the target population) include inflammatory back pain and positivity for HLA-B27.[7] The goal of treatment of axSpA is to relieve pain and stiffness and prevent or delay complications and spinal deformity. Treatment is most successful before the disease causes irreversible damage. Newer medication studies are including all patients with axSpA and not distinguishing them by category. The ICD-11 coding system now includes a code for axSpA (FA92.0) rather than separate categories.

The first biologic therapy for axSpA was the tumor necrosis factor inhibitors (TNFi). These agents have been second-line therapy after NSAID failure and are effective. For example, 58.2 percent of adalimumab-treated patients achieved an Assessment in Spondyloarthritis International Society (ASAS) 20 response, compared with 20.6 percent of placebo-treated patients ($p < 0.001$).[8] The ASAS20 is defined as an improvement of at least 20 percent, and an absolute improvement of at least 10 units on a 0 to 100 scale, in at least three of the following domains; patient global assessment, pain assessment, function, and inflammation. More patients in the adalimumab group (45.2%) than in the placebo group (15.9%) had at least a 50 percent improvement in the Bath Ankylosing Spondylitis Disease Activity Index at week 12 ($p < 0.001$). Significant improvements in the ASAS40 response at weeks 12 and 24 were also demonstrated ($p < 0.001$).

The interleukin (IL) 23/17 axis and related cytokines have been implicated in the pathogenesis of SpA. Genes such as HLA-B27 may contribute to excess innate immune activation and IL-23 production, altered IL-23 responses, and increased production of IL-17 and related cytokines.[9] IL-17A has been shown to be the most important of the IL-17 family for axSpA. Elevation of IL-17A producing cells and IL-23 and IL-17A levels have also been shown in blood of AS patients. There is also an increased expression of IL-23 and IL-17A in diseased tissues.

The IL-17A antagonists secukinumab (Cosentyx®) and ixekizumab (Taltz®) inhibit IL-17A homodimers and IL-17A/F heterodimers. IL-17A inhibitors have been shown to be effective and are approved for treating adults with active AS or active nr-axSpA with objective signs of inflammation.[10-14] IL-17A inhibition improves subjective symptoms and objective signs (MRI, C- reactive protein) of axial inflammation, but the effect on radiographic progression in AS is still unknown. The effect size with the IL-17A inhibitors is similar to TNFi. IL-17A inhibitors do have efficacy in TNFi non responders,

Exhibit 4: Treatment Recommendations[20]

Adults with Active AS
• NSAIDs + physical therapy are first-line therapy – no preference for specific NSAID – continuous preferred over on demand in active disease
• No role for conventional DMARDs
• No systemic corticosteroids, but consider local injections
• Start TNFi if disease remains active on NSAIDs – insufficient response (or intolerance) to two or more NSAIDs at full dose over one month – no preference for specific TNFi (except for recurrent uveitis, IBD) – TNFi preferred over IL-17A antagonists and tofacitinib
• Primary TNFi failure or TNFi contraindication ==> IL-17A inhibitor over tofacitinib
• Secondary TNFi failure ==> switch to alternative TNFi

TNFi = tumor necrosis factor inhibitor; NSAID = nonsteroidal anti-inflammatory;
DMARD = disease-modifying antirheumatic drug (sulfasalazine, methotrexate, leflunomide, apremilast);
PT = physical therapy; IBD = inflammatory bowel disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

but it is less than in a TNFi naïve population. There are no head-to-head studies between the TNFi and IL-17A inhibitors.

Contrary to expectation, IL-23 inhibitors failed in axSpA clinical trials.[15,16] This includes both ustekinumab (Stelara®) and risankizumab (Skyrizi®), which have been shown to be effective in PsA. The reasons for efficacy in peripheral SpA but inefficacy in axSpA is not known, but there are many speculated reasons. Most importantly, it appears that IL-23 plays a role during initiation of axSpA but does not appear important for perpetuation of disease. IL-23 inhibition has been shown to prevent disease in HLA-B27+ rats but is ineffective after onset of arthritis.[17]

The newest class of therapy approved for axSpA is the Janus kinase inhibitor (JAKi). A large number of cytokines, including many of those implicated in the pathogenesis of SpA, signal through JAK pathways.[18] Tofacitinib (Xeljanz®) was FDA-approved on December 14, 2021 to treat adults with active AS who have had inadequate response or intolerance with one or more TNFi. It was already approved for treating psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis. Approval for AS was based on data from a Phase III, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of tofacitinib 5 mg twice daily versus placebo in 269 adult patients with active AS. The study met its primary endpoint showing that at week 16 the percentage of patients achieving an ASAS20 response was significantly greater with tofacitinib (56.4%) versus placebo (29.4%, $p < 0.0001$).[19] In addition, the percentage of patients achieving an ASAS40 response was significantly greater with tofacitinib (40.6%) versus placebo (12.5%) ($p < 0.0001$), a key secondary endpoint of the study. This is a similar effect size to TNFi and IL-17A inhibitors. Patients treated with tofacitinib also showed significant improvements in other clinical measures and outcomes related to disease activity, mobility, function, fatigue, and health-related quality of life, compared with the placebo group. Approval of the other two currently available JAKi (baricitinib and upadacitinib) for AS is likely to occur in the near future, as is an indication for nr-axSpA.

The American College of Rheumatology, the Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network published updated treatment guidelines for axSpA in 2019 (Exhibit 4).[20] These guidelines give preference to TNFi over IL-17A inhibitors or tofacitinib after NSAID plus physical therapy failure. Tofacitinib was not yet FDA-approved nor were the results of the Phase III trial previously discussed available at the

time of these recommendations. The place of JAKi in the therapy paradigm is still to be determined but may be as an equal alternative to IL-17A inhibitors.

As with other inflammatory diseases, treat-to-target (T2T) is becoming a main goal of axSpA treatment. An international task force has recommended the treatment target should be clinical remission/inactive disease of musculoskeletal (arthritis, dactylitis, enthesitis, axial disease) and extra-articular manifestations.[21] Low/minimal disease activity may be an alternative treatment target. Some challenges to T2T in axSpA exist. Although there are several treatment options, they have not really been studied for disease remission but as ASAS20 and 40 achievements. Disease activity measures are rarely used in clinical practice and are a requirement to prove disease remission. Some patients have slow disease progression despite ongoing disease activity. There is a lack of predictive biomarkers for rapid radiographic progression. Additionally, there is a lack of conclusive evidence that treatment reduces radiographic progression and that T2T improves long-term outcomes. Lastly, there are no data on the cost-effectiveness of T2T.

Conclusion

Axial spondyloarthritis, including AS and nr-axSpA, is underrecognized and typically take years to diagnose. It is important to identify and treat affected patients to reduce patient burden and potential for spinal deformity. There are several treatment options which now include the JAK inhibitors.

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References

1. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis (Part II): Validation and final selection. *Ann Rheum Dis*. 2009;68(6):777-83.
2. Wang R, Ward MM. Epidemiology of axial spondyloarthritis: an update. *Curr Opin Rheumatol*. 2018;30(2):137-43.
3. Feldtkeller E, Khan MA, van der Heijde D, et al. Age at disease onset and diagnosis delay in HLA-B27 negative versus positive patients with ankylosing spondylitis. *Rheumatol Int*. 2003;23(2):61-6.
4. Sykes MP, Doll H, et al. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? *Rheumatology (Oxford)*. 2015;54(12):2283-4.
5. Redeker I, Callhoff J, Hoffmann F, et al. Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. *Rheumatology (Oxford)*. 2019;58(9):1634-8.
6. Magrey MN, Danve AS, Ermann J, Walsh JA. Recognizing axial spondyloarthritis: A guide for primary care. *Mayo Clin Proc*. 2020;95(11): 2499-508.
7. Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. *Nat Rev Rheumatol*. 2012;8(5):262-8.
8. van der Heijde D, Kivitz A, Schiff MH, et al; ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: Results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2006 ;54(7):2136-46.
9. Smith JA, Colbert RA. Review: The interleukin-23/interleukin-17 axis in spondyloarthritis pathogenesis: Th17 and beyond. *Arthritis Rheumatol*. 2014; 66(2):231-41.
10. Baeten D, Sieper J, Braun J, et al; MEASURE 1 Study Group; MEASURE 2 Study Group. Secukinumab, an Interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med*. 2015;373(26):2534-48.
11. van der Heijde D, Cheng-Chung Wei J, Dougados M, et al; COAST-V study group. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16-week results of a Phase III randomized, double-blind, active-controlled, and placebo-controlled trial. *Lancet*. 2018;392(10163):2441-51.
12. Deodhar A, Poddubnyy D, Pacheco-Tena C, et al; COAST-W Study Group. Efficacy and safety of ixekizumab in the treatment of radiographic axial spondyloarthritis: Sixteen-week results from a Phase III randomized, double-blind, placebo-controlled trial in patients with prior inadequate response to or intolerance of tumor necrosis factor inhibitors. *Arthritis Rheumatol*. 2019;71(4):599-611.
13. Deodhar A, van der Heijde D, Gensler LS, et al; COAST-X Study Group. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): A randomized, placebo-controlled trial. *Lancet*. 2020;395(10217):53-64.
14. Deodhar A, Blanco R, Dokoupilová E, et al Improvement of signs and symptoms of non-radiographic axial spondyloarthritis in patients treated with secukinumab: Primary results of a randomized, placebo-controlled Phase III study. *Arthritis Rheumatol*. 2021;73(1):110-20.
15. Deodhar A, Gensler LS, Sieper J, et al. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71(2): 258-70.
16. Baeten D, Østergaard M, Wei JC, et al. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: Results of a randomized, double-blind, placebo-controlled, proof-of-concept, dose-finding Phase II study. *Ann Rheum Dis*. 2018;77(9):1295-1302.
17. van Tok MN, Na S, Lao CR, et al. The initiation, but not the persistence, of experimental spondyloarthritis is dependent on interleukin-23 signaling. *Front Immunol*. 2018;9:1550.
18. Veale DJ, McGonagle D, McInnes IB, et al. The rationale for Janus kinase inhibitors for the treatment of spondyloarthritis. *Rheumatology (Oxford)*. 2019;58(2):197-205.
19. Deodhar A, Sliwinska-Stanczyk P, Xu H, et al. Tofacitinib for the treatment of ankylosing spondylitis: a Phase III, randomized, double-blind, placebo-controlled study. *Ann Rheum Dis*. 2021;80(8):1004-13.
20. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis. *Arthritis Care Res (Hoboken)*. 2019;71(10):1285-99.
21. Smolen JS, Schöls M, Braun J, et al Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis*. 2018;77(1):3-17.

Evolving Considerations in the Treatment and Management of Hereditary Angioedema: Managed Care Strategies in an Evolving Treatment Paradigm

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Summary

Hereditary angioedema (HAE) is a rare, lifelong, disabling, and potentially life-threatening condition caused by a deficiency of C1 esterase inhibitor (C1-INH). Numerous treatment options are now available for treating acute attacks and preventing future attacks. Selection of treatment options will depend on individual patient factors such as the number and severity of attacks plus other factors.

Key Points

- Once HAE is identified, acute treatment and prophylaxis should be individualized considering unique patient factors.
- All patients require a management plan on how to deal with both acute attacks and any known triggers.
- All patients should have availability of two doses of effective on-demand acute therapy.
- Short-term and long-term prophylaxis is appropriate for many patients.

HEREDITARY ANGIOEDEMA IS A RARE condition characterized by the presence of angioedema without urticaria in the form of acute attacks that are sometimes preceded by prodromal symptoms. This angioedema can be quite severe, affecting the face, oropharynx (causing risk of asphyxiation), extremities, gastrointestinal system, and genitourinary tract. These prolonged attacks increase in intensity over 24 hours, and typically resolve in two to four days without treatment. Notably, they are unresponsive to treatment with antihistamines, corticosteroids, or epinephrine. Attacks typically occur unpredictably and vary in frequency. They are usually intensified by the use of oral contraceptives and hormone replacement therapy and are often precipitated by trauma or stress. In most cases, a family history of HAE is identified.

Angioedema is the result of fluid extravasation into deep dermis and subcutaneous tissues. As shown in Exhibit 1, there are many different causes of angioedema which must be excluded to diagnose HAE.[1,2] Most forms of angioedema are mediated by

Exhibit 1: Causes of Angioedema[1,2]

- IgE-mediated: Foods, drugs, insect stings
- Non-IgE mediated: Radiocontrast media
- Chronic spontaneous urticaria/angioedema
- Physical urticaria/angioedema
- Aspirin/nonsteroidal anti-inflammatories
- Angiotensin converting enzyme (ACE) inhibitor-induced
- C1-INH Deficiency
  - Hereditary - Types I, II
  - Acquired
- Hereditary with normal C1-INH
- Idiopathic
  - Histaminergic/mast Cell-mediated
  - Non-histaminergic

Exhibit 2: HAE Misdiagnosis[7]

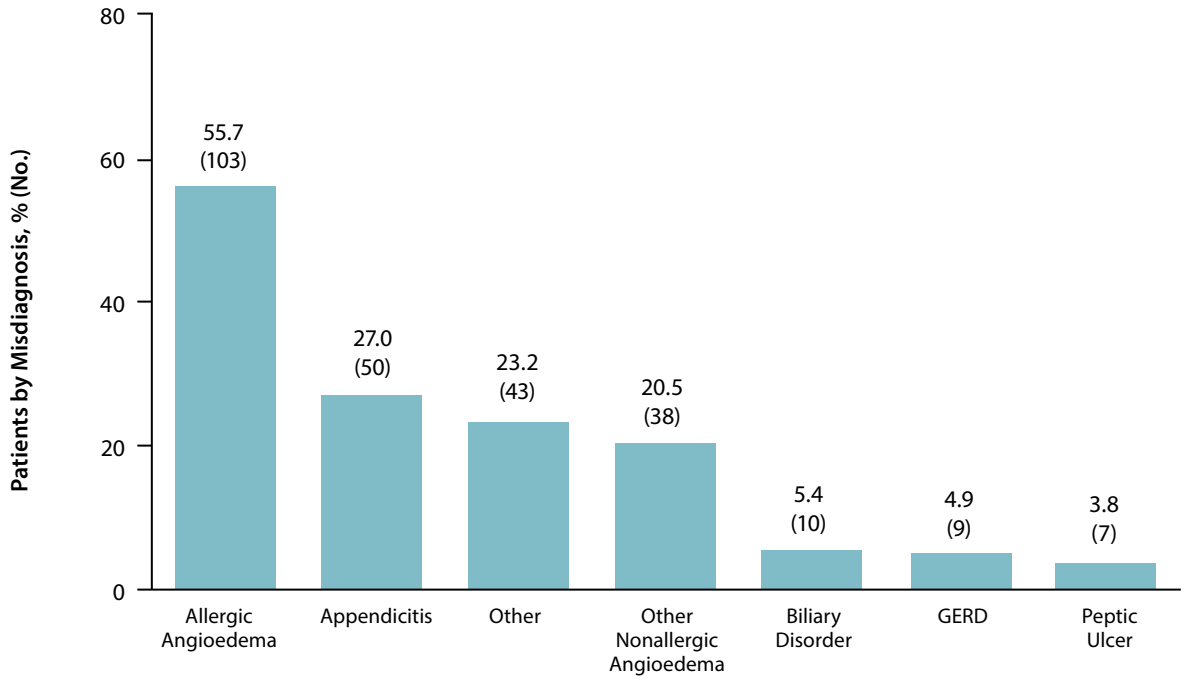

Exhibit 3: C1-Inhibitor Deficiency

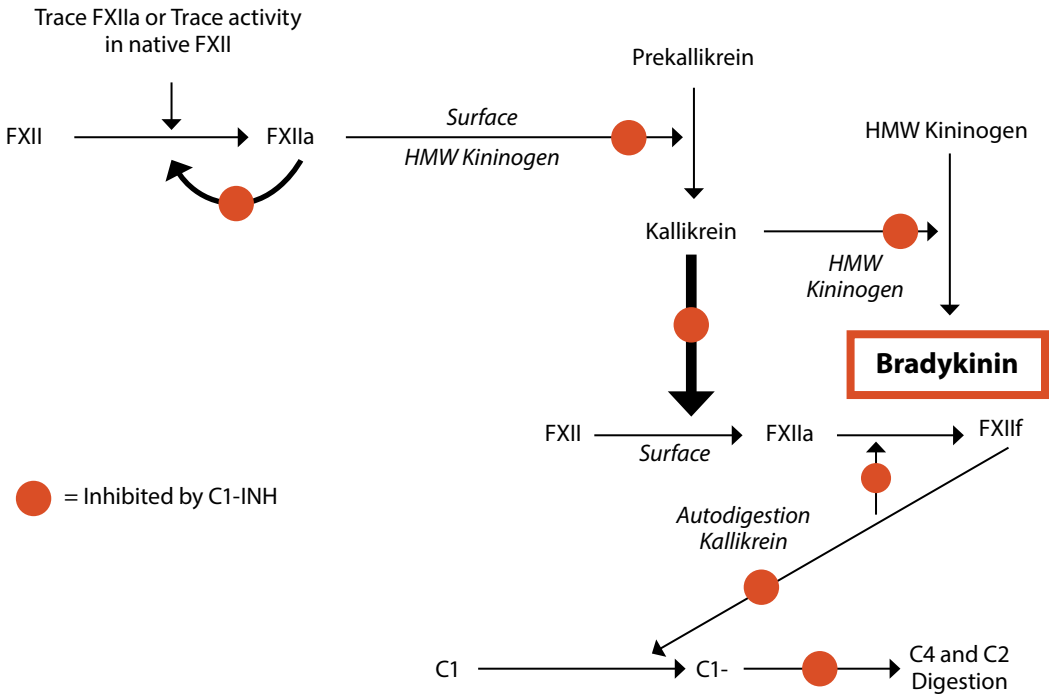

Exhibit 4: Acute Therapies

Drug	Mechanism	Disadvantages	Advantages
Plasma-derived C1-INH (Berinert®)	• Provides C1-INH	• Needs IV access • Dependent on plasma supply • Infectious risk • Potential infusion reactions	• Extensive clinical experience • Relatively long half-life
Recombinant C1-INH (Ruconest®)	• Provides C1-INH	• Needs IV access	• No human virus risk • Scalable supply
Ecallantide (Kalbitor®)	• Plasma kallikrein inhibitor	• Requires administration by a healthcare provider • Potential for anaphylaxis/allergic reactions • Antibody formation	• No infectious risk • Subcutaneous administration • Quick onset of action
Icatibant (Firazyr®)	• Bradykinin B2 receptor antagonist	• Local injection reactions	• No infectious risk • Stable at room temperature • Prefilled syringe for self subcutaneous administration

either histamine or bradykinin. This is an important distinction as it determines what treatment(s) will be effective for the patient. HAE is mediated by bradykinin.

Facial, extremity, oropharyngeal, laryngeal, and abdominal attacks can occur. The skin and abdomen are the most common locations followed by laryngeal.[3] With abdominal attacks, mild to severe pain, abdominal distension, tenderness, and vomiting may occur. The symptoms can mimic other abdominal conditions, resulting in misdiagnosis and unnecessary surgery.[1] Airway angioedema can cause death. In one survey, 1.3 percent of diagnosed patients died from asphyxiation and more importantly 31 percent of those undiagnosed also died.[4]

In approximately 50 percent of HAE patients, the symptoms first occur during childhood, usually between four and 11 years of age.[5,6] Early onset of symptoms (in first year of life) may mean a more severe course of HAE. Symptoms and frequency of attacks increase during periods of intense physiological development, such as between age three and six years and at the onset of puberty.[1] HAE is frequently misdiagnosed. In one study, 44 percent of patients had one or more misdiagnosis prior to HAE diagnosis (Exhibit 2).[7] The median diagnostic delay was 13.3 years in those with prior misdiagnosis compared to 1.7 years if no misdiagnosis.

HAE is an autosomal dominant disease caused by C1-INH gene mutations, which lead to deficiency in C1-INH.[8] Families of those diagnosed with HAE should be screened for the disease. C1-INH inhibits all active enzymes of the bradykinin-forming cascade (Exhibit 3). With a C1-INH deficiency, bradykinin levels increase. Bradykinin causes endothelial cell "leak" through vasodilatation and increased vascular permeability.[9] C1-INH functional assays are used to diagnose HAE.

A negative impact on health-related quality of life (HRQOL) by HAE has been documented in numerous studies. Many contributing factors include debilitating, painful, dangerous, and unpredictable symptoms; challenges in diagnosis; access to effective treatment; and treatment burden. HAE also increases risk of depression and loss of productivity. Because of their most recent HAE attack, workers lost a mean of 3.3 days and students lost a mean of 1.9 days.[10] Overall, HAE results in significant humanistic burden across physical and mental health domains and negatively impacts productivity.

The therapeutic goals of HAE treatment are to return normalcy to life, reduce hospitalization and disability, and prevent death and excessive pain. The three treatment strategies for HAE include on-demand treatment to resolve angioedema symptoms as quickly as possible during an attack, short-term prophylaxis to prevent an attack when the patient

Exhibit 5: Prophylactic Therapies

Drug	Mechanism	Patient Age	Potential Safety Concerns	Disadvantages	Advantages
Plasma-derived nanofiltered C1-INH (intravenous) (Cinryze®)	Inactivation and consumption of C1-INH	6 years and older	• Infectious risk • Infusion reactions • Thrombosis	• Needs IV access • Dependent on plasma supply • Frequent breakthrough attacks	• Extensive clinical experience • Long half-life
Plasma-derived nanofiltered C1 INH (subcutaneous) (Haegarda®)	Inactivation and consumption of C1-INH	6 years and older	• Infectious risk • Infusion reactions • Thrombosis	• Needs IV access • Dependent on plasma supply	• Improved steady-state C1-INH levels • No IV access required
Lanadelumab	Monoclonal antibody; binds plasma kallikrein and inhibits its proteolytic activity	12 years and older	• Unknown safety in pregnancy • Anti-drug antibodies/ hypersensitivity	• Injection site reactions	• No human virus risk • Subcutaneous administration • Less frequent dosing
Berotralstat	Plasma kallikrein inhibitor	12 years and older	• Abdominal pain, vomiting, diarrhea	• Drug interactions	• Oral administration
Danocrine	Unknown	All ages	• Hepatic toxicity, elevated LDL, weight gain, hypertension • Virilization, amenorrhea • Psychological effects	• Contraindicated in pregnancy, lactation, children, cancer	• Oral administration
Tranexamic acid	Inhibits activation of plasminogen and activity of plasmin	All ages	• Thrombosis, myalgias, abdominal pain, diarrhea	• Inferior efficacy compared to other agents • Off-label for HAE	• Oral administration

will be exposed to a known trigger, and long-term prophylaxis to decrease the frequency and severity of ongoing attacks.[11] All patients need on-demand treatment, and many will also need long-term prophylaxis. Short-term prophylaxis should be prescribed for those with known triggers. Known or suspected triggers include physical trauma (surgical or dental procedures, accidental), emotional stress, medications (estrogens, angiotensin-converting enzyme inhibitors), and infections. Treatment for HAE must be individualized to provide optimal care and normalize HRQOL.

Four agents are available for acute treatment, but only one of these can be self-administered (Exhibit 4). Treatment of early symptoms of an attack, with any licensed therapy, results in milder symptoms, more rapid resolution, and shorter duration of attack, compared with later treatment.[12] All therapies have been shown to be well tolerated, with minimal risk of serious adverse events. Exhibit 5 provides overviews of the advantages and disadvantages of the available prophylactic treatments for HAE. All currently available prophylactic agents are associated with breakthrough attacks; therefore, an acute treatment plan is essential for every patient. Subcutaneous administration of C1-INH is a significant advancement in therapy of intravenous administration because it does not require intravenous access which can become an issue over time with patients. It is effective in reducing attacks compared to placebo.[13] Prophylactic subcutaneous C1-INH improves patient HRQOL compared with on-demand alone treatment.[14]

Lanadelumab (Takhzyro®) is a human monoclonal antibody that targets plasma kallikrein to prevent angioedema in patients with HAE. It was approved in the United States (U.S.) in 2018 as the first monoclonal antibody indicated for prophylactic

treatment of HAE. In the clinical trial that led to FDA approval, subcutaneous lanadelumab for 26 weeks significantly reduced the attack rate and improved HRQOL compared with placebo.[15]

Berotralstat (Orladeyo™) is the newest prophylactic therapy for HAE. This agent is an oral once-daily plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years and older. Berotralstat demonstrated a significant reduction in attack rate at both 110 mg (1.65 attacks per month; $p = .024$) and 150 mg (1.31 attacks per month; $p < .001$) relative to placebo (2.35 attacks per month).[16] One hundred and fifty milligrams is the standard dose but the 110 mg dose is recommended in patients with moderate or severe hepatic impairment and in patients taking chronically administered P-glycoprotein or breast cancer resistance protein (BCRP) inhibitors (e.g., cyclosporine).

The U.S. Hereditary Angioedema Association Medical Advisory Board has published recommendations on management of HAE.[11] Patients need to be educated about triggers and how to avoid them, and they need to know when to use short-term prophylaxis. About 40 percent of patients can identify what triggers their attacks, but most attacks are unpredictable. All patients should have availability of two doses of effective on-demand acute therapy and should be educated on when to use the doses. Identifying an attack early can be difficult but each attack should be treated as soon as possible. Prompt treatment to prevent attack progression is recommended with self-administered therapy. Attacks should be treated irrespective of the site of swelling. Incorporation of long-term prophylaxis into the patient's regimen should be undertaken based on individualized decision-making reflecting a physician-patient partnership. First-line prophylactic therapies are C1-INH, lanadelumab, and berotralstat. Danocrine and tranexamic acid should be used as second-line due to higher rates of adverse events and lower rates of efficacy, respectively. Management plans need to be individualized to lessen the burden of illness, aim to provide patients with HAE a normal HRQOL, and consider treatment burden. Acute treatment and prophylaxis should be selected considering unique patient factors, such as attack history, proximity to a medical/infusion center, impact of HAE on HRQOL, and other patient circumstances, preferences, and expectations.

Conclusion

HAE is a rare, lifelong, disabling, and potentially life-threatening condition caused by a deficiency of C1-INH. Once HAE is identified, acute treatment and prophylaxis should be individualized considering unique patient factors. All patients require a management plan on how to deal with both acute attacks and any known triggers, and they should have two doses of acute treatment readily available.

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References

1. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(3 Suppl):S51-131.
2. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. *Allergy*. 2018;73(8):1575-96.
3. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119(3):267-74.
4. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks, and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130(3):692-7.
5. Busse PJ, Christiansen SC. Hereditary Angioedema. *N Engl J Med*. 2020;382(12):1136-48.
6. Frank MM. Hereditary angioedema. *Curr Opin Pediatr*. 2005;17(6):686-9.
7. Zanichelli A, Longhurst HJ, Maurer M, et al; IOS Study Group. Misdiagnosis trends in patients with hereditary angioedema from the real-world clinical setting. *Ann Allergy Asthma Immunol*. 2016;117(4):394-8.
8. Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2000;105(3):541-6.
9. Zhao Y, Qiu Q, Mahdi F, et al. Assembly and activation of HK-PK complex on endothelial cells results in bradykinin liberation and NO formation. *Am J Physiol Heart Circ Physiol*. 2001;280(4):H1821-9.
10. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc*. 2010;31(5):407-14.
11. Busse PJ, Christiansen SC, Riedl MA, et al. U.S. HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-50.e3.
12. Longhurst H. Optimum use of acute treatments for hereditary angioedema: Evidence-based expert consensus. *Front Med (Lausanne)*. 2018;4:245.
13. Longhurst H, Cicardi M, Craig T, et al; COMPACT Investigators. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med*. 2017;376(12):1131-40.
14. Lumry WR, Craig T, Zuraw B, et al. Health-related quality of life with subcutaneous C1-inhibitor for prevention of attacks of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2018;6(5):1733-41.e3.
15. Banerji A, Riedl MA, Bernstein JA, et al; HELP Investigators. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: A randomized clinical trial. *JAMA*. 2018;320(20):2108-21.
16. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled Phase III trial. *J Allergy Clin Immunol*. 2021;148(1):164-172.e9.

Navigating an Increasingly Complex Treatment Paradigm in the Management of Type 2 Diabetes: Optimizing Cardiovascular and Renal Outcomes with SGLT2 Inhibitors

Richard E. Pratley, 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

Diabetes is an important disease due to the substantial risk of developing serious chronic complications, including cardiovascular disease and microvascular disease, such as retinopathy and nephropathy. There has been a great deal of progress in the management of type 2 diabetes over the past two decades in part because of the introduction of several new classes of medicines. However, there are still many treatment challenges to face.

Key Points

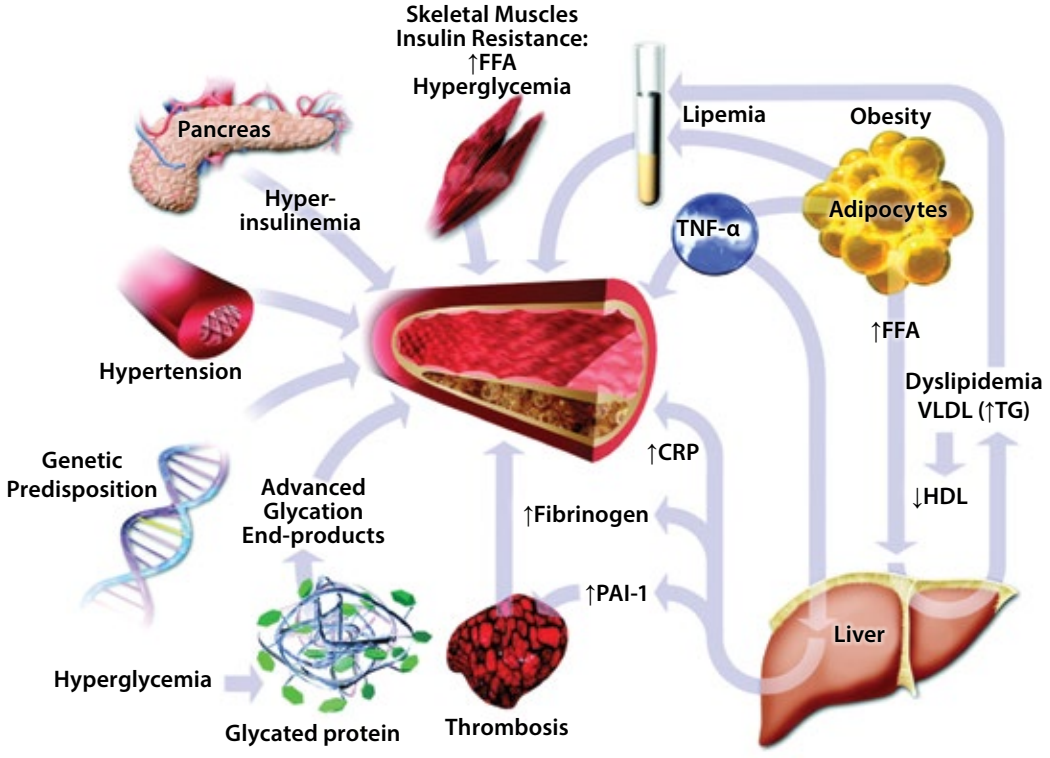
- Foundation therapy for type 2 diabetes remains lifestyle change and metformin.
- Recent clinical trials demonstrate that cardiovascular disease (CVD) and chronic kidney disease (CKD) risk are reduced with certain glucose-lowering classes, including the sodium glucose cotransporter 2 inhibitors (SGLT2) inhibitors and the glucagon-like peptide-1 receptor agonists (GLP-1 RAs.)
- These agents should be considered as initial therapy in selected patients.

DIABETES IS ONE OF THE MOST COMMON chronic diseases in the United States (U.S.) affecting over 34.2 million people (10.5% of the U.S. population), and this number is projected to continue to increase.[1] The vast majority (90 to 95% of cases in adults) are people with type 2 diabetes mellitus (T2DM). More concerning is that over 88 million people aged 18 years or older have prediabetes (34.5% of the adult U.S. population). Diabetes results in serious chronic complications including CVD and microvascular disease, such as retinopathy and nephropathy. It is the third leading cause of death (including contributing causes) in the U.S. The total estimated cost of diabetes in the U.S. is $327 billion per year (2017).[2] Of this total, $237 billion was for direct medical costs and $90 billion was reduced productivity.

One challenge in diabetes management is that many patients are not at optimal glucose control. The American Diabetes Association recommends a hemoglobin A1c (A1c) target of 7 percent, for most patients with diabetes.[3] However, it is estimated that over 14 million patients have an A1c above 7 percent and just over three million have an A1c above 10 percent.[4,5] This illustrates that there is still a significant unmet need to improve glycemic control in many patients. Also, most patients with T2DM struggle with weight issues. In fact, it is estimated that 16 million patients with diabetes in the U.S. can be classified as obese, and more than four million are considered severely obese, with a BMI above 40.[1,4] It is now well established that modest weight loss of as little as 5 percent can improve glycemic control. Anti-hyperglycemic agents also result in substantial weight loss and are needed in clinical practice.

Serious microvascular and macrovascular complications of T2DM have a devastating effect on quality of life and impose a heavy burden on healthcare systems. Diabetic retinopathy is present in 21 percent of people at the time diagnosis and

Exhibit 1: Macrovascular Disease in Patients with Diabetes[20]



FFA = free fatty acids; TNF = tumor-necrosis factor; VLDL = very low-density lipoprotein; TG = triglyceride; CRP = C-reactive protein; HDL = high-density lipoprotein; PAI-1 = plasminogen activator inhibitor-1.

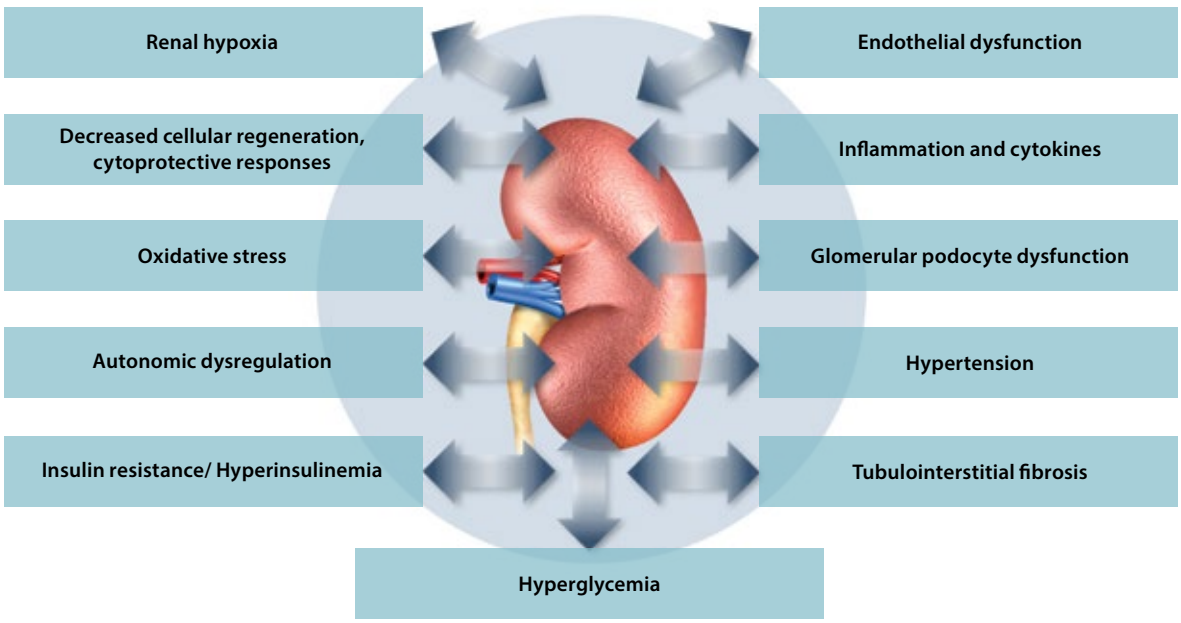
diabetic retinopathy is the leading cause of new blindness among adults aged 20 to 74 years.[6,7] Diabetic nephropathy is present in 18 percent of people diagnosed with diabetes and is a leading cause of end-stage renal disease (ESRD).[8,9] Diabetes is associated with a two to fourfold increase in cardiovascular mortality and stroke.[10] Seventy-five percent of individuals with T2DM die from cardiovascular causes. Diabetic neuropathy affects approximately 70 percent of people with diabetes and is a leading cause of nontraumatic lower extremity amputations.[11] Early detection and treatment of diabetes is essential in order to reduce the impact of its serious complications.

Rates of diabetes complications including myocardial infarction (MI), stroke, amputation, ESRD, and deaths from hyperglycemic crises all decreased markedly between 1990 and 2010.[12] These rates were decreased by multifaceted improvements in diabetes care, risk-factor management, self-management education and support, and better integration of care.[13] Progress seemed to stall after 2010 and some rates actually worsened which is partly due to rising rates in young and middle-aged adults.[13]

Cardiovascular complications are still much too common in people with T2DM which calls for more focus on reducing this risk. Glycemic control alone is not necessarily the answer to reducing cardiovascular risk. Glycemic control (A1c ~ 7%, even lower) reduces microvascular complications in T2DM with relative risk reduction (RRR) of 25 to 60 percent.[14-19] The impact of glycemic control itself on macrovascular complications in T2DM is small to nonexistent.[14-19] For the most part, any benefit of RRR is in the order of approximately 15 percent. This is for nonfatal myocardial infarction (MI), and also requires long-term efforts before it can be observed. Tight glucose control has also not been shown to reduce heart failure (HF) incidence rates; HF hospitalization and death were unchanged by tight glycemic control in randomized trials such as Advance and Accord.[17,18] Pharmacological interventions that target the dyslipidemia and hypertension associated with T2DM have been shown to reduce risk of macrovascular complications.[20] There are numerous mechanisms by which diabetes contributes to the development of macrovascular disease (Exhibit 1).[20]

Diabetes is a predictor of poor clinical outcomes

Exhibit 2: Mechanisms by Which Diabetes May Lead to CKD[29]



in HF patients, and those with diabetes have higher rates of HF.[21,22] Despite declining rates of hospitalizations for cardiovascular complications, HF remains the main reason for hospitalization in patients with diabetes in both men and women.[23] Heart failure with preserved ejection fraction (HFpEF) is most common in those with T2DM (55%).[24] HF with reduced EF (HFrEF) combined with diabetes leads to higher rates of cardiovascular death or need for hospitalization compared to HFpEF with diabetes mellitus (DM) and either type of HF without diabetes mellitus (DM).[25]

The combination of HF and DM is particularly bad because of metabolic inflexibility. To maintain its high energy demand, the heart orchestrates adenosine triphosphate (ATP) production using multiple energy substrates, namely fatty acids, carbohydrates (glucose and lactate), ketones and amino acids.[26] The contribution of these individual substrates to ATP production can dramatically change, depending on such variables as substrate availability, hormonal status, and energy demand, which is called metabolic flexibility. In heart failure, cardiac function is reduced, which is accompanied by discernible energy metabolism perturbations and impaired metabolic flexibility. Diabetes worsens metabolic flexibility.

Chronic kidney disease (CKD) is another complication which continues to evade significant rate reductions. Diabetes is the leading cause of kidney failure in the U.S., and diabetic kidney disease shortens life span by 16 years.[27,28] Diabetes causes kidney disease through many different mechanisms (Exhibit 2).[29] Approximately 75 percent of those with CKD also have some type of CVD.[27] CVD and DM work in combination to worsen CKD. In patients with low output heart disease, compensatory pressor responses via the sympathetic nervous system and the renin-angiotensin-aldosterone-system (RAAS) are activated.[30] These systems act as vasoconstrictors of the afferent and efferent arterioles, respectively, to preserve glomerular filtration rate (GFR). The increased GFR, via efferent vasoconstriction, results in decreased renal perfusion. Subsequently, low renal blood flow contributes to tubular hypoxia and progressive loss of nephrons and renal dysfunction. Activation of the sympathetic nervous system and the RAAS also increases sodium and water retention, resulting in increased central venous pressure, renal congestion, and venous pressure. Increased renal venous pressure reduces glomerular filtration rate. Renal congestion activates both sympathetic nervous system and RAAS, which contribute to tubulointerstitial inflammation and progressive reduction in GFR. Comorbidities and medications may exacerbate the tubular and glomerular changes and contribute to the progressive renal dysfunction.

In order to show benefit and not harm, manufacturers are now required to evaluate the cardiovascular effects of new diabetes therapies

which have led to the discovery that certain classes can reduce CVD and HF which is reflected in the updated American Diabetes Association (ADA) management guidelines. The trials discussed below have led to earlier use of glucagon like peptide one receptor agonists (GLP-1 RAs) and sodium glucose co-transporter two (SGLT-2) inhibitors.

GLP-1 RAs increase glucose-dependent insulin secretion, decrease glucose-dependent secretion of glucagon, slow gastric emptying and increase satiety. These agents have broad actions like native GLP-1 which target many of the underlying issues with T2DM. The satiety effects of this class result in moderate weight loss of five to seven pounds over six to 12 months (at doses approved for glucose management). Modest improvement in blood pressure and no intrinsic increased risk of hypoglycemia are other benefits.

Treatment with a GLP-1 RA has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with T2DM. In terms of cardiovascular outcomes, GLP-1 RA treatment reduces major adverse cardiovascular events (MACE) by 12 percent, CV death by 12 percent, stroke by 16 percent, myocardial infarction by 9 percent, mortality by 12 percent, and heart failure hospitalization by 9 percent.[31] Renal outcomes (development of new-onset macroalbuminuria, decline in estimated kidney function, progression to ESRD, or death attributable to kidney causes) are reduced by 17 percent, mainly due to a reduction in urinary albumin excretion. They also result in slower worsening of kidney function outcome (either doubling of serum creatinine or ≥ 40 percent decline in estimated glomerular filtration rate) by 13 percent.

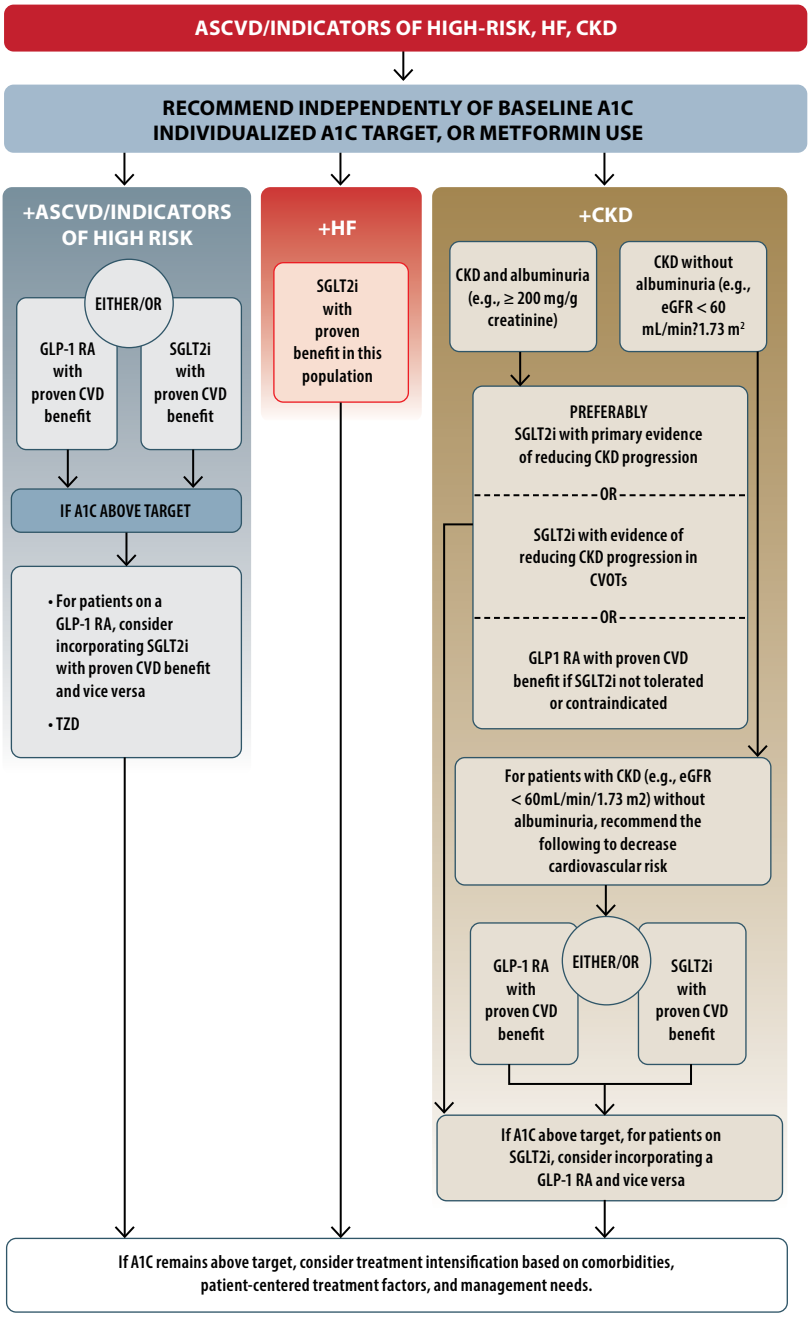
The SGLT2 inhibitors are the most recent medication class for T2DM, exerting their A1C lowering effect through glucosuria by lowering the renal threshold for glucose excretion. The kidneys play an essential role in maintenance and regulation of glucose homeostasis.[32, 33] Normally, virtually all of the filtered glucose is reabsorbed into blood by the proximal convoluted tubules mediated by an active process in the brush border membrane of the tubular epithelium and a facilitated process in the basolateral membrane. SGLT2 is responsible for reabsorbing up to 90 percent of the glucose filtered at the glomerulus. The remaining 10 percent is reabsorbed by SGLT1 that is expressed on the luminal (brush border) surface of cells of the S3 segment of the proximal tubule.

Five large-scale trials [Dapagliflozin Effect On Cardiovascular Events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS), Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME), Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV)] have studied the cardiorenal outcome of SGLT2 inhibitor treatment.[34-38] From these trials, SGLT2 inhibitors have been shown to protect against CVD and death in diverse subsets of patients with T2DM, regardless of CVD history. A recent meta-analysis found SGLT2 inhibitors were associated with a reduced risk of MACE (except ertugliflozin). In addition, results suggest significant heterogeneity in associations with CV death.[39] The largest benefit across the class was for reduction in risk for hospitalization for HF and kidney outcomes, with benefits for hospitalization for HF risk being the most consistent observation across the trials. The benefits of SGLT2 inhibitors appear to occur whether HFrEF or HFpEF, but are better for HFrEF.[38,40] For HF, the SGLT2 inhibitors prevent diabetes- associated ventricular remodeling.[41]

In terms of kidney outcomes, the SGLT2 inhibitors reduce the progression of CKD by 25 to 40 percent and decrease risk of development of ESRD.[39] The kidney benefits of SGLT2 inhibitors appear to be from improved glomerular loading conditions, reduced hyperfiltration, and decreased inflammatory and fibrotic responses of proximal tubular cells.[41,42] Given the known contribution of CKD towards HF development and progression, SGLT2i effects at the level of the kidney form a very attractive hypothesis when postulating mechanisms for the HF benefit. The combination of a diuretic effect plus a slowing of renal function deterioration help explain the HF benefit of these agents.[43]

Overall, with the SGLT2 inhibitors, efficacy in terms of MACE across the class is modest. In the EMPA-REG OUTCOME trial, MACE reduction was significant due to effect on CV death and no effect on MI or stroke.[36] In CANVAS, MACE reduction was significant due to contribution from MI, CV death, and stroke.[35] DECLARE and VERTIS CV only found trends in MACE reduction.[34,38] For CV death, only the EMPA-REG OUTCOME trial found significant reduction, driving heterogeneity in the beneficial effect for the class.[36] There is a consistent, substantial effect across the class for HF hospitalization reduction. Benefits are independent of baseline atherosclerotic cardiovascular disease (ASCVD) and prior HF. In patients with albuminuria or compromised kidney function, the risk reduction is larger.

Exhibit 3: Selecting Initial Therapy[3]



In addition to glucose lowering, the SGLT2 inhibitors are associated with modest reductions in blood pressure (-4 to -2 mmHg), body weight (~ 2 kg), and triglycerides. They also do not cause hypoglycemia when used alone. Adverse events include polyuria, dehydration, genital mycotic infections, reversible decreases in GFR, small increases in low-density lipoprotein cholesterol (LDL-C), and diabetic ketoacidosis.

The ADA guidelines for 2022 state that first-line therapy depends on comorbidities, patient- centered treatment factors and management needs and includes metformin and comprehensive lifestyle modification.[3] Although many patients can be

managed on oral metformin, a majority of patients will eventually require combinations to achieve target goals because of the progressive nature of the disease. The ADA guidelines now recognize that early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. GLP-1 RAs and SGLT2 inhibitors are recommended for initial therapy for individuals with T2DM with or at high risk for ASCVD, HF, and/or CKD independent of baseline A1C, A1C target, or metformin use.[3] As shown in Exhibit 3, the SGLT2 inhibitors are preferred in the cases of HF and CKD.[3] The American College of Cardiology and the American Heart Association guidelines on the primary prevention of CVD also recommend use of SGLT2 inhibitors or GLP-1 RAs in addition to metformin in those with T2DM not at goal A1C.[44]

Primary care providers (PCPs) deliver clinical care to approximately 90 percent of individuals with T2DM, and this will increase over time with the growth of an aging population. T2DM management has become increasingly complex with PCPs managing glucose control, facilitating lifestyle changes, navigating multiple medication classes (including combination therapies) and medical device options, addressing comorbid conditions, and managing CVD risk all in very time limited office visits. Managed care has a significant role in helping PCPs optimize quality care to improve outcomes and control costs through education and usage-data analysis. Given the CVD and kidney benefits of SGLT2 inhibitors and GLP-1 RAs which could result in substantial savings over time by avoiding the substantial costs of ESRD, HF, and other CVD, managed care should be identifying if appropriate patients are receiving these agents. An international study (which did not include data from the U.S.) found that one in three adults with T2DM already had CVD, yet only about 20 percent of subjects were on a GLP-1 RA (these agents may also be underused in the U.S.).[45]

Conclusion

T2DM has a complex pathogenesis, and glucose-lowering options have expanded markedly over the past 15 years. Foundation therapy remains lifestyle changes and metformin. Beyond metformin, several options are available. Recent clinical trials demonstrate that CVD and CKD risk are reduced with certain glucose-lowering classes, including the SGLT2 inhibitors and GLP-1 RAs. With any treatment decision, it is important to weigh both the risks and benefits of each agent and design a treatment regimen individualized to the patient.

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References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020.
2. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*. 2018;41(5):917-28.
3. American Diabetes Association. Standards of Medical Care in Diabetes — 2022 Abridged for Primary Care Providers. *Clin Diabetes*. 2022;40(1):10-38.
4. Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? *Diabetes Care*. 2008;31(1):81-6.
5. Chen Y, Rolka D, Xie H, Saydah S. Imputed state-level prevalence of achieving goals to prevent complications of diabetes in adults with self-reported diabetes — United States, 2017–2018. *MMWR Morb Mortal Wkly Rep*. 2020;69:1665-70.
6. UK Prospective Diabetes Study 6. Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. *Diabetes Res*. 1990;13(1):1-11.
7. Fong DS, Aiello L, Gardner TW, et al; American Diabetes Association. Diabetic retinopathy. *Diabetes Care*. 2003;26 Suppl 1:S99-S102.
8. Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens*. 1993;11(3):309-17.
9. Molitch ME, DeFronzo RA, Franz MJ, et al; American Diabetes Association. Diabetic nephropathy. *Diabetes Care*. 2003;26 Suppl 1:S94-8.
10. Kannel WB, D'Agostino RB, Wilson PW, et al. Diabetes, fibrinogen, and risk of cardiovascular disease: The Framingham experience. *Am Heart J*. 1990;120(3): 672-6.
11. Mayfield JA, Reiber GE, Sanders LJ, et al; American Diabetes Association. Preventive foot care in people with diabetes. *Diabetes Care*. 2003;26 Suppl 1:S78-9.
12. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med*. 2014;370(16):1514-23.
13. Gregg EW, Hora I, Benoit SR. Resurgence in Diabetes-Related Complications. *JAMA*. 2019;321(19):1867-8.
14. Duckworth W, Abraira C, Moritz T, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129-39.
15. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-86.
16. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-89.
17. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-72.
18. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-59.
19. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-

glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* 1998;352(9131):854-65.
20. Libby P, Plutzky J. Diabetic macrovascular disease: the glucose paradox? *Circulation*. 2002;106(22):2760-3.
21. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycemic drug therapy. *Lancet.* 2015;385(9982):2107-17.
22. Bauters C, Lamblin N, Mc Fadden EP, et al. Influence of diabetes mellitus on heart failure risk and outcome. *Cardiovasc Diabetol.* 2003;2:1.
23. Burrows NR, Li Y, Gregg EW, Geiss LS. Declining rates of hospitalization for selected cardiovascular disease conditions among adults aged ≥ 35 years with diagnosed diabetes, U.S., 1998-2014. *Diabetes Care.* 2018 ;41(2):293-302.
24. Arnold SV, Echouffo-Tcheugui JB, Lam CSP, et al. Patterns of glucose-lowering medication use in patients with type 2 diabetes and heart failure. Insights from the Diabetes Collaborative Registry (DCR). *Am Heart J.* 2018;203:25-29.
25. MacDonald MR, Petrie MC, Varyani F, et al; CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: An analysis of the candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) program. *Eur Heart J.* 2008;29(11): 1377-85.
26. Karwi QG, Uddin GM, Ho KL, Lopaschuk GD. Loss of Metabolic Flexibility in the Failing Heart. *Front Cardiovasc Med.* 2018;5:68.
27. United States Renal Data System. 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.
28. Wen CP, Chang CH, Tsai MK, et al. Diabetes with early kidney involvement may shorten life expectancy by 16 years. *Kidney Int.* 2017;92(2):388-96.
29. Thomas MC, Brownlee M, Susztak K, et al. Diabetic kidney disease. *Nat Rev Dis Primers.* 2015;1:15018.
30. Waldum B, Os I. The cardiorenal syndrome: what the cardiologist needs to know. *Cardiology*. 2013;126(3):175-186.
31. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol.* 2019;7(10):776-85.
32. Lee YJ, Lee YJ, Han HJ. Regulatory mechanisms of Na(+)/glucose cotransporters in renal proximal tubule cells. *Kidney Int Suppl.* 2007;(106):S27-35.
33. Wright EM. Renal Na(+)-glucose cotransporters. *Am J Physiol Renal Physiol.* 2001;280(1):F10-8.
34. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-57.
35. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017;377(7):644-57.
36. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-28.
37. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380(24):2295-306.
38. Cosentino F, Cannon CP, Cherney DZI, et al; VERTIS CV Investigators. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: Results of the VERTIS CV Trial. *Circulation.* 2020;142(23):2205-15.
39. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: A meta-analysis. *JAMA Cardiol.* 2021;6(2):148-158.
40. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139(22): 2528-36.
41. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. *Diabetologia*. 2018;61(10):2108-17.
42. Fioretto P, Zambon A, Rossato M, et al. SGLT2 inhibitors and the diabetic kidney. *Diabetes Care.* 2016;39 Suppl 2:S165-71.
43. Sattar N, Petrie MC, Zinman B, Januzzi JL Jr. Novel Diabetes Drugs, and the Cardiovascular Specialist. *J Am Coll Cardiol.* 2017;69(21):2646-56.
44. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;74(10):1376-414.
45. Mosenzon O, Alguwaihes A, Leon JLA, et al; CAPTURE Study Investigators. CAPTURE: A multinational, cross-sectional study of cardiovascular disease prevalence in adults with type 2 diabetes across 13 countries. *Cardiovasc Diabetol.* 2021;20(1):154.

Patient-Focused Treatment Decisions in Advanced Renal Cell Carcinoma: Expert Strategies on New and Emerging Combinations

Toni Choueiri, 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

The treatment of advanced renal cell carcinoma (RCC) has evolved dramatically over the past decade. Combination therapy with immunotherapy and oral tyrosine kinase inhibitors or dual immunotherapy has replaced chemotherapy and targeted agent monotherapy as first-line treatment. Both of these strategies are improving overall survival.

Key Points

- First-line treatment of advanced RCC is now combination therapy.
- The choice of which combination to use will depend on many factors.

RENAL CELL CARCINOMA (RCC) IS THE most common type of kidney cancer in adults. RCC accounts for 80 percent of all cases of kidney cancer and approximately 70 percent of RCC cases are of clear cell histology.[1] In 2022, approximately 79,000 new cases of kidney cancer (50,290 in men and 28,710 in women) will be diagnosed, and about 13,920 people (8,960 men and 4,960 women) will die from this disease.[2]

Treatment options for RCC include surgery, molecular-targeted therapy, immunotherapy, radiation, thermal ablation, and active surveillance. The treatment paradigm for advanced disease has undergone a dramatic transformation in recent years. The combination of targeted therapy and immunotherapy or dual immunotherapy is considered standard of care in patients with metastatic clear cell RCC (Exhibit 1).[1] Chemotherapy is now used only occasionally, in certain other tumor types.

Based on research showing that most clear cell RCC had a mutation resulting in constitutive production of cytokines stimulating angiogenesis, several agents that targeted angiogenesis pathways were developed. Three targeted therapies are part of the first-line recommended regimens – axitinib (Inlyta®), cabozantinib (Cabometyx®), and lenvatinib (Lenvima®). Because RCC is an immunogenic tumor and spontaneous regressions have been documented thus immunotherapies were investigated to treat this cancer. Various checkpoint inhibitor immunotherapies have been studied. Programmed death one (PD-1) inhibitors in combination with vascular endothelial growth factor (VEGF) inhibitors have synergistic activity in clear cell RCC.[3] T-cell mediated cancer cell killing appears to be enhanced through reversal of VEGF-mediated immunosuppression, increased T-cell tumor infiltration through normalization of the tumor vasculature, and increased T-cell priming and activation via dendritic cell maturation.

Nivolumab (Opdivo®), a PD-1 inhibitor, is recommended in combination with the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab (Yervoy®) in patients with poor or intermediate risk. These patients have one or more prognostic factors such as low performance status or elevated calcium, platelet, or lactate dehydrogenase. In the Phase III CheckMate 214 trial there was a significantly higher overall survival (OS) and objective response rate (ORR) with the immunotherapy combination compared with sunitinib.[4] The 18-month OS rate was 75 percent with nivolumab plus ipilimumab compared with 60 percent with sunitinib. The ORR was 42 percent versus 27 percent and complete response rates were

Exhibit 1: NCCN First-Line Therapy for Advanced Clear Cell RCC[1]

Risk	Preferred Regimens*
Favorable	Axitinib + pembrolizumab (category 1) Cabozantinib + nivolumab (category 1) Lenvatinib + pembrolizumab (category 1)
Poor/Intermediate	Axitinib + pembrolizumab (category 1) Cabozantinib + nivolumab (category 1) Lenvatinib + pembrolizumab (category 1) Ipilimumab + nivolumab (category 1) Cabozantinib

* The guidelines also list other recommended regimens and agents useful in certain circumstances

Exhibit 2: Comparing the Immunotherapy/Tyrosine Kinase Inhibitor Trials[5-7]

	CheckMate 9ER	KEYNOTE-426	CLEAR
	Cabo + Nivo	Axi+Pembro	Len+Pembro
Median follow-up	18m	13m	27m
Fav/Int/Poor Classification	23%/58%/19%	32%/55%/13%	31%/59%/9%
PFS (median difference from sunitinib)	8.3 months	4 months	14.7 months
Better Quality of Life	Yes	No	Not Yet Reported
Safety:			
All-causality AEs ≥ Grade 3, % versus sunitinib	75.3 versus 70.6	75.8 versus 70.6	82.4 versus 71.8
AEs leading to d/c of either drug / both, % versus sunitinib	19.7/5.6 versus 16.9	30.5/10.7 versus 13.9	37.2/13.4 versus 14.4

Cabo = Cabozantinib; Axi = Axitinib; Len = Lenvatinib; Nivo = nivolumab; Pembro = Pembrolizumab;
Fav = favorable; Int = intermediate; PFS = progression-free survival; AEs = Adverse events

9 percent and 1 percent. The best results with this combination were in those patients with intermediate and poor-risk disease which led to FDA approval for this group of patients. Sunitinib produced better OS and response rates, compared to the combination in those with favorable-risk disease. The OS by programmed death-ligand 1 (PD-L1) expression was higher in intermediate/poor-risk patients whose tumors expressed PD-L1 greater than or equal to 1 percent.

In the KEYNOTE-426 trial, treatment with pembrolizumab (Keytruda®) plus axitinib resulted in significantly longer OS and progression-free survival (PFS) compared to sunitinib in the first-line setting for metastatic RCC.[5] The 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. At 18 months, 82.3 percent and 72.1 percent were still alive, respectively. Median PFS was 15.1 months in the pembrolizumab-axitinib group and 11.1 months in the sunitinib group. Objective response rates with pembrolizumab-axitinib and sunitinib were 59.3 percent versus 35.7 percent, respectively. The overall frequency of toxic effects was similar in the two groups. Pembrolizumab gained accelerated FDA

Exhibit 3: Comparing Dual Immunotherapy with Immunotherapy/Tyrosine Kinase Inhibitor

IO+IO	IO+TKI
PROS	
• Improved OS	• Improved OS
• Mature follow-up data available	• High ORR
• Durable responses	• Longer PFS
• Potential to stop therapy	• Lower irAE rate
CONS	
• Higher irAE rate	• Unclear AE attribution
• Lower PFS/response rate	• Less mature follow-up
	• Chronic TKI toxicity

IO = immunotherapy; TKI = tyrosine kinase inhibitor; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; irAE = immune-related adverse events; TKI = tyrosine kinase inhibitor.

approval in April 2019 for first-line treatment of advanced RCC in combination with axitinib.

In the CLEAR trial, lenvatinib plus pembrolizumab was compared to lenvatinib plus everolimus and sunitinib.[6] PFS was longer with lenvatinib plus pembrolizumab than with sunitinib (median, 23.9 versus 9.2 months; $p < 0.001$) and was longer with lenvatinib plus everolimus than with sunitinib (median, 14.7 versus 9.2 months; $p < 0.001$). OS was longer with lenvatinib plus pembrolizumab than with sunitinib ($p = 0.005$) but was no longer with lenvatinib plus everolimus than with sunitinib ($p = 0.30$); final OS data have not yet been reported. Grade 3 or higher adverse events occurred in 82.4 percent of the patients who received lenvatinib plus pembrolizumab, 83.1 percent of those who received lenvatinib plus everolimus, and 71.8 percent of those who received sunitinib.

In the CheckMate 9ER trial which compared nivolumab plus cabozantinib with sunitinib, the median PFS was 16.6 months with the combination and 8.3 months with sunitinib ($p < 0.001$).[7] The probability of survival at 12 months was 85.7 percent with nivolumab plus cabozantinib and 75.6 percent with sunitinib ($p = 0.001$). The OS data for this trial are not yet complete. Efficacy benefits with nivolumab plus cabozantinib were consistent across subgroups. Patients reported better health-related quality of life with nivolumab plus cabozantinib than with sunitinib.

Factors that influence first-line treatment selection in advanced RCC include clinical evidence, patients' response to the first-line therapy before metastatic disease developed, patient characteristics, disease-risk criteria (favorable versus others), availability of clinical trials, patient preference, quality of life, physician experience, safety profile, cost/availability of the treatment, and prior pembrolizumab in adjuvant setting. Pembrolizumab is recommended by the National Comprehensive Cancer Network (NCCN) guidelines and FDA-approved as adjuvant therapy at those at intermediate-high or high-risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.[1] This earlier use does complicate the choice of therapy in the advanced RCC setting.

Exhibit 2 compares some information from the three immunotherapy/kinase inhibitor trials.[5-7] Although there are no head-to-head trials with these three regimens, all three are more effective than sunitinib in terms of PFS; however, final survival data has not yet been reported for all the trials. The cabozantinib/nivolumab regimen appears to be better tolerated based on rates of adverse events which results in therapy discontinuation.

For patients with intermediate or poor-risk disease, dual immunotherapy (nivolumab/ipilimumab) is a Category 1 option in addition to immunotherapy/TKI choices. Exhibit 3 compares these options. Both options have been shown to improve OS, so the choice primarily relies on adverse event profiles. Dual immunotherapy has the highest rate of immune-related adverse events because two different mechanisms of taking the breaks off the

immune system are being used.

Toxicity of tyrosine kinase inhibitors (TKIs) and immunotherapy can be significant. Toxicity of immunotherapy is more complex than with TKIs and has a different management including interruption, discontinuation, corticosteroids, and infliximab. Adverse events with TKIs are usually managed with dose reductions. Some toxicities are common for both immunotherapy and VEGF-targeted agents (e.g., gastrointestinal, liver), and it can be difficult to distinguish which agent is causing the problem.

Several additional trials are ongoing examining various other TKIs plus immunotherapy regimens. One of these is studying cabozantinib/nivolumab/ipilimumab compared to nivolumab/ipilimumab. Additional regimens will be approved in the near future and may make their way into first-line therapy for advanced RCC.

Conclusion

There is a wealth of evidence investigating different combinations for the first-line treatment of advanced RCC, including the CheckMate 214, KEYNOTE-426, Checkmate 9ER and CLEAR studies. All the combination regimens have replaced the use of sunitinib in this setting. Many factors may influence a physician's choice of treatment and personalization of care. Toxicity of TKI and immunotherapy can be significant but can be managed by ancillary therapy and dose individualization.

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References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. Version 4.2022. Available at www.nccn.org. Accessed 02/13/2022.
2. American Cancer Society. Key Statistics About Kidney Cancer. Available at cancer.org. Accessed 2/13/2022.
3. Zhou X, Hou W, Gao L, et al. Synergies of antiangiogenic therapy and immune checkpoint blockade in renal cell carcinoma: from theoretical background to clinical reality. *Front Oncol.* 2020;10:1321.
4. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med.* 2018;378(14):1277-90.
5. Rini BI, Plimack ER, Stus V, et al, for the KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med.* 2019;380 (12):1116-27.
6. Motzer R, Alekseev B, Rha SY, et al; CLEAR Trial Investigators. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med.* 2021;384(14):1289-300.
7. Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med.* 2021;384(9):829-41.

Evolving Treatment Paradigms in the Management of Multiple Sclerosis: How New and Emerging Therapies are Changing the Treatment Landscape

Benjamin Greenberg, MD, MHS

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

Summary

Multiple sclerosis (MS) is a devastating disease which needs to be treated early in the neurodegeneration process. Numerous effective therapies are available and need to be selected based on various patient factors, including disease severity. Managed care can have a role in managing adherence with disease-modifying therapies and overall costs by eliminating barriers to DMT use.

Key Points

- MS is a costly disease both in terms of disability and financially for both the patient and healthcare system.
- Individual costs come from healthcare utilization and increasing disability (which is preventable).
- Strategies to reduce cost to patients and obstacles to care improve outcomes (and hence, cost to patients).

MULTIPLE SCLEROSIS (MS) IS A PROGRESSIVE syndrome with neurodegeneration and multi-dimensional disability which starts early in the disease course. It is an autoimmune syndrome that involves the adaptive and innate immune system, The symptoms of MS are variable from person to person depending on which part of the nervous system is involved (Exhibit 1).

Despite all the advances in understanding MS, MS should be called a syndrome and not a disease because there are multiple pathologies which can cause the same symptoms. In some patients, neurodegeneration in driven by B cells and in others it is T cells or some other mechanism. Currently, clinicians are unable to identify the specific immune system drivers via diagnostic testing in a given individual. There are responders and non-responders to each of the approved disease-modifying therapies (DMTs) which can help identify which part of the immune system is the issue. If MS were a result of one individual cause, every patient would respond to a given therapy.

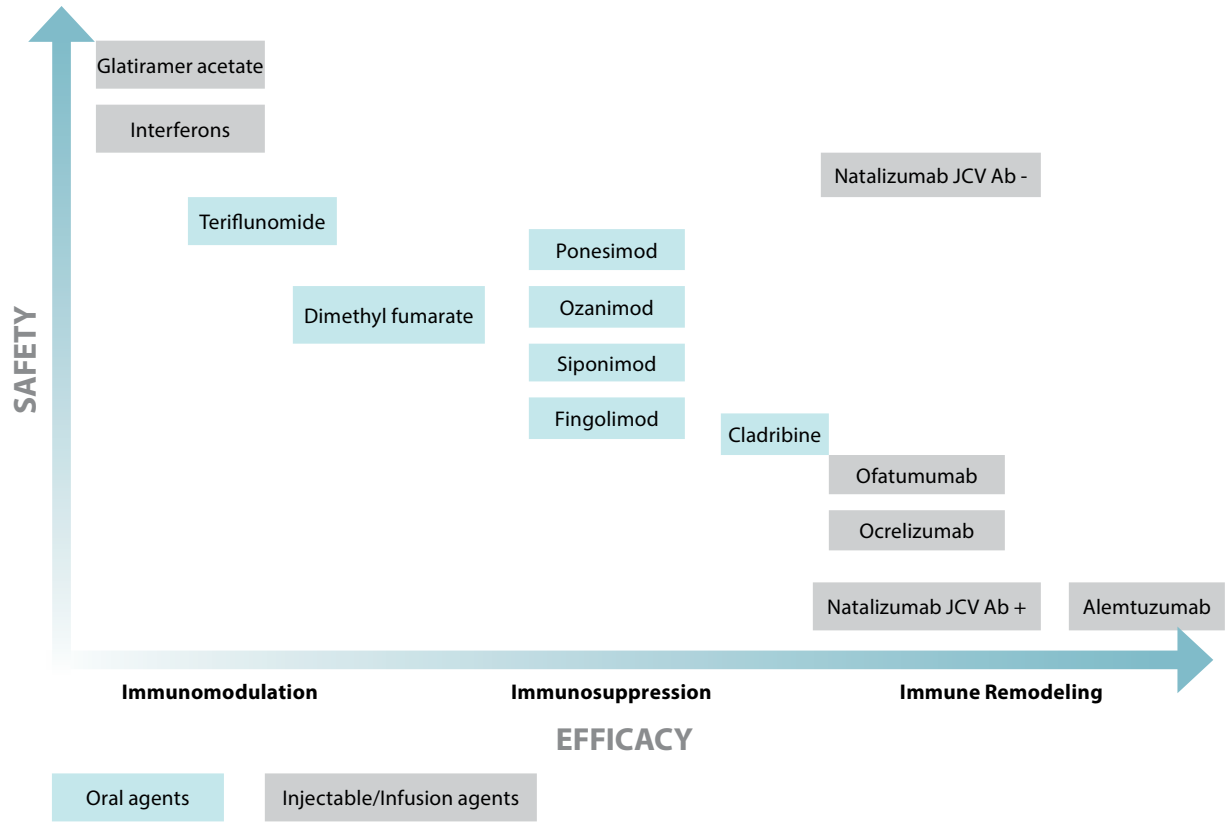
Trial and error are used to find which therapy a patient will respond to, but this takes time and unfortunately the earlier adequate therapy is initiated the better the chances of reducing long-term disability.[1] Treatment with ineffective therapy, delaying treatment, or treatment interruptions results in permanent disability and higher annual relapse rates (ARR) that cannot be reversed compared to those who receive early effective therapy. Preserving quality of life (QOL) is another reason for identifying effective therapy as soon as possible.

MS has major impact on QOL, productivity, and employment. In one survey, 39 percent of those

Exhibit 1: Symptoms of Multiple Sclerosis

• Weakness	• Bowel/bladder dysfunction
• Numbness	• Pain
• Vision loss	• Fatigue
• Double vision	• Depression
• Difficulty walking	• Cognitive difficulties
• Imbalance	• Sexual dysfunction
• Tremor	• Heat intolerance

Exhibit 2: Classifying Disease Modifying Therapies

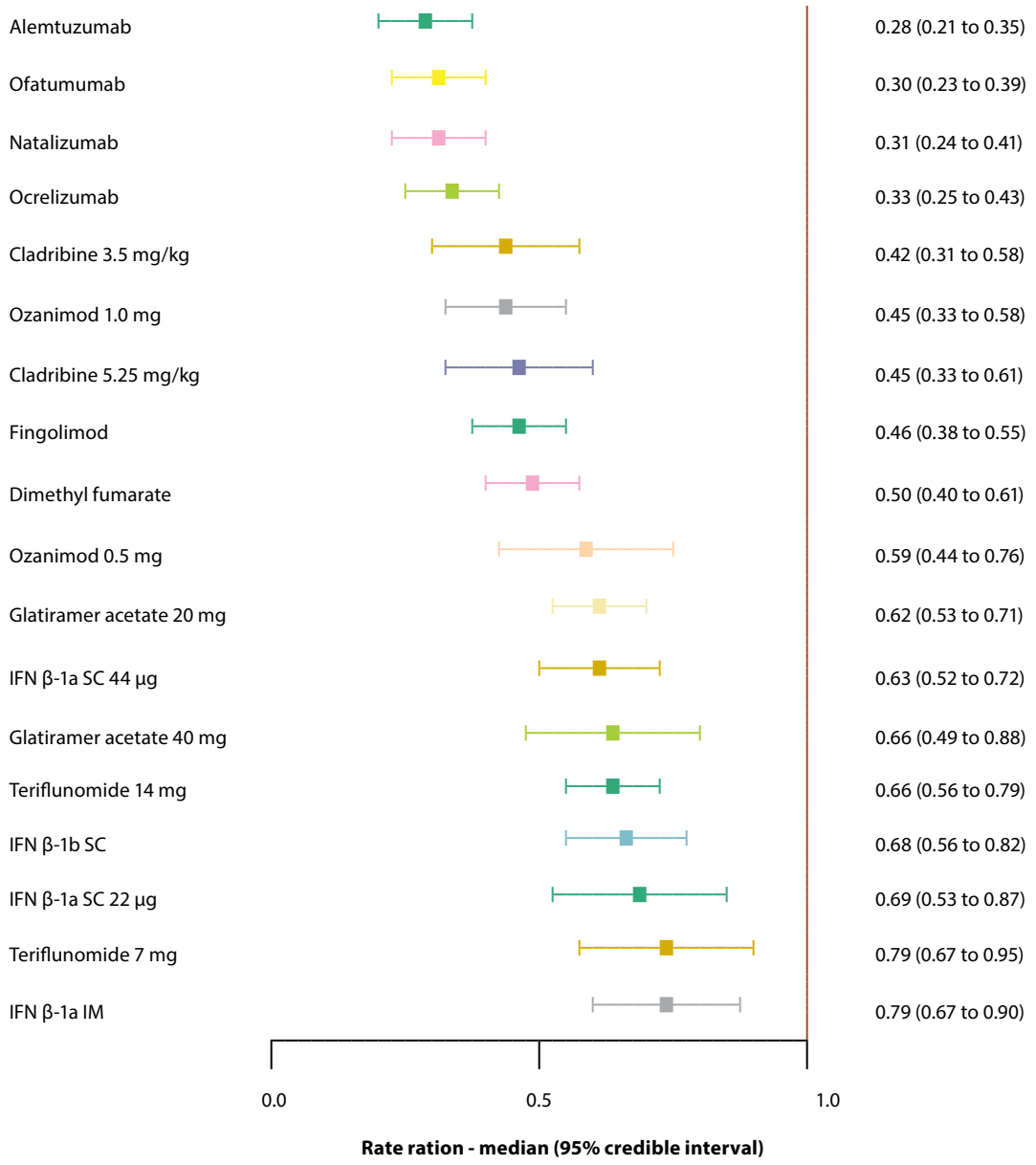


JCV AB = John Cunningham virus antibody

with MS were not employed.[2] Only 50 percent of those 51 to 60 years of age were employed. Thus, MS has a major impact on employment and financial status for those in the prime of their lives. Fatigue and difficulty with movement were the two most common reasons that prevented employment, but approximately one-third of those with MS leave employment because of cognitive issues.

MS is also costly financially to patients, and this is not just due to loss of employment. MS is second to heart failure in annual direct costs.[3] Degree of disability impacts total costs and healthcare costs in patients with moderate or severe MS-related disability are 15 percent and 20 percent higher, respectively, than in patients with mild disability.[4] DMT costs account for 89 percent, 82 percent, and 78

Exhibit 3: ARR Comparisons[6]



IFN = interferon

percent of outpatient pharmacy costs in patients with mild, moderate, and severe disability, respectively.[4] The annual costs of MS are also significantly higher in those who are non-adherent with DMT.[3]

Over much of the last decade, price increases for most DMTs have been greater than 10 percent annually. The median annual cost of a DMT is $91,835.[5] In addition to creating a financial burden for the healthcare system, high DMT costs negatively impact patients through unaffordable out-of-pocket costs and excessive restrictions by insurance companies.[5] The trends of increasing costs represent a risk for decreasing adherence which, as previously discussed, increases overall healthcare costs.

The treatment of MS has evolved dramatically over the last 30 years. There are now 13 DMTs which have varying safety and efficacy. Exhibit 2 shows a comparison of the relative safety and efficacy. Exhibit 3 shows a comparison of the ARR efficacy compared to placebo.[6] A similar ranking of agents

Exhibit 4: No Evidence of Disease Activity[8-12]

- Cladribine 48% at 4 years
- Natalizumab approx. 55% at 4 years
- Alemtuzumab 68% at 2 years
- Fingolimod 33% at 2 years
- Dimethyl Fumarate 23% to 28% at 2 years
- Teriflunomide 18% to 24% at 2 years
- Ocrelizumab 48% at 2 years
- Interferon Beta 1a 27% at 2 years

is also seen with disability progression compared to placebo.[7] Comparing the various outcomes with DMTs has to be done carefully because the majority of the data are not from head-to-head trials, and the studies had different trial designs and patient populations. Trial designs and evolving diagnostic criteria over time have changed the patient population in DMT studies. The ARR for placebo groups in the studies has declined from 1.27 to 0.33 – 0.54, which suggests that people enrolled in trials are being identified earlier with milder disease.

ARR has been the outcome measure used by various regulatory agencies around the world to approve MS therapy, but it may not be the best outcome measure. No evidence of disease activity (NEDA) has become the goal with treat-to-target in MS. It is increasingly being reported in clinical trials and in practice. NEDA is complete absence of detectable disease activity while on DMT. The criteria include NEDA on an MRI, no clinical relapses, and no disability worsening. Achievement of NEDA with the approved agents is not optimal and is less than 50 percent, except with the most effective agents – alemtuzumab and natalizumab (Exhibit 4).[8-12] Similar to other measures, those DMTs which are most efficacious produce the highest NEDA rates. Long-term follow-up studies have shown that there is sustained benefit of DMT in terms of suppressing relapses.

In addition to efficacy, safety of a given agent has to be considered. Patients and clinicians need to have discussions regarding the potential adverse events of the various therapy options. As shown in Exhibit 1, the most efficacious agents are risker in terms of adverse events because of their more potent effect on the immune system. Additional DMTs are under investigation. One class of interest are the Bruton's tyrosine kinase (BTK) inhibitors. The closest to market is evobrutinib, a highly selective inhibitor of BTK. BTK contributes to the development and function of B lymphocytes which attack and destroy the neuroprotective myelin sheath that surrounds nerve cells in the brain and spinal cord in MS. Other BTK inhibitors are already FDA-approved for treating B-cell cancers. The BTK inhibitors also inhibit autoantibody production and, on the innate immune side, shift the macrophage phenotype from proinflammatory to an anti-inflammatory state. In a Phase II trial comparing evobrutinib to dimethyl fumarate (DMF) and placebo, the ARR at week 24 was 0.37 in the placebo group, 0.57 in the evobrutinib 25mg group, 0.13 in the evobrutinib 75mg once-daily group, 0.08 in the evobrutinib 75mg twice-daily group, and 0.20 in the DMF group.[13]

An effective therapy that is easy to adhere to and an effective monitoring plan is needed to achieve the best outcomes in MS treatment. The monitoring plan needs to include an action plan for changing therapy if the goals are not achieved. Therapy should be individualized to the patient based on covariates including baseline risk of disease, reproductive considerations, and comorbid conditions. There is no ideal DMT for every patient. Managed care can play a role in achieving good outcomes with MS treatment by enhancing medication adherence and eliminating barriers related to out-of-pocket costs. Both of these targets may actually reduce overall costs.

Clinicians should monitor MRI disease activity from the clinical onset of disease to detect the accumulation of new lesions in order to make treatment decisions in people with MS using DMTs. Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience one or more relapses, two or more unequivocally new MRI-detected lesions, or increased disability on examination, over a one-year period of using a DMT. Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use.[14]

Conclusion

Multiple sclerosis is a potentially disabling but extremely treatable condition. DMT development has created a multitude of various therapies with distinct mechanisms of action, varying safety profiles, and differing efficacy. This diversity allows for more comprehensive treatment of the population of MS patients. The health system costs are massive and driven by DMT costs. Individual costs come

from healthcare utilization and increasing disability (which is preventable). Strategies to reduce cost to patients and obstacles to care improve outcomes (and hence, cost to patients).

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References

1. O'Connor P, Goodman A, Kappos L, et al. Long-term safety, and effectiveness of natalizumab redosing and treatment in the STRATA MS Study. *Neurology.* 2014;83(1):78-86.
2. MSIF 2016 Global Employment Report.
3. Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. *J Med Econ.* 2013;16(5):639-47.
4. Berkovich R, Fox E, Okai A, et al. Identifying disability level in multiple sclerosis patients in a U.S.-based health plan claims database. *J Med Econ.* 2021;24(1): 46-53.
5. Hartung DM. Health economics of disease-modifying therapy for multiple sclerosis in the United States. *Ther Adv Neurol Disord*. 2021;14:1756286420987031
6. Samjoo IA, Worthington E, Drudge C, et al. Efficacy classification of modern therapies in multiple sclerosis. *J Comp Eff Res.* 2021;10(6):495-507.
7. Institute for Clinical and Economic Review. Disease-modifying therapies for relapsing-remitting and primary-progressive multiple sclerosis: Effectiveness and value. Final evidence report. March 6, 2017.
8. Havrdová E, Arnold DL, Bar-Or A, et al. No evidence of disease activity (NEDA) analysis by epochs in patients with relapsing multiple sclerosis treated with ocrelizumab vs interferon beta-1a. *Mult Scler J Exp Transl Clin.* 2018;4(1):2055217318760642.
9. Dekker I, Leurs CE, Hagens MHJ, et al. Long-term disease activity and disability progression in relapsing-remitting multiple sclerosis patients on natalizumab. *Mult Scler Relat Disord*. 2019;33:82-87.
10. Nixon R, Bergvall N, Tomic D, et al. No evidence of disease activity: indirect comparisons of oral therapies for the treatment of relapsing-remitting multiple sclerosis. *Adv Ther*. 2014;31(11):1134-54.
11. Havrdova E, Arnold DL, Cohen JA, et al; CARE-MS I and CAMMS03409 Investigators. Alemtuzumab CARE-MS I 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. *Neurology.* 2017;89(11):1107-16.
12. Giovannoni G, Soelberg Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. *Mult Scler.* 2018;24(12):1594-604.
13. Montalban X, Arnold DL, Weber MS, et al; Evobrutinib Phase II Study Group. Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. *N Engl J Med*. 2019;380(25):2406-17.
14. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2018;90(17):777-88.

Recent Advances in the Treatment and Management of Acute Myeloid Leukemia: Expert Perspectives for Improved Clinical and Economic Outcomes

Harry P. Erba, MD, PhD

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

Summary

The past decade has witnessed considerable advances in unraveling molecular and genetic underpinnings of acute myeloid leukemia (AML). With a better understanding of the disease, several targeted therapies have been developed which are enhancing survival in AML. Most of these are well-tolerated oral agents.

Key Points

- Cytogenetic and mutational data are important for prognosis and treatment selection.
- Rapid turnaround of results is needed to guide initial therapy.
- Patients at low-risk of relapse can be identified by response to standard chemotherapy alone, potentially avoiding risk of allogenic hematopoietic stem cell transplantation (HSCT).
- Hypomethylating agents and the B-cell lymphoma 2 (BCL2) inhibitor venetoclax can be safely given to older AML patients with high rates of durable responses.

ACUTE MYELOID LEUKEMIA, A HEMATOlogic malignancy with excess immature white blood cells, is the most common leukemia affecting adults. It can present with signs and symptoms of bone marrow failure (anemia, neutropenic infection, thrombocytopenic hemorrhage), pulmonary or cerebral leukostasis, extramedullary disease (leukemic infiltration of skin, gingiva, liver, spleen, lymph nodes, and central nervous system), disseminated intravascular coagulation, tumor lysis syndrome, and abnormalities of serum chemistries (hypokalemia and spurious hypoxia, hypoglycemia, or hyperkalemia). Several of these presentations are indications for inpatient admission and immediate treatment. Since these patients have a proliferative disease, treatment typically needs to begin quickly after diagnosis, unlike with a chronic leukemia.

In AML, there is a block in normal differentiation of cells, proliferation of early progenitor cells (blasts), and a block in normal apoptosis of cells. Diagnosis of AML requires at least 200 leukocytes on blood smear and 500 nucleated cell differential on bone marrow analysis and a bone marrow or blood blast count of greater than 20 percent.[1] Various cytogenetic and molecular abnormalities are important for prognosis and treatment selection. Based on mutations and abnormalities, patients with AML can have favorable, intermediate one or two, or adverse-risk disease (Exhibit 1).[1,2] Favorable disease has the longest disease-free survival after treatment and best overall survival (OS) and adverse-risk disease has the shortest of these.[3,4]

An example of one important mutation in AML is FMS-like tyrosine kinase 3 (FLT3). FLT3 is a tyrosine kinase enzyme that resides on the surface of cells and acts as a receptor.[5] FLT3 is activated by allosteric dimerization upon binding of the FLT ligand (FL). FLT3 is normally expressed in bone marrow hematopoietic stem cells but not in differentiated cells and plays a key role in the control

Exhibit 1: AML Risk Stratification by Cytogenetics and Mutations[1,2]

Risk Status	Cytogenics	Molecular Abnormalities
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11	Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low} or Biallelic mutated CEBPA
Intermediate	t(9;11)(p21.3;q23.3); MLLT3-KMT2A Cytogenetic abnormalities not classified as favorable or adverse	Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without adverse-risk genetic lesions)
Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) −5 or del(5q); −7; −17/abn(17p) Complex karyotype, monosomal karyotype	Wild-type NPM1 and FLT3-ITD^{high} Mutated RUNX1 Mutated ASXL1 Mutated TP53

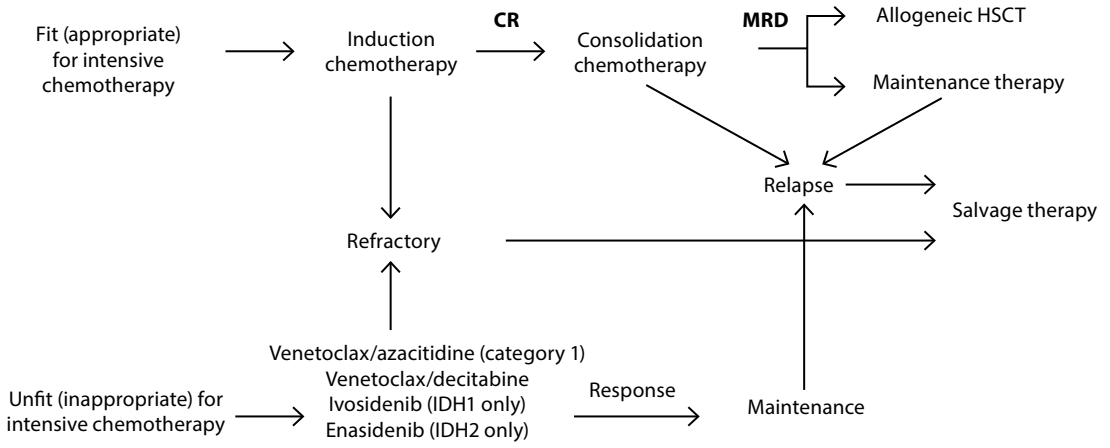
of hematopoiesis. FLT3 is highly expressed on AML blasts and FL can enhance survival and proliferation of AML. FLT3 mutations include internal tandem duplication (ITD), tyrosine kinase domain (TKD) and juxtamembrane domain point mutation. FLT3 ITD mutations occur in 25 to 30 percent of AML cases and results in poor prognosis and high rates of relapse after treatment.[6,7] With FLT ITD mutations, the receptor is still dependent on the presence of FL for complete activation. FLT3 TKD mutations occur in 5 to 10 percent of cases. A TKD mutation activates FLT3 kinase directly. Juxtamembrane domain point mutations are much rarer. Testing for FLT3 mutations should be done by polymerase chain reaction (PCR) at the time of diagnosis and relapse (including suspected relapse). PCR results are available more rapidly than next-generation sequencing (NGS), and NGS may underestimate or miss the presence of a FLT3-ITD mutation. For patients with previously untreated AML, FLT3 analysis should not wait for karyotype results.

Whereas cytogenetics and molecular abnormalities are pretreatment predictors of outcomes, measurable residual disease (MRD), previously termed minimal residual disease, is a new post-treatment predictor. Patients who achieve complete hematologic remission after treatment for AML often harbor residual cancer cells in the bone marrow or peripheral blood that can result in relapse. MRD denotes the presence of leukemia cells down to levels of 1:104 to 1:106 white blood cells (WBCs), compared with 1:20 in morphology-based assessments. MRD status at the end of induction and consolidation chemotherapy predicts duration of disease remission and OS and can be used to make decisions about need for additional therapy including stem cell transplant. MRD positivity after a complete response (CR) to chemotherapy in a patient with AML is associated with a higher-risk of relapse and shorter survival.[8,9] MRD can be evaluated using a variety of multiparameter flow cytometry and molecular protocols, but these approaches have not been qualitatively or quantitatively standardized, making their use in clinical practice challenging.[10]

Once diagnosed, treatment is initiated. Patients are divided into whether they are able to undergo intensive chemotherapy or not (Exhibit 2).[2] Those who are able will undergo induction chemotherapy and the regimen chosen depends on the patient's age, antecedent myelodysplastic syndromes, and presence of various other risk markers. If a CR is achieved then the patient moves on to consolidation chemotherapy. With a CR or MRD positive to consolidation, the patient may be eligible for an allogenic HSCT, especially for those with poor or intermediate-risk disease.

For those not eligible for HSCT, maintenance therapy after chemotherapy can reduce risk of

Exhibit 2: AML Treatment Algorithm



HSCT = hematopoietic stem cell transplant, CR = complete response; MRD = measurable residual disease

relapse. Oral azacitidine (Onureg®) maintenance therapy has been shown to produce significantly longer overall and relapse-free survival than placebo among older patients with AML who were in remission after chemotherapy. Overall survival was improved by 9.9 months and relapse-free survival by 5.4 months.[11] This agent delays relapse that was otherwise going to occur. Those that benefit the most from azacitidine maintenance are those who are MRD positive at the end of consolidation or only received induction. It is now recommended in the National Comprehensive Cancer Network (NCCN) guidelines for maintenance is those with intermediate or adverse risk who are in remission after chemotherapy and no HSCT is planned.[2] Taking azacitidine can be a tough sell for the patient because of potential adverse events (gastrointestinal, neutropenia, thrombocytopenia), costs, and that it is only postponing a relapse.

Several oral therapies that target underlying mutations in AML have changed the treatment landscape especially for those who are unable to tolerate chemotherapy. Less than 40 percent of Medicare patients received any kind of treatment before the availability of targeted agents.[12] The only available agents were the hypomethylating agents (HMAs) azacitidine and decitabine which did not improve OS when used alone. Ivosidenib, enasidenib, gilteritinib, and venetoclax are targeted therapies that have been approved by the FDA for treating AML. Enasidenib (Idhifa®) is an oral, selective inhibitor of mutant- isocitrate dehydrogenase two (IDH2) enzymes and ivosidenib (Tibsovo®) targets IDH1. Approximately 20 percent of patients with AML have an isocitrate dehydrogenase one (IDH1) or IDH2 mutation.[13-15] Gilteritinib (Xospata®) is a next- generation, more specific FLT3 inhibitor than previously available sorafenib (Nexavar®) and midostaurin (Rydapt®). Venetoclax (Venclexta®) is an oral B-cell lymphoma two (BCL2) inhibitor which selectively binds and inhibits BCL2, a pro-apoptotic protein, leading to the initiation of apoptosis. In combination with hypomethylating agents, it produces a very high rate of response (50% to 60%) and improves OS.

The NCCN preferred regimens for induction in those who are over 60 years of age, and who are not candidates for intensive remission induction chemotherapy, are venetoclax plus azacitidine or decitabine.[2] Venetoclax in combination with azacitidine is the only category one regimen for induction in this group of patients. If an IDH1 or IDH2 mutation is present, ivosidenib or enasidenib, respectively, are options. Although initially used in relapsed/refractory AML, ivosidenib and enasidenib have been shown to produce deep durable remission as initial treatment.[15,16] If the patient has response to the chosen regimen, it will typically be continued until disease progression. For those who do not respond, a regimen for relapsed/refractory AML or enrollment in a clinical trial would be selected. Gilteritinib is an option for those with FLT3 mutation who have relapsed. Gilteritinib, ivosidenib, and enasidenib are also under study in combination

Exhibit 3: Prevention of Tumor Lysis Syndrome

Prior to commencing venetoclax
• For patients with hyperleukocytosis, start hydroxycarbamide or flat-dose ara-C, e.g., until the WBC is < 25 x 109/L prior to starting venetoclax.
• Commence TLS prophylaxis with pre-hydration and uricosuric agents and normalize potassium, inorganic phosphorus, and uric acid levels according to institutional practice.
• For some molecularly defined AML subsets with high sensitivity to venetoclax, consider lowering the starting WBC to < 10 x 109/L to lower TLS risk prior to initiation of venetoclax.
• Ramp-up initial venetoclax dosing in steps.
• Monitor for TLS complications pre-dose (< 4 h) and 6 to 8 h after each ramp-up dose with additional monitoring until normalization of abnormal biochemistry.
• If significant biochemical or clinical TLS is observed, delay further venetoclax dosing until resolution.

with azacitidine in newly diagnosed AML with the respective targeted mutation (FLT3, IDH1, IDH2). These combinations will become first-line regimens based on early data from the trials.[17]

An important adverse event with treatment of AML is differentiation syndrome (DS). It is possibly caused by a large, rapid release of cytokines from leukemia cells. Symptoms include unexplained fever, peripheral edema, hypotension, acute respiratory distress with interstitial pulmonary infiltrates, vascular capillary leak syndrome leading to acute renal failure, or pleuropericardial effusion. DS occurs in about 20 percent of those who receive either ivosidenib or enasidenib.[18] In an analysis of data from studies, baseline bone marrow blasts ≥ 48 percent and peripheral blood blasts ≥ 25 percent and 15 percent for ivosidenib and enasidenib, respectively, were associated with increased risk of DS.[18] FLT3 inhibitors can also induce DS in AML.[19] Because DS can be fatal, it is important that clinicians recognize this syndrome and educate patients on symptoms that require attention. High-dose intravenous dexamethasone is the primary treatment of DS.

Venetoclax can cause tumor lysis syndrome (TLS), which occurs when large numbers of cancer cells are killed rapidly. Clinically, the syndrome is characterized by rapid development of hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute kidney injury. Those at higher risk for this complication (WBC > 25 x 10^9/L, uric acid > 7.5 mg/dL, creatinine >1.4 mg/dL) will need therapy to lower the white blood cell count before starting on venetoclax (Exhibit 3).[20] All patients, especially those with an elevated risk of TLS, should be hospitalized until at least completion of ramp-up dosing.[20]

Conclusion

Cytogenetic and mutational data are not only prognostically important, but they drive treatment decisions with intensive therapy. Rapid turnaround of results is needed to guide initial therapy.

Patients at low-risk of relapse can be identified by response to standard chemotherapy alone, potentially avoiding risk of allogenic HSCT. Risk stratification and detection of measurable residual disease are used to determine if HSCT is needed. Hypomethylating agents and the BCL2 inhibitor venetoclax can be safely given to older AML patients with high rates of durable responses. Age alone should not determine eligibility for potentially curative approaches, including allogeneic HSCT.

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References

1. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424-47.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 1.2022. Available at nccn.org.

3. Grimwade D, Hills RK, Moorman AV, et al; National Cancer Research Institute Adult Leukemia Working Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116(3):354-65.
4. Medeiros BC, Othus M, Fang M, et al. Prognostic impact of monosomal karyotype in young adult and elderly acute myeloid leukemia: The Southwest Oncology Group (SWOG) experience. *Blood*. 2010;116(13):2224-8.
5. Pemmaraju N, Kantarjian H, Ravandi F, Cortes J. FLT3 inhibitors in the treatment of acute myeloid leukemia: The start of an era? *Cancer*. 2011;117(15):3293-304.
6. Garcia JS, Stone RM. The development of FLT3 inhibitors in acute myeloid leukemia. *Hematol Oncol Clin North Am*. 2017;31(4):663-80.
7. Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med*. 2012;366(12):1079-89.
8. Terwijn M, van Putten WL, Kelder A, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: Data from the HOVON/SAKK AML 42A study. *J Clin Oncol*. 2013;31(31):3889-97.
9. Ivey A, Hills RK, Simpson MA, et al; UK National Cancer Research Institute AML Working Group. Assessment of minimal residual disease in standard-risk AML. *N Engl J Med*. 2016;374(5):422-33.
10. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2018;131(12):1275-91.
11. Wei AH, Döhner H, Pocock C, et al; QUAZAR AML-001 Trial Investigators. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26):2526-37.
12. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: A population-based study. *Haematologica*. 2012;97(12):1916-24.
13. Stemer G, Rowe JM, Ofran Y. Efficacy, and safety profile of ivosidenib in the management of patients with acute myeloid leukemia (AML): An update on the emerging evidence. *Blood Lymphat Cancer*. 2021;11:41-54.
14. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med*. 2009;361(11):1058-66.
15. Ward PS, Patel J, Wise DR, et al The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell*. 2010;17(3):225-34.
16. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. 2020;135(7):463-71.
17. Stein EM, Huang Y, Borate U, et al. Enasidenib (ENA) monotherapy with addition of azacitidine in non-responders is effective in older patients with newly diagnosed IDH2 mutated acute myeloid leukemia (AML): A completed Phase 2/1b sub-study of the beat AML Master Trial. 62nd ASH Annual Meeting. December 5-8, 2020. Abstract 636.
18. Norsworthy KJ, Mulkey F, Scott EC, et al. Differentiation syndrome with ivosidenib and enasidenib treatment in patients with relapsed or refractory IDH-mutated AML: A U.S. Food and Drug Administration systematic analysis. *Clin Cancer Res*. 2020;26(16):4280-8.
19. Kondo T, Onozawa M, Fujisawa S, et al. Myelomonocytic differentiation of leukemic blasts accompanied by differentiation syndrome in a case of FLT3-ITD-positive AML treated with gilteritinib. *Hematology*. 2021;26(1):256-60.
20. DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood*. 2020;135(2):85-96.

Recent Advances in the Treatment and Management of Relapsed/Refractory Multiple Myeloma: Expert Perspectives on the Role of New Therapies

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For a CME/CEU version of this article, please go to
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Summary

New, more effective, and less toxic therapies have revolutionized the management of multiple myeloma in the past decade. Triple therapy with proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies is now the standard treatment. Despite the availability of new treatments, most patients will develop refractory disease to the therapies that currently comprise the standard of care.

Key Points

- Triple therapy with agents from the backbone treatments have become the norm.
- Several new therapies, including the first chimeric antigen receptor T- cell therapy (CAR-T), have been FDA-approved for treating relapsed/refractory MM in recent years.
- Numerous new agents are on the horizon.

MULTIPLE MYELOMA (MM) IS AN UNcommon cancer of plasma cells.[1] In the United States (U.S.) in 2021, there were about 34,920 new cases (19,320 in men and 15,600 in women) and 12,410 deaths (6,840 in men and 5,570 in women). The five-year survival with early-stage disease is 74 percent and with late-stage disease it is 51 percent. Exhibit 1 lists the risk factors for MM.[1]

The treatment paradigm for newly diagnosed active MM is to determine whether a patient is eligible for a stem cell transplant, however, those not eligible receive induction and maintenance therapy (Exhibit 2).[2] The goal of treating newly diagnosed MM, whether stem cell transplant eligible or ineligible, is to gain the best depth of response by using an effective induction regimen followed by consolidating the response with a transplant or medication and offering maintenance strategies to prolong the first progression-free survival (PFS) benefit.

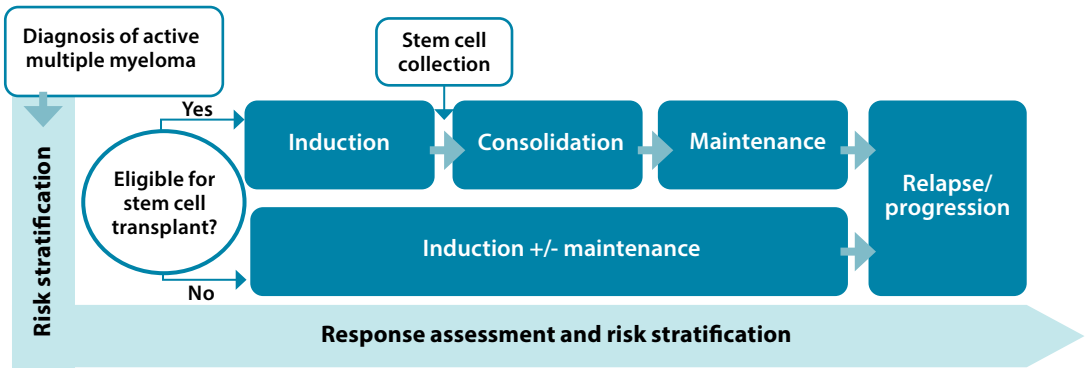
Treatment regimens for newly diagnosed and relapsed/refractory MM consist of two or more treatment backbone agents and oral dexamethasone (Exhibit 3).[3] Dexamethasone has a therapeutic effect on MM cells. Numerous trials have shown that two backbone agents are better than just one agent in improving PFS. Bortezomib (Velcade®), carfilzomib (Kyprolis®), and ixazomib (Ninlaro®) are proteasome inhibitors which induce apoptosis of MM cells. Lenalidomide (Revlimid®) and pomalidomide (Pomalyst®) are immunomodulators which induce immune responses, prevent inflammation, and enhance the activity of T cells and natural killer (NK) cells. Daratumumab (Darzalex®) and isatuximab (Sarclisa®) are anti-CD38 monoclonal antibodies; CD38 is overexpressed on MM cells. Elotuzumab (Empliciti®), a humanized IgG1 monoclonal antibody, directly activates NK cells through both the signaling lymphocytic activation molecule family member 7 (SLAMF7) pathway and Fc receptors. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with NK cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC). The preferred primary therapy for newly diagnosed transplant candidates is bortezomib/

Exhibit 1: Multiple Myeloma Risk Factors[1]

Age	Most patients diagnosed aged ≥ 65 years; < 1% diagnosed before age 35 years
Gender	Slightly more common in men
Race	More than twice as common in African American patients than white patients
Family history	Modest link with family history
Obesity	Being overweight or obese increases lifetime risk
Plasma cell diseases	History of MGUS or SP increases risk of multiple myeloma

MGUS = Monoclonal Gammopathy of Undetermined Significance; SP = Solitary Plasmacytoma

Exhibit 2: MM Treatment Paradigm[2]



lenalidomide/dexamethasone and for nontransplant candidates it is the same regimen or daratumumab/lenalidomide/dexamethasone. For either category of patient, the preferred maintenance therapy is lenalidomide, which is continued until progression. Dual maintenance of bortezomib and lenalidomide is recommended for high-risk MM.

After initial treatment, most patients will have a disease relapse. Indications for retreatment are either clinical or biochemical. A clinical relapse is defined as development of new soft tissue plasmacytomas or bone lesions, definite increase (≥ 50%) in size of existing plasmacytomas or bone lesions, hypercalcemia (≥ 11.5 mg/dL), decrease in hemoglobin of ≥ 2 g/dL or to < 10 g/dL due to myeloma, rise in serum creatinine by ≥ 2 mg/dL due to myeloma, or hyperviscosity requiring therapeutic intervention.[4] Patients can have a biochemical relapse without a clinical relapse. A biochemical relapse is identified by doubling of myeloma protein in two consecutive measurements separated by two months with the reference value of 5 g/L, or in two consecutive measurement increases in any of the following: absolute levels of serum M protein by ≥ 10 g/L, urine M protein by ≥ 500 mg/24 h, or involved serum immunoglobulin-free light chain (FLC) level by ≥ 20 mg/dL plus abnormal FLC ratio or by 25 percent, whichever is greater.

Exhibit 3: Treatment Backbones for Multiple Myeloma[3]

Frontline and Early Relapse

Proteasome Inhibitors	Immunomodulatory Agents	Monoclonal Antibodies
• Bortezomib	• Lenalidomide	• Daratumumab
• Carfilzomib	• Pomalidomide	• Isatuximab
• Ixazomib		• Elotuzumab

Exhibit 4: Strategies for Treatment Selection in Relapsed/Refractory MM[5,6]

Individualized Approach	Treatment Choice Based on Prognosis	Treatment Choice Based on Previous Treatment Response
✓ Patient age	**Patients with poor prognosis**	**Patients with response for ≥ 12mo, no significant toxicity**
✓ Patient fitness	✓ Triplet/quadruplet regimen until disease progression	✓ Re-treatment feasible
✓ Comorbidities	✓ Novel treatments may be more appropriate	**Patients with progression on therapy, or short response**
✓ Treatment history	**Patients with indolent disease characteristics**	✓ Switch drug class
• Depth and duration of response	✓ Treatment-free intervals may be appropriate	✓ Second-generation agent in same class
• Treatment toxicities		
✓ Aggressiveness of the relapse		
✓ Patient expectations		

The selection of treatment for relapsed/refractory MM (R/R MM) is influenced by whether the relapse is early or late, patient factors, and prior treatments (Exhibit 4).[5,6] Early relapse is one which occurs within 12 months of finishing initial treatment. The most important factor in choosing therapy is that the selected therapy has to be shown to produce stable disease or better and be well tolerated.

The treatment options at relapse are enrollment in a clinical trial, stem cell transplant, repeating first-line treatment, switching to a second-generation agent in the same drug class (e.g., lenalidomide to pomalidomide), or switching to an alternative drug class. Patients can receive multiple lines of therapy for R/R MM.

Recent studies favor the use of daratumumab as part of the regimen for R/R MM based on response.[7,8] The National Comprehensive Cancer Network (NCCN) guidelines list several daratumumab regimens as Category 1 preferred regimens, but does not specify any recommended regimen in early or late relapse.[3]

Patients who are triple or quad refractory to the backbone agents have very poor prognosis (median overall survival = 9 months).[9] Approaches have been conventional chemotherapy, salvage autologous stem cell transplant, recycling previous regimens, and clinical trial, each of which have generally had short-lived efficacy.[10] Selinexor, belantamab mafodotin, and idecabtagene vicleucel are three newer options for those who have been treated with at least four prior therapies and have refractory disease.

Selinexor (Xpovio®) reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus and reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells. It is FDA-approved in combination with dexamethasone for the treatment of adult patients with R/R MM who have received

at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. In patients with triple-refractory disease, treatment with the combination of selinexor and dexamethasone resulted in a 26.2 percent overall response rate and 4.4 month median duration of response.[11] In a trial comparing selinexor/bortezomib/dexamethasone to bortezomib/dexamethasone triple-refractory MM, the three-drug combination improved PFS (13.93 months versus 9.46 months).[12] Selinexor has been studied in combination with various other backbone agents and regimens with daratumumab, carfilzomib, and pomalidomide are listed as options in the NCCN guidelines.[3]

Selinexor can cause significant adverse events, including thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, immunosuppression, and neurological toxicity. Aggressive supportive care is required, especially in the first month, to help patients tolerate this agent. This includes aggressive antiemetic prophylaxis prior to start of medication, hydration and salt tablets for hyponatremia, management of appetite and weight loss, monitoring of blood counts and electrolytes, and aggressive infection monitoring.[13]

Belantamab mafodotin (Blenrep®) is a B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate that was FDA-approved in August 2020 for the treatment of adult patients with R/R MM who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. In an open-label, two-arm, Phase II study in 196 patients with disease progression after three or more lines of therapy and who were refractory to immunomodulatory drugs and proteasome inhibitors, and refractory or intolerant (or both) to an anti-CD38 monoclonal antibody, 31 percent of 97 patients in the 2.5 mg/kg cohort and 34 percent of 99 patients in the 3.4 mg/kg cohort achieved an overall response.[14] Many belantamab mafodotin-based combinations are under evaluation in Phase I, II, and III clinical trials in either late or early R/R MM patients.

Uniquely, belantamab mafodotin causes ocular toxicity (keratopathy in 27%) in addition to the typical hematologic toxicities of MM treatment. It is dosed intravenously once every three weeks and an ocular exam from an eye care professional is required before each dose. A baseline examination should be done within three weeks prior to the first dose. Eye care professionals can include ophthalmologists as well as optometrists. The eye care professional uses an available form to indicate the corneal exam findings and grading and conveys to hematologist/oncologist to inform potential dose modifications. Dose modification guidance for corneal events is provided in the Prescribing Information and is based on corneal examination findings and best corrected visual acuity. Overall, the ocular toxicity is manageable with adequate dose reductions or delays since most patients who developed keratopathy in the trials recovered on treatment and discontinuations were rare.

Cell-based immunotherapies, such as chimeric antigen receptor (CAR) T-cells, are showing impressive activity in the R/R MM setting. Challenges to their widespread use remain, including toxicity, manufacturing time, and cost. Idecabtagene vicleucel (Abecma®), which targets BCMA, is the first FDA-approved CAR-T treatment for R/R MM. In a study in 33 patients who had received a median of seven prior therapies, the objective response rate was 85 percent, including 45 percent with complete responses.[15] Six of the 15 patients who had a complete response have had a relapse since treatment. The median PFS was 11.8 months. All 16 patients who had a response (partial response or better) and who could be evaluated for minimal residual disease (MRD) had MRD-negative status (≤ 104 nucleated cells). CAR T-cell expansion was associated with responses, and CAR T cells persisted up to one year after the infusion. In another Phase II trial in 128 R/R MM patients who had disease after at least three previous regimens, idecabtagene vicleucel treatment resulted in a 73 percent overall response rate with 33 percent having a complete response or better.[16] MRD-negative status (<105 nucleated cells) was confirmed in 26 percent who were treated and 79 percent of those with a complete response or better. The median PFS was 8.8 months. Common toxic effects included neutropenia (91%), anemia (70%), and thrombocytopenia (63%). Cytokine release syndrome was reported in 84 percent, including 5 percent who had events of Grade 3 or higher. Neurotoxic effects developed in 18 percent and were of Grade 3 in 3 percent but no neurotoxic effects higher than Grade 3 occurred. Numerous other CAR-T based treatments for R/R MM are under study.

Venetoclax (Venclexta®) is a selective and orally bioavailable small-molecule inhibitor of B-cell lymphoma two (BCL-2) currently FDA-approved for treating chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and acute myeloid leukemia (AML). It also can target BCL-2 in MM and is in trials. It has encouraging clinical efficacy in t(11;14) translocated MM as monotherapy and in

a broader patient population in combination with bortezomib/dexamethasone.[17,18] Approximately, 20 percent of myeloma patients will exhibit t (11;14) associated with high BCL-2 expression. Venetoclax in combination with dexamethasone is recommended as a treatment option for R/R MM with t (11;14) in the NCCN guidelines.[3]

At least five anti-BCMA bispecific T-cell engagers (BiTEs) are in various stages of development. Two BiTEs, which target other areas, are also under development. Iberdomide is an investigational immunomodulator which is a potent cereblon E3 ligase modulator.[19] This is the same mechanism of action as lenalidomide and pomalidomide, but this agent is more potent. It is in very early clinical trials and none have as yet been published.

Conclusion

Management of R/R MM continues to be a challenge, but several new therapies, including the first CAR-T, have been FDA-approved in recent years. There are numerous options which can allow patients to be treated with multiple lines of therapy. Triple therapy combinations have become the norm, and numerous additional options are on the horizon.

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References

1. American Cancer Society. Multiple Myeloma. Available at cancer.org/cancer/multiple-myeloma/. Accessed 2/9/2022.
2. Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2016;91(7):719-34.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Available at nccn.org. Accessed 2/9/2022.
4. Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. *Haematologica.* 2016;101(4):396-406.
5. Goldschmidt H, Ashcroft J, Szabo Z, Garderet L. Navigating the treatment landscape in multiple myeloma: which combinations to use and when? *Ann Hematol.* 2019;98(1):1-18.
6. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia.* 2016;30(5):1005-17.
7. Nooka AK, Kaufman JL, Hofmeister CC, et al. Daratumumab in multiple myeloma. *Cancer.* 2019;125(14):2364-82.
8. Nooka AK, Joseph NS, Kaufman JL, et al. Clinical efficacy of daratumumab, pomalidomide, and dexamethasone in patients with relapsed or refractory myeloma: Utility of re-treatment with daratumumab among refractory patients. *Cancer.* 2019;125(17):2991-3000.
9. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia.* 2019;33(9):2266-75.
10. Mikhael J. Treatment options for triple-class refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 2020;20(1):1-7.
11. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med.* 2019;381(8):727-38.
12. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomized, open-label, Phase III trial. *Lancet.* 2020;396(10262):1563-73.
13. Mikhael J, Noonan KR, Faiman B, et al. Consensus recommendations for the clinical management of patients with multiple myeloma treated with selinexor. *Clin Lymphoma Myeloma Leuk.* 2020;20(6):351-7.
14. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): A two-arm, randomized, open-label, Phase II study. *Lancet Oncol.* 2020;21(2):207-21.
15. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med.* 2019;380(18):1726 37.
16. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med.* 2021;384(8):705-16.
17. Vaxman I, Sidiqi MH, Gertz M. Venetoclax for the treatment of multiple myeloma. *Expert Rev Hematol.* 2018;11(12):915-20.
18. Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): A randomized, double-blind, multicenter, Phase III trial. *Lancet Oncol.* 2020;21(12):1630-42.
19. Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. *Leukemia.* 2020;34(4):1197-201.

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