Vol. 28, No. 3, 2025

JOURNAL of MANAGED CARE MEDICINE

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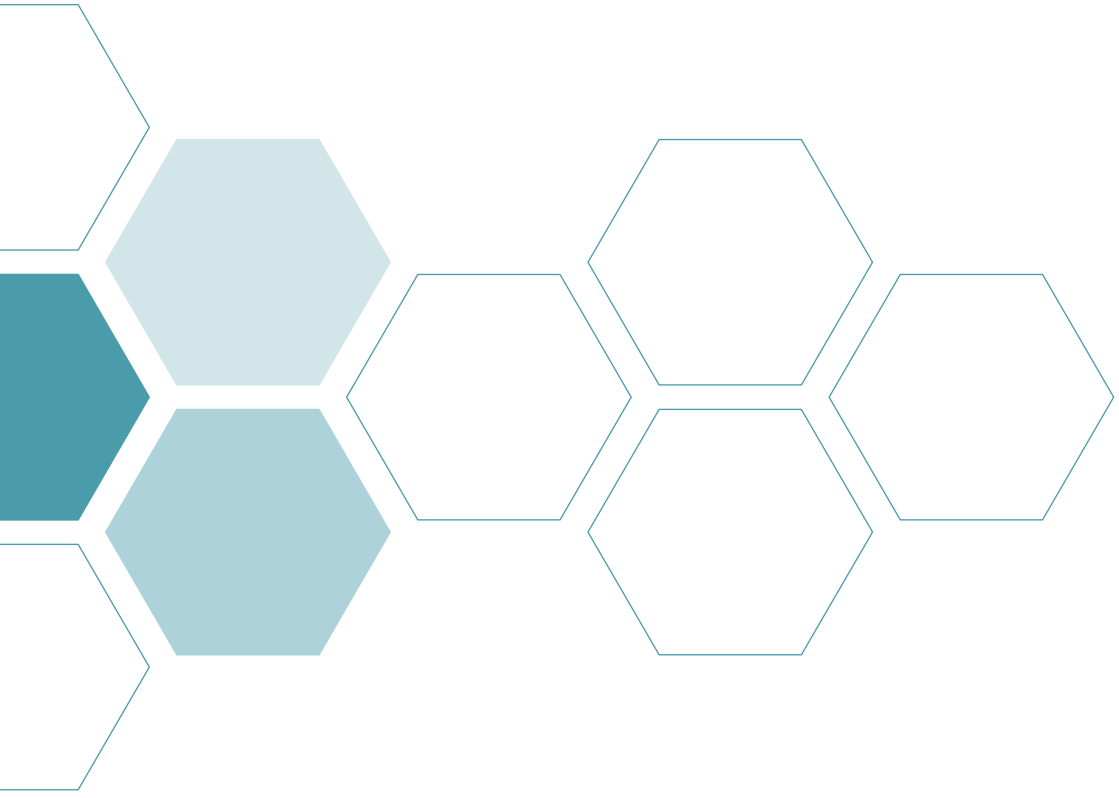

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Innovative Approaches in the Treatment and Management of Multiple Sclerosis: Managed Care Insights for Optimized Clinical and Economic Outcomes

Recent Advances in the Treatment and Management of Early Alzheimer's Disease: Managed Care Insights on the Role of Novel Therapies

Innovative Approaches in the Prevention and Management of HIV: The Role of PrEP and ART for Improved Outcomes

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4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
Thomas Morrow, MD

PUBLISHER
Jeremy Williams

ADVERTISING REPRESENTATIVE
Maria Sercia
American Medical Communications, Inc.
msercia@americanmedicalcomm.com
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JOURNAL MANAGEMENT
Douglas Murphy Communications
Richmond, Virginia
grant.murphy@douglasmurphy.com
(804) 387-7580

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ISSN: 1094-1525. The *Journal of Managed Care Medicine* is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: 15 Bridgehampton Place, Richmond, VA 23229; Tel (804) 387-7580. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316.

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Vol. 28, No. 3, 2025

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Innovative Approaches in the Treatment and Management of Multiple Sclerosis: Managed Care Insights for Optimized Clinical and Economic Outcomes

Benjamin M. Greenberg, MD, MHS

This journal article is supported by an educational grant from Novartis Pharmaceuticals Corporation

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

Summary

A lot has changed in treating those with multiple sclerosis, and this has been very impactful for those affected. Because of disease-modifying treatments MS is routinely ranked in the top three most expensive diseases to treat. All stakeholders must consider how best to care for these patients in a reasonable fashion.

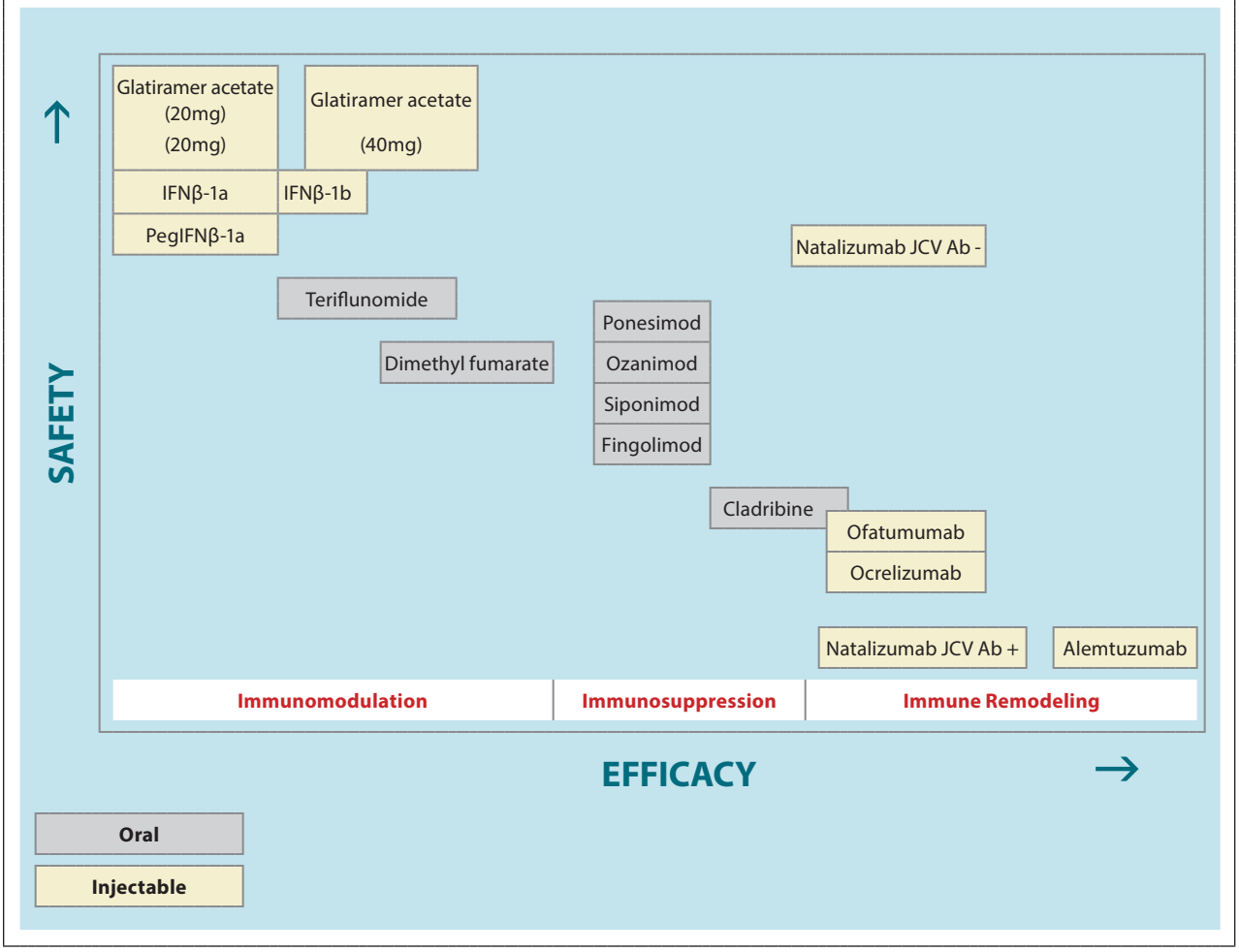
Key Points

- Multiple sclerosis is a life-long, common, potentially disabling condition that is highly treatable.
- Early accurate diagnosis is critical to allow patients access to available therapies and diagnostic criteria which are moving to a biologic definition of the disease.
- Smoldering disease leading to progression has become a critical focus for MS therapeutics.
- Individualized treatments selected by shared decision-making are critical to adherence and best outcomes.
- The treatment algorithm is going to become more complicated.

THE UNDERSTANDING OF THE PATHOLOGY and disease process of multiple sclerosis (MS) has changed dramatically over the last 20 years. MS is now understood as a progressive immune disease with neurodegeneration which is mediated by the adaptive immune system (T and B cells) and the innate immune system. It is characterized by inflammatory plaques or scars in the deep white matter of the brain and spinal cord which can be identified early in the disease process. For many years, the ability to walk had been how clinicians defined disability in MS. Now we know that multidimensional disability (fatigue, depression, cognitive dysfunction) starts early during the disease long before walking is affected.

In MS, early diagnosis and treatment as soon as possible are key for prevention of irreversible nervous system damage and preservation of as much function as possible. The diagnostic criteria have changed dramatically since 1965 when the Schumacher criteria required onset of symptoms between 10 and 50 years of age, objective abnormalities on neurologic examination, signs and symptoms consistent with white matter damage in the central nervous system, and evidence that lesions are disseminated in space (2 or more separate lesions) and time (2 attacks at least 1 month apart). With advances in imaging and biomarkers, MS can now be diagnosed based on one

Exhibit 1: Organizing/Classifying Disease-Modifying Therapies



neurologic event and a pattern on MRI that shows old and new lesions instead of multiple symptomatic attacks.[1] The 2024 revisions of the McDonald criteria allow for even earlier diagnosis. The newest criteria indicate if a patient has evidence of the biology of MS using paraclinical testing and biomarkers, and even with no symptoms, they can be diagnosed with MS.[2]

Disease-modifying therapy for MS has come a long way but there is still a long way to go in preventing disability over the patient's lifetime. The currently available treatments can be divided into three main categories: immunomodulation, immunosuppression, and immune remodeling. In general, the most effective fall into the immune remodeling category but these also a carry significant risk of adverse events (Exhibit 1). The more aggressive agents which cause immune remodeling are the most effective at reducing annual relapse rate and reducing disability progression.[3,4] It is important to note that data on efficacy and safety are primarily from placebo-controlled trials with different trial designs and different populations over a 25-year period. The people who enrolled in the original trials for interferon are vastly different from those enrolled in contemporary trials. Over time the placebo annualized relapse rates in trials have significantly declined from 1.27 in a 1993 interferon trial to 0.36 in a 2012 dimethyl fumarate trial.[5] The reason for this decline is an improvement in diagnostic criteria which has led to earlier diagnosis. In the past clinicians would discuss every available medication with a newly diagnosed patient but now it is more typical to assess the patient's risk tolerance. Some patients will want the most efficacious medications regardless of potential risk whereas others want the least-risky medication.

A better outcome measure to use instead of annualized relapse rate is no evidence of disease activity (NEDA). Clinicians care if the patient has disease activity but relapses with the current

Exhibit 2: No Evidence of Disease Activity from Clinical Trials[6-10]

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

disease-modifying agents are rarely seen. NEDA is defined as no relapses, no progression on the disability scale, no recent changes in brain MRI, and normal age-related brain atrophy. In untreated MS, the rate of brain atrophy is four times normal age-related atrophy. Exhibit 2 shows NEDA rates from some clinical trials.[6-10] Again although these data are not always from active medication comparison trials, the NEDA rates follow with the prior data on the immune remodeling agents being more effective. Long-term data are showing evidence of efficacy beyond 10 years with all the agents.[11,12]

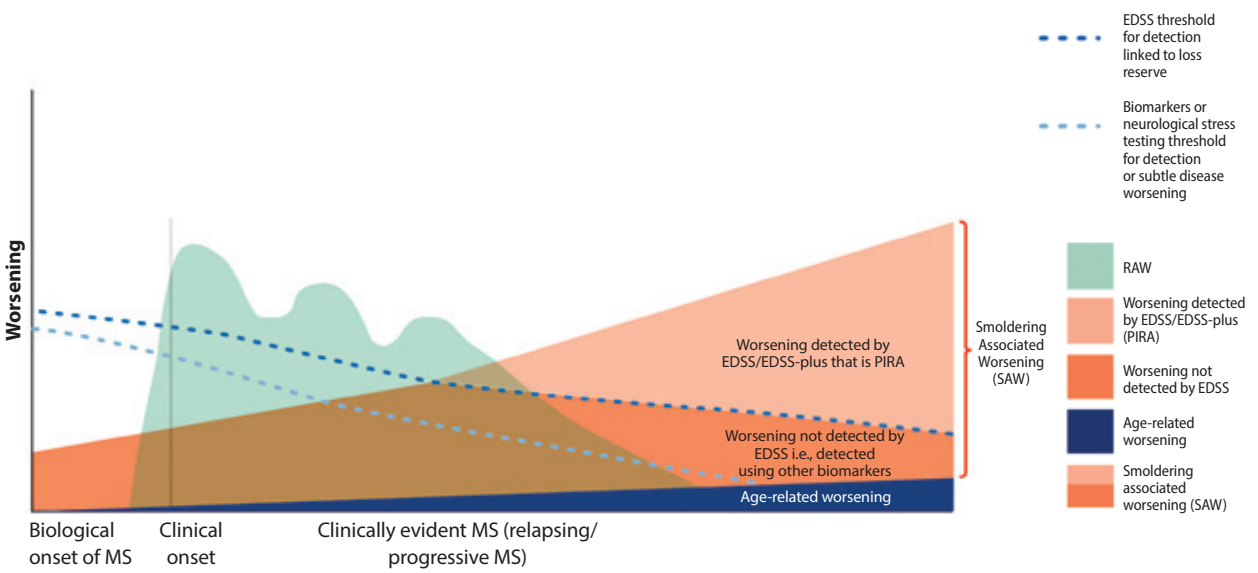
A paradigm change that is occurring in MS treatment is the recognition of smoldering MS. Smoldering neuroinflammation describes the slowly-evolving and chronic inflammatory processes directly linked to innate immune cells such as microglia that cause widespread chronic central nervous system (CNS) inflammation, activating with other immune cells in the CNS and contributing to neurodegenerative processes. This component of MS remains untouched by most current therapies, explaining why disability continues to progress.[13] Because the disease-modifying therapies do such an excellent job of suppressing relapses, slow changes in disability are seen over time [progression independent of relapse activity (PIRA)]. In one cohort study, 50 percent of patients experienced PIRA over the course of 20 years.[14] Additionally, the patients with PIRA acquire more disability than those without PIRA. The focus of care now is on a biologic definition of the disease that is independent of clinical symptomatology and on the neurodegenerative aspects of MS. There needs to be a different paradigm of treatment to target the smoldering worsening of disease (Exhibit 3).[15] The target of therapy is likely to evolve from NEDA (which is targeting inflammation) alone to inclusion of no evidence of smoldering activity (NEDSA) which includes no PIRA, no smoldering associated worsening (SAW), normalization of cerebrospinal fluid and serum biomarkers, and no new smoldering disease activity on MRI.[16]

The newest class of agents closest to market for MS are the Bruton's tyrosine kinase (BTK) inhibitors. BTK inhibition is a unique way of targeting MS; unlike other agents which target cell depletion or migration, these are is targeting enzymes. BTK itself is important in the maturation of B cells which are overactive in MS. BTK inhibitors are already FDA-approved for treating B cell lymphomas and chronic lymphocytic leukemia (CLL). In addition to effects on B cells, BTK inhibitors shift the signaling of myeloid cells from inflammatory cytokine production to anti-inflammatory cytokines which may slow MS damage in the nervous system as the microglia in the brain are less activated.

Several BTK inhibitors are currently under investigation in relapsing, primary progressive, and secondary progressive MS. Phase II trials of evobrutinib and tolebrutinib showed a reduction in the number of new brain lesions compared to placebo and dimethyl fumarate, in the case of evobrutinib.[17,18] Both of these agents have moved to Phase III trials. Development of evobrutinib was stopped because it did not demonstrate superior efficacy compared to teriflunomide in Phase III trials.[19,20] Tolebrutinib also failed to demonstrate superior efficacy in relapsing/remitting MS but was successful in non-relapsing secondary progressive multiple sclerosis (nrSPMS).[21] In this population, a smaller percentage of participants in the tolebrutinib group than in the placebo group had confirmed disability progression sustained for at least six months (22.6% versus 30.7%; hazard ratio, 0.69; $p = 0.003$).[21] Tolebrutinib is under evaluation by the FDA to treat MS and to slow disability accumulation independent of relapse activity in adult patients. The target action date for the FDA decision is September 28, 2025. Other BTK inhibitors in Phase III trials include fenebrutinib and remibrutinib. Liver function abnormalities are the most significant adverse events of this class. It is likely that when approved the BTK inhibitors will be available under a REMS program because of liver toxicity.

The primary goals of treating MS have been to reduce relapses and reduce disability. As discussed, these are shifting to include reducing PIRA. Other goals are choosing effective therapy that promotes adherence, effective monitoring of patients, and an action plan for change of therapy in case of

Exhibit 3: Smoldering Associated Worsening of MS[15]



RAW = relapse associate worsening; EDSS = Expanded Disability Status Scale; PIRA = progression independent of relapse activity

ineffectiveness. Choice of therapy should be individualized to the patient based on aggressiveness of disease, reproductive considerations, comorbid conditions, and patient risk tolerance. Early highly effective therapy reduces long-term relapse rates and disability and all in all will make an enormous difference over the next 20 years in terms of disability accumulation.[22] Patients who do not reach NEDA within two years of diagnosis have the highest risk of disability and continued relapses. The more evidence of disease present at diagnosis the more likely a patient is to have significant disability within 10 years.[23] It is important to initially select a high efficacy medication. Long-term data from ofatumumab trials shows that those who receive ofatumumab early and stay on it or switch to teriflunomide obtain more benefit than those who start on teriflunomide and eventually switch to the more effective ofatumumab.[24]

Whichever therapy is chosen, adhering to that disease-modifying therapy is critical for treatment efficacy and cost-effective care. Worse adherence can lead to relapses, increase in disability, relapse-associated hospitalizations and emergency department visits, and higher medical costs.[25] Patients who do not adhere to therapy have a worse overall quality of life compared to those who are adherent. Reasons for nonadherence to medication can vary, but the most reported include forgetfulness, injection-site pain, and adverse events.

Seventy-five to 90 percent of patients with MS prefer having an active role in treatment decisions (shared decision-making).[26] There is a significant connection between shared decision-making and higher treatment adherence rates. For the oral MS therapies especially, patients must have buy-in to take them daily for years to maintain remission.

Social determinants of health (SDOH), especially access to care, are major determinants of outcomes in MS. For many years studies have shown greater disability accumulation in Black and Hispanic populations. When individual-level SDOH indicators are considered, Black race nor Hispanic ethnicity are not significantly associated with changes in disability.[27] Targeting SDOH is one way to improve outcomes in MS.

Delays in starting therapy which can result from managed care policies matter to patients because it impacts the development of long-term disability. Forcing patients to step through certain therapies before moving on to more expensive therapies is not good practice. Based on prognostic factors, clinicians can predict which patients are likely to be disabled at 10 years and these patients need the most aggressive therapy up-front rather than letting the disease ravage their nervous system whilst testing various less-effective therapies.[23]

Although there are no studies among individuals with MS, systematic reviews in other diseases show that prior authorization and other coverage

restrictions are detrimental to medication adherence and worsen clinical outcomes. A growing body of evidence consistently indicates that cost-sharing can have a negative effect on disease-modifying therapy adherence. Among commercially insured patients with MS, those facing high cost-sharing amounts were 12.7 percent less likely to initiate a disease-modifying therapy in the two years following initial diagnosis relative to those without cost-sharing.[28] There are no studies that quantify the effects of cost-sharing on MS-related outcomes.

Conclusion

Multiple sclerosis is a life-long, common, potentially disabling condition that is highly treatable. Early accurate diagnosis is critical so as to allow patients access to available therapies and diagnostic criteria which are moving to a biologic definition of the disease. Smoldering disease leading to progression has become a critical focus for MS therapeutics. Individualized treatments selected by shared decision-making are critical to adherence and best outcomes. Multiple novel therapies are under development and the treatment algorithm is going to become more complicated.

Benjamin M. Greenberg, MD, MHS, is a Distinguished Teaching Professor and Vice Chairman of Clinical and Translational Research in the Department of Neurology at the University of Texas Southwestern in Dallas, TX.

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Recent Advances in the Treatment and Management of Early Alzheimer's Disease: Managed Care Insights on the Role of Novel Therapies

R. Scott Turner, PhD, MD

This journal article is supported by an educational grant from Eisai

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Summary

Disease-modifying antibody treatments are now available that remove pathologic beta-amyloid from the brain and slow cognitive decline in Alzheimer's disease (AD). There are several issues with widespread use of these agents. The research focus for AD is moving into preclinical disease stages and prevention strategies.

Key Points

- Imaging and biofluid biomarkers of AD are increasingly utilized in screening, diagnosis, prognosis, and testing new treatments.
- Newly approved disease-modifying antibody treatments for mild cognitive impairment (MCI) and AD may be most effective in earlier disease stages.
- Adverse events of these treatments require careful patient selection and intensive clinical and MRI monitoring.
- AD prevention trials are in progress.

IN 2025, AN ESTIMATED 7.2 MILLION Americans aged 65 years and older are living with Alzheimer's disease and this number is expected to grow to 13 million by 2050.[1] The rate of AD increases with age. By age 85, 30 percent of the white population in the United States (U.S.) will have AD.[1] The rates are higher for African Americans (58.6%) and Hispanics (62.9%).

AD is an incredibly expensive disease. In 2025, health and long-term care costs for people living with Alzheimer's and other dementias are projected to reach $360 billion — not including the value of unpaid caregiving.[1] Medicare and Medicaid cover $231 billion (64%) of the direct costs, while out-of-pocket spending is $91 billion. Total annual payments for healthcare, long-term care and hospice care for people living with dementia are projected to increase to $1 trillion by 2050. The total lifetime cost of care for a person living with dementia is about $400,000 with 70 percent carried by family caregivers in the forms of unpaid caregiving and out-of-pocket expenses.

Beyond age alone, there are several known risk factors for AD including family history/genetics (APOE4, race, downs syndrome), diabetes, midlife obesity, metabolic syndrome, traumatic brain injury, smoking, stroke, low education and occupational level, air pollution, and female gender. Age and family history/genetics are the most powerful risk factors. Several risk factors are modifiable such as diabetes or smoking. The presence of APOE4 genes is associated with an earlier onset of brain amyloid deposition by about 15 years compared to those without APOE4; approximately 25 percent of the U.S. population is ApoE4+ (E4/E4, E4/E3, or E4/E2).[2] The rate of AD development is highest in those with the APOE4/E4 genotype.[2]

AD is the number one cause of dementia in the U.S. but there are also many other causes which need to be ruled out before the patient is diagnosed with AD (Exhibit 1). The potentially reversible or treatable causes of dementia such as thyroid disease

Exhibit 1: Other Causes of Dementia

- Lewy body dementia
- Parkinson's disease with dementia
- Frontotemporal dementia
- Pick's disease
- Vascular dementia
- HIV/AIDS
- Mixed dementias (AD and Lewy body dementia, AD and vascular dementia)
- Depression (pseudodementia)
- Drugs (especially anticholinergic - impairing memory)
- Alcoholic dementia
- Chronic traumatic encephalopathy
- Hypothyroidism
- Vitamin B12 deficiency
- Normal pressure hydrocephalus
- Creutzfeldt-Jakob disease, mad cow disease (prion diseases)
- Neurosyphilis

and B12 deficiency are ruled out with laboratory testing. MRI, amyloid testing, and neuropsychiatric testing should be done to confirm the diagnosis.

Exhibit 2 outlines the FDA-approved medications for MCI and AD. As evidenced by the FDA-approval years, there were many failed clinical trials for agents between 2003 and 2023 when the anti-amyloid monoclonal antibodies were approved. The cholinesterase inhibitors and NMDA antagonist medications provide modest improvements in memory and functional status.

The real advance in treating early AD has been the approval of anti-amyloid antibodies. Accumulation of beta-amyloid plaque is one of the pathological factors in AD leading to failure of neurons. The criteria for using the anti-amyloid medications are early AD, demonstrated amyloid in the brain (by either amyloid positron-emission tomography [PET] scan or cerebrospinal fluid analysis), and fewer than three micro-hemorrhages in the brain. These new agents are given by intravenous infusion. Lecanemab is given every two weeks, however, dosing can be switched to every four weeks after 18 months of therapy. Donanemab is given every four weeks. Donanemab can be stopped once removal of amyloid plaques to minimal levels consistent with a visually negative amyloid PET scan is shown. Because these agents can cause amyloid-related imaging abnormalities (ARIA), brain MRI monitoring is required prior to infusions number five, seven and 14 and with any new neurologic signs or symptoms. Those with APOE4 positivity are at higher risk for ARIA which can occur as edema (ARIA-E) or hemorrhage (ARIA-H).

Both lecanemab and donanemab have been shown to slow cognitive decline and effectively remove amyloid from the brains. Lecanemab was studied in a large (n = 1,795), 18-month, multicenter, double-blind, Phase III trial involving persons aged 50 to 90 years with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on PET or by cerebrospinal fluid testing.[3] The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating-Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53; lower scores indicate greater impairment). The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo on the CDR-SB (difference, -0.45; $p < 0.001$). In a sub-study involving 698 participants, there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference, -59.1 centiloids). Other mean differences between the two groups in the change from baseline favoring lecanemab were ADAS-cog14 score, -1.44 ($p < 0.001$); ADCOMS, -0.050 ($p < 0.001$); and ADCS-MCI-ADL score, 2.0 ($p < 0.001$). Lecanemab resulted in infusion-related reactions in 26.4 percent of the participants and ARIA in 12.6 percent.

Donanemab was also investigated in a multicenter, randomized, double-blind, placebo-controlled, 18-month Phase III trial in 1,736 participants with early symptomatic AD (MCI/mild dementia) with amyloid and low/medium or high Tau pathology (another pathologic factor in AD) based on PET imaging.[4] The primary outcome was change in integrated Alzheimer Disease Rating Scale (iADRS) score from baseline to 76 weeks (range, 0 – 144; lower scores indicate greater impairment). There were 24 outcomes (primary, secondary, and exploratory), including the secondary outcome of change in the

Exhibit 2: FDA-Approved Drugs for MCI/AD

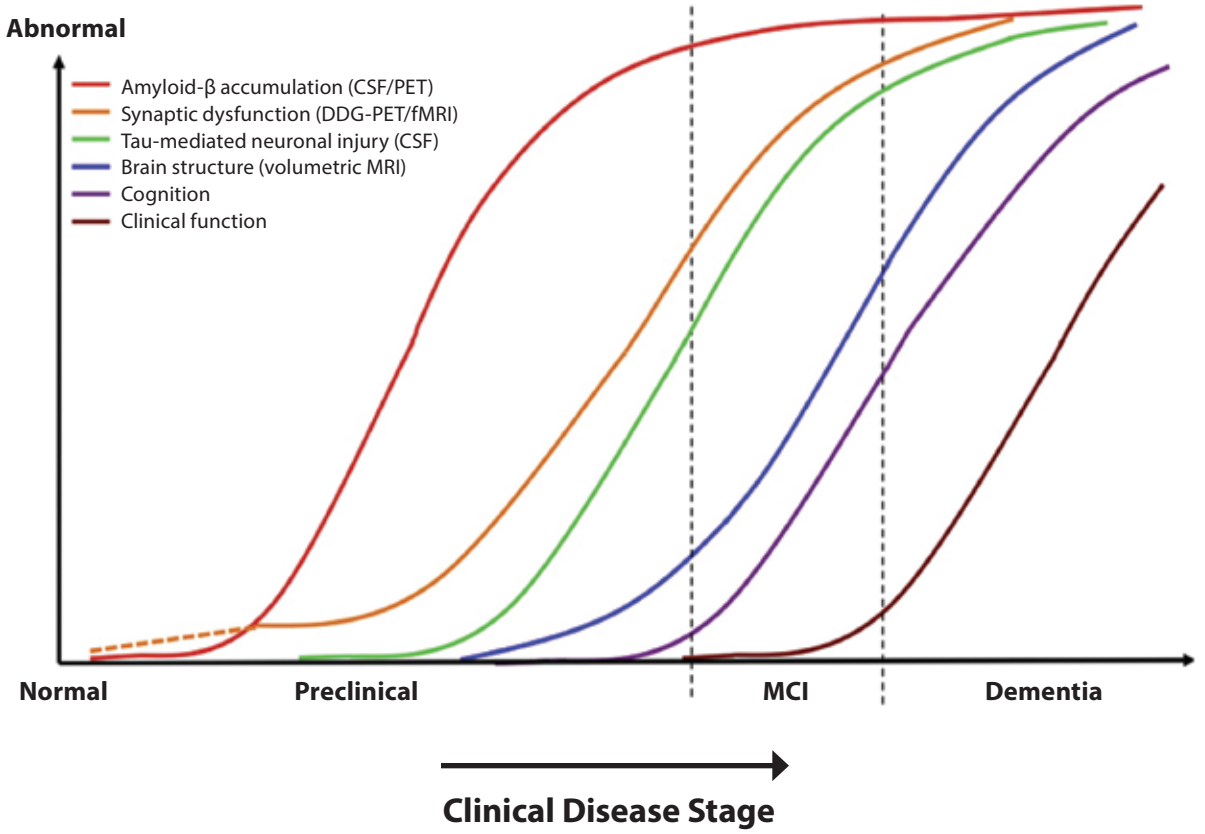
Drug	Mechanism of Action	Indication	FDA-Approved
Donepezil	Cholinesterase inhibitor	All dementia stages	1996
Rivastigmine	Cholinesterase inhibitor	All dementia stages	2000
Galantamine	Cholinesterase inhibitor	Mild-to-moderate	2001
Memantine	NMDA antagonist	Moderate-to-severe	2003
Donepezil/memantine	Combination of Cholinesterase inhibitor and NMDA antagonist	Moderate-to-severe	2014
Lecanemab	Anti-amyloid monoclonal antibody	MCI and mild dementia due to AD	Jul-23
Donanemab	Anti-amyloid monoclonal antibody	MCI and mild dementia due to AD	Jul-24

Exhibit 3: Disease Modifiers in AD

Primary target	Aβ protofibrils	Amyloid plaques
Dosage and frequency	10 mg/kg IV q 2 weeks; q 4 weeks after 18 months	700 mg X 3 then 1400 mg IV q 4 weeks
Discontinue drug with CNS amyloid clearance	No	Yes
Injectable version	Coming	No
Slows cognitive and functional decline	Yes; 27% (CDR-SB)	Yes; 22% (iADRS); 35% for low/medium tau group; 37% (CDR-SB)
Infusion reactions	26%	9%
ARIA ARIA-E ARIA-H	20% 13% 14%	37% 24% 31%
Deaths from ARIA in Phase III	0	3
Annual drug cost	$26,500	$32,000

sum of boxes of the CDR-SB score. Of the 24 gated outcomes, 23 were statistically significant. The least-squares mean change in iADRS score at 76 weeks was -6.02 in the donanemab group and -9.27 in the placebo group (difference, 3.25; $p < .001$) in the low/medium Tau population and -10.2 with donanemab and -13.1 with placebo (difference, 2.92; $p < .001$) in the combined population. Change in CDR-SB score at 76 weeks was 1.20 with donanemab and 1.88 with placebo (difference, -0.67; $p < .001$) in the low/medium Tau population and 1.72 with donanemab and 2.42 with placebo (difference, -0.7; $p < .001$) in the combined population. ARIA occurred in 24.0 percent (52 symptomatic) in the donanemab group and 2.1 percent (0 symptomatic during study) in the placebo group and infusion-related reactions occurred in 8.7 percent with donanemab and 0.5 percent with placebo.

Exhibit 4: Course of AD Biomarker Changes[5]



Overall, the two anti-amyloid therapies slow clinical decline in early symptomatic AD. Exhibit 3 compares the two available agents. It is important to note that there are no available comparative trials so no conclusions about differences in efficacy or safety can be made. In terms of these agents being widely used there are issues with inconvenience of every two-to-four-week infusions, cost of the medications, need for MRI monitoring for adverse events, and significant adverse events, especially ARIA. Another issue with managing patients with early AD is a lack of clinicians. Wait-times for specialty memory clinics are now excessive (more than 6 to 12 months).

Because it may be too late to majorly impact the disease once cognitive impairment is present, the research focus in AD is changing to preclinical disease and prevention. Those in the preclinical stage are cognitively normal but are beginning to have abnormal amyloid and Tau biomarkers. Exhibit 4 shows the course of the biomarker change over time.[5] FDA-approved PET imaging biomarkers for AD include amyloid PET ligands ([18F]-florbetapir, [18F]-flutemetamol, [18F]-florbetaben) and a Tau PET ligand ([18F]-flortaucipir). The amyloid PET scans are done clinically to determine eligibility for anti-amyloid therapies but the Tau PET scans are primarily used for research purposes. Amyloid can also be measured in the cerebrospinal fluid or plasma. The first commercially available blood test for AD entered the market in 2020. This test considers age, ApoE isoform(s), and plasma amyloid ratio (Ab42/Ab40) to support a diagnosis of AD.

One controversial point is when to label someone as having AD. We can now see the pathology of AD years before cognitive decline occurs with biomarker testing. This is leading to labeling someone as having MCI with AD pathology. With the use of biomarkers, patients who have just Tau pathology or non-Alzheimer's pathology are also being identified.

Both anti-amyloid therapies are being investigated for AD prevention. The trials are in cognitively normal people who have amyloid and early-Tau pathology

(AHEAD, TRAILBLAZER-ALZ3). Trontinemab, a combination of gantenerumab, another anti-amyloid monoclonal antibody, and a transferrin receptor module is investigational for early AD. The transferrin receptor module is a shuttle to efficiently cross the blood brain barrier thus a much lower dosage of the anti-amyloid antibody is required compared to the already approved agents. Phase Ib/IIa study results showed that trontinemab achieved rapid and significant amyloid plaque reduction in patients with early AD.[6] This agent is moving into Phase III trials. Remternetug is another anti-amyloid agent being studied for the treatment of early AD, with potential for subcutaneous delivery. There is also a revival of active beta-amyloid vaccination strategies as another way to remove amyloid and Tau from the brain.[7] Numerous clinical trials are ongoing, including those for UB-311, ACI-24.060, and PRX123 vaccines. Vaccination potentially offers a cheaper, easy-to-administer option for millions of people at risk for AD compared to anti-amyloid monoclonal antibodies. Alzheimer's vaccines are still in the preliminary stages and will require large, years-long trials to show efficacy and safety.

Conclusion

Imaging and biofluid biomarkers of AD are increasingly utilized in screening, diagnosis, prognosis, and testing new treatments. Newly approved disease-modifying antibody treatments for MCI and AD may be most effective in earlier disease stages. AD prevention trials are in progress. The major concern with adverse events of the anti-amyloid antibodies for early AD are ARIA which require careful patient selection and intensive clinical and MRI monitoring.

R. Scott Turner, PhD, MD, is professor of neurology and director of the Memory Disorders program at MedStar Georgetown University Medical Center in Washington D.C.

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Innovative Approaches in the Prevention and Management of HIV: The Role of PrEP and ART for Improved Outcomes

Eric S. Daar, MD

This journal article is supported by educational grants from ViiV Healthcare; Gilead Sciences

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

Summary

HIV infections continue to occur in the United States (U.S.), primarily in certain groups and regions. It is important to identify infections and get patients into care. Achieving viral suppression in those already infected and avoiding infection in those at risk through use of pre-exposure prophylaxis (PrEP) are important ways to tackle the epidemic. Managed care should consider the benefits of using long-acting agents for both treatment and PrEP.

Key Points

- New HIV infections continue to be an issue in the U.S.
- Undetectable viral load equals untransmittable disease.
- Easing the use of PrEP should be a goal for managed care.
- The cost effectiveness and increased efficacy of the long-acting PrEP and ART agents should be considered when making formulary decisions.

THE HIV INFECTION PANDEMIC HAS BEEN ongoing for over 40 years. Currently it predominately affects those in sub-Sahara Africa but there are still a substantial number of new cases annually in the U.S. The estimated new HIV infections decreased 12 percent from 36,300 in 2018 to 31,800 in 2022.[1]

HIV continues to have a disproportionate impact on certain populations, in particular racial and ethnic minorities, and gay, bisexual, and other men who have sex with men (MSM). About 60 percent of new cases are among communities of color. Additionally, about half of the new cases are occurring in the southeastern U.S. Population and regional factors impact how diagnosis, treatment, and prevention strategies need to be targeted.

Unlike many other infectious diseases, vaccination against HIV has not yet been successful. Where tremendous success has been achieved is in treating the infection with antiretroviral therapy (ART) which has changed HIV from a death sentence to a chronic disease. We now know that when a person with HIV has an undetectable viral load, they are not infectious and do not transmit the disease. ART can also be used effectively to prevent infection in those at risk (PrEP) but there is still much work to be done in this area.

Exhibit 1 shows the four pillars of ending the HIV epidemic in the U.S.[2] The overall goal is to reduce new infections to 3,000 per year by 2030. Finding previously undiagnosed cases and prevention in those at risk are the two areas where clinicians and managed care can be most impactful.

In terms of treating those who are identified as infected, the standard of care is to initiate therapy on the day of diagnosis or very soon thereafter. Large clinical trials have shown that early initiation of ART is more effective than a late start for preventing both AIDS and non-AIDS related complications.[3,4] There

Exhibit 1: Key Steps to Ending the HIV Epidemic in the United States[2]

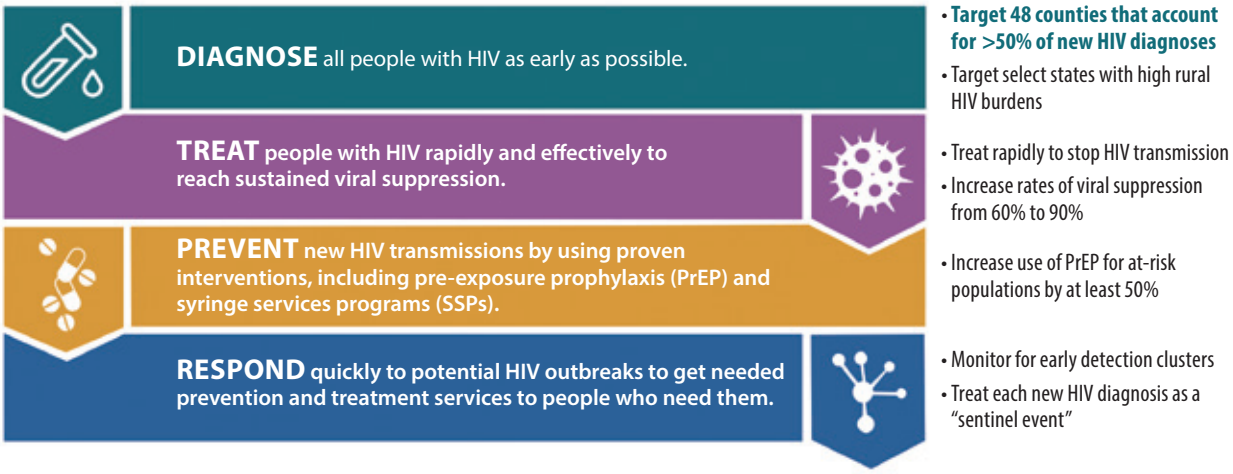

Exhibit 2: Initial Regimens[5]

Recommended for most people with HIV
Bictegravir/emtricitabine/tenofovir alafenamide
Dolutegravir + (emtricitabine or lamivudine) + tenofovir (alafenamide or disoproxil fumarate)
Dolutegravir/lamivudine[†]
If history of cabotegravir-long-acting PrEP
Darunavir/cobicistat (or ritonavir) + (emtricitabine or lamivudine) + tenofovir (alafenamide or disoproxil fumarate) pending INSTI resistance testing

[†]Not for persons with rapid start, pre-treatment HIV RNA >500K copies/mL or known to have active HBV coinfection, or no genotype available.

are also improved clinical outcomes with a rapid initiation of therapy including easier achievement of viral suppression. The rationale for immediate ART in settings with the resources to do this is to increase uptake of ART, decrease the time required to link to care and viral suppression, and improve rate of suppression.[5,6] Early start also reduces transmission to sexual partners. Overall, early start helps the patient and the general population. The treatment guidelines for initial treatment of HIV infection are shown in Exhibit 2.[5]

For most people with HIV, initial regimens composed of an integrase strand transfer inhibitor (INSTI), specifically bictegravir or dolutegravir, with two (and in some cases one) nucleoside or nucleotide reverse transcriptase inhibitors are recommended. These regimens are highly effective (90% or greater viral suppression rates) while also having minimal adverse events and a low rate of viral resistance. The regimen for those who have a history of using cabotegravir long-acting PrEP is different due to the potential for resistance.

Potential benefit for simplicity or adverse event resolution with a new option in those who are virologically suppressed are two reasons for therapy switches. Because there is some risk in switching therapies in those who are virologically suppressed, there needs to be a good reason for switching. An

Exhibit 3: Barriers and Potential Solutions to PrEP Uptake

Key Barriers	Potential Solutions
Limited awareness of PrEP	Education (patient/provider) Communication between providers
Low-risk perception	Education (patient/provider)
Stigma	Increase cultural understanding Improve communication/understanding between patient and provider
Provider bias and mistrust of healthcare system	Education (patient/provider) Address systemic biases (e.g., education, advocacy, and diverse healthcare professional staff)
Limited access to medical care	Education (patient/provider) Extending access to PrEP Technological alternatives (e.g., telemedicine) Address competing priorities (e.g., food, shelter, safety, other healthcare, childcare)
Financial barrier	Awareness/guidance of financial aid options
Concern about side events	Education (patient/provider)

example of benefit is switching from daily oral therapy to long-acting injectable.

For some patients, the long-acting injectable regimen of cabotegravir and rilpivirine (LA-CAB/RPV) is an improvement over the once-a-day oral combinations. This regimen is given as two intragluteal injections every four to eight weeks. The value for the patient is only thinking about their HIV treatment six to 12 days a year. There are more long-acting injectables under investigation which will be administered even less frequently. LA-CAB/RPV is currently only indicated for those who are virologically suppressed with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine; there are limited data on those who are treatment naïve, have poor adherence, or viremic.

A recent trial in a non-adherent population used significant effort, including paying subjects to take their therapy, to achieve viral suppression so they could be switched to long-acting therapy. This trial found that long-acting cabotegravir and rilpivirine administered every four weeks had superior efficacy to daily oral ART among people living with HIV who had previously been unable to maintain viral suppression while taking an oral daily regimen.[7] This data shows we can exploit the properties of long-acting therapy for those who are non-adherent because they are at risk for dying.

Although only FDA-approved in those with virologic suppression, long-acting therapy is an option for those with viremia based on one trial in 59 non-adherent patients.[8] At 48 weeks of treatment, 47 met the primary outcome of viral suppression with LA-CAB/RPV persistence (80%). Five had viral failure with resistance (3 with RPV-associated and 2 with CAB- and RPV-associated mutations), and one was lost to follow-up. The population in this trial had many issues leading to non-adherence and lack of viral suppression. Fifty-three percent had unstable housing, 61 percent used stimulants, and 10.2 percent used opioids. In those initiating LA-CAB/RPV with initial viremia, 48-week viral suppression (< 50 copies/mL) was seen in 92 percent.

The Department of Health and Human Services and International AIDS Society USA guidelines recommend considering off-label CAB/RPV-LA with intensive services in those unable to take

Exhibit 4: PrEP Options[6,11]

<table>
<tr><th colspan="2">Oral FTC/TDF</th><th>Oral FTC/TAF</th><th>Injectable Cabotegravir</th></tr>
<tr><th></th><th>Daily</th><th>On-Demand</th><th>Daily</th><th>Every 2 Months</th></tr>
<tr><td>Men who have sex with men</td><td rowspan="5">FDA On-Label
Guideline Recommended
(DHHS, IAS-USA)</td><td>FDA Off-Label
Guideline Recommended
(IAS-USA)</td><td rowspan="3">FDA On-Label
Guideline Recommended
(DHHS, IAS-USA)</td><td rowspan="5">FDA On-Label*
Guideline Recommended
(DHHS, IAS-USA)</td></tr>
<tr><td>Transgender women</td><td rowspan="4">FDA Off-Label
Not Recommended</td></tr>
<tr><td>Heterosexual men</td></tr>
<tr><td>Heterosexual women</td><td rowspan="2">FDA Off-Label
Not Recommended</td></tr>
<tr><td>Transgender men</td></tr>
</table>

People who use intravenous drugs: Assess and consider sexual risk.
CDC indicates likely to benefit from any FDA-approved PrEP option with or without a sexual risk indication.
*Injectable lenacapavir – not yet included in guidelines
FTC = emtricitabine; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide

orally despite efforts, high risk of progression (e.g., CD4 < 200 or AIDS), and virus susceptible to CAB and RPV.[5,6] The guidelines also recommend referral for substance use and mental health support. Although a long-acting injectable may improve adherence and viral suppression rates in those with a history of poor adherence, the patient still must return to the clinic for injections. If the patient is late getting the injections, they are at elevated risk for developing resistance.

For those who have confirmed virologic failure with ART an expert consultation is recommended for selecting therapy. At least a three-drug regimen will be required to get the patient to virologic suppression. Fixing virologic failure is not only important to the individual patient but is a population/community issue because of disease transmission potential. For patients who are resistant to a fully active second generation INSTI or boosted protease inhibitor, there are several newer medications including lenacapavir, maraviroc, fostemsavir, and ibalizumab for multidrug resistance. Although these agents are very expensive, they are life saving for the patient and are important for targeting the infection in those with significant past treatment exposure. These agents are to be used in combination with other ART. The percentage of patients with significant resistance is much lower for those who started treatment in the last 10 years because of the high barrier to resistance of the newer standard ART regimens.

In 2022, for every 100 people diagnosed with HIV only 76 percent received some HIV care, 54 percent were retained in care, and 65 percent achieved viral suppression. These data highlight the need for continued prevention and care efforts to reach the national goal of ending HIV by achieving 95 percent viral suppression rates.[1] The groups likely to be out-of-care and virally unsuppressed in the U.S. include certain demographic groups (younger age, Black/African American, Cisgender women, and transgender and gender diverse). The big three key barriers to appropriate HIV control are unstable housing, substance use disorders, and mental health disorders.

Preventing HIV infections by using PrEP is another of the key steps in ending the HIV epidemic. PrEP, when it is taken consistently, is very effective in preventing infection. The goal is to increase the use of PrEP in at-risk populations by at least 50 percent.[1] About 2.5 million people in the U.S. are estimated to be at risk for HIV infection and eligible for PrEP.[9] In 2024, 23 percent of the at-risk population was receiving PrEP.[10] There was a 17 percent increase in uptake from 2023 to 2024. Those at substantial risk for acquiring HIV are sexually active adults and adolescents who had anal or vaginal sex in the past six months AND any of the following: sexually active partner with HIV (especially if partner has an unknown or detectable viral load), bacterial sexually transmitted illness in past six months, and history of inconsistent or no condom use with sexual partner(s).[11] There is a direct relationship between PrEP penetrance and reducing HIV infection rates in a community.[12] The Southeast U.S. is one area where PrEP uptake lags.[13] Getting more at-risk people on PrEP is important. Exhibit 3 shows some barriers and potential solutions for increasing PrEP uptake.[14,15]

Taking a sexual history and offering PrEP are necessary first steps in increasing PrEP use. Clinicians should not limit sexual history assessments to only selected patients. All people who desire PrEP should be offered PrEP whether they have substantial risk or not. The current PrEP options are shown in Exhibit 4. Another option beyond daily pills is on-demand dosing—two tenofovir disoproxil fumarate/emtricitabine tablets before sexual exposure, one 24 hours after, and another 48 hours after.

Large trials have found long-acting cabotegravir (LA CAB) as PrEP was more effective than oral daily medications—efficacy is likely because of improved adherence.[16,17] The estimated annual cost for the first year of LA CAB is approximately $25,900 and in subsequent years $22,200. This agent is given as two injections one month apart and then on an every-two-month schedule. Even though injections are more expensive, it is a cost-effective intervention due to the increase in efficacy and avoiding infections which require treatment.

The newest PrEP option which is not yet included in the guidelines is for twice-yearly injections of long-acting lenacapavir. Studies have found it effective and well tolerated across a broad range of populations, including pregnant and lactating women, adolescents (16+), and young people, and it was preferred over daily oral medication among trial participants. In a trial comparing lenacapavir every 26 weeks or daily oral tenofovir disoproxil fumarate/emtricitabine in cisgender men, transgender women, transgender men, and gender-nonbinary persons, there were two HIV infections in the lenacapavir group (0.10 per 100 person-years) and in nine participants in the oral PrEP group (0.93 per 100 person-years).[18] The background HIV incidence in the screened population (4,634 participants) was 2.37 per 100 person-years. In a trial of cisgender women in South Africa and Uganda, no cases of HIV were seen in the lenacapavir group.[19]

Long-acting lenacapavir is indicated for PrEP to reduce the risk of sexually acquired HIV-1 in adults and adolescents (> 35kg) who are at risk for HIV-1 acquisition. As with all PrEP regimens, individuals must have a negative HIV-1 test prior to initiating. An oral loading dose is required. On day one of initiation, the patient takes two 300 mg lenacapavir tablets in addition to being given two subcutaneous injections. An additional two tablets are to be taken the next day. After that, it is two injections twice a year. The list price for a year of therapy is $28,218 compared to $360/year for generic oral PrEP.

Oral PrEP is widely available around the U.S. LA CAB access is more limited primarily because of cost and it is likely this will also be the case with long-acting lenacapavir. In a cost-effectiveness study of LA CAB, a Markov model estimated that LA CAB prevented 4.5 more primary and secondary HIV-1 infections per 100 PrEP users than generic oral PrEP, which yielded 0.2 fewer quality-adjusted life-years (QALYs) lost per person.[20] Additional per-person lifetime costs were $9,476 (2022 U.S. dollars), resulting in an incremental cost-effectiveness ratio of $46,843 per QALY gained. Results remained consistent in sensitivity and scenario analyses, including in underserved populations with low-oral PrEP usage. No cost-effectiveness studies from a U.S. perspective for long-acting lenacapavir have been published but given similar cost and effectiveness, it will likely also be cost-effective.

The future of PrEP is for more long-acting products. Microarray topical patches and subcutaneous implant formulations of LA CAB are under investigation.

Conclusion

Given the significant consequences for an individual and the community in general of an HIV infection, easing the use of PrEP should be a goal for managed care. The cost effectiveness and increased efficacy of the newer long-acting PrEP and ART agents should be considered when making formulary decisions.

Eric S. Daar, MD, is the Chief, Division of HIV Medicine at the Harbor-UCLA Medical Center and a Professor of Medicine at the David Geffen School of Medicine at UCLA in Los Angeles, CA.

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Innovative Approaches in Treatment and Management of HER2-Positive and HER2-Low Breast Cancer: Managed Care Insights in an Evolving Paradigm

Lee S. Schwartzberg MD, FACP

This journal article is supported by educational grants from Daiichi Sankyo; AstraZeneca

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 breast cancer has moved into personalized medicine. Important areas are the management of HER2-positive and HER2-low disease for which antibody drug conjugates are available and making a difference in outcomes while being less toxic overall than conventional chemotherapy.

Key Points

- Marked improvement in outcomes for HER2+ cancers are attributable in part to ADCs, especially trastuzumab deruxtecan.
- HER2-low metastatic breast cancer is a new category of treatable patients.
- In the HER2-low population, trastuzumab deruxtecan has superior efficacy compared to chemotherapy.
- Delaying progression and improving survival in metastatic breast cancer provides financial benefits to patients.
- Novel therapies in metastatic breast cancer have good cost-to-effect ratios.

BREAST CANCER IS THE MOST COMMON cancer in United States (U.S.) women accounting for 15 percent of all new cancer cases.[1] In 2025, an estimated 316,950 women will be diagnosed with invasive breast cancer, and 42,170 women are projected to die from the disease. About 6 percent of cases are already metastatic at the time of diagnosis and 20 to 30 percent of patients will develop metastatic disease after earlier stage treatment. There are about 200,000 women living with metastatic disease in the U.S. The five-year survival rate for breast cancer is 91.7 percent.

Biologically distinct subgroups of breast cancer include hormone receptor positive/human epidermal growth factor receptor two negative (HR+/HER2–), HR+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC). The focus of this article is HER2+ and the newer treatable HER2-low disease.

HER2 was identified as a driver of breast cancer in the 1980s. Overexpression of HER2 protein or amplification of the HER2 gene promotes the growth of cancer cells. HER2 is expressed on all breast cancer cells but the amount of HER2 varies. HER2 levels are detected by measuring the amount of protein on the cell surface using immunohistochemistry (IHC) and the number of HER2 gene copies in cancer cells by *in situ* hybridization (ISH). Until recently, HER2 was thought of as being positive or negative. Positive was defined as IHC3+ or IHC2+ plus positive ISH testing; about 15 percent of cases are HER2+. Now there is the new HER2-low category which came from studies showing benefits of HER2 targeting agents in those with low levels of HER2 expression. HER2-low is defined as IHC2+/negative

Exhibit 1: Antibody Drug Conjugate Component and Functions[3]

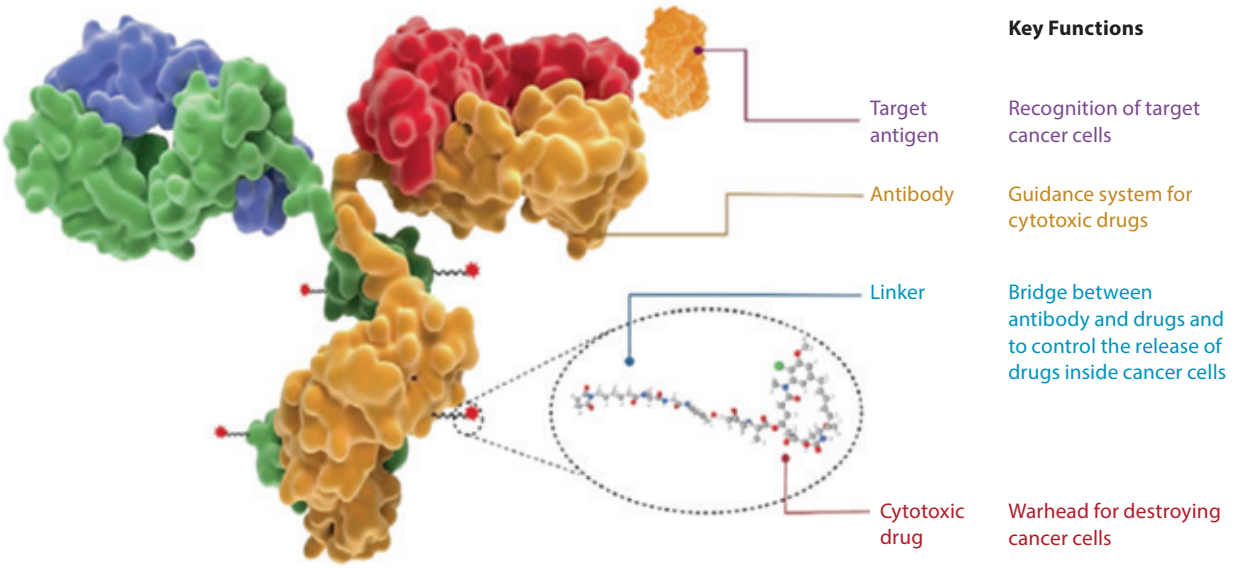
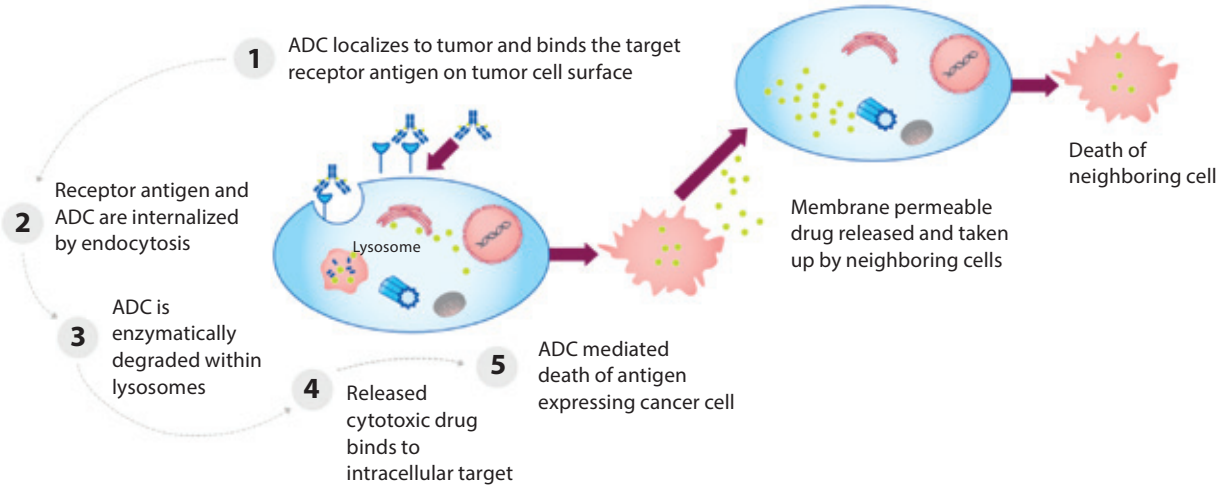


Exhibit 2: Bystander Effect Provides Activity Across Variable HER2 Expression[4]



IHC or IHC+1. Approximately 50 percent of breast cancer patients have HER2-low. HER2-low is, most commonly, also hormone receptor positive (up to 85%). Based on the advances in treatment of HER2+ metastatic breast cancer, those newly diagnosed can expect to have median survival of more than eight years. Prior to the introduction of HER2 targeted therapy, the median survival was one year.[2]

Antibody drug conjugates (ADCs) are akin to a smart bomb for cancer treatment. An ADC is composed of a monoclonal antibody against a target antigen (for example, HER2), a linker, and a cytotoxic drug (Exhibit 1).[3] The antibody binds to the target antigen and the ADC enters the cell releasing the cytotoxic drug. Many of the cytotoxic agents used in ADCs are so toxic they cannot be given alone intravenously being similar to a typical chemotherapy agent. In breast cancer, ADCs have been shown to have a bystander effect where nearby cells are killed by membrane permeation of the cytotoxic agent which provides activity even when HER2 expression is low (Exhibit 2).[4]

Standard first-line treatment for HER2+ metastatic breast cancer is trastuzumab and pertuzumab, which target HER2 in different ways, in combination with chemotherapy because of improved overall survival (OS) compared to older regimens. Second-line treatment is now trastuzumab deruxtecan instead of the previous standard of care trastuzumab emtansine based on a comparison trial showing better survival and lower toxicity.[5] Both are ADCs but trastuzumab deruxtecan also can kill neighboring non-HER2+ tumor cells through bystander killing. Additionally, it delivers a higher chemotherapy payload than ado-trastuzumab emtansine.

In the trial comparing trastuzumab deruxtecan and traztusumab emtansine in patients with HER2+ metastatic breast cancer previously treated with trastuzumab and a taxane, the percentage of those who were alive without disease progression at 12 months was 75.8 percent with trastuzumab deruxtecan and 34.1 percent with ado-trastuzumab emtansine (HR, 0.28; $p < 0.001$).[6] The percentage of patients who were alive at 12 months was 94.1 percent and 85.9 percent, respectively (HR, 0.55; prespecified significance boundary not reached). At the final data analysis, median progression-free survival (PFS) was 29.0 versus 7.2 months (HR, 0.30), the 36-month PFS rate was 45.7 percent versus 12.4 percent, and median OS was 52.6 versus 42.7 months (HR, 0.73) with trastuzumab deruxtecan versus trastuzumab emtansine, respectively.[7]

In the DESTINY-Breast04 trial, patients with previously treated HER2-low metastatic breast cancer who were treated with trastuzumab deruxtecan had significant improvements in survival compared to those treated with chemotherapy alone. The median PFS was 10.1 months in the trastuzumab deruxtecan group and 5.4 months in the physician's choice chemotherapy group (HR, 0.51; $p < 0.001$), and OS was 23.9 months and 17.5 months, respectively (HR, 0.64; $p = 0.003$).[8] In this trial, patients who were hormone receptor positive or negative benefited. Based on this study, this agent was FDA-approved for adults with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH negative) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

As of January 2025, trastuzumab deruxtecan is also FDA-approved for HER2-ultralow (IHC 0 plus membrane staining) unresectable or metastatic breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting. This approval was based on results from the DESTINY Breast 06 trial which included both HER2-low and HER2-ultralow HR positive metastatic breast cancer which had been previously treated with one or more lines of endocrine-based therapy and no previous chemotherapy for metastatic breast cancer. This trial included 713 subjects with HER2-low disease and 153 with HER2-ultralow. Among the patients with HER2-low disease, the median PFS was 13.2 months in the trastuzumab deruxtecan group and 8.1 months in the physicians' choice chemotherapy group (HR, 0.62; $p < 0.001$); the results were consistent in the exploratory HER2-ultralow population (13.2 versus 8.3 months).[9] Data for OS in the overall population are immature (28.9 versus 27.4 months).[10]

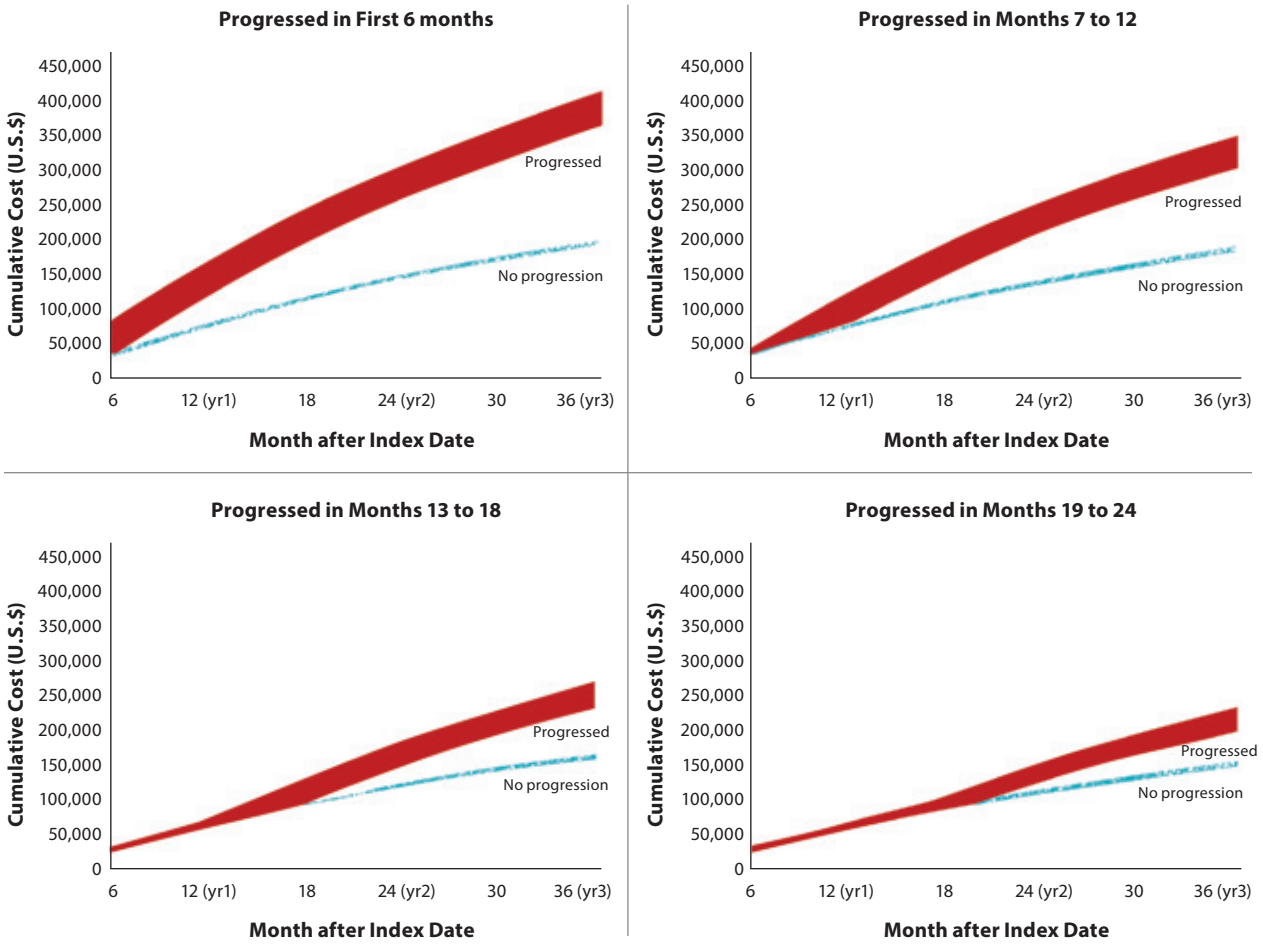
The National Comprehensive Cancer Network (NCCN) Guidelines for HR+, HER2-low metastatic breast cancer which is hormone refractory recommend chemotherapy as first-line treatment unless BRCA mutations are present.[5] Second-line therapy is trastuzumab deruxtecan (Category 1). The guidelines also recommend trastuzumab deruxtecan for second-line treatment of triple negative breast cancer with HER2-low and no BRCA mutations. The NCCN Guidelines have not yet addressed the issue of using this agent in the HER2-ultralow population.

In terms of adverse events, interstitial lung disease and left ventricular dysfunction are important ones to note that occur with agents that target HER2, including trastuzumab deruxtecan. Additionally, trastuzumab deruxtecan is a highly emetogenic ADC; three to four anti-emetic agent prophylaxis should be used to reduce issues.[11]

Another area for utilization of trastuzumab deruxtecan is when brain metastases are present. Brain metastases are a common problem in HER2+ metastatic disease. About 47 percent of patients will develop them after first-line treatment with trastuzumab. The NCCN preferred regimens for those with brain metastases are tucatinib in combination with trastuzumab and capecitabine (Category 1) if previously treated with one or more regimens or trastuzumab deruxtecan, each if previously treated with one or more regimens.[12] Trastuzumab deruxtecan moved from an other recommended regimen to preferred in the most recent update of the NCCN Guidelines.

Healthcare costs and time lost from work are significant for those with all types of metastatic breast cancer. Total costs (medical and productivity) across all age groups and phases of care were estimated at $63.4 billion (95% sensitivity range = $59.4 to $67.4 billion) in 2015 and predicted to increase to $152.4 billion (95% sensitivity range = $111.6 to

Exhibit 3: Delaying Progression is Associated with Lower Healthcare Costs[14]



$220.4 billion) by 2030, an increase of 140 percent.[13] Estimated costs are higher for younger and midlife women who are still in the work force than for older women. More women in their early 30s and 40s are being diagnosed with breast cancer.

Costs are also higher for those patients who have disease progression in the metastatic setting; one study found 60 percent higher costs.[14] The main driver of the progression cost increases are hospital outpatient visits. Delaying progression of metastatic breast, lung, and colon cancer is associated with lower healthcare costs (Exhibit 3).[14] Delaying disease progression can also help keep patients healthy enough to continue working. Having medications that improve OS is important but delaying progression is also an important endpoint in terms of patient health and well-being and financially for the healthcare system.

A budget impact model of using trastuzumab deruxtecan for the HER2-low metastatic population previously treated with chemotherapy in a 10-million-member plan found that the two-year cost would be an extra $6 million. This factored out to be a 2.5 cent per member per month cost over two years. Another analysis found that the inclusion of this ADC for HER2+ metastatic breast cancer patients who have progressed on two or more prior anti-HER2 regimens, in need of a next-line treatment caused a modest increase in healthcare budget.[15]

Conclusion

Metastatic breast cancer remains a huge societal problem in the U.S., with substantial human and financial costs. ADCs are a newer class of drugs that are more effective and overall, less toxic than conventional chemotherapy. Marked improvement in outcomes for HER2+ cancers are attributable in part to ADCs, especially trastuzumab deruxtecan. HER2-low metastatic breast cancer is a new category of treatable patients, with trastuzumab

deruxtecan showing superior efficacy compared to chemotherapy. The financial and workforce impact of delaying progression and improving survival in metastatic breast cancer is well documented. Budget impact models predict small incremental costs for novel therapies leading to a good cost to effect ratio.

Lee S. Schwartzberg, MD, FACP, is the chief of Medical Oncology and Hematology for Renown Health–William N. Pennington Cancer Institute and is a professor of clinical medicine at the University of Nevada–Reno in Reno, NV.

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Navigating Recent Advances in Hyperlipidemia Care: Managed Care Considerations on the Impact of PCSK9 Modulation on Cardiovascular Outcomes and Lowering LDL-C

Pam R. Taub MD, FACC

This journal article is supported by educational grants from Merck Sharp & Dohme LLC; Novartis Pharmaceuticals Corporation

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Summary

Statins remain the cornerstone of lipid therapy but many patients will require additional non-statin agents to achieve appropriate LDL cholesterol goals and reduce non-HDL cholesterol. Screening patients for elevated lipoprotein a [Lp(a)] is now recommended and lowering this lipoprotein when elevated is important to reduce atherosclerotic cardiovascular disease risk.

Key Points

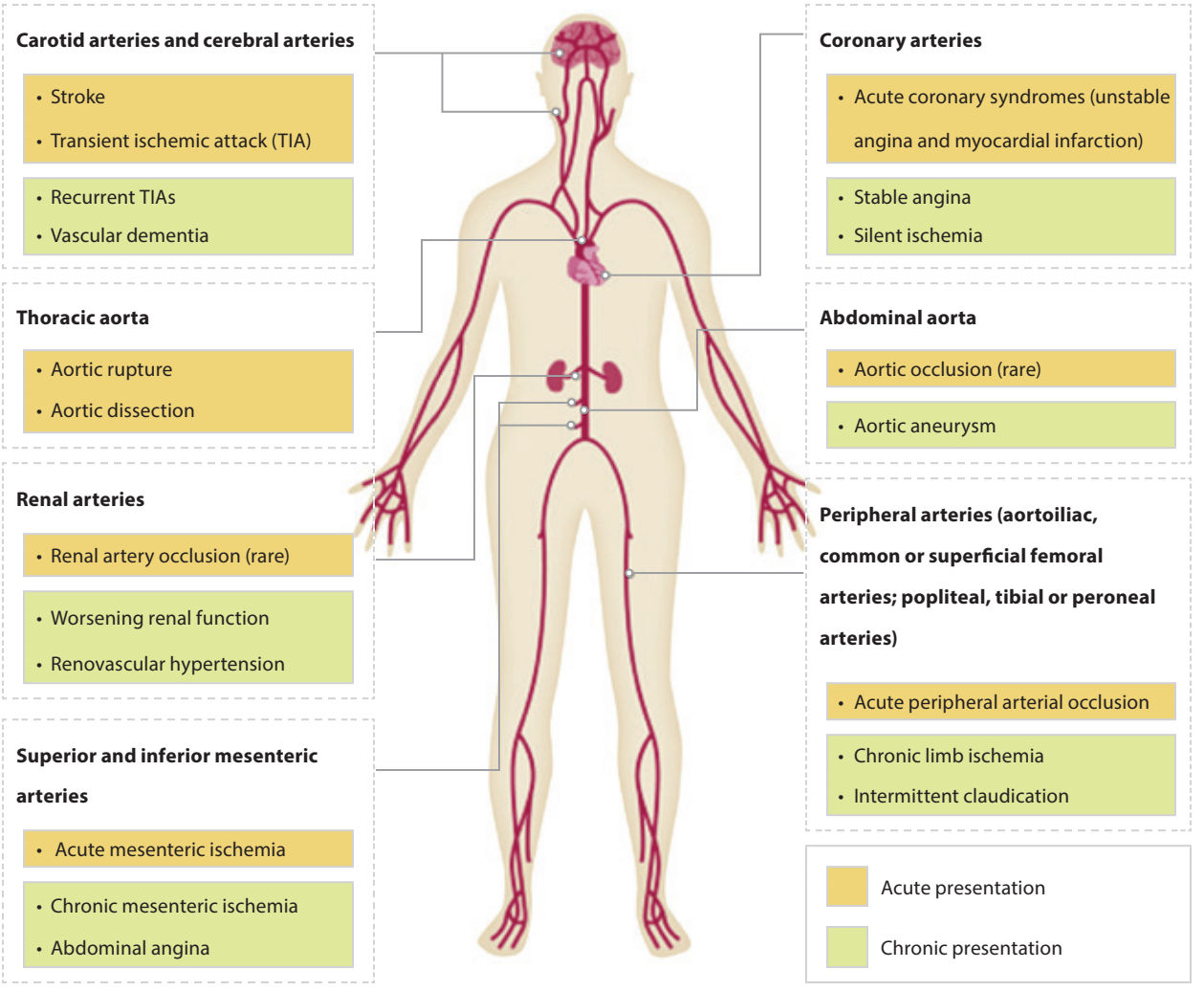
- Statins are the cornerstone of lipid therapy.
- Ezetimibe is a useful non-statin adjunct.
- PCSK9 inhibitors reduce LDL cholesterol and non-HDL cholesterol, reduce Lp(a), have a favorable safety profile, and cause beneficial plaque remodeling.
- Bempedoic acid and inclisiran are promising newer agents for LDL-C and Lp(a) lowering.
- Achieving an LDL as low as possible is important for secondary prevention.
- Lp(a) is a marker of residual risk.

ATHEROSCLEROSIS IS A DIFFUSE DISEASE driven by inflammation, atherogenic lipoproteins, and in the acute phase – platelet aggregation. At the core of atherosclerotic plaques is cholesterol and the core way to reduce plaque is to remove the cholesterol from the body with lipid lowering therapies. Inflammation also plays a role by making plagues more active.

Subclinical plaque may not be detected on stress testing or coronary angiography. Stress testing is only going to identify luminal narrowing of the arteries (stenosis) and thus is not useful for identifying atherosclerosis until it is significantly advanced. Plaque can cause outward expansion of the artery wall which accommodates the growth of the plaque and minimizes luminal narrowing. Luminal stenosis does not occur until late in the process of atherosclerosis. Unfortunately, most myocardial infarctions and strokes occur in arteries without significant stenosis (< 50%).[1] It is also important to remember that atherosclerosis is a systemic disease (Exhibit 1).[1] Clinicians used to think they could place a stent or do a bypass and the disease was fixed. Systemic therapy is required so all the arteries in the body are addressed and not just one artery where there happens to be the most narrowing.

Other issues in assessing atherosclerosis and risk for events are low-density lipoprotein cholesterol (LDL-C) values. Because it is calculated rather than measured, it is not an ideal biomarker. Clinicians and

Exhibit 1: Atherosclerosis is a Systemic Disease[1]

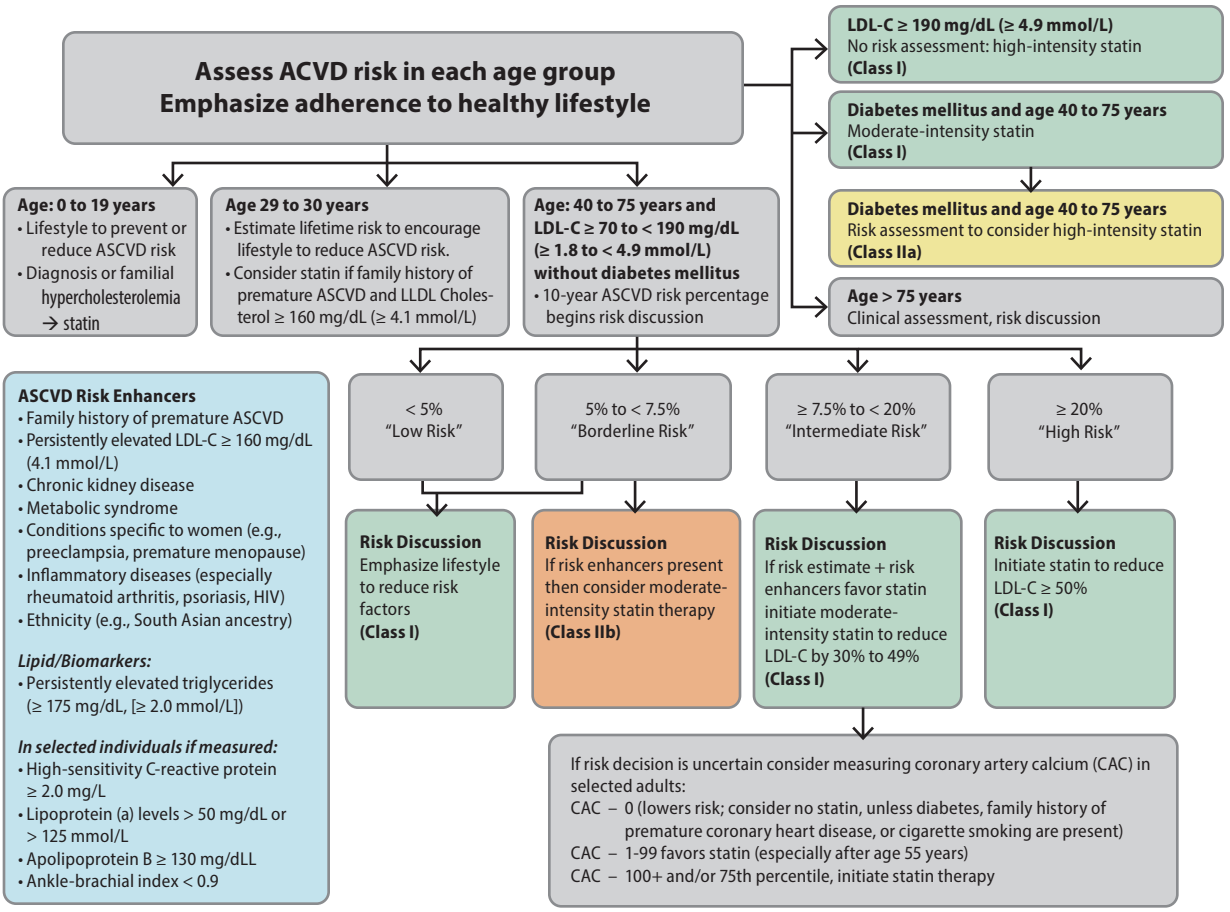


patients can be fooled by very low values because they are not providing a complete picture. For example, if a patient has elevated triglycerides, their LDL-C will be falsely low because the calculation is highly influenced by triglyceride levels. There are other measures which can give a better picture including apolipoprotein B, LDL particle number, and non-high density lipoprotein cholesterol (non-HDL-C). Non-HDL-C is the best measure because it is included in a standard lipid profile without any additional cost. Non-HDL-C is the amount of cholesterol in atherogenic particles and is the HDL-C level subtracted from total cholesterol. If a patient has an LDL-C of 70 mg/dL, the non-HDL-C should be 100. If the patient has a non-HDL greater than 100, the LDL-C is not providing the full picture. The non-HDL-C targets are about 30 mg/dL higher than the LDL-C targets. Newer equations such as the Hopkins Martin or National Institutes of Health (NIH) equations for LDL-C are being used by some laboratories for lipid profile reporting and are more accurate than older equations. The use of multiple biomarkers of risk is needed for better risk-factor stratification.

There are many aspects of reducing atherosclerotic cardiovascular disease (ASCVD) risk. In addition to lifestyle interventions and lipid management, other targets include inflammation, metabolism (type 2 diabetes, metabolic syndrome), platelets, and coagulation. It is important to note that the process of atherosclerosis development starts early in life thus lifestyle interventions are important in children and throughout the lifespan.

There is a continuum of risk including primary prevention (no evidence of overt atherosclerosis, no ASCVD events), high-risk primary prevention

Exhibit 2: Primary Prevention of Atherosclerotic Cardiovascular Disease[2]



Note: Color corresponds to class of recommendation: green = Class I (strong); yellow = Class IIa (moderate); orange = Class IIb (weak)

(advanced subclinical atherosclerosis, numerous high-risk factors), and secondary prevention (ASCVD events). The high-risk primary prevention patient is just waiting to have an event. Identifying and aggressively treating the high-risk primary prevention patient is needed to prevent events. Exhibit 2 outlines primary prevention strategies.[2] The problem area patients are the 40- to 50-year-olds who fall into the intermediate-risk area. Non-HDL-C, apolipoprotein B, and coronary artery calcium scoring can be helpful in identifying which of these intermediate-risk people are actually high-risk.

Coronary artery calcium scoring (CAC) is a reasonably priced test (~$100) and is covered by most insurance companies. Calcium deposited in a coronary vessel shows that the patient has had some atherosclerotic injury to that vessel. A patient with a CAC score of 300 or more has the same risk for an ASCVD event as someone with a prior history of an ASCVD event and thus classifies the patient high-risk primary prevention.[3] Preventing a first heart attack or stroke in these high-risk primary prevention patients can save significant money for managed care.

Some people confuse CAC with CT based coronary angiography which is a more expensive test. Coronary angiography not only looks for calcium deposits but also measures coronary stenosis and characterizes coronary plaque. A high CAC does not mean a patient has coronary stenosis. Any patient who has metabolic syndrome should also be classified as high-risk (Exhibit 3). These patients have a two-fold risk of developing cardiovascular disease over five to 10 years and a five-fold increase in risk of type 2 diabetes mellitus. At least 34 percent of the United States (U.S.) adult population has metabolic syndrome.

Lipid lowering is one of the most important interventions for reducing ASCVD risk. Statins are the backbone of therapy but are imperfect

Exhibit 3: Metabolic Syndrome Criteria

Three or more of the following criteria:

- Waist circumference ≥ 102 cm (Men) or ≥ 88 cm (Women)
- Triglycerides ≥ 150 mg/dL*
- HDL-C < 40 mg/dL (Men), < 50 mg/dL (Women)*
- SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg*
- Fasting glucose ≥ 100 mg/dL*

*or taking a medication to address this problem

Waist circumference cutoff for South Asian population is ≥ 90 cm for males and ≥ 80 cm for females

medications. The PCSK9 inhibitors and ezetimibe, a cholesterol absorption inhibitor, are two options for those with statin intolerance or who cannot reach LDL-C goals on statins alone. The PCSK9 inhibitors (evolocumab, alirocumab) and synthesis inhibitors (inclisiran) remove PCSK9 which degrades LDL-C receptors on hepatocytes. The LDL-C receptors are important for clearing LDL bound cholesterol from the circulation. Addition of the PCSK9 inhibitors to statin therapy reduces cardiovascular events more than statins alone.[4-6] These agents reduce LDL-C by 55 to 60 percent and stabilize vulnerable plaque.

The introduction of inclisiran has helped significantly improve patient adherence with lipid lowering therapy. This agent is given twice a year by injection. Inclisiran must be administered by a healthcare provider so it is under a "buy and bill" program where it is billed to Medicare Part B and not Part D. It is FDA-approved as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH). Exhibit 4 compares the dosing and pricing of these agents. Of note, evolocumab and alirocumab have wider FDA-approved indications including homozygous familial hypercholesterolemia (HoFH), pediatric HeFH, and for secondary prevention. Although these agents are expensive, the cost has been declining.

Enlicitide decanoate (MK-0616) is an investigational oral PCSK9 inhibitor in Phase III trials. In a Phase IIb, randomized, double-blind, placebo-controlled, multicenter trial of enlicitide, LDL-C was reduced up to 60.9 percent from baseline at eight weeks and the medication was well tolerated during eight weeks of treatment and an additional eight weeks of follow-up.[7]

Statin intolerance is real and can lead to nonadherence with therapy. It is a clinical syndrome that can manifest on a continuum.[8] Some patients experience partial intolerance while others are completely intolerant. Partial intolerance is defined as the ability to tolerate a lower dose of statin than is required to achieve the desired therapeutic objective. Complete intolerance is when the patient is unable to tolerate any statin dose or regimen. About 20 percent of patients prescribed a statin stop it due to adverse events, especially muscle symptoms. In one study of patients on high-dose statins, 10.5 percent reported myalgias.[9] Muscular pain prevented even moderate exertion during everyday activities in 38 percent of those with myalgias, while 4 percent were confined to bed or unable to work. Statin rechallenge can be done in patients with a history of statin-associated muscle symptoms to confirm true statin intolerance. In one trial of statin rechallenge, 43 percent of the subjects had recurrence of muscle symptoms and thus statin intolerance.[10] Patients with statin intolerance (high percentage are women) are undertreated and need more aggressive LDL lowering.[11]

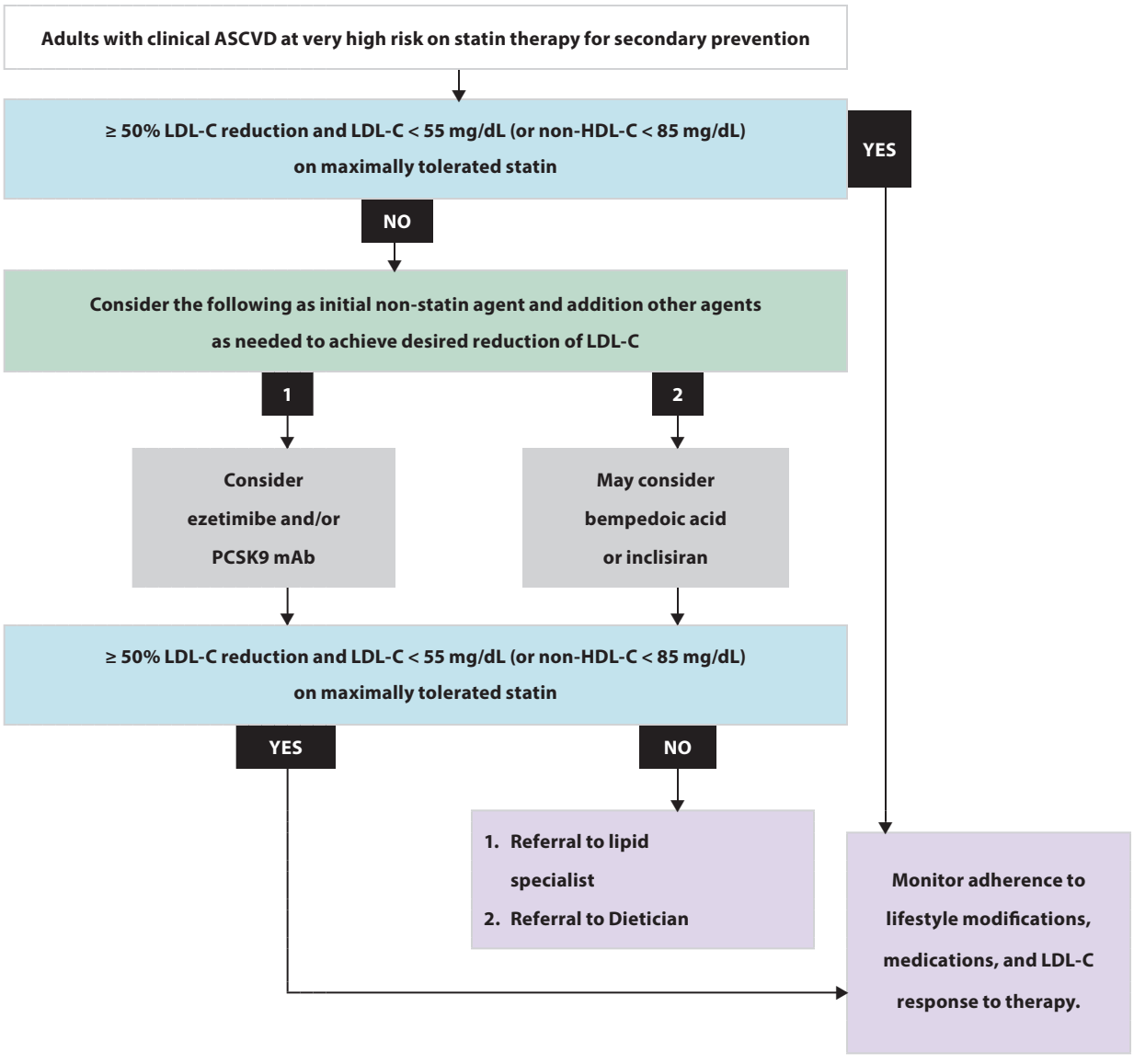
To try and avoid muscle-related adverse events, it is important to check thyroid function and vitamin D levels before starting patients on statins. The rate of muscle-related symptoms appears higher in those with abnormal thyroid function tests and vitamin D deficiencies. These issues should be corrected before starting statin therapy. Starting with low doses is also important.

To identify a tolerable statin regimen, it is recommended that clinicians consider using several different strategies (e.g., different statin, dose, and/or dosing frequency).[8] Non-statin therapy may be required for patients who cannot reach therapeutic objectives with lifestyle and maximal tolerated statin therapy. Non-statin therapies with outcomes data from randomized trials showing reduced cardiovascular events are favored. In high- and very-high-risk patients who are statin intolerant, clinicians should consider initiating non-statin therapy while additional attempts are made to identify a tolerable statin to limit the time of exposure to elevated levels of atherogenic lipoproteins.[7] Bempedoic acid which does not cause muscle-related adverse events is one of the options for statin-intolerance. There are data showing ASCVD benefits and bempedoic acid has an FDA-approved indication to reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with established ASCVD or at high risk for an event but without established ASCVD

Exhibit 4: PCSK9 Targeting Agents

	PCSK9 Inhibitors	Inclisiran
Dosing	Every two weeks or once a month	Three doses in first year followed by 2 doses in subsequent years
Cost (List Price)	$5,850 yearly	$9,750 in year one; $6,500 in subsequent years
Price to the Patient	Copays can range from $5 to $500 per month	For Medicare patients with part B coverage copay is 0

Exhibit 5: 2022 ACC Expert Consensus Decision Pathway for Secondary Prevention[13]



(high-risk primary prevention).[11] This agent is available as monotherapy or as a combination product with ezetimibe.

Real-world data shows that many patients are not achieving appropriate LDL-C goals. In a trial of patients with ASCVD who were receiving lipid lowering therapy, only 22.4 percent and 14.4 percent of the subjects with LDL-C values greater than 100 mg/dL or 70 to 99 mg/dL, respectively, had their lipid lowering therapy intensified.[12] Only 21 percent and 33.9 percent achieved LDL-C levels less than 70 mg/dL over the two-year study period. The minimum goal LDL-C for those with established ASCVD and high-risk features is 55 mg/dL (Exhibit 5).[13] As low as possible is the real goal with most lipid clinicians aiming for 25 to 30; LDL-C levels below 30 mg/dL will lead to plaque regression. The only way to achieve these LDL-C goals in secondary prevention for most patients is with combination therapy. This may be statin plus ezetimibe, statin plus PCSK9 modulator, PCSK9 modulator plus bempedoic acid, or even statin/ezetimibe/PCSK9 modulator.

Some clinicians and many patients worry about potential for cognitive issues with very low LDL-C levels. Importantly, the brain has its own circulation of cholesterol separate from the rest of the body and can synthesize cholesterol without relying on the peripheral pool of cholesterol. There are now many neurocognitive studies with the PCSK9 inhibitors where LDL-C levels of 20 mg/dL are achieved which show no negative impact on sophisticated neurocognitive tests. Additionally, the natural LDL-C level is approximately 20 mg/dL; this is the level at which humans are born.

Aggressive LDL-C lowering lowers but does not eliminate ASCVD risk. For example, in the Improve-It trial with ezetimibe in combination with statins, events still occurred in 32.7 percent of secondary prevention patients who achieved LDL-C of 53 mg/dL.[14] Residual risk is related to untreated risk factors such as increased triglycerides, elevated lipoprotein a [Lp(a)], non-HDL-C, and hyperglycemia. Many patients who have a heart attack or stroke despite controlled LDL-C have elevated Lp(a) that was not detected.

Lp(a) is more thrombotic than LDL-C.[15] Elevated Lp(a) is currently the strongest, single, inherited risk factor for early CAD and aortic stenosis.[16] Elevations in Lp(a) result in two- to four-fold higher risk of ASCVD events. Elevated Lp(a) occurs in 63 million people in the U.S. and occurs more commonly among African Americans and South Asians. The National Lipid Association guidelines recommend measuring Lp(a) levels at least once in every adult for risk stratification.[17] Levels less than 30 mg/dL are considered minimal risk, between 30 to 50 mg/dL are intermediate risk, and 50 mg/dL or more are elevated risk. Currently measurement rates are low, warranting improved screening strategies for cardiovascular disease prevention. Cascade screening of first-degree relatives of patients with elevated Lp(a) can identify additional individuals at risk who require intervention.

Patients with elevated Lp(a) should receive early, more-intensive risk factor management, including lifestyle modification and lipid-lowering drug therapy, primarily to reduce LDL-C levels because of the interaction between elevated LDL-C and Lp(a). Aspirin 100 mg/day should be considered based on a risk/benefit discussion. Aspirin has been shown to reduce ASCVD events in those with genetic markers for Lp(a) elevation.[18] In addition to lowering LDL-C, PCSK9 inhibitors lower Lp(a) 25 to 30 percent, inclisiran lowers it 25 percent, and lipid apheresis lowers it 35 to 40 percent.[19] These therapies can be added to statins. Lipid apheresis is FDA-approved for high-risk patients with familial hypercholesterolemia and documented coronary or peripheral artery disease whose Lp(a) level remains 60 mg/dL or more and LDL-C of 100 mg/dL or more on maximally tolerated lipid-lowering therapy. There are also additional agents in Phase III clinical trials which lower Lp(a) including one that would be given once a year.

Managed care policies may restrict some of the more advanced medicines to secondary prevention patients when high-risk primary patients could also benefit. Advanced tools for risk stratification are helping to advance treatment of high-risk patients by justifying coverage for these medications.

The future of lipid-lowering therapy is for agents given only once a year and gene editing to eliminate genetic risk. It is an exciting time for those in preventive cardiology.

Conclusion

Statins are the cornerstone of therapy in patients with hyperlipidemia and ezetimibe is a useful non-statin adjunct to statin therapy. PCSK9 modulators reduce LDL cholesterol and non-HDL, Lp9a), have a favorable safety profile, and cause beneficial plaque remodeling. Bempedoic acid and inclisiran are promising new agents. Achieving an LDL as low as possible is important for secondary prevention. Lp(a) is a marker of residual risk and needs to be measured and treated.

Pam R. Taub MD, FACC, is Founder and Director of Step Family Cardiac Rehabilitation and Wellness Center and is Director of Preventive Cardiology and a Professor of Medicine at the UC San Diego Health System in San Diego, CA.

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Evolving Considerations in the Management of Chronic Lymphocytic Leukemia Optimizing Clinical and Economic Outcomes with BTK Inhibitors

John N. Allan, MD

This journal article is supported by educational grants from Pharmacyclics LLC and Janssen Biotech, Inc.; AstraZeneca; Lilly

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Summary

Chronic lymphocytic leukemia is a B cell cancer primarily affecting older people. Oral targeted therapies that change B cell signaling are now first-line treatment. Fixed duration regimens combining two classes of targeted therapy are now an option.

Key Points

- Covalent BTK inhibitors have been shown to be safe and effective with continuous therapy.
- The selective covalent BTK inhibitors have similar efficacy to ibrutinib but have an advantage of fewer adverse events.
- A non-covalent BTK inhibitor is now available to achieve response and disease control in presence of certain resistance mutations.
- New fixed treatment duration approaches may mitigate overall cost without significant impairment to clinical outcomes.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a rare cancer composed of monomorphic small mature B cells that co-express CD5 and CD23.[1] It accounts for 1.2 percent of all cancers diagnosed in the United States annually.[2] In 2025, an estimated 23,690 new cases of CLL and 4,460 deaths from CLL will occur. The five-year relative survival rate with CLL is 89.3 percent which has significantly improved over time. In the era of novel targeted agents, the five-year survival rate will increase to 95 percent.

CLL is more common in adults with a median age of 70 years at diagnosis and is more common among men than women, particularly white men. Molecular tests predict which patients need to be treated immediately and those who can be observed. Patients with CLL today can live an almost normal life-span.

Despite progress in improving survival with CLL, real-world data suggest more work needs to be done. Data published in 2020 from the informCLL™ Registry showed that prognostic testing rates were poor despite being recommended by the available practice guidelines and approximately one-third of high-risk patients [del(17p) and TP53 mutations] received chemoimmunotherapy (CIT), which was not aligned with CLL treatment recommendations.[3] An updated report in 2023 found that one-third of patients with del(17p) or TP53 mutation did not receive National Comprehensive Cancer Network (NCCN)-recommended regimens.[4] Prognostic testing was again low with the majority of patients in the registry lacking mutation data and therefore may have received suboptimal treatment. Additional unmet needs have been shown in patients with CLL refractory to the most effective treatments [Bruton's tyrosine kinase (BTK) inhibitors and venetoclax]. In one trial, the effective duration of therapy after these agents fail is only 5.5 months,[5] and as such better therapies for refractory CLL are needed.

B cell signaling is crucial for normal B-cell development and adaptive immunity. In CLL, malignant B cells display many features of normal

Exhibit 1: NCCN Recommended First-Line Regimens[9]

Type	Preferred First-Line
CLL with del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab Venetoclax + obinutuzumab Venetoclax + acalabrutinib ± obinutuzumab Zanubrutinib
CLL without del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab (Category 1) Venetoclax + obinutuzumab (Category 1) Venetoclax + acalabrutinib ± obinutuzumab (Category 1) Zanubrutinib (Category 1)

mature B lymphocytes, including the expression of functional B-cell receptors.[6] Thus various targeted treatments have been developed that alter this signaling. Targeted treatment options include oral BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib), an oral B cell lymphoma 2 inhibitor (venetoclax), and an injectable anti-CD20 monoclonal antibody (obinutuzumab).

Although initially used for relapsed/refractory disease, BTK inhibitors have moved to first-line therapy and transformed treatment of CLL by improving survival compared to CIT. This class of agents has also proved to be effective in high-risk CLL. Ibrutinib, the first BTK inhibitor to market, improves overall survival (OS) over chemotherapy and CIT in both older and younger patients; long-term OS in those treated with ibrutinib first-line matches survival for age matched cohorts without CLL.[7,8] Essentially, the BTK inhibitors have turned CLL into a chronic disease where this cancer is not the cause of a patient's death.

The NCCN Guidelines recommend acalabrutinib and zanubrutinib, more selective second generation agents, over ibrutinib for patients newly starting on BTK inhibitors (Exhibit 1).[9] Ibrutinib was moved from preferred regimens to other recommended regimens in the guidelines based on its toxicity profile compared to the other two BTK inhibitors from two comparison trials (Elevate-RR, Alpine).[10,11] In patients who are already taking ibrutinib with no major adverse events, ibrutinib can be continued until disease progression.

Acalabrutinib was the second BTK inhibitor approved and is dosed twice daily to maintain BTK inhibition. A first-line trial of acalabrutinib with or without obinutuzumab compared it to chlorambucil-obinutuzumab (Elevate-TN). At six years of median follow-up, median OS was not yet achieved for all treatment arms in the trial, with significantly longer OS for acalabrutinib-obinutuzumab versus chlorambucil-obinutuzumab (hazard ratio [HR], 0.62, p = .0349).[12] Estimated 72-month OS rates were 83.9 percent, 75.5 percent, and 74.7 percent for acalabrutinib-obinutuzumab, acalabrutinib, and chlorambucil-obinutuzumab, respectively. There is still controversy about which patients benefit the most from the addition of obinutuzumab to acalabrutinib; there are additional cost and adverse events including serious infections which occur when obinutuzumab is used and it requires injection.

Zanubrutinib was FDA approved for CLL in April 2023. Unique to zanubrutinib, it can be dosed once or twice daily but still maintains BTK inhibition throughout the dosing interval even when given once daily. In the first-line trial which compared zanubrutinib to bendamustine/rituximab (BR), at a median follow-up of 61.2 months, median progression-free survival (PFS) was not reached in zanubrutinib-treated patients; median PFS was 44.1 months in BR-treated patients (HR, 0.29; one-sided p = .0001).[13] PFS benefit was seen in those with and without mutated immunoglobulin heavy-chain variable region (IGHV) genes. Median OS was not reached in either treatment arm; estimated 60-month OS rates were 85.8 percent and 85.0 percent in zanubrutinib- and BR-treated patients, respectively.

The newest recommended regimen for first-line treatment of CLL is the combination of fixed duration BTK inhibitors and venetoclax. Although ibrutinib has been studied in combination with

venetoclax, this regimen was not approved by the FDA nor is it a preferred regimen the NCCN Guidelines.[9,14] Fixed duration acalabrutinib-venetoclax (with or without obinutuzumab) was compared to CIT in a first-line trial in those with CLL who did not have a 17p deletion or TP53 mutation. Patients were randomly assigned, in a 1:1:1 ratio, to receive acalabrutinib-venetoclax (acalabrutinib, cycles 1 to 14; venetoclax, cycles 3 to 14), acalabrutinib-venetoclax-obinutuzumab (as above, plus obinutuzumab, cycles 2 to 7), or CIT with the investigator's choice of fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab (cycles 1 to 6).

Estimated 36-month PFS at a median follow-up of 40.8 months was 76.5 percent with acalabrutinib-venetoclax, 83.1 percent with acalabrutinib-venetoclax-obinutuzumab, and 66.5 percent with CIT (HR for disease progression or death with acalabrutinib-venetoclax versus CIT, 0.65, $p = 0.004$; for the comparison of acalabrutinib-venetoclax-obinutuzumab with chemoimmunotherapy, $p < 0.001$).[15] Estimated 36-month OS was 94.1 percent with acalabrutinib-venetoclax, 87.7 percent with acalabrutinib-venetoclax-obinutuzumab, and 85.9 percent with CIT. Neutropenia, the most common adverse event of clinical interest of Grade 3 or higher, was reported in 32.3 percent, 46.1 percent, and 43.2 percent in the three groups, respectively.

First-line treatment of CLL can be either BTK inhibitors (with or without anti-CD20 antibodies) until disease progression or fixed duration venetoclax plus obinutuzumab or fixed duration venetoclax/acalabrutinib with or without obinutuzumab. A key goal with fixed-duration therapy is achievement of undetectable measurable residual disease (MRD), which is associated with prolonged PFS and, in some studies, longer OS. Patients who enter deep remission often have lengthy treatment-free intervals without ongoing toxicities and cost. Intermittent time-limited combination therapy may win over continuous BTK inhibitor monotherapy for many patients. Clinicians do not believe there is any detriment to fixed duration compared to continuous BTK inhibitors but there are no published trials which directly compare these approaches. Continuous BTK inhibitor monotherapy will remain an option for certain patients, such as older individuals seeking simplicity. In high-risk disease, B cell clones recover faster when treatment is stopped compared to low-risk disease, thus continuous BTK inhibitors may be the best choice for high-risk disease but again head-to-head data are not yet available. Beyond del(17p)/TP53 mutation, risk factors for shorter disease response include bulky disease and unmutated IGHV. One approach being investigated for high-risk patients is double or triple therapy until MRD is achieved and then BTK inhibitor maintenance is continued until disease progression. Numerous combination therapy trials are ongoing.

B cell clones in CLL change over the course of the disease based on time, treatment pressures, and underlying biology resulting in treatment resistance mutations.[16] A sizable portion of patients treated with a BTK inhibitor eventually experience treatment failure due to the development of resistance. Ibrutinib, zanubrutinib and acalabrutinib are all irreversible, covalent BTK inhibitors which bind to the C481 site on BTK; 50 percent to 60 percent of resistance mutations seen in BTK inhibitor treated patients are with C481 and activating mutations downstream of BTK.[17] Reversible, non-covalent BTK inhibitors are the next evolution of CLL therapy. These exert inhibition of BTK by different mechanisms from covalent BTK inhibitors. Because they do not act by binding to the C481 site on BTK, they are an option for patients who have developed acquired resistance due to BTK C481 mutations. Pirtobrutinib, the first reversible, non-covalent BTK inhibitor to be approved by the FDA, blocks the ATP binding site of BTK.

Pirtobrutinib was approved for the treatment of adult patients with CLL in December of 2023. The NCCN Guidelines recommend it for second-line or third-line therapy in cases of resistance or intolerance to prior covalent BTK inhibitor therapy.[9] Pirtobrutinib is a highly selective inhibitor which also helps lower the rate of adverse events. In a trial evaluating pirtobrutinib in 317 patients with CLL, including 247 who had previously received a BTK inhibitor, the median number of previous lines of therapy was three (range, 1 to 11), and 40.5 percent had also received venetoclax.[18] The percentage of patients with an overall response to pirtobrutinib was 73.3 percent and the median PFS was 19.6 months. The availability of pirtobrutinib has been a significant benefit for covalent BTK inhibitor refractory patients. The most common adverse events were infections (71.0%), bleeding (42.6%), and neutropenia (32.5%). At a median duration of treatment of 16.5 months (range, 0.2 to 39.9), some concerning adverse events that are typically associated with BTK inhibitors occurred infrequently, including hypertension (14.2% of patients), atrial fibrillation or flutter (3.8%), and major hemorrhage (2.2%). Only nine of 317 patients (2.8%) discontinued pirtobrutinib owing to a treatment-related adverse event. Overall, pirtobrutinib treatment can achieve response and disease control in presence of common C481 mutations.

Exhibit 2: Ten-year Estimates of Cost Based on Initial Therapy and Risk of CLL[22]

Estimated ten-year budget for 2020 cohort of patients with newly diagnosed CLL				
	Low Risk	**Intermediate Risk**	**High Risk**	**Total**
Numbers	6,312	7,574	7,154	21,040
Proportion of patients with CLL estimated to need treatment in the next 10 years within each category	0.18	0.57	0.8	
Cost ($) of first-line treatment when initiated				
Venetoclax-plus-obinutuzumab	269,461,597	1,070,560,441	1,957,581,686	3,297,603,724
Rituximab-plus-chlorambucil	274,001,503	1,088,597,311	1,990,563,146	3,353,161,960
Obinutuzumab-plus-chlorambucil	293,153,326	1,164,686,756	2,129,697,098	3,587,537,180
Ofatumumab-plus-chlorambucil	300,698,096	1,194,661,835	2,184,508,264	3,679,868,195
Bendamustine-plus-rituximab	350,076,339	1,390,839,671	2,543,230,783	4,284,146,793
Ibrutinib	548,727,951	2,180,074,799	3,986,392,863	6,715,195,613
Acalabrutinib	564,271,558	2,241,828,943	4,099,313,887	6,905,414,388
Ibrutinib-plus-obinutuzumab	568,104,512	2,257,057,120	4,127,159,488	6,952,321,120
Ibrutinib-plus-rituximab	573,999,165	2,280,476,348	4,169,982,902	7,024,458,415
Acalabrutinib-plus-obinutuzumab	622,773,156	2,474,253,515	4,524,315,660	7,621,342,331

Unfortunately, novel mutations are now being identified as mechanisms of pirtobrutinib resistance.[19] Novel BTK degraders demonstrate preclinical and potential clinical activity that can potentially address these emerging mechanisms of resistance. Four agents which are under investigation in B-cell malignancies in early clinical trials are BGB-16673, NX-2127, NX-5948, and AC676.[20]

Treatment of CLL carries a significant financial burden with the main drivers of cost being infusions, outpatient visits, hospitalizations, adverse event management, and medication costs. Adoption of targeted agents has dramatically increased the cost of CLL management due to high medication prices, prolonged treatment duration, and an increased number of patients living longer because of medication efficacy.[21] Although CLL is an incurable disease, patients can live a long time with oral therapy. For example, with BTK inhibitors, a patient may be on this therapy for six to eight years before developing resistance and disease progression. With the wholesale acquisition price of the BTK inhibitors ranging from $14,000 to $20,000 monthly, the estimated 10-year costs for a cohort of patients with CLL treated with various regimens is shown in Exhibit 2.[22] Fixed duration therapies such as venetoclax or CIT compared to continuous BTK inhibitor therapy have similar costs in year one of treatment but decline in years two and three whereas the cost of the BTK inhibitor continues.[23] While both venetoclax and acalabrutinib are expensive medications, fixed-duration regimens with these two may offer cost advantages, particularly in the long-term but no cost-effectiveness studies have been published.

Conclusion

The use of BTK inhibitors has changed the management of CLL. The covalent BTK inhibitors have been shown to be safe and effective in long-term data. There is similar efficacy across agents but improved class and adverse event profiles favor the selective agents. Fixed duration of therapy approaches are attractive for cost effectiveness, toxicity mitigation, and durable efficacy. Resistance mechanisms are clear for a majority of BTK inhibitor progressors but a non-covalent BTK inhibitor is now available to achieve response and disease control in presence of common

C481 mutations. Cost for treating CLL are significant and fixed duration approaches can mitigate overall cost without significant impairment to clinical outcomes. Fixed duration venetoclax/acalabrutinib use will increase in the near future.

John N. Allan, MD, is an Assistant Professor of Medicine in the Division Hematology and Medical Oncology at Weill Cornell Medicine in New York, NY.

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Mastering Beta-Thalassemia Therapeutic Strategies: Applying New Evidence into the Treatment Paradigm

Hanny Al-Samkari, MD

This journal article is supported by an educational grant from Agios Pharmaceuticals

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Summary

Thalassemia is a genetic disorder where the body doesn't produce enough of either the alpha or beta globin chains of the hemoglobin molecule. This leads to reduced hemoglobin production and can result in anemia requiring blood transfusions. Newer therapies including an erythroid maturation agent and gene therapy/editing are changing the treatment of beta-thalassemia.

Key Points

- Luspatercept is useful in a subset of transfusion dependent patients.
- Gene therapy and gene editing approaches appear to be a functional cure for transfusion-dependent thalassemia but have significant issues.
- Mitapivat, and potentially other oral PK activators, are highly promising in both transfusion and non-transfusion dependent thalassemia.

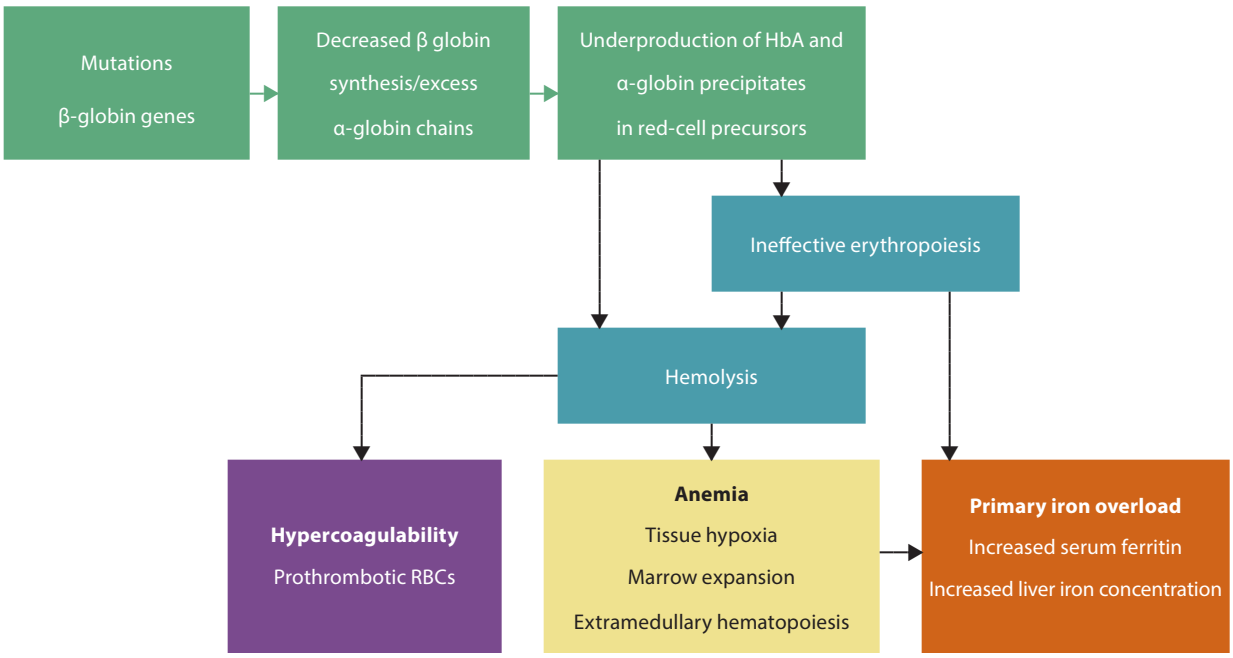
THALASSEMIAS ARE INHERITED HEMOglobin disorders with reduced or absent alpha or beta chains of hemoglobin.[1] Thalassemia is more prevalent in populations from the Mediterranean region, Southeast Asia, the Middle East, and the Indian subcontinent.[2] Previously, most cases of beta-thalassemia in the United States were seen in those of Greek or Italian descent. As a result of immigration trends in the last 50 years, there are more cases of both types in populations with ethnic backgrounds from a variety of different countries.

Gene clusters on chromosomes 16 and 11 encode the alpha (α) and beta (β) globin chains, respectively. In healthy red blood cells (RBCs), the α- and β-globin chains are balanced in a one-to-one ratio. In thalassemic RBCs, reduced or absent synthesis leads to a relative excess of the α-globin (beta-thalassemia) or β-globin and gamma (γ)-globin (alpha-thalassemia) chains. In beta-thalassemia, the globin chain imbalance leads to ineffective erythropoiesis and hemolytic anemia. Ineffective erythropoiesis leads to bone marrow expansion and extramedullary hematopoiesis.

In addition to hemolytic anemia and its consequences, beta-thalassemia results in hypercoagulability and iron overload (Exhibit 1).[1] It is a multi-organ disease and is classified as minor/trait, intermedia, or major and as transfusion dependent or non-transfusion dependent (Exhibit 2).[3] Those with two mutated alleles will be transfusion dependent. Morbidity and mortality in thalassemia is related to the degree of anemia; even a 1 gm/dL difference has an impact on developing complications.[4] Both morbidity and mortality have improved significantly over the years. With transfusion and iron chelation, life expectancy for those with major thalassemia is middle to late adulthood. Seventy percent of deaths from thalassemia are due to cardiovascular disease because chronic anemia and iron overload can lead to cardiomyopathy.

Primary treatments of beta-thalassemia include intermittent or regular RBC transfusions, iron chelation to prevent iron overload, and luspatercept and gene therapy, for selected patients. Splenectomy was more commonly used in the past but is now rarely used. Exhibit 3 outlines the options for

Exhibit 1: Consequences of Beta-Thalassemia[1]



each classification.

The treatment of beta-thalassemia causes a significant patient and health system burden. The need for RBC transfusion every two to three weeks is a burden for patients and the healthcare system. Iron chelation, particularly subcutaneous infusions, is difficult for patients to tolerate and compliance with the prescribed regimen is important to avoid the complications of iron overload. Due to the disease process, iron absorption in the gut is enhanced and patients can develop iron overload even if they are not transfusion dependent.

Luspatercept, an erythroid maturation agent FDA approved in 2019, is indicated for the treatment of anemia in adult patients with beta-thalassemia who require regular RBC transfusions. This agent is a recombinant fusion protein that binds several endogenous transforming growth factor beta (TGF-β) superfamily ligands, thereby diminishing Smad2/3 signaling. It is given subcutaneously every three weeks. In the Phase III placebo-controlled trial used for FDA approval, luspatercept or a placebo was administered for a median of approximately 64 weeks in both groups. The percentage of patients who had a reduction in the transfusion burden of at least 33 percent from baseline during weeks 13 through 24 plus a reduction of at least two red cell units over this 12-week interval was significantly greater in the luspatercept group than in the placebo group (21.4% versus 4.5%, $p < 0.001$).[5] During any 12-week interval, the percentage of patients who had a reduction in transfusion burden of at least 33 percent was greater in the luspatercept group than in the placebo group (70.5% versus 29.5%), as was the percentage of those who had a reduction of at least 50 percent (40.2% versus 6.3%). The least-squares mean difference between the groups in serum ferritin levels at week 48 was -348 µg per liter (95% confidence interval, -517 to -179) in favor of luspatercept. Adverse events of transient bone pain, arthralgia, dizziness, hypertension, and hyperuricemia were more common with luspatercept than placebo. The adverse events were most common in the first three months and declined after that point. Overall, the percentage of patients with transfusion-dependent beta-thalassemia who had a reduction in transfusion burden was significantly greater in the luspatercept group than in the placebo group, and few adverse events led to the discontinuation of treatment.

Most clinicians caring for beta-thalassemia patients will try luspatercept in most patients to reduce transfusion burden. It is most optimal in transfusion dependent beta-thalassemia patients receiving transfusion every three weeks or less, those with red cell alloantibodies or at substantial risk of developing them, and those who struggle with iron chelation therapy. If there is no significant improvement in treatment burden

Exhibit 2: Classification of Beta-Thalassemia

Classification	Laboratory Results	Symptoms and Complications
Trait/Minor (1 mutated allele)	Normal or slightly low Hb Low MCV and MCH	Asymptomatic or mild anemia (Hb >10) Can act as a genetic modifier of other inherited disorders (e.g., sickle cell)
Intermedia (1-2 mutated alleles) Can be Transfusion or non-transfusion dependent (TDT or NTDT)	Low Hb and MCV	Moderate-to-severe anemia (Hb 6-10) Hepatosplenomegaly Acute hemolytic events Leg ulcers Jaundice Cholecystitis (with or without gallstones) Folic acid deficiency Iron overload Growth delays/endocrinopathies (younger patients) Osteoporosis Thrombosis
Major (2 mutated alleles) **Transfusion dependent (TDT)**	Very low Hb, MCV, and MCH	Very severe anemia (Hb 3-6) Severe hepatosplenomegaly Skeletal deformities/osteoporosis Iron overload and its complications Endocrinopathies/growth failure Leg ulcers Biliary disease Thrombosis Life expectancy months to a few years without transfusion With transfusion and without iron chelation, life expectancy is teens to twenties With transfusion and chelation, life expectancy into middle to late adulthood

Hb = hemoglobin; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin

after nine weeks at the maximum dose, this agent should be discontinued. Luspatercept should be avoided in splenectomized patients given increased thromboembolic risk (unless the patient is receiving pharmacologic thromboprophylaxis), children, and women who are pregnant or breastfeeding. This agent works to reduce treatment burden in about 25 percent of patients.

Two one-time gene therapies are FDA approved for beta-thalassemia. Betibeglogene autotemcel (Beti-Cel) was FDA approved in 2022 for the treatment of adult and pediatric patients with transfusion-dependent beta-thalassemia and uses a lentiviral vector encoding β–like globin gene. Exagamglogene autotemcel (Exa-Cel) is indicated for the treatment of patients aged 12 years and older with transfusion-dependent beta-thalassemia and uses CRISPER gene editing to activate fetal hemoglobin production. It was FDA approved in 2023 and is also approved for sickle cell disease with recurrent vaso-occlusive crises. Both are highly effective functional cures (e.g., with Exa-Cel 92.9% of patients were transfusion

Exhibit 3: Standard of Care in Beta-Thalassemia Management

Classification	Therapeutic Approach	Considerations and Challenges
Trait/Minor	Not generally indicated	• Risk of affected offspring • Indication for prenatal screening • Undiagnosed patients with anemia due to nutritional deficiencies (Vitamin B12, folate, or iron) at risk of excess iron supplementation
Non-transfusion dependent	Intermittent RBC transfusions Iron chelation therapy Possible splenectomy Clinical trials	• Risk of affected offspring • Indication for prenatal screening • Development of primary iron overload may begin in young adulthood or earlier • Increased morbidity and mortality due to uncontrolled anemia in patients who do not receive regular transfusions • Increased risk of sepsis and venous thrombosis with splenectomy
Transfusion dependent	Regular RBC transfusions Iron chelation therapy Luspatercept Gene therapy Clinical trials	• Risk of affected offspring • Indication for prenatal screening • Development of primary iron overload in first decade of life • Lifelong chelation requirements and challenges • Increased risk of venous thrombosis

free at 12 months).[6] Unfortunately, there are major barriers to gene therapy because myeloablative conditioning with its acute infectious risks, chronic cancer and sterility risks is required and these gene therapies cost $2.2 to $3.1 million. Better, less toxic conditioning therapy is needed for more patients to even consider gene therapy.

Pyruvate kinase activators (mitapivat, etavopivat, tebapivat) are under investigation for beta-thalassemia. These activators aim to enhance RBC survival and reduce hemolysis by increasing ATP production through glycolysis, a process crucial for RBC energy and function. Mitapivat is already FDA approved for pyruvate kinase (PK) deficiency which leads to hemolytic anemia. This is a well-tolerated oral agent which is taken twice daily. About 40 percent of patients with PK deficiency see a significant increase in hemoglobin and 22 percent are transfusion free.[7] Mitapivat also improved health-related quality of life and iron overload in PK deficiency.

The mechanism of action of mitapivat can improve many of the underlying pathologic issues with thalassemia. Mitapivat has been studied in a Phase II trial in non-transfusion-dependent alpha- and beta-thalassemia (75%).[8] Included subjects had a baseline hemoglobin concentration of 10.0 g/dL or lower. During a 24-week core period, mitapivat was administered orally at 50 mg twice daily for the first six weeks followed by an escalation to 100 mg twice daily for 18 weeks thereafter. Seventy-three percent of the 15 included subjects with beta-thalassemia had a hemoglobin response (increase of 1.3 gm/dL). Improvements in hemoglobin, hemolysis markers, and bone mineral density were sustained during the study and in the long-term extension (72 weeks).[8,9] Data from a Phase III trial has been presented at a professional meeting but not yet published.[10] In the Phase III trial, mitapivat demonstrated statistically significant improvements compared to placebo for hemoglobin response (42.3% versus 1.6%; 2-sided $p < 0.0001$), and for changes from baseline in weeks 12 to 24 average hemoglobin (0.96 g/dL; 2-sided $p < 0.0001$) and weeks 12 to 24 average FACIT-Fatigue score (3.40; 2-sided $p < 0.0026$). Improvements in hemoglobin and hemolysis markers were sustained during the study. The most common adverse events (10% or more of patients) with mitapivat were headache, insomnia, nausea, and upper respiratory

tract infection. This agent was submitted to the FDA for the non-transfusion dependent thalassemia indication in January 2025 and a decision is expected by Fall 2025. Ongoing study is evaluating mitapivat in those who are transfusion dependent. Etavopivat and tebapivat are also under investigation for thalassemia and sickle cell disease.

Conclusion

Beta-thalassemia is a morbid and common red cell disorder worldwide but the era of disease-modifying medications has arrived. Luspatercept is useful in a subset of transfusion dependent patients. Gene therapy and gene editing approaches appear to be a functional cure for TDT but are expensive and require the risks of myeloablative conditioning. Mitapivat, and potentially other oral PK activators, are highly promising in both TDT and NTDT.

Hanny Al-Samkari, MD, is the Peggy S. Blitz Endowed Chair in Hematology/Oncology, Classical Hematologist and Clinical Investigator, Co-Director of the HHT Center of Excellence, and an Associate Professor of Medicine at Harvard Medical School and Massachusetts General Hospital in Boston, MA.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of Multiple Myeloma: Managed Care Insights on the Role of BCMA-Directed Therapy

Ravi Vij, MD, MBA

This journal article is supported by educational grants from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; GSK

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Summary

Treatment of multiple myeloma continues to evolve. New therapies targeting BCMA are making a difference in progression-free survival in second and later lines of therapy. There are questions to resolve about how best to sequence BCMA-targeted therapies with other already well documented therapies.

Key Points

- For second- to forth-line therapy, there are a multitude of three drug combinations and CAR-T cells.
- For fifth-line and later, CAR-T cells and bispecifics are improving outcomes.
- A BCMA-targeting antibody drug conjugate may also return to the market.

MULTIPLE MYELOMA (MM) IS AN uncommon cancer of plasma cells and is the second most common blood cancer in the United States (U.S.). The American Cancer Society's estimates in the U.S. for 2025 there will be 36,110 new cases diagnosed and 12,030 deaths expected to occur.[1] The median age at diagnosis is 69 years.

Initial treatment of MM is stem cell transplant and multidrug combinations of proteosome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies. Most patients with MM will relapse at some point after initial treatment. The regimen chosen will depend on the duration of response from prior treatment, genetic profile of the MM cells, previous treatments and their toxicity in the patient, and various patient factors (pre-existing toxicity, age, concomitant conditions, general health, preferences). There are numerous options for multiple lines of therapy.

In the past, patients with MM refractory to standard treatments had a poor prognosis with overall survival (OS) measured in months.[2,3] Treatment of this group has changed dramatically with the approval of B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR-T) cells (ciltacabtagene autoleucel and idecabtagene vicleucel), bispecifics (elranatamab, teclistamab), and antibody-drug conjugates (belantamab mafodotin). BCMA is found on the surface of MM cells and plays a role in the survival and growth of these cancer cells. With these new agents, survival is now marked in years.

Teclistamab and elranatamab are bispecific BCMA-directed CD3 T cell engagers which bind to BCMA on plasma cells, plasmablasts, and MM cells and CD3 on T cells leading to cytolysis of the BCMA-expressing cells. These two agents are FDA-approved for relapsed or refractory multiple myeloma

after at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. In the long-term follow-up of the Phase I/II trial, with teclistamab used for FDA approval, at a median of 22 months follow-up, 43 percent achieved a complete response or better.[4] The median duration of response was 24 months. The median progression-free survival (PFS) was 12.5 months and median OS was 21.9 months. Compare this to previously available fifth-line response of two to three months of PFS. After a ramp up in dosing, this agent is given subcutaneously weekly for the first six months and then switched to every two to four weeks. Minimal residual disease (MRD) negativity is achieved rapidly with this agent.

In the ongoing Phase II MagnetisMM-3 trial, patients with relapsed or refractory multiple myeloma received subcutaneous elranatamab once weekly after two step-up priming doses.[5] After six cycles, persistent responders switched to biweekly dosing. Results from cohort A, which enrolled patients without prior BCMA-directed therapy (n = 123) have been published. Data from cohort B, which included those with prior BCMA-directed therapy have not been reported. There was a 61 percent objective response rate (ORR) and 35.0 percent had a complete response or better. Fifty responders switched to biweekly dosing, and 80 percent improved or maintained their response for six months or more. With a median follow-up of 14.7 months, median duration of response, PFS and OS have not been reached. Fifteen-month rates were 71.5 percent, 50.9 percent, and 56.7 percent, respectively.

Ciltacabtagene autoleucel (cilta-cel), approved in 2022, and idecabtagene vicleucel (ide-cel), approved in 2021, are BCMA-directed genetically modified autologous T cell immunotherapy. These agents were first studied and approved in heavily pretreated patients (fifth-line or later) but are now approved for use as early as second-line. In the Phase III KarMMa-3 trial, patients with class-exposed (TCE) relapsed and refractory multiple myeloma (R/RMM) and two to four prior regimens were randomized on a two to one ratio to ide-cel or standard regimens.[6] At final PFS analysis (median follow-up, 30.9 months), ide-cel improved median PFS versus standard regimens (13.8 versus 4.4 months; hazard ratio [HR], 0.49; 95 percent confidence interval [CI], 0.38 to 0.63). PFS benefit with ide-cel versus standard regimens (SRs) was observed regardless of number of prior lines of therapy, with greatest benefit after two prior lines (16.2 versus 4.8 months, respectively). ORR benefit was maintained with ide-cel versus SRs (71% versus 42%; complete response, 44% versus 5%). Patient-centric design allowed crossover from SRs (56%) to ide-cel upon progressive disease, confounding overall survival (OS) interpretation. At interim analysis of OS, median was 41.4 (95% CI, 30.9 to not reached [NR]) versus 37.9 (95% CI, 23.4 to NR) months with ide-cel and SRs, respectively (HR, 1.01; 95% CI, 0.73 to 1.40); median OS in both arms was longer than historical data (9 to 22 months). Two prespecified analyses adjusting for crossover showed OS favoring ide-cel (41.4 versus 23.4 months). Importantly, the patients in this trial were daratumumab and lenalidomide refractory which are not typical in second-line patients who have more sensitivity to standard regimens. Ide-cel also improved patient-reported outcomes versus SRs.

Cilta-cel was compared to the physician's choice of effective standard care in a Phase III, randomized, open-label trial in patients with lenalidomide-refractory MM who had received one to three previous lines of treatment. At a median follow-up of 15.9 months (range, 0.1 to 27.3), the median PFS was not reached in the cilta-cel group and was 11.8 months in the standard-care group (hazard ratio, 0.26; $p < 0.001$).[7] Progression-free survival at 12 months was 75.9 percent in the cilta-cel group and 48.6 percent in the standard-care group. More patients in the cilta-cel group than in the standard-care group had an overall response (84.6% versus 67.3%), a complete response or better (73.1% versus 21.8%), and an absence of minimal residual disease (60.6% versus 15.6%). Death from any cause was reported in 39 patients and 46 patients, respectively (HR, 0.78; 95% CI, 0.5 to 1.2). Most patients reported Grade 3 or 4 adverse events during treatment. Among the 176 patients who received cilta-cel in the as-treated population, 134 (76.1%) had cytokine release syndrome (Grade 3 or 4, 1.1%; no Grade 5), eight (4.5%) had immune effector cell-associated neurotoxicity syndrome (all Grade 1 or 2), one had movement and neurocognitive symptoms (Grade 1), 16 (9.1%) had cranial nerve palsy (Grade 2, 8.0%; Grade 3, 1.1%), and five (2.8%) had CAR-T-related peripheral neuropathy (Grade 1 or 2, 2.3%; Grade 3, 0.6%). In updated results from the this trial presented at the 2024 International Myeloma Society Annual Meeting, cilta-cel reduced the risk of death by 45 percent versus standard of care in the studied patient population.[8] At a median follow-up of 33.6 months, the 30-month OS rate with cilta-cel was 76.4 percent compared with 63.8 percent with standard of care (HR, 0.55; $p = .0009$). The earlier the CAR-T cell therapies are given, the better the chance of a sustained response.

Belantamab mafodotin is an antibody drug conjugate (ADC) consisting of an anti-BCMA-

Exhibit 1: Management of CRS With CAR T-Cell Therapy and Bispecific Antibody Therapy[12-14]

■ **Rule out other etiologies:** infection, heart failure, pulmonary edema, possibly treat for infection

Grade	CAR T-Cell Therapy	Bispecific Antibody Therapy
	Supportive Care + Intervention	Supportive Care + Intervention
1	± Tocilizumab*	Withhold until CRS resolution and administer pretreatment medications prior to next dose
2	Tocilizumab ± corticosteroid	Grade 1 interventions + 48-hour hospitalization following next dose according to institutional and manufacturer guidelines
3	Tocilizumab ± corticosteroid	*First Grade 3 occurrence with duration ≤ 48 hours:* Grade 2 interventions + ICU/critical care as needed *Recurrent Grade 3 or Grade 3 with duration > 48 hours:* Grade 4 interventions
4	Tocilizumab + high-dose corticosteroid ICU/critical care	Permanently discontinue; provide ICU/critical care as needed

*IL-6 antibody, for older patients with comorbidities

directed antibody conjugated to a microtubule inhibitor, monomethyl auristatin F which kills MM cells once it is bound to BCMA and enters the cell. It was the first BCMA-targeting agent and was initially approved by the FDA in August 2020 for the treatment of adults with relapsed or refractory MM who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication was approved under accelerated approval based on response rate. In November 2022, the DREAMM-3 Phase III confirmatory trial in relapsed/refractory MM with two prior therapies failed to show better PFS than standard of care, thus failing to meet the requirements of the FDA accelerated approval regulations.[9] As such, the FDA requested that GSK withdraw the U.S. marketing authorization. Two trials have since been published or presented at professional meetings showing PFS benefit of combining belantamab mafodotin with pomalidomide and dexamethasone or bortezomib and dexamethasone in those with one prior line of therapy.[10,11] It is expected that belantamab mafodotin will be re-approved by the FDA based on these two trials. The main toxicity of this ADC is corneal toxicity.

The CAR-T and bispecific agents for MM can cause significant adverse events and have black box warnings about cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Both CRS and ICANS can be life-threatening or fatal. CRS is characterized by fever, hypoxia, and hypotension; primarily Grades 1 and 2 occur with the BCMA-targeting agents. Exhibit 1 shows the management of CRS based on grade.[12-14] Prophylactic tocilizumab is being used more frequently to reduce the incidence of CRS. Exhibit 2 shows the management of neurologic toxicity and ICANS.[12-14] The CAR-T therapies also have additional black box warnings including potentially fatal hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), prolonged and/or recurrent cytopenias, and secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies. These agents are only available through restricted programs under Risk Evaluation and Mitigation Strategies.

The bispecifics are given on a step-up dosing basis to minimize CRS and ICANS and other adverse events. Most clinicians give the bispecifics in the hospital during the step-up dosing phase to monitor CRS and ICANS; this results in a four-day stay with elranatamab and seven-day with teclistamab. The Medicare reimbursement for this hospital stay typically leads to hospitals losing money. Large

Exhibit 2: Management of Neurologic Toxicity and ICANS With CAR T-Cell and Bispecific Antibody Therapy[12-14]

Grade	CAR T-Cell Therapy	Bispecific Antibody Therapy	
	Neurotoxicity	Neurologic Toxicity Excluding ICANS	ICANS
1	Supportive care (± steroids)	Withhold until symptoms resolve or stabilize	Withhold until resolution
2	Steroids (dexamethasone or methylprednisolone)	Withhold until symptoms improve to Grade ≤1	Withhold until resolution + steroids + 48-hr hospitalization with next dose
3	Steroids (dexamethasone)	*First occurrence:* Grade 2 actions + supportive therapy *Recurrence:* Grade 4 actions	*First occurrence:* Grade 2 actions + supportive therapy + steroids *Recurrence:* Grade 4 actions + steroids
4	High-dose steroids (methylprednisolone) ICU/critical care	Permanently discontinue + steroids (dexamethasone or methylprednisolone) ICU/critical care	

Add anticonvulsants (levetiracetam, benzodiazepines)
Low threshold for inpatient management (if outpatient at time of onset)
Multidisciplinary team approach

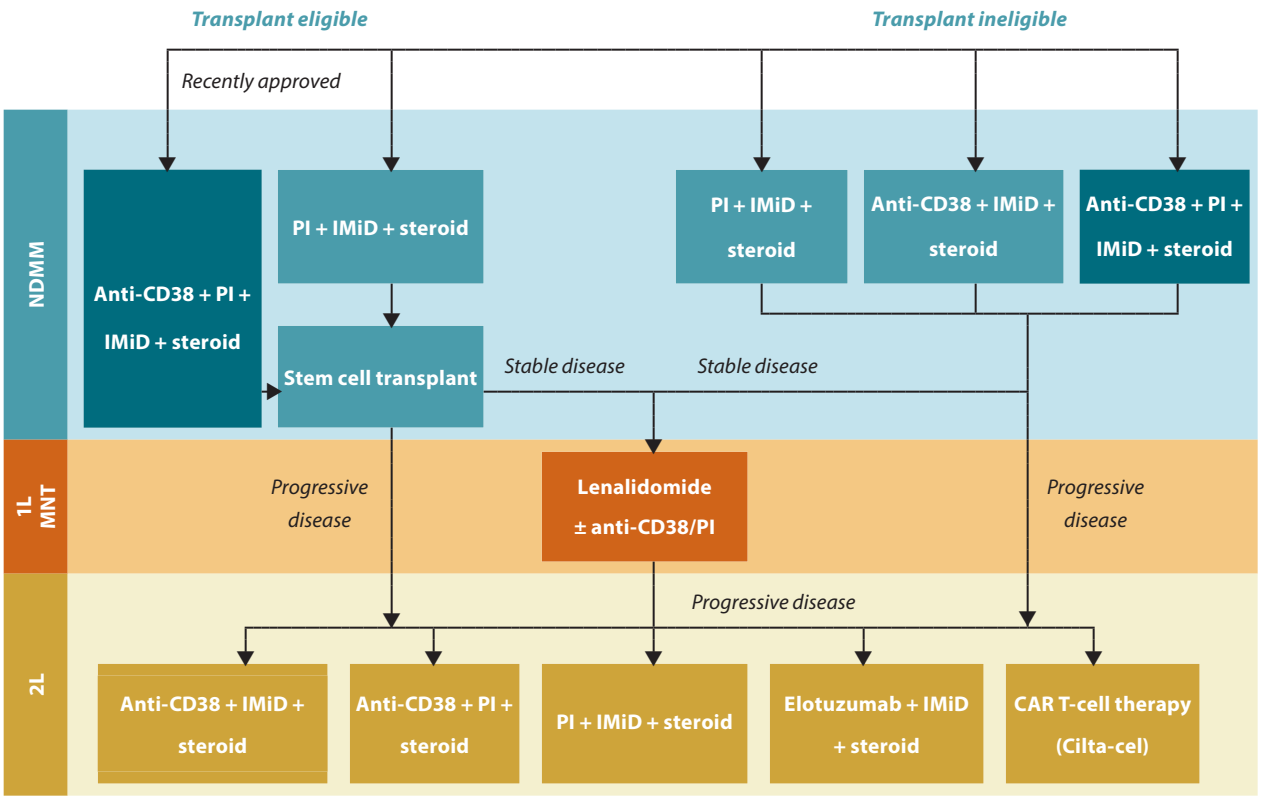
*High-burden, high-risk products; older; comorbidities; etc.

academic institutions, where the bispecifics are primarily used, are trying to develop algorithms for giving them in the outpatient setting. Once the step-up dosing phase is finished, these agents can be given in the community setting because CRS and ICANS are no longer an issue.

Cytopenias can also occur with the BCMA-targeting agents. The cytopenias with the bispecifics occur less frequently than with CAR-T cell therapies. Risk for infection is higher with the bispecifics. Additionally, patients need to have vaccinations up-to-date before starting therapy. Outstanding vaccinations should be completed at least two weeks prior to receiving CAR T-cell therapies or bispecific antibodies. For the CAR-T therapies, post-infusion vaccinations should be delayed for at least three to six months (one year for live vaccines). Herpes simplex and *pneumocystis jirovecii* pneumonia prophylaxis should be given to all patients. Antibacterial and other antifungal prophylaxis are recommended for patients with an elevated risk of infection.

Sequencing therapies for relapsed/refractory MM has become much more complex. Treatment decisions are influenced by what first-line therapy was given. Other factors in choosing a regimen include disease-related and patient-related factors and if the disease is refractory to any medications. Exhibit 3 shows the Category 1 recommendations from the National Comprehensive Cancer Network (NCCN) Guidelines for first- and second-line therapy.[15] As BCMA-directed therapies have moved into earlier lines of therapy (second or beyond), the ideal sequencing of all the therapeutic options remains a question. Although CAR-T therapy is approved for second-line use, many clinicians are not yet using it in this group unless the patient has relapsed within two years of first-line therapy. It is hard to justify the cost and logistical issues of CAR-T therapy in those with first relapse who have gone six or seven years without disease. The bispecifics

Exhibit 3: Key NCCN Category 1 Symptomatic MM Treatment Options[15]



Anti-CD38 = monoclonal antibody (daratumumab,isatuximab); PI = proteosome inhibitor (bortezomib, carfilzomib); IMiD = immunomodulator (lenalidomide, pomalidomide).

Exhibit 4: Comparing BCMA-Directed CAR T-Cell Therapy and Bispecific Antibodies

Differences Between CAR-T Cell and Bispecific Antibody Therapies[1-7]	CAR T-Cell Therapies	Bispecific Antibody Therapies
Convenience factors	Specialized center Caregiver needed Prolonged manufacturing time	"Off the shelf"
Hospitalization	At most centers	Currently for step-up doses at most centers
Length of treatment	One-time administration	Ongoing every 1-2 weeks until progressive disease or discontinuation
Safety/toxicities	CRS, neurotoxicity, cytopenias, infections, secondary hematologic malignancies Requires chemotherapy administration before infusion	CRS, neurotoxicity, cytopenias, infections Lower risk of CRS and neurotoxicity; better tolerated by older patients
REMS	Yes	Yes

are likely to move into earlier than fifth-line within the next few years. In choosing between CAR-T and bispecifics in later lines of therapy there are some pros and cons of each therapy (Exhibit 4). For example, patients with rapidly progressing disease may not be candidates for CAR-T therapy due to the four-to-six-week delay between T cell collection and reinfusion of the modified T cells.

Another issue with sequencing CAR-T and bispecifics is efficacy when one follows the other. PFS with a CAR-T after a BCMA bispecific is significantly lower than PFS in a BCMA-targeting naïve population.[16] There are some emerging data indicating that a year or longer between bispecific and CAR-T along with another type of therapy in that intervening period may allow CAR-T to be effective. On the other hand, there are data supporting good responses with BCMA bispecific after a response to CAR-T therapy especially with at least a one-year gap between therapies.[17,18]

Conclusion

The treatment of multiple myeloma has evolved quickly over the past decade. For second- to forth-line therapy, a multitude of three drug combination options have existed and now CAR-T cells have also gained FDA approval for these patients. In the fifth-line and later, CAR-T cells and bispecifics are changing the landscape of treatment. For patients with multiple myeloma the best is yet to come!

Ravi Vij, MD, MBA, is a Professor of Medicine in the section of Stem Cell Transplant and Leukemia at the Washington University School of Medicine in St. Louis, MO.

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Keeping Pace with Rapid Advancements in the Management of Non-Small Cell Lung Cancer

Gary M. Owens, MD

This journal article is supported by an educational grant from Merck Sharp & Dohme LLC

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Summary

The management of non-small cell lung cancer (NSCLC) continues to evolve with additional use of immunotherapy in the neoadjuvant and adjuvant setting in earlier stages of the disease than advanced/metastatic. Because many treatment options are available and early use is becoming more frequent, treatment of those with NSCLC is becoming more complicated.

Key Points

- Immunotherapy plus platinum-based chemotherapy doublets is standard first-line therapy in advanced NSCLC for those without actionable genetic mutations.
- Targeted therapy is first-line for those with actionable genetic mutations.
- Immunotherapy has moved into earlier stages of the disease as neoadjuvant therapy in combination with chemotherapy and adjuvant therapy.

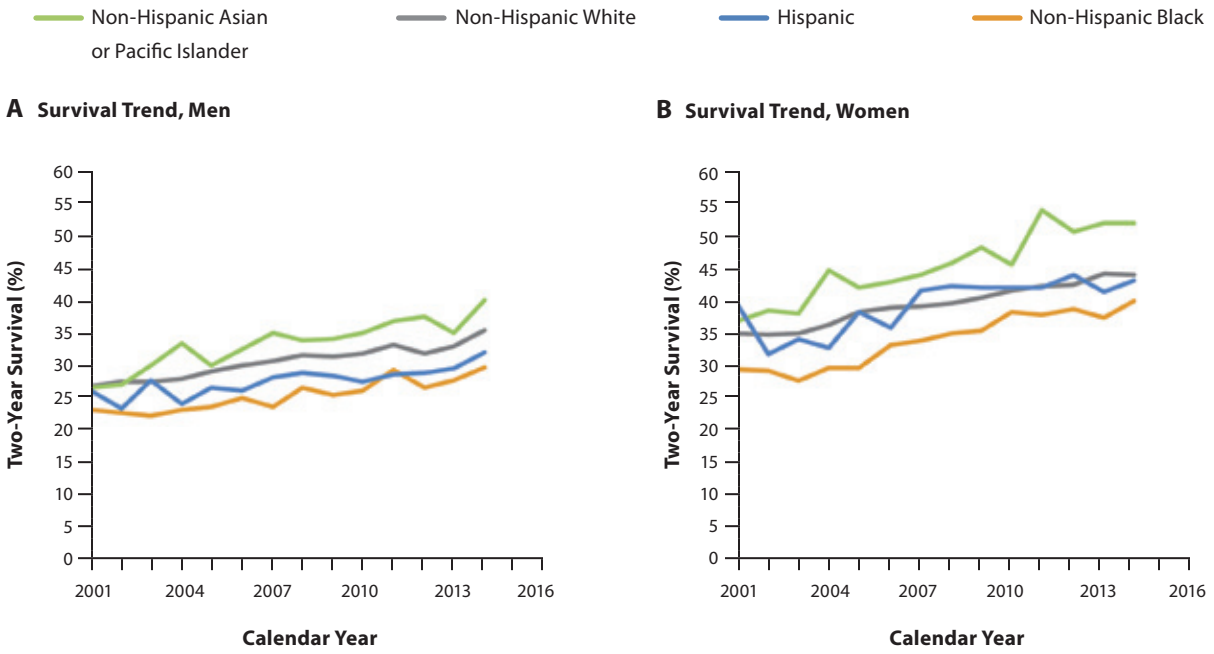
LUNG CANCER IS THE SECOND MOST common cancer in both men and women and the most common type is non-small cell lung cancer (NSCLC).[1,2] NSCLC usually grows and spreads more slowly than small cell lung cancer. An estimated 226,650 new cases of lung cancer will be diagnosed and 124,730 deaths will occur in the United States (U.S.) in 2025.[1] In about 1953, lung cancer became the most common cause of cancer deaths in men, and in 1985, it became the leading cause of cancer deaths in women. Lung cancer deaths have begun to decline in both men and women, reflected by a decrease in smoking.

Managed care costs of treating cancer have been increasing significantly and the patient economic burden related to cancer care is substantial.[3,4] Given the significant out-of-pocket expenses, patient financial toxicity, the detrimental effects of the excess financial strain caused by the diagnosis of cancer on the well-being of patients may occur and has become an important consideration in cancer care.[5] In 2020, lung cancer was the third most costly cancer.[6] With NSCLC, costs are driven primarily by outpatient visits and medication costs, especially for checkpoint inhibitor immunotherapy and targeted agents.[7] Although lung cancer is costly to treat, there are significant socio-benefits of treatment. In one study, population-level mortality from NSCLC in the U.S. fell sharply from 2013 to 2016, and survival after diagnosis improved substantially, which was likely driven by targeted therapies (Exhibit 1).[8]

Unfortunately, about 50 percent of patients with lung cancer have late-stage disease at diagnosis.[9] Early diagnosis of NSCLC is difficult because the symptoms are very non-specific or are attributed to other illnesses or smoking. About 25 percent of people have no symptoms until later disease stages.

The most frequently used system to stage lung cancer is the American Joint Committee on Cancer TNM system, which is based on the size and extent of the primary tumor (T), whether the cancer has spread to nearby (regional) lymph nodes (N), and whether the cancer has metastasized (M) to other organs of the body.[10] Once the T, N and M categories have been defined, this information is combined to assign an overall Stage of 0, I, II, III or IV. Stage IV is metastatic disease. This process is called stage grouping and produces a range of anatomical stage

Exhibit 1: Improvement in Survival Trends[8]



or prognostic groups.

Molecular testing is central to selecting effective therapeutic options in NSCLC. Therapies targeted at molecular mutations which drive cancer growth have consistently demonstrated significantly improved outcomes for patients with NSCLC compared to chemotherapy. Methods for screening NSCLC patients for driver mutations and other abnormalities are continually evolving and there is no single standard platform for testing. Features that make a platform clinically useful are fast turnaround time (two weeks or less), cost efficiency, ability to be performed on clinically available samples, and semi-automation—eliminating reliance upon a single operator.[11] Fifty percent or more of NSCLC cases harbor genomic alterations amenable to targeted therapy. These driver mutations create pathways for targeted therapy.

Driver mutations for which a targeted therapy exists and the presence of programmed cell death ligand 1 (PD-L1) expression, a biomarker of immunotherapy efficacy in NSCLC, are key factors in initial treatment selection for advanced NSCLC. Other key factors are the extent of disease, including the number and sites of metastases; squamous versus nonsquamous histology; performance status; comorbidities; and brain or liver metastases.[12]

If a patient with advanced NSCLC is identified as having a targetable tumor mutation, then targeted therapy is the first-line treatment, except in the case of certain mutations where chemotherapy is first-line.[12] If the patient has no targetable mutations, checkpoint inhibitor immunotherapy with or without chemotherapy and/or bevacizumab is the treatment option, depending on the expression of PD-L1.[12,13] Patients without contraindications to checkpoint inhibitor immunotherapy, good performance status, and PD-L1 expression of 50 percent or more are offered either monotherapy with a checkpoint inhibitor or a platinum-doublet chemotherapy plus a checkpoint inhibitor. The American Society of Clinical Oncology (ASCO) guidelines provide a strong recommendation with high quality evidence for single-agent pembrolizumab or cemiplimab or atezolizumab as first-line therapy for PD-L1 expression of 50 percent or more; their recommendation for immunotherapy plus chemotherapy is a weak recommendation with moderate evidence.[13] In addition to the single agent options, the National Comprehensive Cancer Network (NCCN) Guidelines list these checkpoint immunotherapy options in combination with platinum-doublet chemotherapy as Category 1 recommendations.[12] For patients with PD-L1 expression of less than 50 percent, the combination of a platinum-doublet chemotherapy and a checkpoint inhibitor is standard due to of improved efficacy. For those receiving chemotherapy the choice is again influenced by tumor histology.

Patients with earlier Stage I, II, or III NSCLC are at substantial risk for recurrence and death even

Exhibit 2: Approved Immunotherapy Agents for Neoadjuvant/Adjuvant Therapy

Drug	Indications
Pembrolizumab	Adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC. Neoadjuvant treatment of patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy and then continued as a single agent as adjuvant treatment after surgery.
Atezolizumab	Adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 ≥ 1%, as determined by an FDA-approved test.
Nivolumab	Neoadjuvant with platinum-doublet chemotherapy in adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC. Neoadjuvant with platinum-doublet chemotherapy followed by single-agent nivolumab after surgery as adjuvant treatment, for adults with resectable (tumors ≥ 4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.
Durvalumab	Neoadjuvant with platinum-containing chemotherapy followed by durvalumab continued as a single agent as adjuvant treatment after surgery, for the treatment of adult patients with resectable (tumors ≥ 4 cm and/or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

after complete surgical resection. Approximately 25 percent of patients with Stage IB, 35 to 50 percent of Stage II, and a greater percentage of those with Stage III NSCLC eventually have cancer recurrence and subsequent death from the cancer.[14-16] Adjuvant chemotherapy has been found to improve five-year overall survival (OS) but additional improvements are needed. Therefore, based on success in advanced NSCLC, immunotherapy was investigated to decrease postoperative recurrence and improve survival in patients with resected NSCLC as neoadjuvant (pre-surgery), adjuvant (post-surgery), and perioperative (pre- and post-surgery) options.

Adjuvant atezolizumab every 21 days for one year versus best supportive care (observation and regular scans for disease recurrence) after adjuvant platinum-based chemotherapy was evaluated in 990 adults with completely resected Stage IB (tumors of 4 cm or more) to IIIA NSCLC.[17] After a median follow-up of 32.2 months, atezolizumab treatment improved disease-free survival (DFS) compared with best supportive care in patients in the Stage II-IIIA population whose tumors expressed PD-L1 1 percent or more (hazard ratio [HR] 0.66; $p = 0.0039$) and in all patients in the Stage II-IIIA population (0.79; $p = 0.020$). Atezolizumab-related Grade 3 and 4 adverse events occurred in 11 percent of patients and Grade 5 events in 1 percent. At the interim survival analysis, at a median of 45.3 months follow-up, 25 percent of patients in the atezolizumab arm and 24.9 percent in the best supportive care arm had died.[18] The median OS in the intention to treat population was not estimable; the stratified hazard ratio (HR) was 0.995. The stratified OS HRs were 0.95 in the Stage II-IIIA, 0.71 in the Stage II-IIIA PD-L1 of 1 percent or more, and 0.43 in the Stage II-IIIA PD-L1 of 50 percent or more. The authors concluded that the immature OS data indicate a positive trend favoring atezolizumab in PD-L1 subgroup analyses, primarily driven by the PD-L1 of 50 percent or more Stage II-IIIA subgroup. A systematic review and meta-analysis concluded that adjuvant immunotherapy has been shown to improve DFS in patients with completely resected NSCLC, particularly those who are EGFR mutation negative, had PD-L1 levels of 1 percent to 49 percent, had non-squamous cell carcinoma, or never smoked.[19] In addition to atezolizumab, pembrolizumab is FDA approved for adjuvant therapy (Exhibit 2).

Neoadjuvant addition of immunotherapy to chemotherapy has also been studied in NSCLC. Neoadjuvant treatment can target micro-metastatic disease prior to surgery and can downstage cancer, permitting resection that was previously not possible or considered too extensive.[20,21] Nivolumab plus platinum-based chemotherapy was evaluated in a Phase III trial in patients with Stage IB to IIIA resectable NSCLC.[22] The median event-free survival was 31.6 months with nivolumab plus chemotherapy and 20.8 months with chemotherapy alone (HR, 0.63, $p = 0.005$). At the first prespecified interim analysis, the hazard ratio for death was 0.57 and did not meet the criterion for significance. Grade 3 or 4 treatment-related adverse events occurred in 33.5 percent of the patients in the nivolumab-plus-chemotherapy group and in 36.9 percent of those in the chemotherapy-alone group. A meta-analysis of eight randomized eligible neoadjuvant therapy (chemotherapy and chemoimmunotherapy) trials found that pooled OS and event-free survival favored neoadjuvant chemoimmunotherapy over neoadjuvant chemotherapy.[23] For patients with baseline tumor PD-L1 levels less than 1 percent, there was a significant benefit in event-free survival for neoadjuvant chemoimmunotherapy compared with chemotherapy, but not OS.

Pembrolizumab, durvalumab, and nivolumab have all been evaluated for perioperative therapy—neoadjuvant immunotherapy in combination with platinum-based chemotherapy followed by single agent adjuvant immunotherapy. In 2023, the FDA approved neoadjuvant pembrolizumab in combination with platinum containing chemotherapy for resectable NSCLC followed by single-agent pembrolizumab in the adjuvant setting across all PD-L1 strata after OS results were produced from KEYNOTE-671.[24] Thirty-six month OS estimates were 71 percent in the pembrolizumab group and 64 percent in the placebo group (HR 0.72, one-sided $p = 0.0052$).[25] Median event-free survival was 47.2 months in the pembrolizumab group and 18.3 months in the placebo group (HR 0.59).

In a trial evaluating durvalumab perioperative therapy, 802 subjects with resectable NSCLC (Stage II to IIIB [N2 node stage]) received platinum-based chemotherapy plus durvalumab or placebo administered intravenously every three weeks for four cycles before surgery, followed by adjuvant durvalumab or placebo intravenously every four weeks for 12 cycles.[26] The duration of event-free survival was significantly longer with durvalumab than with placebo (HR 0.68, $p = 0.004$) at the first interim analysis. At the 12-month landmark analysis, event-free survival was observed in 73.4 percent of the patients who received durvalumab, as compared with 64.5 percent of the patients who received placebo. Event-free survival and pathological complete response benefit were observed regardless of stage and PD-L1 expression. Adverse events of maximum Grade 3 or 4 occurred in 42.4 percent of patients with durvalumab and in 43.2 percent with placebo.

Nivolumab has also been studied as perioperative therapy in a Phase III, randomized, double-blind trial. Adults with resectable Stage IIA to IIIB NSCLC received neoadjuvant nivolumab plus chemotherapy or neoadjuvant chemotherapy plus placebo every three weeks for four cycles, followed by surgery and adjuvant nivolumab or placebo every four weeks for one year.[27] At a median follow-up of 25.4 months, the percentage of patients with 18-month event-free survival was 70.2 percent in the nivolumab group and 50.0 percent in the chemotherapy group (HR 0.58, $p < 0.001$). Grade 3 or 4 treatment-related adverse events occurred in 32.5 percent of the patients in the nivolumab group and in 25.2 percent of those in the chemotherapy group.

Neoadjuvant immunotherapy is an important option for resectable NSCLC to target micro-metastases and shrink tumors before surgery and adjuvant immunotherapy to prevent recurrence post-surgery with or without chemotherapy. The NCCN Guidelines recommend that patients with resectable tumors of 4 cm or greater, or node positive should be evaluated for perioperative therapy, with strong consideration for an immune checkpoint inhibitor plus chemotherapy for the neoadjuvant component.[12] Treatment approaches for unresectable Stage III NSCLC are less well-defined. Exhibit 2 shows the FDA-approved indications for checkpoint immunotherapy for neoadjuvant, adjuvant and perioperative therapy in NSCLC.

Because checkpoint inhibitor immunotherapy takes the brakes off the immune system, they produce a wide range of immune-mediated adverse events which must be monitored and managed to avoid significant consequences. The most frequent immune-related adverse events (irAEs) are cutaneous and mimic several types of spontaneous skin disorders.[28] Identifying irAEs in a timely manner and managing them appropriately requires a multidisciplinary approach.

In a 2019 survey, 21 payors were asked about general oncology product management, use of specific management tools, management challenges, and expected use of specific management tools by 2020 through 2022.[29] When compared with other high-cost disease areas such as diabetes, multiple sclerosis, bleeding disorders, rheumatoid arthritis,

psoriasis, and hepatitis C virus, oncology was rated as the highest budget impact category. The top five challenges to payors for oncology management were difficulty comparing products, complex patient population, lack of mature evidence, government regulations, and physician pushback. In addition to managing the inflated costs of immunotherapy, payors are finding it hard to keep up with the constantly evolving field of immuno-oncology. New issues include how to deal with identifying the best candidates for immunotherapy (PD-L1 expression versus microsatellite instability or tumor mutational burden), combination therapies, and lines of therapy.

Conclusion

The treatment of NSCLC continues to change. Immunotherapy plus platinum-based chemotherapy doublets is standard first-line therapy for advanced NSCLC for those without actionable genetic mutations whereas targeted therapy is first-line for those with actionable genetic mutations. Immunotherapy is now recommended as neoadjuvant and adjuvant therapy with and without chemotherapy in the initial stages of the disease for those with resectable disease who can tolerate immunotherapy. Additionally substantial costs complicate fiscal management for this disease.

Gary M. Owens, MD, is President of Gary Owens and Associates in Ocean View, DE.

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Advancing Care in Narcolepsy and Idiopathic Hypersomnia: Optimizing Treatment and Addressing Challenges in Sleep Management

Clete A. Kushida, MD, PhD

This journal article is supported by educational grants from Avadel CNS Pharmaceuticals, LLC; Jazz Pharmaceuticals

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

Summary

Central hypersomnias have a major impact on those affected because of excessive daytime sleepiness. Wakefulness promoting medications are available for treatment but none improve all aspects of these conditions. Individualized treatment is required to achieve the best outcomes.

Key Points

- Medications to reduce excess daytime sleepiness are available.
- Only oxybate and pitolisant are FDA-approved for cataplexy.
- Combination therapy will be required by many patients to manage their symptoms.
- Additional medications will reach the market in a few years.

BECAUSE NARCOLEPSY GENERALLY HAS an onset in childhood or adolescence, it is often misdiagnosed, has no known cure, requires lifelong treatment, and is an important disease from a managed care perspective.[1] Narcolepsy is estimated to occur in 0.02 percent to 0.18 percent of the general population, affecting about 200,000 Americans. Narcoleptic patients report significant role limitations due to physical problems, lowered vitality, lower social functioning, and role limitations due to emotional problems.[2] Patients with narcolepsy are more impaired than patients with epilepsy and are almost as impaired as patients with Parkinson's Disease. Those with narcolepsy commonly experience occupational problems, including impaired performance, decreased earning capacity, and increased rate of job loss due to termination. Misdiagnosis and delayed diagnosis may contribute to the socioeconomic burden of narcolepsy due to postponement of treatment and increased disease burden.

Narcolepsy type 1 (with cataplexy) is characterized by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis, and fragmented sleep. Cataplexy is a sudden decrement in muscle tone often precipitated by emotion, stress, fatigue, or meals. It commonly involves postural muscles and can last from seconds to minutes. Blurred vision, speech difficulty, irregular respiration may be present. The most common sites of cataplexy are legs or knees and jaw, however, falling to the ground is uncommon.[3] Hypnagogic hallucinations are visual or auditory hallucinations when falling asleep. Abnormal feelings in extremities, levitation or extracorporeal sensations can also occur. Extreme anxiety often accompanies sleep paralysis.

Narcolepsy commonly begins in the second decade near puberty but can occur at three to six years of age

Exhibit 1: Epworth Sleepiness Scale[4]

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

0 = would *never* doze

1 = *slight* chance of dozing

2 = *moderate* chance of dozing

3 = *high* chance of dozing

	Chance of Dozing
Sitting and Reading	
Watching Television	
Sitting inactive in a public place (meeting, theater, etc.)	
As a passenger in a car for one hour without a break	
Lying down in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
Total	

(rarely below five years) and at 35 to 45 years of age. There is a slight preponderance in males.

Most cases of narcolepsy are sporadic. One to 2 percent of first-degree relatives of those with narcolepsy type 1 are also affected and 4 percent to 6 percent of first-degree relatives may have isolated symptoms of narcolepsy. HLA DQB1*0602 is the most common HLA marker associated with narcolepsy (~90%) but is not sufficient alone to cause narcolepsy. Additional gene(s) may be required and environmental factors play a role. In some families, a non-HLA gene may confer narcoleptic susceptibility.

Most cases of narcolepsy with cataplexy are associated with a loss of orexin-containing hypothalamic neurons. Orexin is also known as hypocretin. Approximately 90 percent of narcoleptics with cataplexy (almost all with HLA DQB1*0602) have significantly decreased cerebrospinal fluid orexin levels. Orexin neurons drive wakefulness via wake-promoting neurons. Orexin two receptors in the tuberomammillary nucleus in the brain drive long wake bouts. Orexin one receptors in the locus ceruleus promote wakefulness.

Excessive daytime sleepiness (EDS) and sleep attacks are usually the initial symptoms of narcolepsy. Cataplexy may rarely antedate other symptoms but may occur up to 20 years later, though it most often occurs within a year of onset of EDS. Attacks of sleepiness recur throughout the day during a wide spectrum of activities. Naps lead to refractory periods of feeling refreshed from one to several hours. Patients may have persistent drowsiness throughout the day with automatism and decreased concentration, performance, and short-term memory. EDS is associated with fragmented sleep.

Sleepiness can be assessed in several ways. This includes Stanford Sleepiness Scale, Epworth Sleepiness Scale, Multiple Sleep Latency Test (MSLT), Maintenance of Wakefulness Tests (MWT), and continuous polygraphic monitoring. The subjective sleepiness scales have questionable reliability with chronic sleepiness and may not correlate with objective measures of sleepiness. Exhibit 1 shows the Epworth Sleepiness Scale (ESS).[4]

The MSLT consists of four or five scheduled 20-minute naps separated by two hours. An MSLT with a mean sleep latency of less than eight minutes and two or more sleep-onset REM periods (SOREMPs) is diagnostic for narcolepsy. Before undergoing an MSLT, patients should be non-sleep deprived, off stimulants, stimulant-like medications, REM-suppressing medications for two weeks, and

Exhibit 2: Narcolepsy Type 1, Narcolepsy Type 2, and Idiopathic Hypersomnia Diagnostic Criteria

Narcolepsy Type 1 (NT1)
(Narcolepsy with Cataplexy)

A and B must be met

A. EDS ≥ 3 months
B. At least one of the following:
   –Cataplexy and a positive MSLT
      • Low mean sleep latency ≤ 8 mins
      • ≥ 2 SOREMPs on MSLT-PSG
   –Low CSF hypocretin-1/orexin concentration (≤ 110pg/ml or < 1/3 of normal)

Narcolepsy Type 2 (NT2)
(Narcolepsy without Cataplexy)

A–E must be met

A. EDS ≥ 3 months
B. Positive MSLT
   –Low mean sleep latency ≤ 8 mins
   –≥ 2 SOREMPs on MSLT-PSG
C. Cataplexy is absent
D. CSF hypocretin-1/orexin concentration > 110pg/ml or > 1/3 of normal
E. Hypersomnolence and MSLT findings not better explained by other causes:
   –Insufficient sleep, OSA, delayed sleep phase, drug intake/withdrawal.

Idiopathic Hypersomnia

A-F must be met

A. EDS ≥ 3 months
B. Cataplexy is absent
C. < 2 SOREMPs on MSLT-PSG
D. At least one of the following:
   –Low MSLT mean sleep latency ≤ 8 mins
   –Total 24-hour sleep time ≥ 660 minutes (12-14 hours) on 24-hour PSG monitoring or by wrist actigraphy in association with a sleep log (averaged over ≥ 7 days).
E. Insufficient sleep syndrome is ruled out
F. Hypersomnolence and MSLT findings not better explained by other causes:
   –Another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications.

their sleep should be stable without evidence of other disorders. Eighty-four percent of narcoleptic patients have two or more SOREMPs on a single-day MSLT.

Individuals with two or more SOREMPs on MSLTs and EDS may develop cataplexy many years later. A mean sleep latency of 3.1 plus or minus 2.9 minutes was found in individuals with narcolepsy by a meta-analysis. Twenty-four percent of obstructive sleep apnea patients had a positive MSLT.

Narcolepsy without cataplexy represents 10 to 50 percent of the narcoleptic population. Approximately 40 percent are HLA DQB1*0602 positive compared with 12 to 25 percent of controls. Ten to 20 percent of patients without cataplexy (almost all with HLA DQB1*0602) have decreased CSF hypocretin-1 levels of 110 pg/mL or less. The differential for narcolepsy includes other hypersomnias, obstructive sleep apnea and upper airway resistance syndrome, periodic limb movement disorder, and cataplexy mimics. The hypersomnias include idiopathic hypersomnia, recurrent hypersomnia, hypersomnia due to a medical disorder, hypersomnia due to medication or substance, hypersomnia associated with a psychiatric disorder, and insufficient sleep syndrome. Idiopathic hypersomnia (IH) is considered a central hypersomnia similar to narcolepsy types 1 and 2 where there are problems within the brain's sleep-wake regulation system. Sleep inertia is a prominent feature alongside other symptoms such

Exhibit 3: American Academy of Sleep Medicine (AASM) Practice Guidelines[6]

		Outcomes With Clinically Significant Improvement			
Medication (Mechanism of Action)	**Strength of Recommendation**	**EDS**	**Cataplexy**	**Disease Severity**	**Quality of Life**
Modafinil (dopamine (DA) reuptake inhibitor)	Strong	X		X	X
Pitolisant (histamine H3 antagonist/inverse agonist)	Strong	X	X	X	
Oxybate (GABA agonist)	Strong	X	X	X	
Solriamfetol (DA-norepinephrine (NE) reuptake inhibitor)	Strong	X		X	X
Armodafinil (DA reuptake inhibitor)	Conditional	X		X	
Dextroamphetamine (enhance DA, NE, serotonin)	Conditional	X	X		
Methylphenidate (enhance DA, NE, serotonin)	Conditional			X	

as prolonged sleep duration (more than 12 hours) and unrefreshing naps. Sleep inertia is characterized by grogginess, confusion, and impaired cognitive function upon waking, which can last for minutes or even hours. Exhibit 2 compares the diagnostic criteria for central hypersomnias.

Treating narcolepsy and IH is not just managing daytime sleepiness but also limiting the impact the disease has on quality of life, work and/or school, and social aspects of life. Treatment goals for these central hypersomnias are to:

- Reduce EDS.
- Control cataplexy if present.
- Control nightmares, hallucinations, sleep paralysis, and disturbed nocturnal sleep.
- Improve psychosocial dysfunction and quality of life.
- Improve safety of patients and the public.
- Optimize risk to benefit of pharmacotherapy.[5]

Exhibit 3 shows the 2021 American Academy of Sleep Medicine guideline medication recommendations for managing narcolepsy and IH in adults.[6] No currently available medication impacts all aspects of either disease.

Oxybate, a derivative of gamma-hydroxybutyrate (GHB), is available as sodium oxybate (SXB) and lower sodium oxybate (LXB) which are dosed twice nightly and once-nightly SXB (ON-SXB). The twice nightly oxybate products are given at bedtime and then 2.25 to four hours later and are the only agents indicated for use in children. Low-sodium oxybate is the only agent with an FDA-approved indication for IH but the other agents in Exhibit 3 are typically also used for IH. LXB has 92 percent less sodium than SXB (141 mg versus 1,640 mg at the highest doses); the sodium content of SXB can be an issue for people with hypertension, heart failure, or renal dysfunction. The other medications for central hypersomnias are typically given once a day in the morning to prevent disturbing nighttime sleep.

Selected studies of the medications for central hypersomnias are reviewed here. In a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy, LXB (which is actually calcium, magnesium, potassium, and sodium oxybates) reduced EDS and cataplexy.[7] This study was interesting because it transitioned patients from their current medications to LXB

then to a two-week, double-blind, randomized withdrawal period (DBRWP). Half of the patients were taken off LXB and put on a placebo and finally back to LXB. A statistically significant worsening of symptoms was observed in participants randomized to placebo, with median change in weekly number of cataplexy attacks from stable LXB dose to placebo group of 2.35 versus 0.00 in the LXB group ($p < 0.0001$). There was a median change in Epworth Sleepiness Scale score of 2.0 in the placebo group versus 0.0 in the LXB group ($p < 0.0001$). The most common treatment-emergent adverse events with LXB were headache (20.4%), nausea (12.9%), and dizziness (10.4%).

ON-SXB is an option to improve adherence compared to the twice nightly products but it has a high sodium content. A low-sodium once nightly option is under development. The trial used for FDA-approval of ON-SXB compared four doses of 4.5, 6, 7.5, and 9 g with placebo.[8] All the dose levels of ON-SXB demonstrated clinically meaningful, statistically significant improvement versus placebo (all $p < 0.001$). For ON-SXB 9 g versus placebo, the increase in mean sleep latency was 10.8 versus 4.7 min, 72.0 percent versus 31.6 percent of subjects were rated much/very much improved on Clinical Global Impression-Improvement, change in mean weekly number of cataplexy attacks was -11.5 versus -4.9, and change in the Epworth Sleepiness Scale was -6.5 and -2.7.

Histaminergic neurons are crucial to maintain wakefulness and pitolisant is a histamine H3 receptor inverse agonist. It has been shown to improve wakefulness and reduce cataplexy. In a trial specifically focused on cataplexy efficacy, the weekly cataplexy rate during a stable dosing period compared with baseline was decreased by 75 percent in patients who received pitolisant and 38 percent in patients who received placebo ($p < 0{\cdot}0001$).[9]

Solriamfetol is a dopamine-norepinephrine re-uptake inhibitor indicated to improve wakefulness in adult patients with EDS associated with narcolepsy or obstructive sleep apnea (OSA). A prespecified subgroup analysis of data from a 12-week randomized, double-blind, placebo-controlled, Phase III trial of solriamfetol for EDS in narcolepsy evaluated the efficacy and safety of solriamfetol by cataplexy status.[10] This agent appears to be slightly less effective in those with cataplexy in terms of mean wakefulness test and Epworth Sleepiness Scale improvements. Cataplexy rates were not formally evaluated in the clinical trials for this agent.

Modafinil and LXB have been evaluated for treating IH. Compared to placebo in IH, modafinil decreased sleepiness significantly and improved mean sleep latency in the MWT non-significantly.[11] The Clinical Global Impression improved significantly from baseline to the last visit on treatment. The most frequent adverse events with modafinil were headaches and gastrointestinal disorders. Modafinil is FDA-approved for narcolepsy but not IH.

LXB was evaluated for IH treatment in a Phase III, multicenter, placebo-controlled, double-blind, randomized withdrawal trial.[12] ESS scores decreased from a mean of 15.7 at baseline to 6.1 by the end of the stable-dose period. During the double-blind, randomized withdrawal period, ESS scores worsened in participants randomly assigned to placebo but remained stable in those assigned to LXB (least squares mean difference 6.5; $p < 0{\cdot}0001$). Treatment-emergent adverse events included nausea (22%), headache (18%), dizziness (12%), anxiety (11%), and vomiting (11%).

Many patients will require combination therapy to maximize their wakefulness. One trial compared SXB, modafinil, and the combination in those with narcolepsy.[13] SXB alone and in combination with modafinil improved subjective ratings of excessive sleepiness and an objective measure of the ability to stay awake to similar extents in those with and without cataplexy. The greatest improvements in mean sleep latency were seen in the combination group (3.34 minutes) compared to SXB or modafinil alone. Combination therapy should use agents with different mechanisms of action.

Personalized treatment for patients with central hypersomnias includes consideration of patient needs and preferences, EDS severity, disease comorbidities, cardiovascular risk, and medication factors including adverse events, convenience and ease of use, adherence, and carry-over effects.[14] As mentioned previously, once nightly oxybate may be more convenient than twice nightly allowing the patient to be more adherent. Some patients may find that the stimulant agents (armodafinil, modafinil, etc.) prevent them from going to sleep at night. Each of the medication options for these diseases have limitations and adverse events. Common adverse events include headache, nausea, insomnia, and decreased appetite. All but pitolisant are controlled medications which have prescribing barriers. The oxybate products are only available through restrictive Risk Evaluation and Management Strategy (REMS) programs because of potential for abuse. Individualizing treatment can lead to better symptom control and improved overall well-being.

Additional agents are under investigation and will enter the market in a few years. Orexin agonists which target the underlying pathology of narcolepsy are in early-stage trials. For example,

ORX142, an orexin receptor 2 agonist, is moving into Phase I trials to evaluate safety, tolerability, and pharmacokinetics in healthy volunteers. Another histamine H3 receptor inverse agonist, a norepinephrine reuptake inhibitor, a combination dopamine reuptake inhibitor/astroglial connexin inhibitor, and a sympathomimetic amine with orexin agonist properties are in various stages of investigation.

Conclusion

Central hypersomnias have a major impact on all aspects of a patient's life. Medications to reduce excess daytime sleepiness are available but only oxybate and pitolisant are FDA-approved for cataplexy. Many patients will require combination therapy to manage their symptoms.

Clete A. Kushida, MD, PhD, is a neurologist, Professor, Division Chief, and Medical Director of Stanford Sleep Medicine, and Director of the Stanford University Human Sleep Research Laboratory at Stanford University in Palo Alto, CA.

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