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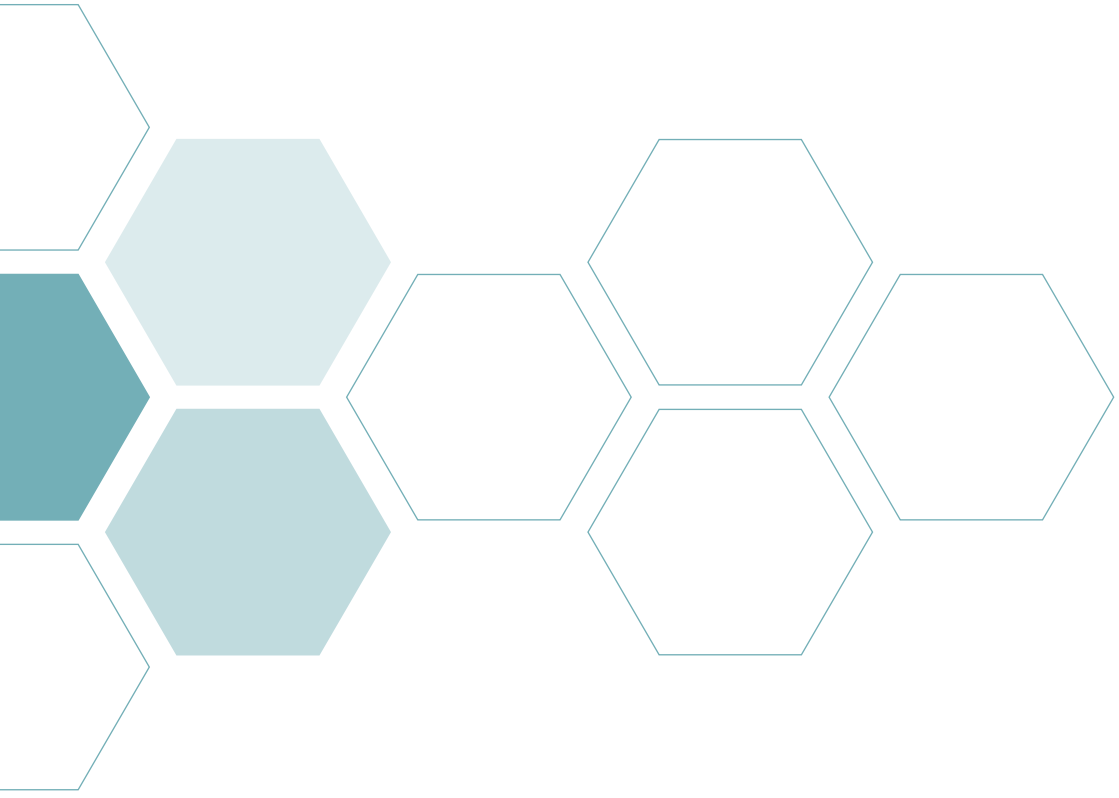
Educating Medical Directors of Employers, Health Plans and Provider Systems



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Editorial Review Board

Novel Therapeutic Options for the Management of Inflammatory Bowel Disease

Joel Pekow, MD

For a CME/CNE version of this article, please go to http://namcp.org/home/education, and then click the activity title.
Supported by an educational grant from Takeda Pharmaceuticals.

Summary

Treatment options for inflammatory bowel disease, like many other autoimmune diseases, have been evolving rapidly. Multiple additional agents, some with novel mechanisms, will likely be reaching the market in the new few years. All the options will hopefully improve remission rates.

Key Points

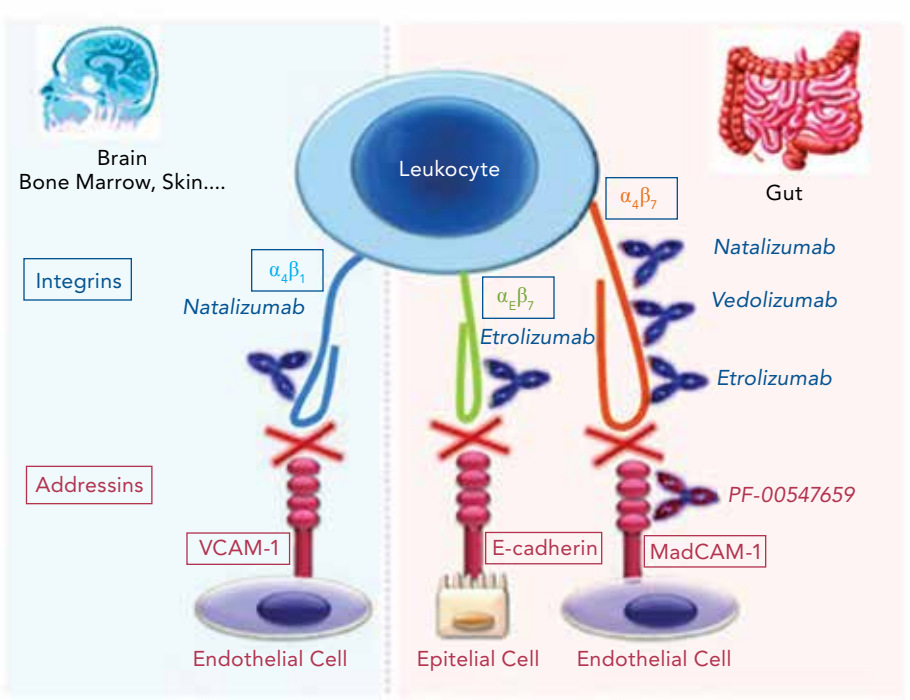
- The goal of IBD therapy is to achieve mucosal healing.
- Remission rates with mucosal healing are not optimal with current agents.
- Numerous agents are on the horizon which are in the same class as agents already approved or targeting novel mechanisms of action.

INFLAMMATORY BOWEL DISEASE (IBD) IS A chronic inflammatory condition of the gastrointestinal tract that has traditionally been divided into two principal categories – ulcerative colitis (UC) and Crohn's disease (CD) – even though there is a great deal of overlap between the two. Ulcerative colitis is a diffuse mucosal inflammation limited to the colon. Crohn's disease, by contrast, is a patchy transmural inflammation that may affect any part of the gastrointestinal tract. Its most common distributions are either the small bowel alone (regional ileitis or enteritis), the colon (Crohn's disease of the colon or colitis), or both the large and small bowel simultaneously (ileocolitis). Both have similar clinical symptoms including diarrhea, cramping, bloody diarrhea, and urgency.

It is ideal to start treatment of IBD early in the process while the disease is still in the inflammatory phase. Reasons for treatment include symptom improvement, nutritional status improvement, and minimization risks of short-term and long-term complications. Short-term complications include adverse effects related to corticosteroid use, extraintestinal manifestations, venous thromboembolism, and flares of disease. Long-term complications include strictures, colon cancer, bowel obstruction, and short bowel syndrome (from extensive bowel resections).

Until recently, clinical trials of CD treatment focused on clinical symptoms, but there is poor correlation between symptoms and mucosal inflammation in CD.[1] The focus now is on mucosal healing, rather than just symptom control. Early mucosal healing is a predictor of the disease course in CD. Those who had mucosal healing within the first year of the disease had a lower risk of requiring disease-related colon resection.[2] Hospitalization and overall surgery rates are also decreased in those with mucosal healing.[3] Additionally, mucosal healing leads to higher rates of long-term disease remission.[4] In UC, 25 percent of patients achieve clinical remission without endoscopic remission.[5] Like with CD, early

Exhibit 1: Anti-Integrin Therapies[7]



VCAM-1 = vascular cell adhesion molecule 1
MadCAM-1 = mucosal vascular addressin cell adhesion molecule 1

mucosal healing predicts long-term outcomes and disease course in patients with UC.[2,5]

There are many different medications under development for IBD. There are ones targeting mechanisms similar to approved drugs - anti-tumor necrosis factor (TNF), anti-integrin, and anti-IL-12/23 agents. Others are targeting novel mechanisms in IBD, including SMAD7 inhibition, sphingosine-1 phosphate receptor modulation, Janus kinase (JAK) inhibition, phosphatidylcholine supplementation, and anti-NKG2D.

The currently available anti-TNF agents which have an indication for IBD are infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), and golimumab (Simponi®). In 2014, infliximab sales were $8.1 billion and adalimumab sales were $11.8 billion. Two biosimilars for infliximab have been approved - infliximab-abda (Renflexis®) and infliximab-dyyb (Inflectra®) – and one for adalimumab - adalimumab-atto (Amjevita®). Additional biosimilars for both of these are in development. The FDA approval process for biosimilars requires demonstration of structural and functional biosimilarity without differences in clinical outcomes between the biosimilar and the originator biologic.

Currently marketed anti-TNF drugs are highly effective for the treatment of IBD. However, despite their success, these drugs have two significant drawbacks. One is that they must be infused or injected, whereas patients prefer oral medications. More importantly, they cause rare but serious side effects, such as risk of serious infection, because they dampen the immune system throughout the body, not just in the intestines where the disease occurs. In contrast, oral anti-TNF agents which are under development target the gut, potentially improving safety and efficacy over existing anti-TNF therapies. An oral anti-TNF agent (AVX-470) in clinical trials is a polyclonal antibody generated from purifying the antibody from the colostrum of cows immunized with recombinant anti-TNF. In vitro, it has similar neutralizing capabilities as infliximab and is effective in murine models of colitis. It has been studied in a Phase 1b study in 30 patients with UC with promising but low (~14%) endoscopic healing.[6]

Integrins, a class of cell surface molecules which facilitate how immune cells move from the blood to tissue, are an attractive target for IBD. The first integrin inhibitor FDA approved was natalizumab (Tysabri®) infusion, which is indicated for multiple sclerosis and CD. It blocks both brain and gut integrins, but the brain effect can lead to progres-

sive multifocal leukoencephalopathy (PML), a rare but potentially fatal adverse effect. More recently, vedolizumab (Entyvio®) infusion was approved for both UC and CD. It selectively binds to α4β7 which binds to mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) in the gut, so it is a gut-specific therapy (Exhibit 1).[7] Importantly, the onset of response with anti-integrin therapy is slow and may not be until week 14 of therapy. Maintenance of response appears to be durable.

Etrolizumab is one anti-integrin agent under investigation in Phase III trials. It is a humanized monoclonal antibody against the β7 subunit of integrins α4β7 and αEβ7 designed to selectively control disease in the gut of patients with moderate to severe IBD.[8] Etrolizumab can be self-administered once per month via the subcutaneous route which would be an advantage over the already approved agents. In an UC trial, patients treated with etrolizumab had higher clinical remission (21% vs 0%) than those treated with placebo.[9] In this trial, 10 percent of patients had complete healing of the mucosa. Anti-TNF naïve patients appear to do better on this agent than those previously exposed and mucosal αE expression at baseline was associated with response. Data from two Phase III clinical trials with this agent were presented at the 2017 United European Gastroenterology Week.[10-11] Compared to vedolizumab, etrolizumab in animal studies results in decreased CD8+ cells homing to the gut.[12] Because the different integrin inhibitors bind to different receptors they will likely have different therapeutic effects.

There is a monoclonal antibody against MAdCAM-1 (PF-00547659) in development for IBD. In UC, 27.8 percent of patients receiving this agent compared with 8.2 percent of those receiving placebo achieved mucosal healing.[13] In CD, there was no overall benefit with this agent.[14] It does appear to be more effective in those with CD with C-reactive protein (CRP) greater than 18 with 24 to 39 percent remission versus 14 percent of placebo group. The Phase III studies with this agent have not started.

Interleukins, including IL-12 and IL-23, are important in the inflammatory process in IBD. Ustekinumab (Stelara®), FDA approved for CD and psoriasis, induces early remission with an intravenous induction dose and is effective at maintaining remission when given subcutaneously every eight weeks.[15] At least two additional therapies targeting IL-12 or IL-23 signaling are also under development - MEDI2027 and BI655066.[16]

Multiple agents with novel mechanisms of action are also under investigation. Mongersen is an anti-SMAD7 (mothers against decapentaplegic homolog 7) oligonucleotide.[17] SMAD7 is very high in the mucosa of patients with CD where it blocks the anti-inflammatory effects of transforming growth factor beta (TGF-beta). Mongersen is an oral therapy that in Phase II trial results induced clinical remission in 55 to 65 percent of subjects compared to 10 percent of those receiving placebo over 28 days.[18] This study did not include endoscopic evaluation. Phase III trials are underway that do assess mucosal healing.

Sphingosine-1 phosphate (S1P) receptor modulators are also under development for IBD. S1P receptors modulate the egress of lymphocytes from the lymph nodes to effector sites.[19] When a S1P modulator is given, lymphocytes stay in the lymph nodes. The first sphingosine phosphate modulator approved by the FDA was fingolimod for multiple sclerosis, but this agent is a nonspecific modulator which leads to bradycardia and hypotension through interaction with S3P. A S1P specific modulator, ozanimod, is being investigated in UC and has shown benefit in remission induction and mucosal healing.[20] Other investigational S1P modulators include MT-1303 for CD and APD-334 for UC.

The class most likely to make it to market first is the Janus kinase (JAK) inhibitors. JAK is part of a signaling cascade that leads to multiple proinflammatory cytokines.[21] There are four different JAKs, and the agents under development for IBD have different selectivity. One JAK inhibitor, tofacitinib (Xeljanz®), is already approved to treat moderate to severe rheumatoid arthritis (RA). Tofacitinib has been evaluated for UC.[22] If approved for UC, it will likely be used at a higher dose than what is currently used for RA and does not appear to be effective for CD.[23] Filgotinib and ABT-494 are in Phase III and Phase II trials, respectively, for CD and RA.[24,25] Both of these agents are JAK1 selective. Peficitinib, a JAK3 selective agent, is in trials for psoriasis and UC.[25]

An anti-NKG2D monoclonal antibody (NNC0142-0002) under investigation prevents activation of immune cells. In active CD, a single 2mg/kg subcutaneous dose reduced the Crohn's Disease Activity Index (CDAI) score significantly by 12 weeks. Patients with elevated calprotectin (>250ug/g), as a marker of more significant inflammation, did better.[26]

All the previously discussed agents have been for moderate to severe IBD, but there are large numbers of patients with a milder disease course. Those with mild disease are typically treated with mesalamine. Modified release phosphatidylcholine has been under development for several years. Phosphatidylcholine is a component of the mucosal barrier. In one published trial, mucosal healing was 13 percent better with this agent than with placebo and histologic

remission was 20 percent better.[27] This agent is now in Phase III trials.

Conclusion

Mucosal healing is the most important outcome of IBD therapy. Disease remission rates continue to be less than ideal. At best about one-third of our patients achieve disease remission. There will be continued focus on using our therapies more effectively and developing tools for a personalized treatment approach to target to those who would most likely benefit and to optimize doses. There are many exciting new treatments for IBD in development which will hopefully make it to market.

Joel Pekow, MD, is a Gastroenterologist in Chicago, Illinois and is affiliated with the University of Chicago Medical Center.

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Exploring New Advances in Current and Novel Treatments for the Management of Epilepsy

Dennis J. Dlugos, MD, MSCE

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

The management of epilepsy can be complicated, particularly by medication resistance and associated conditions. There are now numerous antiepileptic medications which can control seizures in a high percentage of patients, and there are also surgical procedures and non- medication treatments which can be effective. A team approach is needed to optimally manage this disease.

Key Points

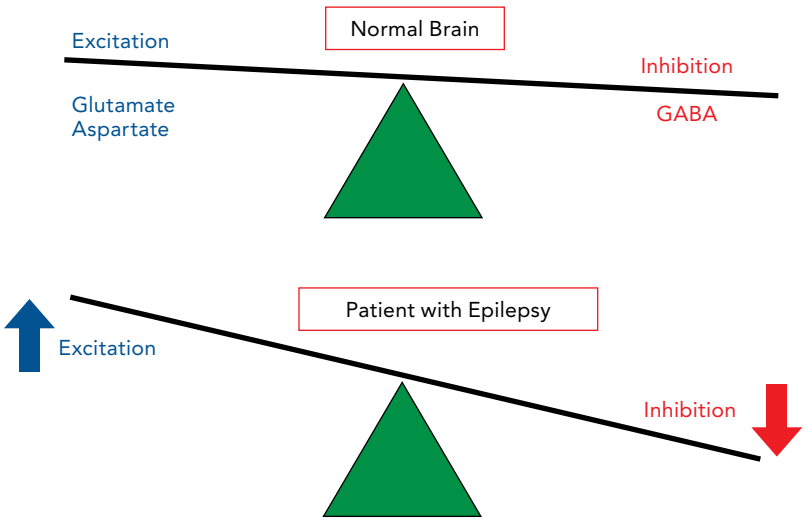
- Optimal epilepsy treatment depends on accurate classification, an individualized treatment plan, and medication adherence.
- Minimizing treatment adverse effects is essential for treatment adherence.
- Associated conditions require multi-disciplinary treatment.
- An epilepsy treatment team is essential.

EPILEPSY IS DEFINED AS TWO OR MORE UNprovoked seizures or one unprovoked seizure and a biological predisposition to have additional seizures. The biological predisposition is proven with an abnormal EEG or brain MRI scan. Seizures caused by head trauma or infections are considered provoked and thus are not epilepsy. Our understanding of how seizures occur is not well defined. At a basic level, seizures occur when there is an imbalance between excitatory and inhibitory neurotransmitters in the brain (Exhibit 1).

Epilepsy is surprisingly common; it is the fourth most common neurological disorder behind migraine, stroke, and Alzheimer's disease. One in 26 people will develop epilepsy at some point in their lifetime and over two million people in the United States (U.S.) have epilepsy. One hundred and fifty thousand new cases are diagnosed annually; children and older adults are the fastest group segments of the new onset epilepsy population.

The International League against Epilepsy has published a classification of seizure types as focal, generalized, or unknown type.[1] Focal seizures, which used to be called partial seizures, start in a single area of the brain. These can secondarily generalize to involve the whole brain. Generalized seizures affect the whole brain. There are six categories for seizure etiology – structural, genetic, infection, metabolic, autoimmune, and unknown. In structural seizures, the patient has a structural abnormality that leads to an abnormal MRI and may have been born with the abnormality or acquired it such as by having a stroke. Single gene genetic mutations leading to seizures have been shown in 30 to 40 percent of those under age 5 with seizures. Autoimmune-related seizures are considered uncommon and are typically treatment resistant. Interestingly, those with unknown cause for their epilepsy are more likely to respond to treatment than other etiologies and the disease may go away over time, especially in children. Seizures also have motor and non-motor manifestations and the patient may or may

Exhibit 1: Excitation/Inhibition Imbalance



GABA = gamma amino-butryic acid

not lose awareness during and immediately after the seizure. Most seizures do not look like the classic tonic-clonic seizure. With focal seizures, the patient suddenly has very off behaviors, such as making unusual noises or shouting out specific words. There are also bland seeming seizures where the patient has repetitive purposeless motions like arm movements. Overall, seizures are widely varied and the individual's seizure type is important in terms of medical risk and treatment goals.

Seizures are just the tip of the epilepsy iceberg. Having epilepsy leads to many other related issues. Several associated conditions include developmental delays, learning differences (learning disability to extreme giftedness), socialization challenges (difficulties with making friends and having relationships), unemployment, and psychiatric disease (depression, anxiety). The odds ratio for developing psychiatric illness is significantly higher during the two years before and after the diagnosis of a seizure disorder. There is a spectrum of severity and associated symptoms, but more than 50 percent of patients have these. Controlling seizures tends to bring these associated conditions to the surface because in the face of active seizures everything else is ignored. Treatment of the associated symptoms is important for the overall care of the patient.

Because of the complicated nature of seizures, typically patients will require management by an epilepsy treatment team. This team can be composed of the patient, parents, family, and extended family; nurse; social worker; psychologist; neuropsychologist; educational or vocational specialist; dietician; genetic counselor; and physician(s). Not every patient will need a dietician or genetic counselor, depending on the seizure type.

Treatment is primarily the use of antiepileptic drugs (AEDs). There is now a wide range of AEDs with varying mechanisms of action (Exhibit 2).[2,3] Essentially, AEDs are raising inhibitory function of gamma-aminobutyric acid (GABA) or decreasing excitation in the brain.

In clinical practice the mechanism of action is not as important as whether a particular drug works in a particular seizure type. Exhibit 3 illustrates which AEDs work for different types of seizures. Finding the right AED can take some trial and error. Forty-seven percent of patients with newly diagnosed appropriately classified epilepsy will be seizure free with the first agent prescribed and an additional 13 percent will have seizure control on the second agent that is tried.[4] Treatment resistance is a lack of control after two different AED trials. This occurs in about 40 percent of patients. Those with treatment resistance may require rational duo-therapy or surgical assessment if the type of epilepsy is amenable to surgery.

Those with medication-resistant epilepsy have persistent seizures which can lead to cognitive decline and neuro-biochemical changes in the brain. These patients have impaired quality of life, excessive medication burden with multiple adverse effect potential, increased mortality, a restricted lifestyle, psychosocial dysfunction, and dependent behavior.[5]

Exhibit 2: Mechanisms of Action of Anti-Epileptic Drugs[2,3]

Mechanism of Action	Agents
Blockers of repetitive action of sodium channel	Phenytoin Carbamazepine Oxcarbazepine Lamotrigine Topiramate
Enhancers of slow inactivation of sodium channel	Lacosamide Rufinamide
GABA-A receptor enhancers	Phenobarbital Benzodiazepines
Glutamate modulators	Topiramate Lamotrigine Felbamate
T-calcium channel blockers	Ethosuximide Valproate
N- and L-calcium channel blockers	Lamotrigine Topiramate Zonisamide Valproate
GABA reuptake inhibitors	Tiagabine
Drugs binding to unique receptors	Gabapentin and pregabalin (alpha-2-delta receptor) Levetiracetam (synaptic vesicle 2A receptor)
Carbonic anhydrase inhibitors	Topiramate Zonisamide
GABA-transaminase inhibitors	Vigabatrin

GABA = gamma-aminobutyric acid

Thus, medication-resistant epilepsy is dangerous and expensive.

There are a few non-AED options for medication-resistant epilepsy. Epilepsy surgery is a valid treatment for focal seizures where there is a specific area of the brain that can be identified as where the seizure starts. If the specific area of the brain is not responsible for language, movement or vision, it can be removed. Optimally, there is a 70 to 80 percent chance of being seizure free after surgery.

If the part of brain where the seizure starts is critical for function, responsive neurostimulation is an option. A neurostimulator is implanted in the brain which delivers electrical stimulation to stop seizures. Responsive neurostimulation is a big advance for a small number of patients who have medication–resistant epilepsy that originates in a vital part of the brain. Vagal nerve stimulation can also be used to reduce seizures by 50 percent in about 50 percent of the patients treated with this therapy. Approximately 10 percent of patients will have a 90 percent reduction in seizure frequency. A significant advantage of neurostimulation is that it does not have medication-related adverse effects.

There are now a few documented precision therapies in epilepsy that are based on specific uncommon genetic subtypes.[6] This includes vitamin B6 for pyridoxine-dependent epilepsy with ALDH7A1 mutations, a ketogenic diet for glucose transporter deficiency secondary to SLC2A1 mutations, and everolimus for seizures related to tuberous sclerosis complex (TSC). TSC is a rare genetic disorder caused by overactivation of the mammalian target of rapamycin (mTOR) pathway that promotes cell growth. The condition leads to seizures, cortical malformations, and neuronal hyperexcitability. Everolimus is an mTOR inhibitor which is FDA approved for adults with TSC-related kidney tumors (angiomyolipoma); the antiseizure effect of this agent was discovered when patients with the kidney tumors were treated and had significant reductions in seizures. Everolimus is also approved for treating several cancers. There are case reports of using quinidine and memantine for seizures second-

Exhibit 3: AED Options by Seizure Type

Focal seizures (with or without 2nd gen)	Focal and/or generalized seizures	Syndrome-specific use
Carbamazepine (CBZ)	Valproate (VPA)	Ethosuximide (ETX) – absence
Oxcarbazepine (OXC)	Levetiracetam (LEV)	Methsuximide – absence, generalized tonic-clonic
Gabapentin (GBP)	Lamotrigine (LTG)	Acetazolamide – absence, generalized tonic-clonic
Phenytoin (PHT)	Topiramate (TPM)	Adrenocorticotropic hormone (ACTH) – infantile spasms
Phenobarbital (PB)	Zonisamide (ZNS)	Vigabatrin (VGB) – infantile spasms
Pregabalin (PGB)	Clobazam (CLB) and other benzos	Prednisone – infantile spasms
Lacosamide (LCM)	Rufinamide (RFN)	Stiripentol – Dravet syndrome
Vigabatrin (VGB)	Felbamate (FBM)	
Brivaracetam (BRV)	Perampanel (PMP)	
Eslicarbazepine (ESL)		

ary to KCNT1 mutations and GRIN2A mutations, respectively. This list of precision therapies will be getting longer as more genetic mutations that cause seizures are identified.

Ketogenic diets can be used for some seizure types, particularly in children with medication resistance. The "classical" ketogenic diet, called the "long-chain triglyceride diet," provides 3 to 4 grams of fat for every 1 gram of carbohydrate and protein. That is about 90 percent of calories from fat. Thirty percent of patients are either seizure free or have a 90 percent reduction in seizure frequency, which is an important reduction in seizures. How ketosis reduces seizures is unknown. Because this diet can be very difficult to adhere with and requires close follow-up with a dietician, dietary therapy is not first-line therapy but should be considered when medication resistance is an issue.

Cannabis high in cannabidiol (CBD) but low in tetrahydrocannabinol (THC), the psychotropic component, is a therapy for seizures that many patients or parents of children with epilepsy may ask about. The interest in CBD came about from a family in Colorado who used this in their child with Dravet syndrome, also known as severe myoclonic epilepsy of infancy. She became seizure free using CBD, which was documented by her treating physician. One trial has been done with pharmaceutical grade CBD compared to placebo as add-on therapy for Dravet syndrome in 120 patients. Over a 14-week treatment period, CBD reduced convulsive seizures by 39 percent compared with a 13 percent reduction with placebo.[7,8] Thus, it appears to have some efficacy and the adverse effects were cognitively friendly. A similarly designed trial in Lennox-Gastaut syndrome, severe epilepsy that begins in childhood characterized by multiple types of seizures and intellectual disability, found a similar result. Importantly, a 40 percent reduction in seizures is not a magic bullet. A CBD product is under evaluation by the FDA under the trade name Epidiolex for Lennox-Gastaut syndrome and Dravet syndrome.

It is desirable that AEDs have high efficacy and low rates of adverse effects, but this is not always the case. Unfortunately, the adverse effects of AEDs can be more disabling than seizures. The chronic adverse effects such as drowsiness, dizziness, ataxia, and altered cognition are the ones that decrease quality of life and lead to nonadherence.

AED mechanism of action does play a role in adverse effects. Ataxia, dizziness, and drowsiness are typical adverse effects of sodium channel blockers. Giving two agents with the same mechanism of action increases the rate of the typical adverse effects and results in lower adherence rates thus clinicians should avoid combining two agents with the same

mechanism of action.[9] Depression and AED side effects independent of seizure control correlate with health- related quality of life in epilepsy.[10] The epilepsy quality measures from the American Academy of Neurology include asking about and managing adverse effects and screening for psychiatric conditions at each visit.[11] Management of adverse effects includes lowering the dose if possible or switching to a different mechanism of action AED.

Adherence with AEDs is vital for success in managing epilepsy. It is important that an appropriate AED for the seizure type(s) and patient's associated conditions which is more likely to provide seizure control is selected. If possible, once or twice daily dosing is preferable to enhance adherence. Adherence with once a day AEDs is 87 percent compared with 81 percent for twice daily dosing.[12] Because medication adherence is so important, clinicians should be pro-active with adherence strategies, including old ones such as medication boxes and new ones such as cell phone reminders. Clinicians need to recognize the challenge of adhering with daily medications, especially in someone who has one or two seizures per year. Setting realistic expectations about side effects is an important component of patient education. Most AEDs cause some adverse effects, but the goal is tolerable, acceptable adverse effects. Clinicians also need to facilitate adaptive coping and self-management. A therapist, psychologist, or social worker will be needed to help patients and families change maladaptive behaviors that frequently occur with seizure disorders.

Conclusion

Optimal epilepsy treatment depends on accurate epilepsy classification, an individualized treatment plan, and medication adherence. Minimizing treatment-related adverse effects is essential for treatment efficacy. Associated conditions can be as disabling or more disabling than seizures and require multidisciplinary treatment. An epilepsy treatment team is essential to success in managing these patients.

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Improving Patient Outcomes with Novel Treatment Strategies in the Management of Multiple Sclerosis

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

A wide range of effective disease-modifying therapies are available for the relapsing/remitting subtype of multiple sclerosis (MS) and one is available for primary/progressive MS. Managing appropriate access to these expensive medications is a major issue for payers. Payers need to identify new strategies to manage these agents, especially as more agents reach the market.

Key Points

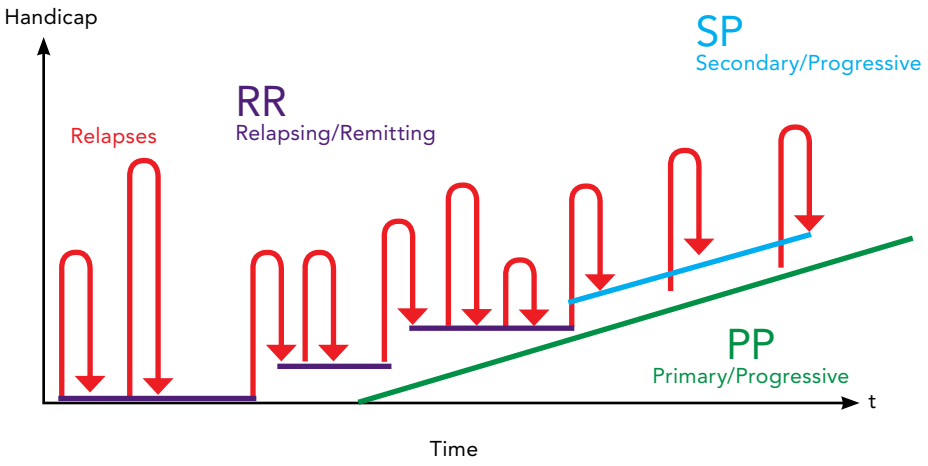
- Understanding of the pathophysiology of MS is changing and is essential to future management by payers.
- All the available MS medications reduce the annualized relapse rate, disability, and MRI evidence of disease in relapsing/remitting MS.
- One agent is now available for primary/progressive MS.
- Payers need to adopt new strategies such as managing MS treatments based on mechanism categories, managing site of service, emphasizing achieving no evidence of disease activity, and supporting patient medication adherence and persistence.

MULTIPLE SCLEROSIS (MS) IS AN AUTOIMmune neurodegenerative disorder of the central nervous system (CNS). Over 400,000 people in the United States (U.S.) have MS with 8,500 to 10,000 new cases identified annually. Worldwide, there are one to 2.3 million cases. Women with MS outnumber men three to one. MS is most commonly diagnosed during the prime of life (between ages 15 and 45).

Several subtypes of MS are recognized. Clinically isolated syndrome (CIS) is the first MS attack and most often presents with long tract symptoms/signs, optic neuritis, or brainstem, cerebellar, or spinal cord syndrome, While CIS is by definition isolated to a single attack in time, it is not necessarily isolated in space. Approximately one-quarter of patients present with multifocal abnormalities. Radiologically isolated syndrome (RIS) is characterized by incidental brain MRI findings highly suggestive of multiple sclerosis in the absence of signs or symptoms of the disease. Eighty-five percent of MS cases present as relapsing/remitting MS (RRMS), which is characterized by episodes of relapse (Exhibit 1). Without treatment, 50 percent of these patients develop secondary-progressive MS (SPMS), with significant disability within 10 years. SPMS is when an initial relapsing patient transitions to slow worsening disease. The natural history of MS is to start out as relapsing, then transition to the secondary/progressive subtype. The remaining 10 to 15 percent of patients will have primary/progressive MS. These patients have a slow worsening (typically in gait) from onset. Primary progressive has about equal gender onset and a decade later age of onset. Additionally, these patients may have superimposed relapses.

The diagnosis of MS requires evidence of damage in at least two separate areas of the CNS, evidence

Exhibit 1: MS Subtypes



that the damage occurred at least one month apart, and other diagnoses have to be ruled out. Evidence of CNS damage can be seen on MRI scan and may include enhancing and non-enhancing lesions. Other diagnoses should be considered if there is family history of neurologic disease other than MS, a well demarcated spinal level in the absence of disease above the foramen magnum, prominent back pain that persists, symptoms and signs that can be attributed to one anatomical site, age over 60 years of age or less than 15 years at the onset of disease, rapidly progressive disease, or symptoms of systemic disease such as weight loss or fever.

Our understanding of the pathophysiology of MS is changing and is essential to future management by payers. Both T and B cells appear to be involved in the pathogenesis of MS (Exhibit 2). The predominant hypothesis of how MS starts is that auto-reactive T lymphocytes cross the blood-brain barrier (BBB) and trigger inflammatory events which results in axonal demyelination and neuronal damage. Normally, the BBB prevents entrance of T cells into the nervous system. Infection or another environmental trigger decreases the integrity of the BBB allowing T cell entry. When the blood–brain barrier regains its integrity, usually after the infection has cleared, the T cells are trapped inside the brain.

The immune system attacks the nervous system, forming plaques or lesions commonly involving brain white matter. These attacks destroy oligodendrocytes causing demyelination. Re-myelination occurs in the early phase of the disease but is never complete restoration. Repeated attacks lead to less re-myelination and to disability. T cell attacks on myelin trigger additional inflammatory processes, stimulating other immune cells and soluble factors like cytokines and antibodies. Leaks form in the BBB causing swelling, activation of macrophages, and more activation of cytokines and other destructive proteins

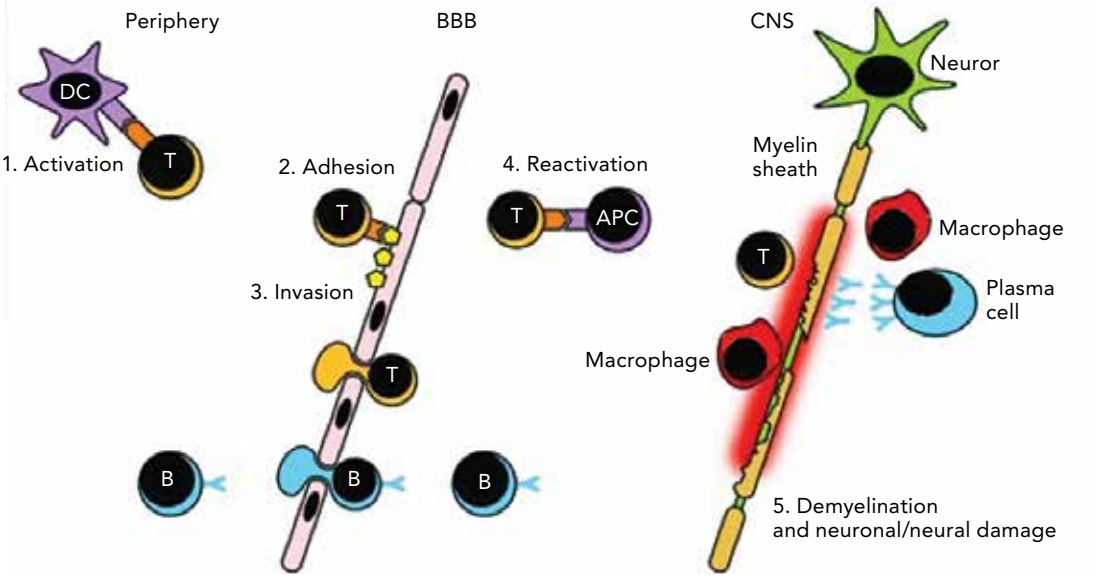
CNS lesions in MS patients contain B cells, plasma cells and antibodies. The level of B-cell involvement may vary in MS patients. Besides differentiating into antibody-secreting plasma cells, B cells may contribute to the development and progression of CNS autoimmune disease as antigen-presenting cells for activation of T cells. Newer MS therapies target B and T cells.

The goal of treatment of MS is to reduce the relapse rate or prevent relapse completely to prevent disability. Starting in 1995, the development of disease-modifying therapy (DMT) that targeted the immune defects in MS revolutionized treatment. The first-generation agents [interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), and glatiramer acetate (Copaxone®] have extensive evidence for treating MS and still have a large number of users and new starts. These agents reduce the annualized relapse rate, disability, and MRI evidence of disease in RRMS and are also known as platform agents. [1]

Interferon beta, administered by self-injection, was the first class of medications approved by the FDA for MS. The most common adverse effects are injection site reactions and flu-like symptoms. Neutralizing antibodies may reduce the bioavailability of interferon.

Interferon beta diminishes the ability of activated

Exhibit 2: Immune Cells in MS



DC = dendritic cell
T = T cells
B = B cells
APC = antigen presenting cell

T cells to cross the blood-brain barrier and enter the central nervous system parenchyma.

Glatiramer, also self-injected, is a polymer of four amino acids that is an inducer of specific T helper 2 type suppressor cells. Common adverse effects are injection site reactions, chest pain, flushing, dyspnea, and palpitations. It is the only MS treatment with pregnancy category B.

Natalizumab (Tysabri®) is an integrin α4 blocker which stops circulating lymphocytes from entering the CNS. Given as monthly infusions, it provides effective relapse suppression (68% reduction compared to placebo).[2] Progressive multifocal leukoencephalopathy (PML) is a rare potentially fatal adverse effect that occurs in about 0.1 percent of patients. This adverse effect occurs in people with John Cunningham viral infections (JC virus). The JC Virus is a polyomavirus and infection is almost universal, but the virus is dormant in the majority of the adult population. Risk of PML can be assessed with JC virus testing. The risk of PML appears to increase with time on treatment; the rate is very low in the first year and increases after two or more years of therapy.

The second generation of MS agents began with the approval of oral DMT, including fingolimod, teriflunomide, and dimethyl fumarate. Fingolimod (Gilenya®), an oral sphingosine-1-phosphate receptor modulator, induces rapid and reversible sequestration of lymphocytes in lymph nodes and prevents activated and autoreactive cells from migrating to the CNS. Lymphocytes remain functional and may still be activated as part of an immune response. Relapse reduction is 55 percent with this agent. Because of potential for bradycardia and atrioventricular block, the first dose must be given in the hospital. Other adverse effects of concern are macular edema and hypertension. Teriflunomide (Aubagio®) inhibits pyrimidine synthesis and binds dihydroorotate dehydrogenase thus inhibiting T-cell division. Fumarate is a naturally occurring molecule that is essential for cellular oxidative respiration (citric acid cycle). Dimethyl fumarate's (DMF, Tecfidera®) is formulated into enteric-coated oral microtablets contained in a capsule. The compound (and its metabolite, monomethyl fumarate) activates the nuclear (Nrf2) pathway and has been identified as a nicotinic acid receptor agonist in vitro, but the precise mechanism of action is unknown. These oral agents have the advantages of oral convenience, very good efficacy, and good tolerability. On the negative side, there is limited experience with using the oral agents and no long-term safety or efficacy data.

The newest wave of MS treatments are better targeted to the underlying immune issues in MS. Alemtuzumab (Lemtrada®), a recombinant human-

Exhibit 3: Ensure Access to All Categories for Appropriate Patients

Drug Category	Agent(s)	Comments
Immunomodulators	Interferon-beta, glatiramer acetate, dimethyl fumarate, daclizumab	All generally considered "first-line" except daclizumab
Inhibitors of Cell Replication	mitoxantrone, teriflunomide	Mitoxantrone rarely used in 2017
Cell depletion agents	alemtuzumab, ocrelizumab	Act on T and B cell lines More agents in the pipeline
Altered Cell Trafficking	natalizumab, fingolimod	More agents in the pipeline

ized monoclonal antibody that targets CD52, a glycoprotein present at high levels on the surface of mature T and B lymphocytes and cells of the monocyte lineage and eosinophils. Treatment with alemtuzumab produces a rapid and prolonged immune cell depletion, particularly for T cells. Alemtuzumab is administered as an intravenous injection over two hours and is given as two infusions one year apart. Alemtuzumab provides durable efficacy through five years after treatment, with around 60 percent of patients having no disease activity over that period of time.[3] This medication has black box warnings about cytopenias, infusion reactions, and infections. Treated patients require anti-infective prophylaxis to reduce risk of infection due to the severe and prolonged lymphopenia. There is a recommended maximum dose of 90 mg/week to avoid risk of pancytopenia. Alemtuzumab is pregnancy category C.

Daclizumab (Zinbryta®) is an anti-CD25 agent that was first approved for prevention of renal allograft rejection by the FDA in 1997. It inhibits T-cell and B-cell activation by interleukin-2 (IL-2) by binding to the IL-2 receptor α-chain. It was FDA approved for treating relapsing forms of MS in 2016 and reduces annualized relapse rate by 45 percent compared with interferon beta.[4]

Ocrelizumab (Ocrevus®) is a humanized anti-CD20 monoclonal antibody that targets mature B lymphocytes and hence is an immunosuppressive drug. It depletes B cells via antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. It was the first therapy specifically approved for PPMS and was also approved for RRMS in early 2017. Treatment with this agent leads to a statistically significant reduction in disease activity as measured by brain lesions (measured by MRI scans) and a 46 to 47 percent reduction in relapse rate compared to interferon.[5] Among patients with PPMS, ocrelizumab was associated with modestly lower rates of clinical and MRI progression than placebo.[6]

Numerous agents are also under investigation for MS treatment. This includes firategrast (anti-α4β-integrin), ofatumumab (anti-CD20), ibudilast (selective PDE4 inhibitor), and opicinumab (human aglycosyl IgG1 monoclonal antibody).

MS treatments are actively managed by most managed care plans because of the cost related to these agents. Most plans have a preferred agent for starting therapy and stepped approaches. Almost all of these agents must have prior authorization before they are approved for reimbursement.

There are no guidelines for the treatment of MS because there is currently insufficient Class I evidence for a detailed MS treatment algorithm. The lack of definitive clinical evidence to guide MS treatment decisions has become increasingly important as the number of therapeutic options continues to increase annually. Payers struggle with which drug is right for which patient, while balancing cost, outcomes and access.

Several years ago, Miller and colleagues used a modified Delphi approach to develop consensus statements regarding MS management approaches from a panel of U.S. managed care pharmacists and physicians presently or previously involved in the

formulary decision-making process at their organization.[7] Some of the consensus statements from the group which are still relevant include 1) DMT therapy initiation for patients with CIS is a provider decision; 2) most patients with clinically definite MS should be treated with a DMT and 3) access to natalizumab should be limited to use for the FDA approved indication. Most importantly, the payers in this study identified medication adherence and the need for patient adherence support as vital to successful MS treatment.

The current method of managing MS medications is to divide them up into platform therapies, oral agents, and infusion agents. It is probably better to divide up the therapies as immunomodulators, inhibitors of cell replication, cell depletion agents, and altered cell trafficking (Exhibit 3). As we think about formulary management moving forward, it will be important to have patient access to agents in each category.

Managed care plans must conduct their own assessments of literature and data with the newer agents and their roles in therapy. They can work with physicians to assess the role(s) of newer therapeutic agents. Plans should consider establishing quality metrics to improve outcomes and use patient education and support programs to enhance adherence.

Plans actively managing medication adherence will go a long way toward maximizing the benefit of these expensive agents. Payers make a large "lifetime investment" in MS treatments because treatment has to be continued for many years. Quite often, patients stop their MS medications because they do not feel better, the adverse effects make them feel worse than the disease, a relapse occurred and the patient thought the medication was not working, insurance coverage issues, and inability to afford co-payments. In one retrospective trial examining natalizumab adherence, those patients who were adherent and persistent with therapy had significantly lower costs related to relapses.[8]

Managing the site of service for the infused MS treatments is another cost containment option for payers. A retrospective analysis on the impact of site of care on utilization adherence and cost in four geographic areas found that hospital outpatient administration was the most costly and that a physician's office and home infusion were less expensive.[9] Thus, managing site of service of infused agents can have substantial cost impact,

MS probably should have a goal similar to rheumatoid arthritis's "treat-to-target." In MS, this is called no evidence of disease activity (NEDA). This is complete absence of detectable disease activity while on a DMT. The criteria are no MRI lesion activity (Gd-enhancing lesions, new/enlarged T2 lesions), no clinical relapses, and no disability worsening. The hope is that achieving NEDA and maintaining it will maximize long-term outcomes, such as neurologic function and health-related quality of life through effective prevention of MS-related CNS tissue damage. NEDA rates are increasingly being reported in clinical trials and beginning to be used at MS centers. Managed care plans could adopt NEDA rates as a quality measure of MS care.

Conclusion

The management of MS continues to evolve with the development of additional DMTs. DMTs reduce the annualized relapse rate, disability, and MRI evidence of disease in relapsing/remitting MS, but at a significant cost. Formulary management of these agents is necessary to manage the ongoing use of them. Payers need to adopt new strategies such as managing MS treatments based on mechanism categories, managing site of service, emphasizing achieving NEDA, and supporting patient medication adherence and persistence.

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Navigating a Complex Treatment Landscape in Advanced Non-Small Cell Lung Cancer

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Summary

The treatment of non-small cell lung cancer (NSCLC) continues to advance and get more complicated. Treatment advances have improved survival. Treatment is now selected based on histology and molecular biomarkers; however, for the majority of patients, treatment is still chemotherapy rather than targeted therapy or immunotherapy.

Key Points

- Advanced NSCLC is an increasingly complex disease.
- Histology and selected molecular biomarkers (EGFR, ALK, ROS1, and PD-L1) drive therapeutic choices.
- Platinum-based doublet chemotherapy remains the standard for the majority of patients.
- Anti-VEGF and anti-EGFR antibodies play a selective role in therapy.
- Immunotherapy is now a first-line and second-line standard therapy for some patients

LUNG CANCER IS THE MOST COMMON cause of cancer-related mortality in the United States (U.S.). It accounts for more deaths than breast, prostate, and colorectal cancers combined. The median age of diagnosis is 70 years, with the major risk factor being smoking. However, 25,000 to 30,000 never-smoking Americans will develop lung cancer this year. Unfortunately, most patients are at an unfavorable stage at the time of diagnosis, primarily because screening is not routinely practiced.

Stage IV or metastatic non-small lung cancer (NSCLC), the focus of this article, is a treatable but not curable disease. The goal in Stage IV care is controlling the disease to improve patient symptoms and quality of life and limiting adverse effects of treatment.

Overall, lung cancer is histologically and molecularly a very heterogeneous disease and has historically been shrouded by therapeutic nihilism. Traditionally, lung cancer has been divided into small cell and non-small cell and then non-small cell is further divided by histology. With advances in genetic testing, NSCLC is now divided into numerous molecular subtypes.

The numerous molecular subtypes are important in determining treatment. According to the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology guidelines, patients with NSCLC and adenocarcinoma histology should have at least epidermal growth factor receptor (EGFR) mutation and ALK fusion testing at the time of diagnosis, not just when a treatment decision is needed.[1] The National Comprehensive Cancer Network (NCCN) guidelines also recommend proto-oncogene tyrosine-protein kinase (ROS) testing for these same patients.[2] Testing for anaplastic lymphoma kinase (ALK) rearrangements, ROS rearrangements, and EGFR mutations can be considered in patients with squamous cell histology

Exhibit 1: Summary of Benefits of Liquid Biopsy in a Clinical Setting

Tissue	ctDNA
Invasive • Costs • Complications • Delays	No Invasive Blood Draw
Qualitative	Qualitative
Limited by sample collection and heterogeneity	Not limited by sample collection and heterogeneity (tumor summary); real-time monitoring
Total Time to Treatment (TTT) 3 - 8 weeks	TTT: ≤ 14 days

if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported. Testing for other mutations including v-Raf murine sarcoma viral oncogene homolog B (BRAF), V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), MET proto-oncogene, receptor tyrosine kinase (MET), and RET proto-oncogene (RET) may also be appropriate. A challenge in lung cancer management is making sure large enough biopsy samples are obtained for all the necessary genetic testing.

Immunohistochemistry testing for programmed death ligand-1 (PD-L1) expression is recommended before first-line treatment in patients with metastatic NSCLC with negative or unknown test results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements to determine if immunotherapy is appropriate. Retesting should take place after a targeted therapy intervention at the time of relapse to assess for tumor evolution in the molecular profile.

Molecular testing is important because it has an impact on survival.[3] Those patients who have a mutation for which targeted therapy exists and who receive that therapy have longer median overall survival (mOS) compared to patients without such mutations.

Another way of testing for mutations is with liquid biopsy. Tumor cells release small fragments of DNA into circulation which can be detected using liquid biopsy (circulating tumor DNA, ctDNA).[4,5] Cancer-associated genetic alterations can be detected in ctDNA, including point mutations, copy number variations, chromosomal rearrangements, and methylation patterns. Blood and urine can both be used for ctDNA testing. Circulating tumor cells can also be used to evaluate genetic changes with treatment.[6] Exhibit 1 lists some of the benefits of ctDNA compared with tissue biopsy. When to use a liquid or tissue biopsy is a case-by-case decision.

Tissue biopsy has been the gold standard for diagnosis and staging in human malignancies. Accurate histologic classification and molecular profiling is paramount in NSCLC. Tissue procurement often has its limitations, both biologically as well as practically. Tissue and ctDNA testing should be viewed as complementary. Understanding the strengths and limitations of both are necessary for optimal patient management.

There is targeted therapy for NSCLC with EGFR and ALK mutations. In approximately 10 percent of adenocarcinoma cases, EGFR is mutated, which allows unregulated cell growth.[7] Certain EGFR mutations make tumors sensitive to tyrosine kinase inhibitors (TKIs), whereas others such as the insertion 20 mutation confer resistance to TKIs. Gefitinib, erlotinib, and afatinib are the available TKIs and are first-line therapy for EGFR mutation-positive NSCLC. Afatinib is the most efficacious and gefitinib causes the lowest toxicity, but most oncologists use erlotinib because of familiarity with this agent.

Resistance to TKI therapy occurs in a great deal of patients. The majority are caused by T790M, a specific acquired mutation, but there can be other acquired resistance mechanisms.[8] There can even be histologic transformation to small cell disease. Osimertinib (Tagrisso®), a third-generation TKI, is approved for treating T790M mutation-positive patients.

ALK rearrangement occurs in 2 to 7 percent of NSCLC cases, depending on the population tested. Common features of this type of NSCLC are younger age (50s) at onset, never smokers, adenocarcinoma, and central nervous system (CNS) metastasis. It is identified by immunohistochemistry testing. Crizotinib (Xalkori®) has been a standard therapy for patients with metastatic ALK+ NSCLC since it was FDA approved. It results in a 74 percent overall response rate (ORR), 10.9 month progression-free survival (PFS) and 84 percent survival probability

Exhibit 2: Selected Other Mutations in NSCLC

Oncogene	Prevalence %	Therapies in Clinical Development	Therapies in Preclinical Development
KRAS mutations	25 - 30	MEK, P13K, FAK inhibitors	KRAS G12C inhibitors, MEK and PI3K inhibitors, JAK/TBK1/KK inhibitors
ROS1 rearrangements	1 - 3	Ceritinib	ROS inhibitors, Hsp90 inhibitors
HER2 mutations	1 - 3	ERBB/HER2 inhibitors (neratinib, afatinib, dacomitinib, trastuzumab, TDM-1), mTOR/PI3K inhibitors	HER2 inhibitors, Hsp90 inhibitors
BRAF mutations	1 - 3	Vemurafenib, dabrafenib, MEK inhibitors (selumetinib, trametinib), dasatinib	RAF inhibitors
RET rearrangements	1	Cabozantinib, vandetabin, sunitinib, ponatinib	RET inhibitors, Hsp90 inhibitors
MET amplification	1	Crizotinib, tivantinib, onartuzumab, other MET inhibitors	MET inhibitors
MET exon 14 mutation	3	Crizotinib, cabozantinib	MET inhibitors
NTRK1 rearrangements	<1	Crizotinib	TRKA inhibitors

at 12 months in the first-line setting.[9] This agent is really a MET inhibitor that has some ALK activity, so there has been great interest in developing ALK-specific agents. Ceritinib (Zykadia®), alectinib (Alecensa®), and brigatinib (Alunbrig®) are all FDA approved second-generation ALK inhibitors. The ORR for these three agents are in the 50 to 56 percent range and PFS in the range of 6.9 to 12.9 months. These agents are also active in CNS disease. Comparison data from studies between these agents and crizotinib are now being published. In a Japanese trial, alectinib was more efficacious than crizotinib.[10] The doses used in Japan are half those used in the U.S. and their population is genomically very different from the U.S. A trial of alectinib versus crizotinib in a U.S. and European population found that alectinib reduced the risk of cancer progression or death by 53 percent compared with crizotinib.[11] Alectinib extended the median time to progression by about 15 months (median progression-free survival was 25.7 months with alectinib and 10.4 months with crizotinib). At 12 months, the incidence of brain metastases was much lower with alectinib than with crizotinib (9% vs 41%). Alectinib, ceritinib, and crizotinib are all listed as first-line agents for ALK rearrangement disease in the NCCN guidelines.[2] Alectinib is particularly active in the CNS. Side effect profiles may impact selection of a first-line ALK inhibitor.

The ALK rearrangement population is different from the EGFR population when it comes to therapy resistance. There are several possible mechanisms of resistance including amplification of the ALK fusion, mutation of the ALK kinase domain, and bypass signaling (where the tumor cells are using other growth pathways). Only about 25 percent of cases have a second mutation in ALK and about 15 different mutations have been found. In the past, most clinicians did not believe that, beyond the clinical trial setting, re-biopsy was informative to the treatment decisions in the ALK rearrangement population. This approach will likely change as the use of the second-generation ALK agents increases. Emerging data suggest that newer ALK inhibitors alter the spectrum of resistance mutations, inducing more ALK resistance mutations.[12]

Crizotinib is effective for NSCLC with ROS-1 translocation. This mutation only occurs in 1 or 2 percent of cases. There are numerous other mutations that have been identified in NSCLC for which targeted therapies are under development or currently approved for other indications and used off label (Exhibit 2).[13,14]

Immunotherapy is the other new area of treatment of NSCLC. PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and T cell function. Antibodies to PD-1 or PD-L1 binds PD-1 receptors on T cells and disrupts negative signaling to restore T cell antitumor function. Three agents are currently FDA approved (Exhibit 3). These agents work best in those with high expression of PD-L1 (> 50 %), which occurs

Exhibit 3: Immunotherapy Agents Currently Approved in Advanced NSCLC

- **Nivolumab (Opdivo)*** – 2nd line, all histologies, every two week schedule, complementary diagnostic (28-8)
- **Pembrolizumab (Keytruda)*** – 1st and 2nd line, all histologies, every three week schedule, companion diagnostic (22C3)
- **Atezolizumab (Tecentriq)^** – 2nd line, all histologies, every three week schedule, complementary diagnostic (SP142)

*anti-PD-1
^anti-PD-L1

in 15 to 25 percent of cases. Pembrolizumab (Keytruda®) is recommended in the NCCN guidelines as first- line therapy in patients with metastatic NSCLC without activating mutations and PD-L1 expression greater than 50 percent. It is first line because it has been shown to be better than platinum-based doublet chemotherapy in this population with a superior PFS, OS, and ORR. [15] In the trial leading to this NCCN recommendation, six complete responses were observed with pembrolizumab.[15] Treatment-related adverse effects were lower with pembrolizumab compared with chemotherapy. In the second-line setting, all three immunotherapies are approved and work modestly in those who do not have high expression.

Approximately two-thirds of NSCLC patients do not have the biomarkers for which targeted therapy nor immunotherapy are indicated. Chemotherapy is still the treatment choice. Platinum-based doublet chemotherapy is the standard. Three to four cycles of therapy lead to similar survival outcomes compared to six or more cycles, so most therapy should be discontinued after four cycles. Importantly, chemotherapy does not negatively impact quality of life and can improve symptom control by shrinking tumors.

Bevacizumab (Avastin®), an anti-vascular endothelial growth factor (VEGF) agent, is also effective in nonsquamous NSCLC for appropriate candidates.[16] It is not appropriate for those with squamous disease because of high rates of hemoptysis. This agent decreases blood vessel growth and thus "starves" tumors. It is typically given in combination with chemotherapy.

Maintenance therapy has been demonstrated to improve PFS and OS. Bevacizumab and pemetrexed (Alimta®), a chemotherapy agent, are approved for maintenance therapy in non-squamous NSCLC. Combination maintenance therapy has been shown to improve PFS but not OS, so a single-agent therapy is most commonly used.

Second- and third-line therapies are also an option for these patients at the time of relapse. The guidelines are frequently being updated on which therapies are recommended at what line, so clinicians and managed care should consult the most recent versions to know the current recommendations.

Conclusion

Advanced NSCLC is an increasingly complex disease. Histology and selected molecular biomarkers (EGFR, ALK, ROS1, PD-L1 and others) drive therapeutic choices. Platinum-based doublet chemotherapy remains the standard for the majority of patients. Anti-VEGF and anti-EGFR antibodies play a selective role in therapy. Immunotherapy is now a first-line therapy for selected patients with high PD-L1 expression and second-line therapy.

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Improving Diagnosis and Treatment Strategies for Major Depressive Disorder

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

Major depressive disorder (MDD) is a costly disease in terms of quality of life, morbidity, and mortality. Several strategies can improve care, including measurement-based care and selecting antidepressants and augmentation therapy based on safety and efficacy data.

Key Points

- Changes in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria allow for specifiers, including mixed features (MF).
- Distinguishing MDD from MDD-MF or bipolar disorder impacts treatment choice.
- Measurement-based care can improve outcomes.
- Switching antidepressants versus augmentation in the face of inadequate response remains a conundrum.
- New antidepressants and augmentation strategies provide additional choices and can be characterized using safety and efficacy data.

DEPRESSION IS THE MOST COMMON DIagnosis among patients seen by psychiatrists in the United States (U.S.) and is a serious, chronic, disabling illness affecting more than 300 million people worldwide.[1,2] Depression results in a substantial burden of disease to both the individual and society.[3] Despite treatment, residual symptoms are common and cause significant psychosocial and occupational functional impairment.[4,5] Residual symptoms also increase risk for recurrent depression episodes.

The DSM-5 includes nine different types of depressive disorders and nine different specifiers.[6] The specifiers include such things as with atypical features or with catatonia. Core mood criterion for major depressive disorder (MDD) now includes hopelessness as a subjective report in addition to feeling sad or empty, potentially broadening the diagnosis. DSM-5 allows for clinical judgment in distinguishing normal reactions to significant loss from a disorder in need of clinical attention, whereas the prior version had a carefully worded bereavement exclusion. The nine new specifiers of MDD allow characterization of additional symptoms. The elimination of the not otherwise specified (NOS) designations have been replaced with other specified disorders and unspecified disorders. The criteria for MDD are shown in Exhibit 1.[6]

The addition of the MF modifier to the diagnostic criteria was an important advance. There are people with depression who clearly have features of bipolar disorder but are not bipolar. MDD with the mixed features (MDD-MF) is different from MDD and bipolar disorder and has treatment and prognosis implications. Criteria are met for MDD-MF if the patient is having a major depressive episode and three or more of the following manic/hypomanic symptoms are present during the majority of days of the current or most recent episode of depression: increased mood; increased self-esteem or grandiosity; talkative/pressured speech; flight of ideas/racing thoughts; increased energy or goal-directed activity; increased activities with high potential for painful consequences; and decreased need for sleep (not insomnia). These patients typically have

Exhibit 1: Major Depressive Disorder Criteria[6]

A. ≥ 5 of 9 symptoms present for 2-week period and ≥ 1 of the symptoms is either (1) depressed mood or (2) loss of interest/pleasure; other symptoms such as change in weight/appetite, insomnia/hypersomnia, agitation/retardation observed by others, fatigue/loss of energy, worthlessness/guilt, inability to think/concentrate/make decisions, thoughts of death/suicide

B. Significant distress or impairment

C. Not attributable to the physiological effects of a substance or to another medical condition

D. Exclude schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders

E. There has never been a manic episode or a hypomanic episode

a younger onset age, recurrent episodes, greater risk for suicidality, more functional impairment and unemployment, more alcohol/substance use comorbidity, more cardiovascular disease, and a rapid cycling course often compared with typical MDD. Treatment of MDD-MF should be the same as for treatment of bipolar disorder including avoidance of antidepressant monotherapy, which can provoke a manic episode.

MDD-MF has to be distinguished from bipolar disorder. Bipolar disorder is defined by having major depressive episodes and manic/hypomanic episodes. Bipolar type I is when there is a history of manic episodes. Bipolar type II is when there is a history of hypomanic episodes, but no manic episodes.

It is easy to misdiagnose bipolar disorder for MDD because patients can present with a depressive episode as the first manifestation. Up to 69 percent of persons with bipolar disorder are misdiagnosed initially.[7] It requires almost 10 years, a mean of 3.5 diagnoses and four clinicians before receiving the right diagnosis.[7] Comorbidity is common with bipolar depression and can be confusing. Fifty to 70 percent of patients have at least one comorbid psychiatric or mental condition.[8] Examples include anxiety, substance use, obesity, and cardiovascular disease. As many as one in five primary care patients who have clinically significant depressive symptoms and are receiving antidepressant treatment actually have bipolar I or bipolar II disorder.[9] Overall, an incorrect diagnosis leads to an incorrect prognosis and incorrect treatment.

Measurement-based care (MBC) is a relatively new practice in psychiatry because traditionally managing psychiatric conditions did not have easy measures like blood pressure. It can be helpful in improving outcomes with depression treatment. Components of MBC may include antidepressant dosage, depressive symptom severity, medication tolerability and safety, and adherence to treatment.[10] Steps of MBC include screening and identification of MDD, antidepressant selection based upon treatment history, assessment-based medication management, and ongoing care. MBC can also be used to monitor the disease course and effects of treatment and guide treatment change.[11]

Patient-reported outcome scales can be helpful in getting patients to be honest about their symptoms. These scales, such as the patient health questionnaire-9 (PHQ-9), can be used to determine medication efficacy.[12] The PHQ-9 asks about anhedonia, depressed mood, sleep, feeling tired, appetite change, guilt or worthlessness, concentration, slowed down or restless, and suicidal thoughts. This scale is scored with 0 to 3 points per questions for a total of 27 points. Higher scores indicate worse depression; a score greater than 15 indicates major depression. In a trial comparing usual care with MBC, response rates (controlling for demographic variables) were 59.7 percent and 67.0 percent, respectively [number needed to treat (NNT) = 14].[13]

The mainstay approaches to treating MDD are pharmacotherapy, with or without psychotherapy. Selection of initial treatment should consider clinical features, and patient preference and experience.[14] An antidepressant is recommended as initial treatment for mild to moderate MDD, and definitely for severe MDD. Since effectiveness is similar across antidepressants, the initial selection should largely be based on anticipated side effects and their tolerability for the individual and on the pharmacological properties of the medication such as half-life and drug interactions. Additional factors, such as prior medication response, cost and patient preference should also be considered. Antidepressant effectiveness is similar between and within classes. Response

Exhibit 2: Likelihood to be Helped or Harmed[16]

Antidepressant	NNT vs. Placebo for response	NNH vs. Placebo for discontinuation because of an adverse event	LHH
Duloxetine	5.7	24.5	4.3
Escitalopram	6.7	30.7	4.6
Levomilnacipran	9.8	18.2	1.8
Sertraline	5.3	6.5	1.2
Venlafaxine	5.7	7.8	1.4
Vilazodone	8.0	26.1	3.3
Vortioxetine	8.4	42.7	5.1

NNH = number needed to harm
NNT = number needed to treat
LHH = likelyhood to be helped or harmed

Exhibit 3: Reasons for Nonresponse[14]

- Inaccurate diagnosis
- Unaddressed co-occurring medical or psychiatric disorders, including substance use disorders
- Inappropriate selection of therapeutic modalities
- Inadequate dose of medication or frequency of psychotherapy
- Pharmacokinetic/pharmacodynamic factors affecting medication action
- Inadequate duration of treatment
- Nonadherence to treatment
- Persistent or poorly tolerated side effects
- Complicating psychosocial and psychological factors
- Inadequately trained therapist or poor "fit" between patient and therapist

rates in clinical trials typically range from 50 to 75 percent. First-line antidepressants (selective serotonin reuptake inhibitor, selective norepinephrine reuptake inhibitor, mirtazapine or bupropion) are optimal for most patients.

There are a few newer antidepressants including vilazodone (Viibryd®), levomilnacipran (Fetzima®), and vortioxetine (Trintellix®). Because these agents are only available as branded products, they are more costly than the older generic agents. The role for them is as an option for second-line therapy. Vilazodone and vortioxetine cause lower rates of weight issues and sexual dysfunction. Each of these also have slightly different mechanisms of action than previous agents. Dosing for each of these requires titration to minimize adverse effects, particularly nausea.

Choosing among medications for MDD can be done using the likelihood of success (response, remission) and problematic adverse effects.[15] Number needed to treat (NNT) is used to describe the possibility of success and the lower the NNT, the better. The likelihood of encountering problematic adverse effects is the number needed to harm (NNH). This number is very different from drug to drug and the higher the NNH, the better. A caveat - if an individual patient prefers one medication over the other, choosing based on NNT and NNH does not matter.

Combining the two measures (NNT and NNH) can produce a likelihood to be helped or harmed (LHH): For example, vortioxetine is 5.1 times more likely to result in a therapeutic response than a discontinuation because of an adverse effect.[16] Thus, its LHH is 5.1. Values for some antidepressants are shown in Exhibit 2.[16] These data are from placebo controlled trials.

An important goal of MDD treatment is to eliminate symptoms or reduce them to a very low level. Residual symptoms are a risk factor for recurrent episodes.

Exhibit 4: Augmentation Agents[18-21]

Adjunctive Agent	Level of Evidence	NNT	NNH	LHH
Aripiprazole 2-20 mg/d	1	7	43	6.1
Brexpiprazole 1-3 mg/d	1	12	53	4.4
Quetiapine-XR 300 mg/d	1	9	8	0.9
Olanzapine-Fluoxetine (6-18/25-50 mg/d)	1	11	12	1.1
Risperidone	1	8	*	*
Blupropion	2	*	*	*
Lithium	2	*	*	*
Mirtazapine/mianserin	2	*	*	*
Modafinil	2	*	*	*
Triiodothyronine	2	*	*	*
TCAs (e.g., desipramine)	2	*	*	*
Other antidepressants	3	*	*	*
Other stimulants (methylphenidate, etc.)	3	*	*	*
Ziprasidone	3	*	*	*

* data not available

Not everyone responds to the initial antidepressant. Exhibit 3 lists some of the reasons for nonresponse to antidepressants.[14] Medication strategies to address nonresponse to treatment include dose optimization, change to another antidepressant, augment by adding depression-focused psychotherapy, or augment by adding a non-monoamine oxidase inhibitor antidepressant or a non-antidepressant medication, such as a second-generation antipsychotic, lithium, or a thyroid hormone.[14] Nonresponders to antidepressant monotherapy during acute treatment of major depression are often switched to a new antidepressant. A meta-analysis of several trials found that switching was not superior to continuation.[17] Other trials have shown that for an individual patient sequential prescribing of different classes of antidepressants can increase the response rate, but it can be a long process.

Augmentation is the other option. This approach is especially helpful if the patient is responding to an antidepressant but needs additional symptom reduction. When augmenting, not all agents have the same level of evidence or recommendation for use (Exhibit 4).[18-21] Level 1 evidence is a meta-analysis with narrow confidence intervals and/or two or more randomized clinical trials (RCT) with adequate sample size, preferably placebo controlled. Level 2 evidence is a meta-analysis with wide confidence intervals and/or one or more RCT with adequate sample size. Level 3 is the lowest quality evidence with small-sample, randomized trials or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies. Only the second-generation antipsychotic agents olanzapine, aripiprazole, quetiapine extended release, and brexpiprazole are FDA approved for depression treatment in combination with an antidepressant. The first-line agents based on efficacy, tolerability, and cost are aripiprazole, quetiapine, and risperidone. Olanzapine is not considered first line because of the high rates of

weight gain with this agent. Brexpiprazole is considered second line because it is a newer agent with less data and is more expensive. Using LLH, aripiprazole should be the first antipsychotic chosen (Exhibit 4).

Adjunctive antipsychotics are underused. In an online survey about adjunctive antipsychotic prescribing for patients with MDD and inadequate response to antidepressants, 24 percent of physicians considered adding an antipsychotic, but only 13 percent actually prescribed it.[22] Physicians tend to reserve antipsychotics for more severe illness and greater functional impairment, and for those who have already failed a number of treatment options. Symptoms such as depressive features, anxiety, psychotic symptoms, and irritability also prompted physicians to prescribe antipsychotics. The number one reason cited for prescribing an adjunctive antipsychotic was better efficacy/symptom control, and the top reason for not prescribing was a preference for waiting to see if symptoms improved. Augmenting with an antipsychotic is effective for moderate to severe MDD and should be considered earlier than most clinicians currently use them.

Conclusion

Changes in DSM-5 allow for specifiers, including Mixed Features (MF). Distinguishing MDD from MDD-MF or bipolar disorder is important because it impacts the treatment choice. Measurement-based care can improve outcomes. Switching versus augmentation in the face of inadequate response remains a conundrum. New antidepressants and augmentation strategies provide additional choices and can be characterized using NNT, NNH, and LHH.

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Controlling Severe Asthma through Advanced Diagnosis and Treatment Strategies

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Summary

Those with severe asthma typically require specialist care and are major users of health care resources. Managing those with severe asthma can be a challenge for managed care. There are now two therapies specifically for those with severe asthma, but patients need to be selected carefully for these expensive therapies.

Key Points

- Severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations.
- Severe asthma can be difficult to control.
- There are phenotypes and endotypes of asthma.
- Endotype targeted therapy with two biologics is now available.

THE INCIDENCE OF ASTHMA HAS BEEN dramatically rising since 1970.[1] This reflects increased urbanization, increased risks such as maternal smoking and poverty, and increased infection control. Anywhere in the world that infectious diseases get controlled, then allergy or atopic diseases such as asthma come to the forefront. Asthma is a Western phenomenon. On a positive note, the death rate from asthma has plateaued because of the availability of effective therapies.

Severe asthma will be the focus of this article. Asthma is considered severe when treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) are required to prevent the disease from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy. Approximately 5 to 10 percent of all asthma patients have severe disease; unfortunately, about 50 percent of those have uncontrolled severe asthma (Exhibit1). [2,3]

Among patients with severe, difficult-to-treat asthma, there are high rates of medication and health care utilization, high rates of work absences, and lower rates of quality of life compared with those with mild or moderate asthma. This group will typically require the newer, much more expensive biologic treatments in addition to typical therapies to achieve control. Although those with severe asthma represent only 5 to 10 percent of all asthma sufferers, they account for a significant portion of the economic cost associated with this condition.[4-6] Exhibit 2 compares the annual per patient costs of mild to moderate asthma to that of severe asthma.[5,6]

There are at least two different ways to classify severe asthma. Exhibit 3 illustrates the differences between the World Health Organization (WHO) and the Innovative Medicine Initiative (IMI) classifications.[7, 8] The WHO classification includes treatment-resistant asthma. These are patients for whom inhaled corticosteroids, in ap-

Exhibit 1: Severe Asthma[2,3]

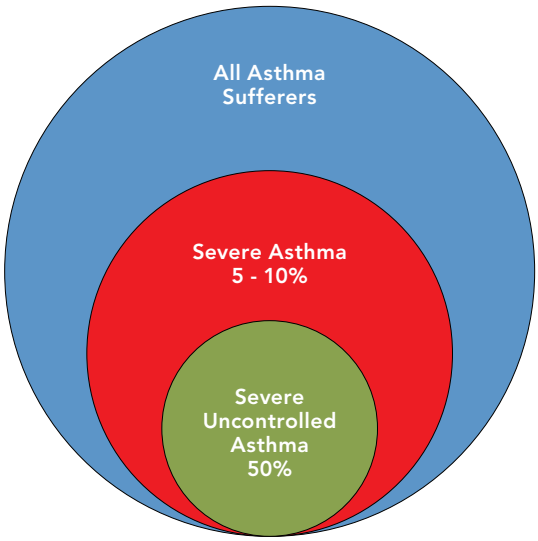


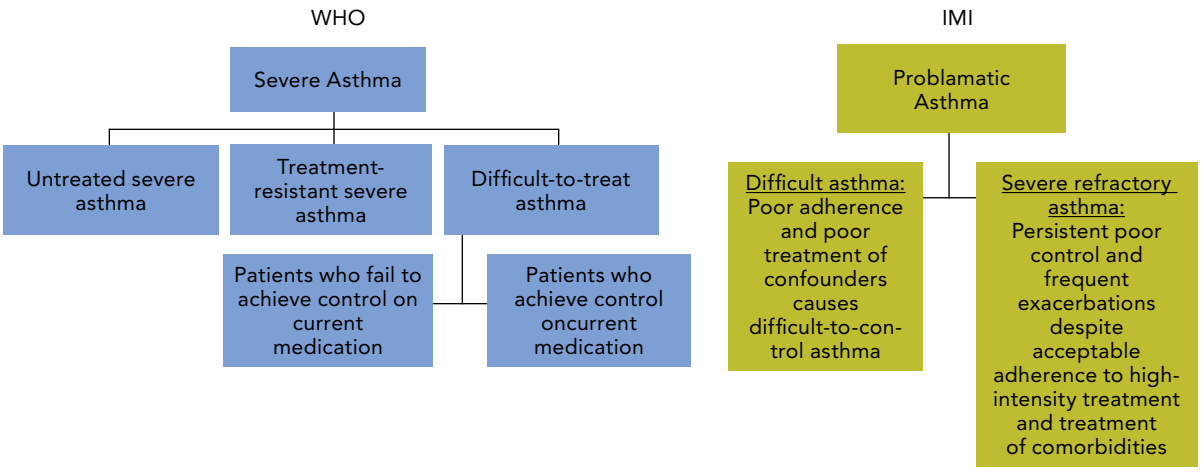
Exhibit 2: Annual Per Patient Cost Comparison[5,6]

Facet of Care	Mild to Moderate Asthma	Severe Asthma
Inpatient	$174	$3,610
Outpatient	$337	$1,417
Emergengy Department	$219	$1,693
Medications	$2,130	$4,090
Total	$2,860	$10,811

propriate doses and with good inhaler technique, are not effective. Another part of the WHO classification is difficult-to-treat asthma. Patients with difficult-to-treat asthma typically have comorbid disease, such as obesity, nasal polyps, sinusitis, allergies, GERD, and diastolic dysfunction, which complicates their treatment. To be considered severe refractory asthma under the IMI criteria, the diagnosis of asthma should be confirmed and there should be adequate adherence and treatment of comorbidities. A patient with severe refractory asthma requires high-intensity treatment managed by an asthma specialist to prevent the patient from becoming uncontrolled. High-intensity therapy is a high-dose inhaled corticosteroid (ICS) and a long-acting beta2-agonist (or leukotriene modifier) or systemic corticosteroids. The definition of 'uncontrolled' asthma according to IMI is poor symptom control as measured by the Asthma Control Questionnaire (ACS, consistently >1.5) or 'not well controlled' according to published guidelines and frequent or severe exacerbations.[8]

Much of the research today on severe asthma is focusing on targeting the underlying immunopathology of the disease. Asthma immunopathology involves lower airway inflammation that arises from genetic predisposition, environmental exposures, and possible alterations in the microbiome. Most asthmatics have type 2 inflammation, named for the type 2 T helper cell lymphocyte. It is associated with certain elevated cytokine profiles (interleukin [IL]-4, IL-5, IL-14) and elevated inflammatory cells (eosinophils, mast cells, basophils, and immunoglobulin E [IgE]-producing plasma cells).

Exhibit 3: World Health Organization Versus Innovative Medicine Initiative Classification of Severe Asthma[7,8]



The Th2 cytokine pathway is the main target for asthma treatment.[9]

The body's response to ongoing inflammation in asthma leads to tissue remodeling in the lower airways and primarily involves the mucosa and submucosa. Histopathological changes in asthma include smooth muscle hypertrophy and hyperplasia, goblet-cell hyperplasia, hypertrophy of submucosal mucus glands, subepithelial fibrosis and collagen deposition, and increased blood vessels in the submucosa. Adequate control of asthma early in the disease process will hopefully limit these histopathological changes.

There are many different asthma phenotypes and endotypes which are clinically relevant in terms of presentation, triggers, and treatment response. Phenotype describes clinical and morphologic characteristics and unique responses to treatment. Phenotypes do not necessarily relate to the underlying pathological mechanisms. Also, phenotypes can overlap or change over time.

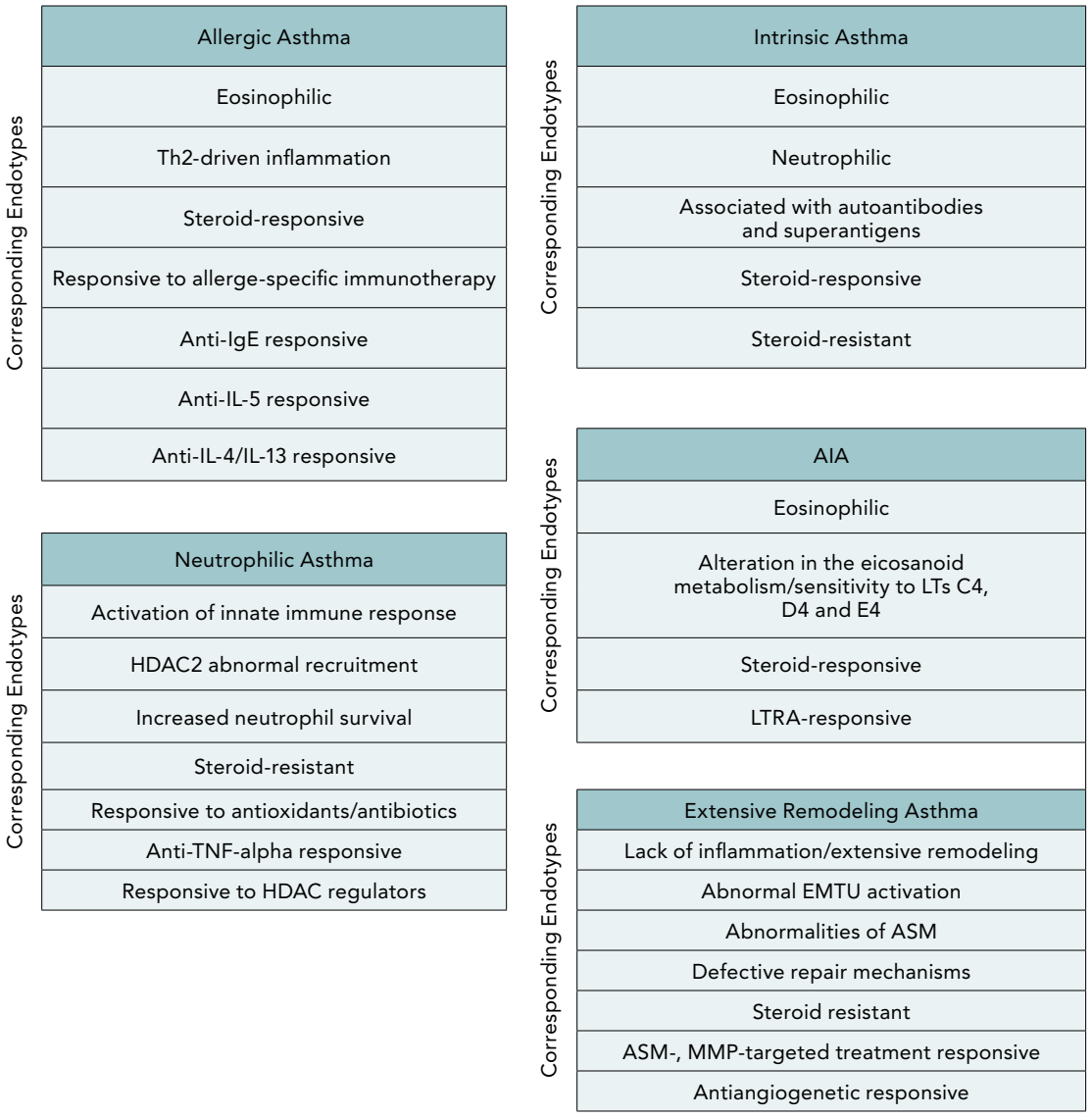
Allergic asthma is one phenotype. It starts in childhood and is often accompanied by allergic rhinitis and/or atopic eczema.[10] The initial symptoms are driven by allergen exposure which leads to increased airway inflammation which can persist even in the absence of the allergen. On histologic characterization, there is mucosal infiltration with eosinophils, CD4+ cells, and mast cells. There is also expression of high-affinity IgE receptors indicating epithelial damage. These patients have goblet-cell hyperplasia, reticular basal membrane thickening, and smooth muscle hypertrophy. The key pathogenic mechanism in allergic asthma is Th2-driven inflammation. Diagnosis requires determination of atopic status.

Intrinsic (nonatopic) asthma often begins in the second half of life and is often accompanied by chronic sinusitis, nasal polyps, and aspirin sensitivity.[10] The histologic characteristics are similar to allergic asthma (increased Th2 cells, mast cell activation, infiltration of eosinophils). Interleukin-2 (IL-2) and interferon gamma (IFN-gamma) are increased in bronchoalveolar lavage fluid, but IL-4 is not increased. This suggests ongoing T-cell stimulation. The key drivers of inflammation are unknown in intrinsic asthma. Local immunoglobulin E (IgE) synthesis has been hypothesized, but there are no validated biomarkers.

Non-eosinophilic asthma is characterized by the absence of airway eosinophilia. Neutrophilia can be observed in nearly 60 percent of symptomatic adults with this phenotype. Pathogenesis is thought to be activation of innate immune responses with a possible role of bacteria, viruses, and diet. Established biomarkers for this phenotype are Il-8, IL-17A, and leukotriene B4. A key diagnostic tool for this phenotype is induced sputum.

Aspirin-intolerant asthma (AIA) affects 5 to 10 percent of adult asthmatics. It is more common in nonatopic asthmatics and often starts in the third decade of life. This is sometimes referred to as aspirin-exacerbated respiratory disease (AERD). The common disease course is rhinitis following a viral respiratory illness and then development of chronic nasal congestion, anosmia, rhinorrhea, nasal polyps; asthma; and sensitivity to aspirin. Histologic characterization is an intense eosinophilic inflammation

Exhibit 4: Asthma Endotypes[11]



of nasal and bronchial tissues. AIA appears to occur as a result of overproduction of cysteinyl leukotrienes (Cys-LTs). It is diagnosed with a lysine–aspirin bronchial challenge test.

Extensive remodeling asthma has extensive airway remodeling with minimal inflammation. Subtypes include thickened small airways, alveolar detachment and loss of elastin, and airway smooth muscle hypertrophy. The pathophysiology of this phenotype is unclear. Inappropriate tissue repair mechanisms may be involved. This phenotype is diagnosed with dynamic evaluation of airway physiology and high-resolution computed tomography. The spirometry results for someone with extensive remodeling asthma look a lot like that for chronic obstructive pulmonary disease (COPD).

There are also asthma endotypes. An endotype is a disease subtype defined by an intrinsically distinct pathogenic mechanism. The Th2 inflammatory complex has been proposed as a distinct asthma endotype that correlates to treatment response and disease outcomes.[11] Type 2 endotype biomarkers have been proposed, although the reliability and validity of such biomarkers are still being evaluated. Potential biomarkers include sputum and blood eosinophils, fractional exhaled NO (FeNO), serum periostin, Th2 gene signature in bronchial and nasal epithelial cells, and salivary inflammatory profile.

With some of the biologic agents under investigation for asthma, these biomarkers may be approved as companion diagnostics. For example, high serum periostin levels are predictive of dupilumab response.

Exhibit 4 shows the endotypes which occur with allergic and intrinsic asthma.[11] There are specific biologic therapies for IgE responsive allergic asthma (Omalizumab [Xolair®]) and IL-5 responsive allergic asthma (mepolizumab [Nucala®]). Dupilumab is investigational for anti-Il-4/IL-13 responsive asthma. It has already been FDA approved for the treatment of severe atopic dermatitis. Numerous other agents are under study for various endotypes.

Endotype-driven therapy selection has been studied in one trial. In this trial, patients with a history of recurrent severe exacerbations and eosinophilic inflammation were treated with mepolizumab which lowered blood and sputum eosinophil counts and significantly lowered the rate of clinically significant exacerbations. [12] In a stepped-care approach like the Global Initiative for Asthma, omalizumab and mepolizumab are only indicated in the last step of therapy.[13] Because they are only effective for specific endotypes, patients should have documented indications for these agents.

Some patients will not achieve good symptom control and minimal exacerbations even on maximal therapy. In these cases it is important to distinguish between true severe, refractory asthma and uncontrolled asthma. Uncontrolled asthma is a more common reason for persistent symptoms and exacerbations.

Before therapy is stepped up, several things should be assessed to determine why the patient's asthma is not controlled. First is to confirm the diagnosis. Next it is important to investigate for persistent environmental exposure to tobacco smoke, allergens, or toxic substances and to review potential comorbidities and complicating conditions that are undertreated. Obesity, gastroesophageal reflux disease (GERD), anxiety/depression, food allergies, rhinitis, sinusitis, and nasal polyps all are commonly found in patients with asthma, particularly those with difficult-to-treat or severe asthma.

Lastly, adherence with the current regimen should be assessed. Patients can have unintentional poor adherence because of misunderstanding instructions, forgetfulness, absence of a daily routine, or medication costs. Intentional poor adherence may come from a perception that the treatment is unnecessary, denial or anger about asthma or its treatment, inappropriate expectations, concerns about side effects (real or perceived), dissatisfaction with health care providers, stigmatization, cultural or religious issues, cost, or medication/regimen factors. Medication/regimen factors include difficulty using inhaler devices, burdensome regimens (e.g., multiple doses per day), and the need for multiple different inhalers.

Conclusion

The personal, social, and economic burden of severe asthma is disproportionately high.

New insights into asthma pathophysiology emphasize the role of type 2 inflammation. Identification of distinct phenotypes and endotypes provide novel ways of categorizing asthma and open avenues for the potential of phenotype- and endotype-driven therapy. It is important to distinguish between truly severe refractory asthma and uncontrolled disease prior to therapeutic intensification.

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Updates in the Management of Hormone Receptor-Positive (HR+) Advanced Breast Cancer

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

Therapy for hormone receptor-positive (HR+) metastatic breast cancer continues to evolve. Better understanding of the pathways of hormone resistance has led to the development of new therapies that are prolonging survival significantly. Additional new classes of therapy are on the horizon.

Key Points

- Numerous lines of therapy are available for HR+ metastatic breast cancer.
- CDK 4/6 kinase inhibitors are changing the metastatic breast cancer landscape, but at a significant financial cost.
- PI3K and HDAC targeting agents will likely be coming to market.

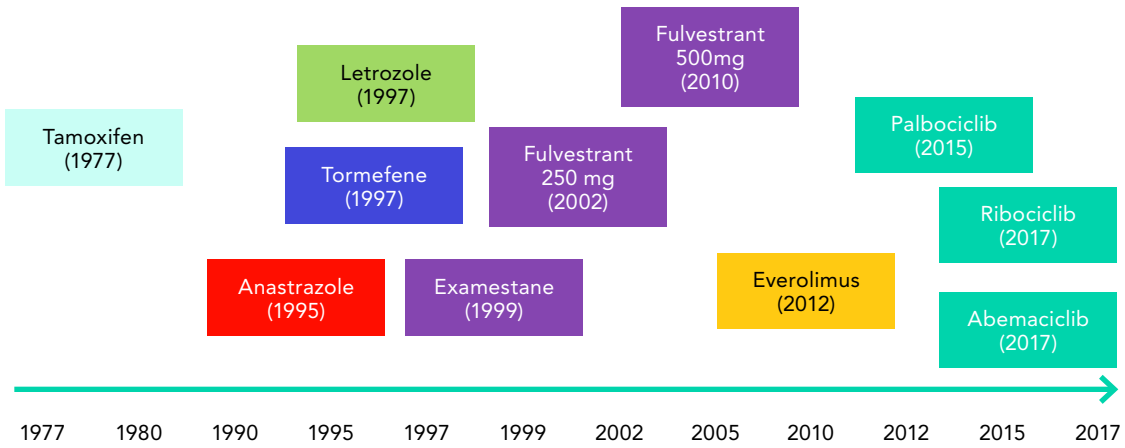
SURVIVAL WITH METASTATIC BREAST cancer has improved significantly with improved treatments.[1] One factor in survival is the type of breast cancer, whether hormone receptor-positive (HR+), human epidermal growth factor receptor 2 positive (HER2+), or without those markers (triple negative). Those with hormone responsive disease (HR+) have the best overall survival, and those with triple negative disease have the worst.[2]

HR+ disease with estrogen positive receptors is the most common subset of breast cancer and comprises 65 to 70 percent of patients with metastatic breast cancer. Prognosis for these patients is highly variable and dependent on hormone responsiveness. The median survival for metastatic disease ranges from three to four years and is likely longer. HER2-positive breast cancer is the second most common for which there are several targeted therapies, which in a few cases can actually be curative. For those with triple negative disease, chemotherapy remains the only treatment beyond clinical trials. The remainder of this article focuses on HR+ disease treatment.

There are a few important nuances with HR+ disease. Rebiopsy of the tumor should be done at the time of diagnosis of the initial metastatic site. Discordance of HR status between the primary and metastatic site is significant and occurs in about 15 percent of cases.

Bone-related problems are another nuance of HR+ disease. Bone metastases are more common in HR+ disease (68%) than other types of breast cancer.[3] All patients with HR+ metastatic disease should receive preventive therapy.[4] Bisphosphonates (pamidronate, zoledronic acid) reduce the incidence of skeletal-related events (SREs), prolong the time to development of a SRE, and reduce pain. Denosumab (humanized monoclonal antibody to RANKL) is superior to zoledronic acid in delaying

Exhibit 1: Evolution of Treatments for ER+ Breast Cancer



SREs by 18 percent greater.[5]

Treatment for HR+ disease is selected based on several factors – prior treatment, menopausal status, and tumor burden (visceral crisis).[6] In patients with HR+ advanced breast cancer, hormone therapy is the treatment of choice in the first-line setting, except in the setting of rapidly progressive visceral disease.[6] Hormonal treatment choices are dependent on disease-free interval, duration of response to adjuvant therapy, extent of disease, prior treatment, and menopausal status. Chemotherapy is not the first-line treatment because of the adverse effects and a much higher rate of hospitalization for management of those events. Chemotherapy would be first- line therapy for rapidly progressive visceral disease.

Hormonal treatment options for postmenopausal women include selective estrogen receptor modulators (SERM, tamoxifen, and toremifene), selective estrogen receptor down-regulator (SERD, fulvestrant), aromatase inhibitors (anastrozole, letrozole, and exemestane), progestins (megestrol), and high-dose estrogens (estradiol). The first choice for a postmenopausal woman is usually an aromatase inhibitor but may be a SERM or SERD. The goal in a premenopausal woman is to make her postmenopausal by removing the ovaries or blocking the effects of estrogen. Women with metastatic breast cancer will typically be given multiple lines of hormonal therapies; an individual therapy is effective for 12 to 14 months.

Approximately 30 percent of the time that a patient is on a long-term aromatase inhibitor, the tumor develops activating genetic mutations of the estrogen receptor (ER), leading to an endocrine resistant state.[7] Targeting the endocrine resistant state requires a dual mechanism of action of blocking ER activity and reducing ER protein level. Fulvestrant, a SERD, is an analog of 17-beta estradiol, and as such, binds to the ER causing rapid degradation and loss of the estrogen receptor protein in cancer cells. Researchers are searching for the best way to identify those patients who would benefit the most from fulvestrant, which is more expensive than the aromatase inhibitors.

In the upfront setting, fulvestrant 500 mg daily is superior to anastrozole in terms of median overall survival (mOS, 54.1 months vs 48.4) and time to progression (23.4 months versus 13.1).[8,9] Fulvestrant appears to be significantly better than anastrozole in those without visceral disease, and the two are equivalent for those with visceral disase.[10] Maximizing the benefit of fulvestrant in those with visceral disease by combining it with targeted agents is discussed later.

The standard of care up until about two years ago was to give women with HR+ advanced breast cancer either an aromatase inhibitor or fulvestrant. A better understanding of the estrogen receptor signaling pathways is leading to a change in the standard treatment which combines one of these classes with targeted agents.

The mammalian target of rapamycin (mTOR) pathway is one of the common pathways in estrogen signaling. Exemestane, an aromatase inhibitor, in combination with everolimus, an mTOR inhibitor, has been studied after progression on letrozole or anastrozole. This combination produces an increase in progression-free survival (PFS, 4.6 mo.) and mOS of approximately 4.5 months compared with exemestane alone.[11] The clinically significant point

from this trial was that 10 to 15 percent of patients do not have progression on this combination and can continue on the medication for a long period of time. The everolimus can cause some different adverse effects, including stomatitis and pneumonitis. This combination is now third line for HR+ metastatic breast cancer. Fulvestrant has also been studied in combination with everolimus in those previously treated with an aromatase inhibitor or relapsing while on an aromatase inhibitor with similar results (5.3 mo. PFS improvement).[12] It also works with tamoxifen. Basically, the addition of a targeted therapy to any hormonal therapy can increase PFS.

Another investigational avenue for targeting hormone resistance is with phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitors. Mutations in the PI3K pathway are quite common in HR+ disease (~30%). In patients with circulating tumor DNA with PIK3CA mutations, buparlisib and fulvestrant produced a clinically meaningful PFS improvement over fulvestrant alone (7.0 vs 3.3 mo.).[13] The regimens were equivalent in those without the mutation. Importantly, buparlisib increases liver function tests and causes severe depression and anxiety. The results of this trial bode well for the future investigation of targeting the PI3K pathway in those with pathway mutations.

There are multiple additional classes of agents under investigation for the management of HR+ disease. Histone deacetylase (HDAC) inhibitors are being studied. These agents block gene transcription.[14] Entinostat, a HDAC inhibitor, increased mOS by 8.3 months, but other trials did not show a benefit.[15] So far this class of agents looks to be fairly nontoxic.

An evolution in treating HR+ metastatic disease occurred in 2015 with the approval of the first cyclin-dependent 4 and 6 kinase (CDK 4/6) inhibitor, palbociclib. Exhibit 1 illustrates the progression of treatments for HR+ metastatic breast cancer. CDK4 and CDK6 are cyclin-dependent kinases that control the transition between the G1 and S phases of the cell cycle. The S phase is the period during which the cell synthesizes new DNA and prepares itself to divide during the process of mitosis.[16] CDK4/6 activity is typically deregulated and overactive in cancer cells. Palbociclib (Ibrance®) is an oral agent that was initially approved for use in combination with letrozole for the treatment of ER+, HER2-negative advanced breast cancer as initial endocrine-based therapy in postmenopausal women. It is now approved in combination with fulvestrant for the treatment of HR+, HER2-negative advanced or metastatic breast cancer in women with disease progression following endocrine therapy and in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women. Neutropenia is the one adverse effect of concern with palbociclib, but it resolves quickly once the therapy is stopped.

Ribociclib (Kisqali®) was the second agent in the CDK 4/6 inhibitor class to be approved. It is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR+ HER2-advanced or metastatic breast cancer. There are two big differences between palbociclib and ribociclib. There is probably a class effect where there is QT prolongation in a small number of patients, but the manufacturer of ribociclib studied this adverse effect more intently. It occurred in 3 percent of those treated with ribociclib and frequent EKG monitoring is required for patients on this agent per the package labeling. This requirement is difficult for community oncologists to meet. The advantage of this agent is the ease of dose reduction in the case of neutropenia compared with palbociclib because all doses are based on multiples of 250 mg tablets rather than different strength tablets with palbociclib.

The third agent approved in this class is abemaciclib (Verzenio®), which was FDA approved (September 2017) in combination with fulvestrant for women with HR+, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. In addition, abemaciclib was approved as monotherapy for women and men with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. Where this agent is different from the others in the class is the rate of diarrhea (20%).[17] It requires concomitant use of antidiarrheals to manage.

The best order in which to use these new agents is not yet known. One option is to use an aromatase inhibitor alone first and then switch to the combination of fulvestrant and CDK 4/6 kinase inhibitor at progression. The other option is to do a combination of CDK 4/6 kinase inhibitor and aromatase inhibitor or fulvestrant first. The CDK 4/6 kinase inhibitors are costly (~$10,000/month), so this is an important decision. Outside the United States, the initial use of hormonal therapy is encouraged with reservation of CDK 4/6 kinase inhibitor use for first progression.

Addition of a CDK 4/6 inhibitor to an aromatase inhibitor or fulvestrant improves PFS and mOS in all the approved settings. The bottom line is that this class is changing OS in metastatic breast cancer and has changed the standard of care so that a targeted agent along with hormonal therapy is now indicated as first-line therapy. The NCCN guidelines list the use of these agents in combination with aromatase inhibitors or fulvestrant in postmenopausal women

with HR+, HER2-negative metastatic disease as category one recommendations.[6]

Conclusion

The treatment of metastatic breast cancer has advanced significantly since the early 2000s. Patients are now living longer and have many different lines of therapy available for which they can be changed to once progression occurs. Clinicians and managed care plans struggle with defining value of the very costly newer agents and in how to integrate them into current practice.

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Improving Management Strategies and Patient Adherence in the Treatment of Psoriasis

Steven R. Feldman, MD, PhD

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

Although there are numerous very effective treatments for psoriasis, many patients do not get optimal benefits because they are not compliant nor adherent with long-term therapy. Clinicians and managed care need to institute support systems to help patients achieve treatment success.

Key Points

- Biologics have revolutionized the treatment of moderate to severe psoriasis.
- Adherence and persistence with treatment is essential for success for all levels of disease.
- Clinicians should schedule patients for a one-week follow-up visit after starting any medication.
- Low tech and high tech strategies should be combined to improve adherence.

PSORIASIS, A CHRONIC INFLAMMATORY skin disease, can be a limited localized disease, which only needs topical treatments, or generalized, which is treated with phototherapy or systemic medications. Psoriasis has a major negative impact on quality of life comparable to other medical diseases, including hypertension, heart failure, diabetes, and depression. Overall, moderate to severe psoriasis is a nasty disease that affects not only the skin but also many parts of the body.

Because of the systemic inflammation, severe psoriasis compared with mild disease significantly increases risk of myocardial infarction threefold.[1] As dermatologists care for most patients with severe psoriasis, it is imperative that these patients are screened for CVD risk factors and that they are referred either to a primary care physician or to a cardiologist for management and treatment of risk factors.

Immunopathology of the disease is better understood today, with T cell abnormalities at the center of the pathology.[2] Blocking tumor necrosis factor (TNF) or various interleukins such as IL-12 or Il-23 with biologics significantly reduces immune response in this disease.

The American Academy of Dermatology (AAD) has published guidelines for managing psoriasis, but these have not been updated for several years.[3] A simplified treatment algorithm is presented in Exhibit 1. Extensive disease (moderate to severe) will require phototherapy, methotrexate, or biologicals for disease control.

Phototherapy is a very effective (~60% of patients achieve 75% skin clearing by 12 weeks) but underused treatment. Managed care plans sometimes require a copay for each phototherapy visit, which means that patients get shifted to more expensive biologics with lower copays. It would be much more cost effective for managed care to encourage phototherapy or even require that every moderate to severe psoriasis patient have a three-month trial of phototherapy with a home unit before moving to

Exhibit 1: Psoriasis Management

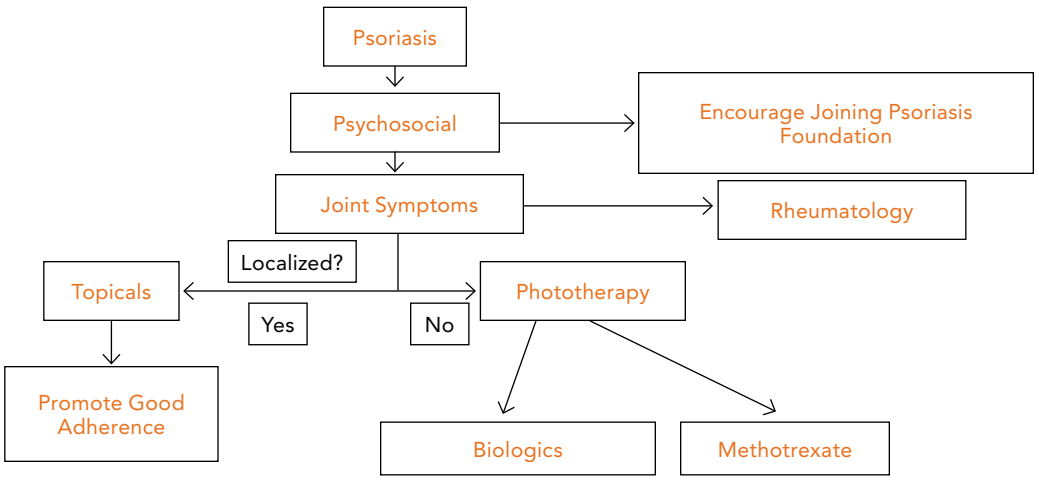


Exhibit 2: Suggestions to Promote Adherence and Persistence[23]

- COPE
  - Connectedness/collaboration, Open-ended questions, Positive attitude, Encourage support
- Schedule return visits
  - Patients more likely to fill the prescription and more likely to take medications
- Focus on initial adherence
  - Promotes positive habits
  - Supports persistence with therapy
- Provide patients with your cell phone number
  - Encourages communication
  - Shows that you are invested in their well-being

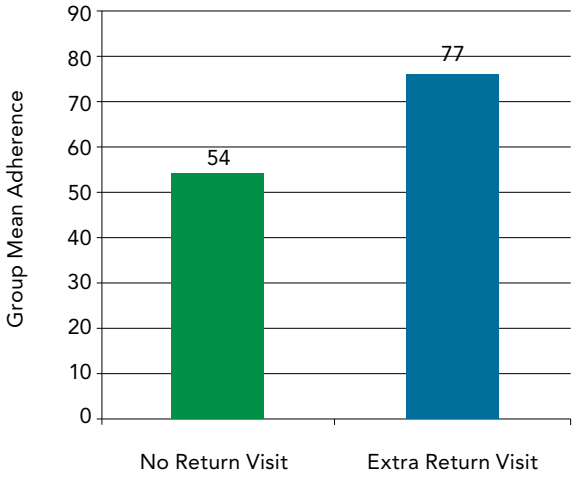
a biologic. Home phototherapy units cost approximately $3,000 to $5,000 as a one-time cost compared with the $50,000 annual cost of a biologic.

The biologic agents, which better target the underlying pathophysiology compared with general immunosuppressants such as methotrexate, were a revolutionary leap forward in disease control with high rates of skin clearing. The agents currently FDA approved for moderate to severe psoriasis or plaque psoriasis include adalimumab (Humira®, biosimilars), brodalumab (Siliq®), etanercept (Enbrel®, biosimilars), golimumab (Simponi®), infliximab (Remicade®), ixekizumab (Taltz®), secukinumab (Cosentyx®), ustekinumab (Stelara®), and guselkumab (Tremfya®). Efficacy is typically measured with the psoriasis area and severity index (PSAI). PSAI 75 and PASI 90 percentages reported in studies are the patients who achieved 75 percent and 90 percent skin clearing. The efficacy of biologics varies from 50 percent of patients achieving PSAI 75 with etanercept to greater than 90 percent with secukinumab and guselkumab.[4-11] These agents are relatively safe and well tolerated. As the agents have become more selective in targeting the immune system, adverse effects, such as infections related to immune suppression, have declined.

Although treatments are remarkably effective, patients do not always get better. This is usually because of a lack of compliance, which consists of both adherence (taking medication as directed) and persistence (continuing to take medication for a long period of time).

Adherence is a major issue in treating localized psoriasis because the therapies are typically topicals which have to be applied once, twice, or more daily. In an anonymous survey of psoriasis patients, 40 per-

Exhibit 3: Improve Adherence with a One Week Return Visit[24]



cent reported noncompliance with topical therapy.[12]

Primary nonadherence is a major issue for all severities of psoriasis. Many patients with all different types of disease do not even fill their initial prescriptions, and psoriasis patients are among the worst.[13]

Secondary nonadherence occurs for many different reasons – adverse effects, not understanding the reason for needing chronic treatment, financial reasons, and memory. Memory aids, such as simple charts for recording when doses are taken, can be helpful. Electronic aids can also be useful. Importantly, clinicians cannot always rely on self-reported adherence because it has been shown to correlate poorly with actual adherence.[14] Even if patients are initially adherent, they tend to become less so over time.[15]

One would think that those with severe psoriasis would be more motivated to be compliant with their therapy, but that has not been shown in several adherence trials with biologics.[16-18] Over a three-year span, the use of biologics falls by about 50 percent.

Another trial found that patients prescribed an every two-week biologic took it at widely varying time intervals.[19]

There are numerous reasons why people have difficulty complying with medications and persisting with therapy. Instead of the barriers, clinicians should focus on the factors that will get people to take their medicines in the first place. Clinicians can encourage adherence and persistence with several easy things. They should establish a relationship with patients, involve patients in treatment planning, and make therapy as easy as possible. A patient's perception of whether the provider is caring increases patient satisfaction and investment in the relationship.[20] It is important to not scare patients with potential adverse side effects. Fast acting agents should be chosen, or the patient should be educated on when the medication should begin working.

Under the category of making therapy easy with topicals, clinicians should choose a formulation that the patient will actually use. Less messy products, such as solutions or spray on foams, are preferred over ointments, creams, emollients, and gels.[21] Prescribing fewer products is also helpful. As the number of topicals are increased from one to three daily, compliance declines.[22] Combination products can be helpful in reducing the number of topicals required. Prescribing products with once a day dosing versus multiple daily dosing can also improve adherence rates.

Exhibit 2 has other suggestions for improving adherence.[23] A follow-up visit in one week instead of four weeks results in better adherence rates (Exhibit 3).[24] Online surveys about medication efficacy and use are another technology that has been shown to improve adherence and provides a "caring touch" but does not require a follow-up visit.[25]

Patients should be given written action plans, particularly for complex regimens. Especially with psoriasis, they need daily skin care, continuous medications, and instructions for disease flares. Patients still need to be accountable in order to be compliant. One way is asking the patient to call within a few days to check in about how their medication is working. Children can be motivated to participate in their care by positive reinforcement and by being provided sticker calendars.

Technology, such as electronic reminders on smartphones, can be helpful. These are especially useful for self-administered biologics, which may only be given every two to four weeks.

Adverse effects and the fear of them can reduce compliance. Adverse effects may also be an opportunity. For scalp psoriasis, tell patients this may sting but that is a sign that their medicine is working and they only have to use it for three days before improvement should occur. Sting really is a sign that they are at least getting the medicine on their scalp and thus will be more likely to have efficacy.

Pharmacists can also be used to increase adherence and persistence. Refill reminders, practical tools to put risk into perspective, coordinated refills so all medications are in sync, and developing a relationship with the pharmacist are all helpful.

Cost can be an issue. Clinicians can help by initially prescribing low-cost generics and by giving the patients a range of options. Patient assistance programs are also an option, including company-sponsored copays or other assistance programs or local indigent pharmacy resources. Sampling medications has positives and negatives. Using samples can help patients know the right way to use the medicine, can get them over the fear of starting a new medicine, and begins to get them in the habit because clinicians know they have at least received the initial supply of medication. Sampling can be negative in that drug interactions with all the other medications the patient is receiving do not necessarily get screened for.

Conclusion

Psoriasis is a terrible disease for which there are effective treatments, but poor adherence is still a major limitation to treatment. Biologics have revolutionized the treatment of moderate to severe psoriasis. Clinicians and managed care providers need to focus on adherence and persistence with therapy for all patients. Actually using the prescribed medication may lead to fewer patients requiring aggressive therapy.

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Individualizing Therapy in the Management of RA: A Closer Look at Emerging Therapeutic Options

Gary M. Owens, MD

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

Early diagnosis and aggressive treatment with biologics, although expensive, should reduce the joint damage and disability that result from rheumatoid arthritis (RA). Managed care will need to implement some strategies to manage the use of biologics, but these agents should be available to patients.

Key Points

- RA is a chronic and costly disease from a payer perspective.
- Biologics for RA are a major driver of specialty pharmacy cost.
- Treatment approaches are changing and guidelines are moving toward earlier and more aggressive treatment.
- Payers are challenged to get the most value from RA treatments.

RHEUMATOID ARTHRITIS (RA), A CHRONIC, progressive, systemic inflammatory autoimmune disease of unknown etiology, affects less than 1 percent of the population in the United States, with women outnumbering men three to one. The onset occurs most frequently between the ages of 30 and 60. RA leads to inflammation of the synovium in diarthrodial joints with damage to affected bone, cartilage, and ligaments. Deformity of the affected joints is common.

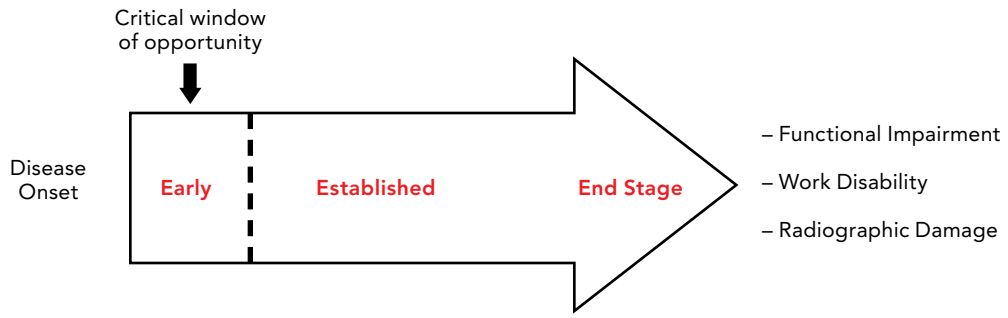
RA can result in significant disability from joint damage. In addition to joints, RA affects multiple organs and has significant extra-articular manifestations. Inflammatory vasculitis, interstitial lung disease, thrombocytosis, fatigue, and anemia are just a few of the effects of this disease. In the pre-biologic era, 50 percent of RA patients were unable to work within 10 years of disease onset.[1] In the biologic era, that number is down to 35 percent.[2]

Additionally, there is significant morbidity and mortality related to the disease. The mortality rate is 1.5 to 1.6-fold higher in RA patients compared with the general population.[3] Individuals with RA are five times more likely to have a heart attack compared with someone without RA, are at increased risk of infection, and have a risk of lymphoma three times greater than the general population.[4-8]

RA is also a costly disease. The annual per patient direct medical cost have been estimated to be $13,012 compared with $4,950 for control groups without RA.[9] the total annual excess direct costs of RA are estimated at $22.3 billion.[9]

The economic burden of RA has grown substantially since the biologic therapies were first introduced in the mid-to-late 1990s. Many payers now report that the biologic drugs to treat RA (and other conditions) are among the top five drug categories by total cost and the number one specialty pharmacy category.[10] In a 2015 paper, Curtis and colleagues used a claims-based algorithm to estimate the mean

Exhibit 1: Therapeutic Window of Opportunity in Early RA[14]



one-year biologic cost per effectively treated patient and found it to range from $43,935 to $101,402.[11]

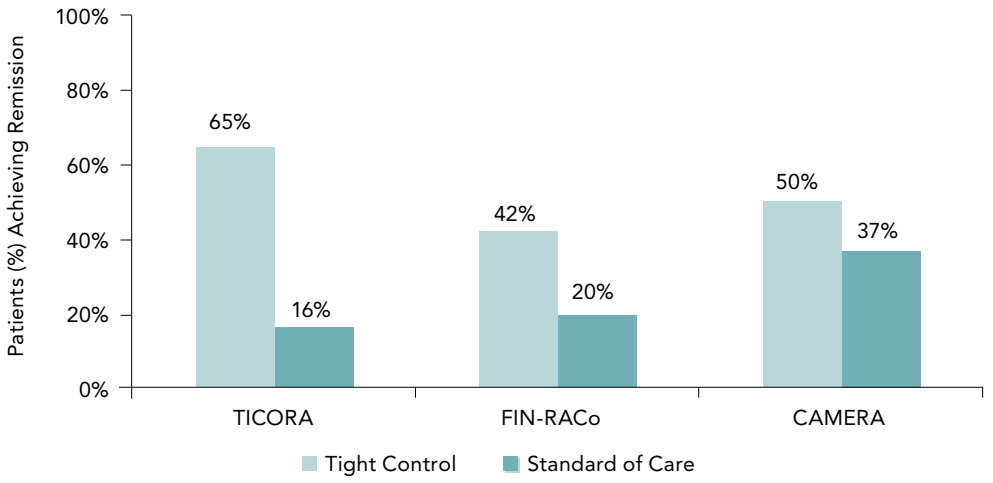
Treatment paradigms for RA are changing. The approach in the past was to start traditional disease-modifying antirheumatic drugs (DMARDs). The current paradigm is early aggressive treatment with biologics in combination with DMARDs. Fifty to 70 percent of patients without treatment have radiographic damage within the first two years after the onset of symptoms.[12] Patients with RA show rapid functional declines that begin early in the course of RA.[13] As shown in Exhibit 1, there is a window of opportunity to intervene to prevent disability.[14] Thus, early identification of the disease and aggressive treatment are important to prevent joint damage and functional disability.

Treatment aims to induce remission or significantly reduce disease activity. Remission is defined as minimal clinical signs and symptoms of synovitis. Biologic drugs have made remission attainable in a way it had never been before. The concept of "treat-to-target" (T2T) of remission is advocated by the American College of Rheumatology guidelines.[15] The key elements of the T2T approach are aiming for a predefined target (remission), monitoring disease activity every one to three months until the target is reached; then every three to six months, and adjusting therapy regularly until the target is achieved. The benefit of using a T2T approach in terms of remission rates is shown in Exhibit 2.[16-18]

There is now a long list of biologics available for managing RA. There are five classes of biologic DMARDs. The tumor necrosis factor alpha (TNF-α) antagonists include adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), and certolizumab pegol (Cimzia®). The interleukin antagonists include anakinra (Kineret®) and toclizumab (Actemra®.) Abatacept (Orencia®) suppresses T cell activation and rituximab (Rituxan®) is an anti B cell monoclonal antibody. Tofacitinib (Xeljanz®) is a Janus kinase (JAK) inhibitor. Biosimilars are now available for etanercept [Etanercept-szzs (Erelzi)] and infliximab [Infliximab-dyyb (Inflectra)]. An anti-TNF inhibitor is typically the first chosen biologic. For patients with an insufficient response to anti-TNF therapy, a non-TNF biologic agent may be more effective than a second anti-TNF agent. In one clinical trial of patients who failed a first anti-TNF agent, 69 percent of patients achieved an effective clinical response with a non-TNF biologic versus 52 percent of patients who took a second anti-TNF agent.[19]

There are numerous management challenges in this disease. There are no standardized outcome measures used in clinical practice, so it is difficult to know the real work efficacy of treatments. There is of course a growing number of biologic agents for which the best order of use is unknown. Additionally, not every biologic agent works for every RA patient. There is little understanding of the cause for variation of drug efficacy between patients. Guidelines on how biologics should be compared to optimize RA treatment outcomes are lacking. Additionally, RA is a chronic disease thus drug costs continue over years. The total cost of care is difficult to assess so it is difficult to know if biologic therapy is preventing future disability-related costs. It is often difficult for payers to merge medical and pharmacy data into a clear picture of total cost, especially in carve-out situations. Benefit design changes and changes of carriers can make it hard to track cost year-over-year. The medical claims system often does not have granular information to allow care costs to be accurately tracked.

Exhibit 2: Treat-to-Target Approach vs Standard of Care[16-18]



The importance of understanding the optimal use of these agents is magnified by their high cost. Physicians, patients, and plan managers need better data to compare the effectiveness of the different biologics.

High budget impact and the lack of clear clinical superiority among biologic alternatives makes RA an attractive target for cost effectiveness research (CER). A 2011 CER analysis found no significant differences in long-term clinical and radiographic outcomes, functional capacity, health-related quality of life, or rates of adverse events among the synthetic disease-modifying therapies.[20] Combination therapies such as a biologic and methotrexate were generally associated with better clinical response rates and outcomes. More CER data is needed to determine the optimal use of biologics.

Undertreatment is also an issue in RA. A "start low, go slow" approach rather than T2T remains common in RA management.[21] Delayed treatment or prolonged undertreatment contributes to uncontrolled inflammation and irreversible tissue damage.[22] Patients not referred to a rheumatologist are less likely to receive disease-modifying therapy within 12 months of symptom onset.[23] Patients frequently receive irregular follow-up and minimal therapeutic adjustment.[24]

Conclusion

RA is a chronic and costly disease from a payer perspective. Drug treatment of RA is a major driver of specialty pharmacy costs. Treatment approaches are changing and guidelines are moving toward earlier and more aggressive treatment. Yet, current RA management is often suboptimal. Payers are challenged to get the most value from RA treatments.

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What is New in the Evolving Treatment Landscape for Moderate to Severe Atopic Dermatitis?

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

It is an exciting time to be managing atopic dermatitis (AD). An explosion of new therapeutic options is about to take place for AD. Several new agents have recently been approved and many more are on the horizon.

Key Points

- AD is the most common chronic inflammatory skin disease.
- An effective nonsteroidal topical agent, crisaborole, is available for mild to moderate AD.
- Effective biologic therapy is now available for moderate to severe AD.
- Multiple additional biologics are on the horizon.

ATOPIC DERMATITIS (AD) IS THE MOST common chronic inflammatory skin disease, often starting in childhood. It is the most common type of eczema and manifests as eczematous rashes, itch, bacterial colonization and secondary infections and can have an intermittent or persistent course.

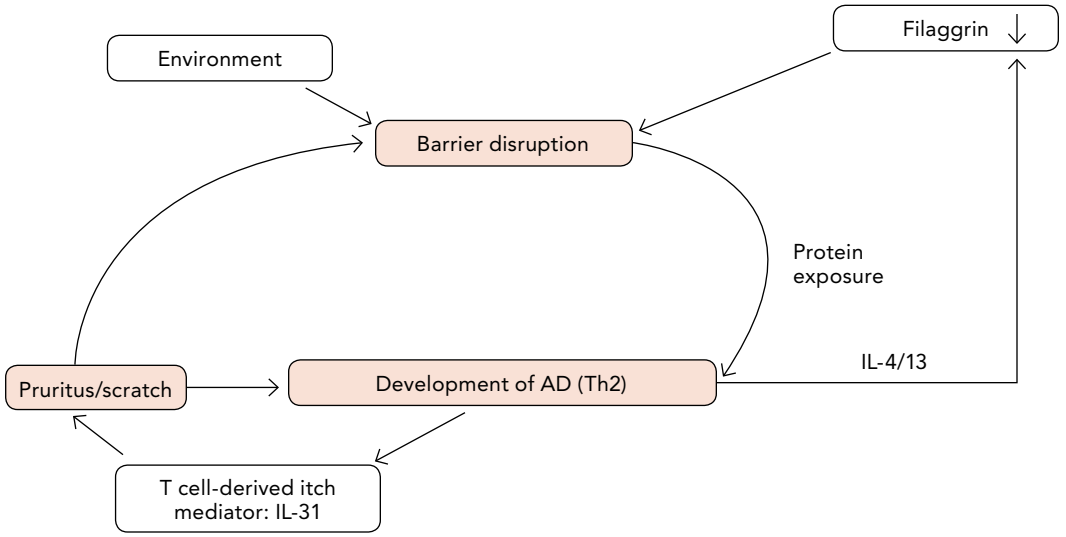
AD occurs in about 20 percent of school-aged children and 10 percent of adults but may be as high as 30 percent of adults.[1] Up to 10 percent of those affected may develop the disease as an adult.[2]

Although in the past the skin was not thought of as a highly immunologic organ; however, it is now known to be very immunologically active. Atopic dermatitis is a skin barrier disease that is thought to be the result of immune dysregulation within the skin. In AD, there is decreased filaggrin due to genetic mutations and type-2 helper T cells (Th2) mediated down regulation which results in increased epidermal hyperplasia and decreased lipid barrier in the skin.

An intact, healthy skin barrier is a critical first line of defense against various microbes, irritants, and allergens. A major factor in maintaining an intact skin barrier is filaggrin. The most immediate result of filaggrin deficiency in AD is decreased stratum corneum hydration. In addition, filaggrin breakdown products play an important role in acidifying the stratum corneum. An increase in the pH of the stratum corneum activates a number of serine proteases. A pH-induced increase in serine protease activity leads to both barrier breakdown and precipitates additional Th2 inflammation. The defective barrier of the skin allows allergens.

The epidermis of AD patients is characterized by significant barrier disruption. Alterations in proteases, pH changes in the skin, and irritants lead to scratching and skin trauma. This skin trauma can allow allergens and bacteria to cross over into the skin and invoke an immunologic response. Without adequate moisture, the skin is dry, red, and readily irritated. It is helpful to think of the barrier defects in AD as resembling a whiffle ball; the skin is covered with holes that let the water in the skin "out" and

Exhibit 1: Interplay Between Barrier, Allergy/Immunology, Pruritus in Atopic Dermatitis[3]



IL = interleukin
Th2 = type 2 helper T cells

the trigger factors "in." The skin barrier abnormality in AD is not just an epiphenomenon (a secondary or additional symptom or complication arising during the course of a malady); it is the initiator of the pathogenesis of the disease state. Overall, AD is a complex interplay between barrier, allergy/immunology, and pruritus (Exhibit 1).[3] Treatment of AD requires repairing the skin barrier disruption.

A major symptom of AD is intense pruritus, which is one of the most challenging aspects of disease management. It is the one aspect of AD that bothers parents of children with AD the most. An impaired skin barrier facilitates the entry of irritants and itch causing agents. A reduction in skin hydration by 10 percent is crucial for the induction of itch.[4]

Nighttime loss of sleep due to itching and scratching is an issue for children and their parents; children may wake up an average of 36 times nightly, disrupting both their sleep and the sleep of their parents. Loss of deep sleep means less growth hormone is secreted with potential for impairment of linear growth. Lack of sleep also means poor coping strategies the next day, impaired school performance, and behavioral issues. It also leads to sleep anxiety and parasomnias. Approximately 30 percent of parents report that their children with AD climb into bed with them because of the itching and inability to sleep.[5] Parents of children with AD lose one to one and one half hours of sleep every night.

Even without itching and scratching, children with AD have more arousals during the night compared with controls.[6] If the disease is not addressed early on, sleep problems will persist even with treatment. Overall, itching has a major impact on quality of life.

Adults with AD also have issues with itching, scratching, and sleep disturbances. Eighty- five percent of those with moderate to severe AD reported problems with everyday itch frequency, 41.5 percent reported 18 hour or greater daily duration of itching, and 55 percent report sleep disturbances five to seven nights per week.[7] Adults with AD with impaired sleep are compromised in their ability to perform certain activities of daily living.

Beyond itching, AD, like other systemic inflammatory diseases, has impact on mortality. In adults, 10-year mortality is increased post hospitalization for AD compared to the general population, but reduced compared to psoriasis.[8] There is also an increased risk of coronary artery disease and myocardial infarction with moderate to severe AD.[9, 10] AD also impacts morbidity. Adults with AD tend to have higher levels of stress, blood pressure, depression, insomnia, obesity, migraines, and asthma than controls.[11,12] Children with AD also have higher rates of obesity, metabolic syndrome, attention deficit hyperactivity disorder (ADHD), depression, anxiety, conduct disorders, and autism.[13,14]

AD also affects work performance. Hand AD in adults is a very common cause for missed days of work. It also impacts quality of life.[15]

AD is also a costly disease. Overall, the health-related cost of AD is estimated at 5.2 billion U.S.

Exhibit 2: Future Therapies for Atopic Dermatitis

Agent	Target
Tofacitinib*	JAK inhibitor
Ustekinumab**	IL-12/IL-23
Apremilast	PDE4 inhibitor
Baricitinib	JAK inhibitor
Tralokinumab	IL-13
Lebrikizumab	IL-13
Nemolizumab	IL-31

* Currently FDA approved for rheumatoid arthritis
** Currently FDA approved for psoriasis
JAK = janus kinase
IL = interleukin
PDE4 = phosphodiesterase type 4

dollars.[16] That breaks down to $349 per patient per month in costs. Eighty-six percent of pediatric dermatology admissions to the hospital are for AD.[17] Overall, there is clear multi-dimensional burden with this disease.

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

Because itching is a major problem in this disease, treatments to help with itching are important. Good skin moisturization is the cornerstone for helping itching. Chilled Noxzema™ is one over-the-counter product which can be used to control itching. As a counterirritant, it replaces the sensation of itching with a cooling, tingling sensation and can be applied as often as needed, does not need to be washed off, and is cost effective for managing itching.

Antihistamines do not adequately control the itching associated with AD and are not recommended for routine use in managing AD.[18] Sedative effects of antihistamines are beneficial for helping children sleep and allowing the family get the rest they need but short-term, intermittent use of sedating antihistamines for sleep should not be substituted for management of AD with appropriate therapies.[18] Topical antihistamines are not recommended because of the risk of absorption and contact dermatitis.

Topical use of various agents is important for repairing the defective skin barrier. Crisaborole (Eucrisa®), a topical benzoxaborole phosphodiesterase type 4 (PDE4) inhibitor, was recently FDA approved for AD. It is indicated to treat mild to moderate AD in adults and children 2 years of age and older. Crisaborole blocks cytokine synthesis by increasing cyclic adenosine monophosphate (cAMP) levels and subsequently protein kinase A levels which negatively modulate signaling pathways that lead to cytokine production. This agent has physiological properties that allow for skin penetration.

Crisaborole reduces inflammation and itching and repairs the skin barrier. This agent results in 7.4 to 13.4 percent improvement in Investigator Static Global Assessment of clear or almost clear (≥ 2 grade improvement) over placebo at 29 days of treatment.[19]

The most common adverse effects with crisaborole are AD flares and application site pain and infections. These occur is less than 5 percent of patients. The rates of topical adverse effects remained very low over two years of treatment.[19] Topical steroid-like adverse reactions, such as application site atrophy and telangiectasia, did not occur during the crisaborole studies.

The revolution in AD treatment began with the FDA approval of the first targeted biologic agent for this disease in March of 2017. . Dupilumab, a fully human monoclonal antibody targeted therapy, is indicated for adult patients with moderate to severe AD whose disease is not well controlled with topical prescription therapies or who cannot use those topical therapies. It is an interleukin-4 alpha (IL-4 α) receptor antagonist which inhibits signaling of IL-4 and IL-13, the Th2-derived cytokines that are important drivers of AD pathology. IL-4 and IL-13 are inhibitors of epidermal differentiation and antimicrobial peptides. IL-4 and IL-13 are elevated in acute and chronic skin lesions of atopic dermatitis. Additionally, patients have increased numbers of CD4- and

CD8+ cells that release these two cytokines. Both IL-4 and IL-13 interact with the IL-4 receptor.

Dupilumab has been studied in the treatment of adults with moderate to severe AD as monotherapy and in combination with topical corticosteroids.[20-24] In the three randomized Phase III pivotal trials of 2,119 adult patients with inadequately controlled moderate to severe AD, this agent significantly improved measures of skin clearing (Eczema Area and Severity Index [EASI] and Investigator Global Assessment [IGA]) and severity of disease at 16 weeks compared to placebo. A dose of 300 mg every week improved the EASI score by 74 percent.

In one study where some patients underwent a skin biopsy, dupilumab treatment resulted in changes in the AD molecular disease profile.[22] It improved the AD molecular disease profile in a dose-dependent manner, expression of genes upregulated in AD lesions was decreased in treated patients, and the molecular changes paralleled improvements in clinical scores.

Dupilumab also has an impact on symptoms and quality of life. It reduced peak itch at 16 weeks relative to placebo by 1.1 to 3.2 points in all doses except the 100 mg dose, improved sleep and health-related quality of life, and reduced anxiety and depression symptoms.[23]

Clinicians and managed care need to get ready for an onslaught of new AD targeted agents. Exhibit 2 lists selected agents in development. Many of these target IL-4 and IL-13 like dupilumab, but a few also target IL-31, which is thought to be important in mediating itching.

Other topical PDE4 inhibitors like crisaborole, including OPA-15406, are under investigation for mild to moderate AD. OPA 15406 ointment has a rapid onset anti-inflammatory and anti-pruritic effect and has been shown to be especially effective in selective inhibition of PDE4 subtype b.[25]

Another promising agent under investigation is tradipitant, a neurokinin-1 (NK-1) receptor antagonist. Substance P and NK-1 receptor interactions in neuronal tissue regulate neurogenic inflammation locally and the pain perception pathway through the central nervous system. An inappropriate overexpression of substance P, either in nervous tissue or peripherally, could result in pathological conditions such as pruritus. An NK-1R antagonist may possess the ability to reduce this over-stimulation of the NK-1R, and as a result address the significant pruritus of AD.

Conclusion

AD is more common in the pediatric population, but most medication treatment trials have been in adults. There are pending studies in pediatric patients. Effective treatments for moderate to severe AD which target underlying pathophysiology are now available. Additionally, a large number of other biologic agents are on the horizon.

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Individualizing Treatment in the Management of Type 2 Diabetes: Novel Therapies for Improved Patient Outcomes

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

The explosion of new therapies for type 2 diabetes mellitus (T2DM) has complicated treatment, but it has also provided the opportunity to better control the disease with appropriate combinations of therapy. A large benefit of some of the new agents is a reduction in cardiovascular outcomes.

Key Points

- Diabetes goals and therapy should be personalized using patient factors, preferences, comorbid conditions, and life expectancy.
- Metformin is usually first-line therapy for T2DM.
- There are multiple options for improving glycemic control after monotherapy failure.
- Selection of second- and third-line therapy depends on goals.
- CV risk reduction should be a major focus of therapy.

THE TREATMENT OF TYPE 2 DIABETES mellitus (T2DM) is improving, but it is also getting more complicated. Over the last 20 years tremendous progress has been made in reducing complications of diabetes.[1] Overall better care of patients with diabetes has led to this improvement. Unfortunately, the number of people in the United States with T2DM continues to grow. Therefore, as health care providers, we need to do more to prevent the development of the disease. Treatment has gotten more complicated as the various metabolic defects of the disease have been understood and therapies to target these defects have been developed.

The multiple metabolic defects that contribute to hyperglycemia in T2DM are shown in Exhibit 1, along with the available therapies that target the individual defects.[2] Insulin and appetite interact in the brain when neurotransmitters in the hypothalamus signal satiety in response to increased insulin. Adding brain and neurotransmitter dysfunction to the pathogenic picture of type 2 diabetes gives us the ominous octet. The decreased incretin effect and the role of the kidneys are both central to initiating and sustaining hyperglycemia in T2DM

Importantly, T2DM is a progressive disease; however, it is a preventable disease (Exhibit 2).[3] Patients do not just wake up one day with the disease. There is a long prodromal phase of impaired glucose tolerance which has much of the same metabolic abnormalities as full blown disease. Complications of the disease do not develop in everyone who has poor control; there are genetic determinants which impact the development of these.

T2DM is also associated with disability and death. T2DM can lead to microvascular complications. In 2005 to 2008, of adults 40 years of age or older

Exhibit 1: Metabolic Defects in T2DM and Medication Activity[2]

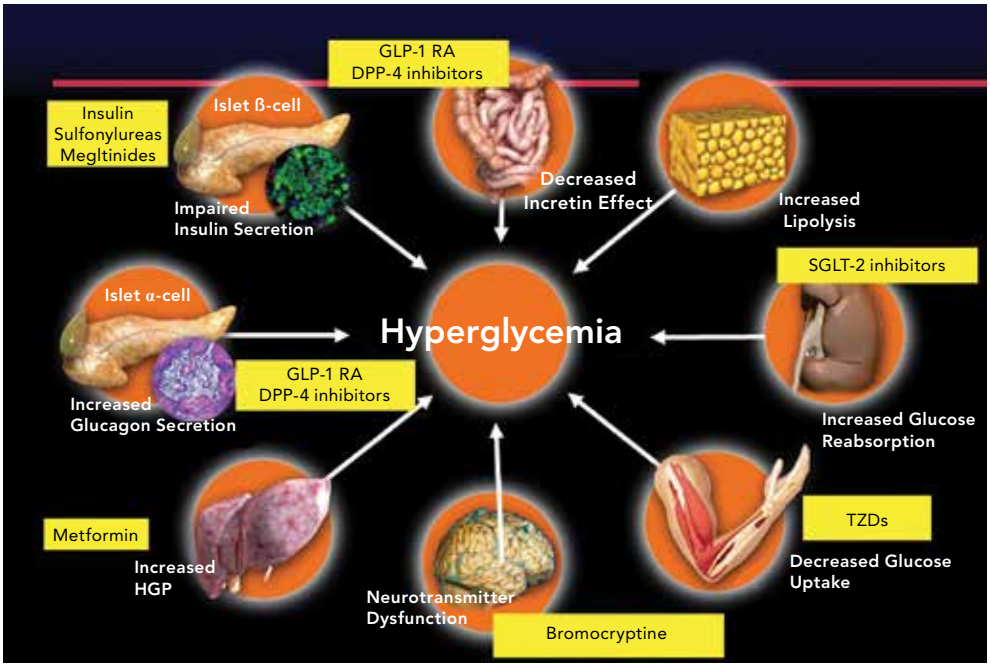
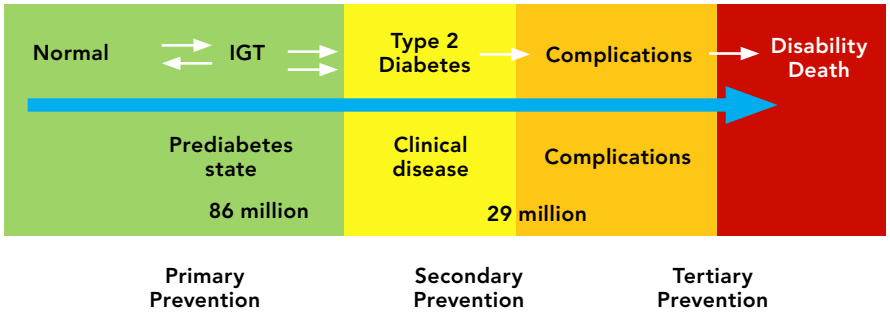


Exhibit 2: Type 2 Diabetes: A Progressive Disease[3]



IGT = impaired glucose tolerance

with diabetes, 4.2 million (28.5%) had diabetic retinopathy, and 655,000 (4.4%) had advanced diabetic retinopathy.[3] In 2010, about 73,000 nontraumatic lower-limb amputations were performed in adults 20 and older with diabetes.[3] About 60 percent of nontraumatic lower-limb amputations among adults 20 and older are in people with diabetes.[3] Diabetes was listed as the primary cause of kidney failure in 44 percent of all new cases in 2011.[3]

Diabetes also causes macrovascular disease. It doubles the risk for coronary heart disease, ischemic stroke, and myocardial infarction.[4] This is the major cause of morbidity and mortality with T2DM.[5]

Exhibit 3 lists the glycemic targets for T2DM treatment.[5] Individualization is key for these goals. Various patient factors need to be taken into account when choosing glycemic goals, such as risk of hypoglycemia, life expectancy, disease duration, comorbidities, patient attitudes, and patient resources. Older patients with multiple comorbidities and limited life expectancy are unlikely to derive as much benefit from tight glucose goals as those who are younger and without complications of the disease. The older patients are also more likely to have ad-

Exhibit 3: Glycemic Targets[5]

- HbA1c < 7% (mean PG ~ 150 - 160 mg/dl [8.3 - 8.9 mmol/l])
  - Pre-prandial PG < 130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
- Individualization is key:
  - Tighter targets (6.0 - 6.5%) - younger, healthier
  - Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.
- Avoidance of hypoglycemia

PG = plasma glucose

verse effects of treatment, especially hypoglycemia.

Over the last 15 years, a number of new classes have been approved, which has complicated treatment. There are now 12 classes of medications for the treatment of T2DM and more are coming.[5-7] The various classes have complementary mechanisms so they can be used in combination to address different metabolic defects and improve glycemic control (Exhibit 1).

Decisions have to be made in regard to what order to use the agents, what combinations to use, and in which patients should each be used.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines recommend starting with lifestyle changes, including healthy eating, weight control, and increased physical activity in most patients.[5] Unless contraindicated, metformin should be added at diagnosis or soon after. If metformin is contraindicated or it is not tolerated, a drug from one of the classes suggested for combination therapy may be substituted as initial therapy. Initial dual therapy can be started in patients with a very high hemoglobin A1C (A1C, e.g. ≥9.0%).

If the A1C target is not achieved after three months, clinicians should consider adding a sulfonylurea (SU), a thiazolidinedione (TZD), a dipeptidyl peptidase-4 inhibitor (DPP4-I), a glucagon-like peptide-1 receptor agonist (GLP-1-RA), Sodium-glucose cotransporter-2 (SGLT-2) inhibitor, or basal insulin. A third drug may be added if the A1C target is not achieved after another three months. At this stage, if insulin therapy is selected, it is usually basal (NPH, glargine, or detemir); insulin is likely to be more effective than most other agents as a third-line therapy, especially when the A1C is very high (e.g., ≥9.0%).

If combination therapy that includes basal insulin has failed to achieve the A1C target after three to six months, a more complex insulin strategy may be considered, usually in combination with one or two noninsulin agents. A more rapid or immediate progression to multiple daily insulin doses may be needed in patients with severe hyperglycemia (e.g., glucose ≥300-350 mg/dL; A1C ≥10.0-12.0% with or without catabolic features, such as weight loss and ketosis).

The American College of Clinical Endocrinologists (ACCE) guidelines recommend more aggressive therapy and tighter glucose control than the ADA guidelines.[8] These guidelines recommend dual therapy for an A1C over 7.5% and triple therapy for values over 9%. There is data to support this approach; those who have good control early in the disease process have lasting benefits in terms of complication reduction. However, the risk of adverse effects with dual and triple therapy have to be considered.

There are some issues with some of the medication classes. Sulfonylureas are effective for about three years but begin to lose efficacy over time. In a study of patients with new onset T2DM comparing glyburide with metformin and rosiglitazone over five years found that the effect of glyburide declined the most over time and rosiglitazone the least.[9] The other issue with sulfonylureas is the risk of hypoglycemia, which is much higher than that for metformin and TZDs.[10] Thirty to 40 percent of patients will develop hypoglycemia with sulfonylureas.

Insulin, sulfonylureas, and TZDs are associated with weight gain. For example, with insulin patients can gain in excess of 8 kg over 12 years.[11] Sulfonylureas and TZDs can lead to 4.8 kg weight gain over five years.[10]

The sulfonylureas, metformin, and TZDs are well-established agents with known side effect profiles and low costs. Exhibit 4 shows data for the major categories of medications that are used as second line after metformin.[5-7] The TZDs are underused because of earlier concerns about increased cardio-

Exhibit 4: Exhibit 4: Choice of Therapy After Metformin[5-7]

	SU	TZD	DPP-4i	GLP-1RA	SGLT-2i	Basal Insulin
Efficacy ($\downarrow HbA_{1c}$)	+++	+++	++	+++	+++	++++
Hypo risk	++	+	+	+	+	+++
Weight effect	↑	↑	↔	↓	↓	↑
Major side effects	Hypo	Edema, Heart failure, Bone fractures	Rare	GI	Urinary and genital infections	Hypo

DPP-4i = dipeptidyl peptidase-4 inhibitor
GI = gastrointestinal
GLP-1RA = glucagon-like peptide-1 receptor agonist
HbA1c = glycosylated haemoglobin
SU = sulphonylurea
TZD = thiazolidinedione
SGLT-2 = sodium glucose co-transporter 2 inhibitors
↑ = weight gain
↓ = weight loss
↔ = weight neutral
+ = low
++ = moderate/intermediate
+++ = high
++++ = highest

vascular risk with rosiglitazone and bladder cancer risk with pioglitazone. Both of these issues have been disproven with long-term studies. This class may actually have cardiovascular benefit.[12,13]

The newest class of anti-diabetic medication is the SGLT-2 inhibitors. These agents block SGLT-2, which is a transporter of glucose from the kidneys back into circulation. Patients with diabetes actually have upregulated SGLT-2 and thus hold onto glucose. The end effect is an increase in glucose eliminated via the kidneys. The secondary effects of lowering blood glucose by this mechanism are increased insulin sensitivity in muscle and liver, decreased gluconeogenesis, and improved β-cell function. [14] Canagliflozin, dapagliflozin, and empagliflozin are the three agents in this class; each is an oral once a day medication and is also available in fixed-dose combinations with metformin. The combination of a SGLT-2 inhibitor and metformin is a very effective combination with weight loss (3-5 kg) and low risk of hypoglycemia.[15,16] Another benefit of the SGLT-2 inhibitors is blood pressure lowering (3-7 mm Hg) because of the mild diuretic effect from higher levels of glucose in urine. Low-density lipoprotein cholesterol (LDL-C) does increase about 3 to 4 percent, which may be related to hemoconcentration. This is not a change of risk factors in the right direction, so there were initially concerns about the cardiovascular disease (CVD) effects of this class. Thus, the FDA required CVD trials for these agents.

In those who already had heart disease, empagliflozin treatment over five years led to a 14 percent reduction in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (MACE), a 38 percent reduction in risk of CV death, and a 35 percent reduction in heart failure.[17] Benefits of this magnitude with antidiabetic medications had not been seen before and this turned the diabetes world upside down. Why this class is so effective in reducing CVD risk is not known, but numerous mechanisms have been proposed.[18]

A rare adverse effect of concern with SGLT-2 inhibitors is diabetic ketoacidosis (DKA). This class interferes with renal clearance of ketones and leads to increased production of ketones. At least 20 cases of DKA in patients with T2DM have been reported to the FDA Adverse Events Reporting System (3/2013 to 6/2014) and 13 cases of euglycemic DKA in patients with T1DM (9 cases) or T2DM (4 cases) have been published.[19,20] Most cases were in women and linked to reduced insulin doses. Other possible links are increased activity, recent illness, alcohol use, and decreased food intake, but some patients had no identifying cause. All patients responded to intravenous rehydration and insulin. Patients with T1DM should be counseled about DKA when SGLT-2 inhibitors are used off-label.

Overall, advantages of the SGLT-2 inhibitor class are good efficacy, decreased glucotoxicity, weight loss, lowered blood pressure, low risk of hypoglycemia, quick onset of efficacy, low risk of drug-drug

interactions and CVD benefits. Disadvantages include cost, lack of efficacy in patients with moderate to severe renal impairment, and risk for DKA and genital mycotic infections. Other issues are unknown long-term safety and durability of response.

One of the other metabolic defects in T2DM is an incretin defect. There is a substantial impairment (40% of normal) in food-induced insulin secretion in those with T2DM. It does not appear to be due to impaired secretion of GLP-1 or gastric inhibitory protein (GIP) but is likely a decreased target effect of these hormones. The defect can be overcome by achieving higher than physiologic GLP-1 levels with injectable GLP-1 agonists (exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide) or by slowing metabolism of the already secreted GLP-1 with oral DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin).

The advantages of the DPP-4 inhibitors include enhanced insulin secretion, decreased glucagon, glucose-dependent action so no hypoglycemia risk, oral and once daily, superior tolerability, weight neutral, and no apparent CVD risk (studies with saxagliptin, alogliptin, and sitagliptin). Disadvantages are high costs, lower efficacy on A1C than some other classes, possibility of pancreatitis, and possibility of heart failure with saxagliptin. Long-term safety out to four years of use appears good. Long-term durability appears to be less than with SGLT-2 inhibitors.

The GLP-1 agonists are all available as injectable products. They are taken either twice a day, once a day, or once a week. Another long-acting agent (semaglutide) is investigational and will likely make it to the market within the next year. The short-acting-agent (exenatide Bid) has more of an impact on postprandial glucose and less effect on fasting glucose. The long- acting agents (all the others) have the most effect on fasting glucose.[21] The GLP-1 agonists have all been compared in trials to exenatide Bid; overall the once daily agents produce the most decline in A1C compared with twice daily exenatide or the once weekly agents, but all are effective in lowering A1C. This class has also been compared to the DPP-4 inhibitors and produces more of a reduction in A1C.

Similar reductions in A1C are seen with GLP-1 agonists and basal insulin with no statistical differences between the classes. In many cases, the GLP-1 agonist may be the injectable of first choice over basal insulin because of the lower risk of hypoglycemia and weight loss with this class, instead of weight gain with insulin.

Hypoglycemia can occur when someone is on a GLP-1 agonist or DPP-4 inhibitor, but it typically only occurs when these classes are used in combination with agents that themselves cause hypoglycemia, particularly sulfonylureas. Nausea is the most common adverse effect with GLP-1 agonists. About 40 percent of patients will have some degree of nausea. The rate is higher for the exenatide short acting compared to the once a week formulations.

Modest weight loss (2 to 4 kg on average) occurs with use of this class. Modest reductions in blood pressure and lipids are also seen with GLP-1 agonist use.[22] This may be related to concomitant weight loss or due to postprandial modulation of triglycerides.

The CV effect of GLP-1 agonist use has also been studied. A 13 percent reduction in MACE, a 22 percent reduction in CV death, and a 15 percent reduction in death from any cause has been shown in one trial with liraglutide.[23] Similar results over two years were shown for reduction in MACE and CV death with semaglutide, the investigational agent. [24] The mechanism by which these agents provide CV protection is unknown but there are numerous theories related to decreased inflammation and other beneficial effects of GLP-1.[25]

The advantages of the GLP-1 agonists include enhanced insulin secretion, decreased glucagon, glucose-dependent mechanism of action, low risk of hypoglycemia, quick onset of action, weight loss, and a CVD benefit. These are probably the best agents for treating T2DM. Disadvantages are the cost ($400-$500/month), psychological barriers to injection, and significant nausea in some patients. From the longer term trials, this class appears to be safe and produces a durable response.

Because of the progressive nature of T2DM, many patients will ultimately require insulin therapy. Several new long-acting basal insulins (degludec, glargine, and detemir), a biosimilar for insulin glargine (Basaglar®), and fixed-dose combinations of basal insulin and GLP-1 agonists (insulin degludec/liraglutide, insulin glargine/lixisenatide) have come to market. Basal insulin with its long duration of action gives less day-to-day variability in glucose levels, lower risk of hypoglycemia, and better glucose control than short-acting insulins; thus, it is typically the first insulin used. Because of their cost, the new long-acting basal insulins are appropriate for patients who need a basal insulin better than NPH. Often this includes people with nocturnal hypoglycemia, variability of fasting glucose levels, or adherence issues, or those who do shift work.

The combination of basal insulin and a GLP-1 agonist is very effective.[26,27] Unlike a GLP-1 agonist alone, the combination with basal insulin can get more patients to goal than with either agent alone. The addi-

tion of the GLP-1 agonist blunts the weight gain from the insulin, so this combination is weight neutral.

Medication and patient factors need to be taken into account when selecting the second agent after metformin. Consideration should be given to the current A1C and the magnitude of reduction needed to reach goal, potential effects on body weight, potential for hypoglycemia (age, lack of awareness of hypoglycemia, disordered eating habits), effects on CVD risk factors, and current comorbidities – CAD, heart failure, kidney disease, and liver dysfunction. The patient's adherence to medications and lifestyle changes, preference for oral versus injected therapy, and economic considerations also play into any medication decisions.

Importantly, in real life, the problem is not in selecting therapy but in actually getting patients on sufficient therapy. It is well known that clinicians tend to delay intensifying therapy for months, especially when it comes to initiating insulin.[28]

Conclusion

Lifestyle changes and education are still the foundation of therapy for T2DM, but medication is necessary to achieve glucose goals in most patients. Diabetes therapy should be personalized using patient factors, preferences, comorbid conditions, and life expectancy. Metformin is still the recommended first-line therapy for T2DM, but there are multiple options for improving glycemic control after monotherapy failure. Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain control. Selection of second- and third-line therapy depends on goals. All treatment decisions should be made in conjunction with the patient with a focus on preferences, needs, and values. CV risk reduction should be a major focus of therapy.

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Novel Treatment Advances and Approaches in Management of Relapsed/Refractory Multiple Myeloma

Ravi Vij, MD, MBA

For a CME/CNE version of this article, please go to http://namcp.org/home/education, and then click the activity title
Supported by educational grants from AbbVie and Amgen.

Summary

Although significant advances have been made in treating multiple myeloma, it is still a fatal disease. To continue making advances, a new paradigm using precision and personalized medicine and novel clinical trial designs is needed.

Key Points

- Most advances in treatment of myeloma have targeted normal plasma cell biology as a result of the empirical paradigm of drug development.
- Future advances in myeloma therapy will be in precision/personalized medicine.
- Tools to make this possible are starting to emerge.
- This will also require novel clinical trial designs.

MULTIPLE MYELOMA (MM), A CANCER OF the plasma cells characterized by excessive numbers of abnormal plasma cells in the bone marrow, is the second most common hematologic neoplasm in the United States. The average age of onset is 70, and the disease affects African Americans at a higher rate than Caucasians. Tremendous progress has been made during the last 20 years, and the median overall survival has increased from approximately three years to more than 10 years.

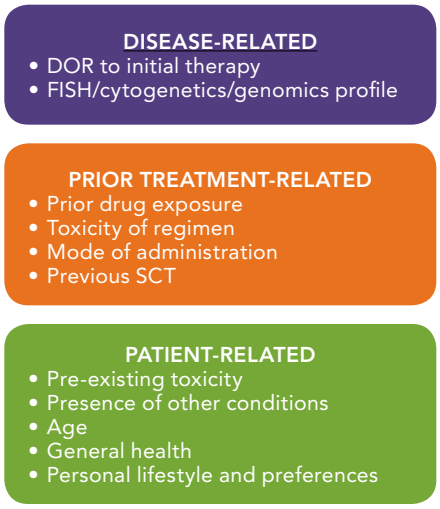
Initial treatment of MM depends on whether the patient is a candidate for a stem cell transplant.[1] Someone who is clearly not a transplant candidate based on age, performance status, and comorbidity would receive conventional chemotherapy. Maintenance therapy will be given after the chemotherapy. Transplant candidates receive non-alkylator based induction chemotherapy for four cycles and then undergo stem cell harvest.

After successful first-line therapy, most patients with MM will eventually relapse. The typical course of MM is repeating periods of remission after treatment and relapses. Over time, with each relapse, the disease becomes more resistant to therapy and the duration of remission is shortened. Five to eight lines of treatment are not uncommon.

Patients can have a clinical or biochemical relapse. A clinical relapse would be treated, whereas with a biochemical relapse (asymptomatic rise in M-protein) the patient may be monitored to determine the rate of rise and nature of the relapse. Patients with known aggressive or high-risk disease based on genomics are considered for salvage therapy, even in the setting of biochemical relapse.

Exhibit 1 outlines some of the factors that have to be considered in choosing treatment in the relapsed/refractory setting.[2] The current treatment approach to relapsed/refractory MM is shown in Exhibit 2.

Exhibit 1: Factors to Consider in Treatment Selection[2]



DOR = duration of response
FISH = fluorescence in situ hybridization
SCT = stem cell transplant

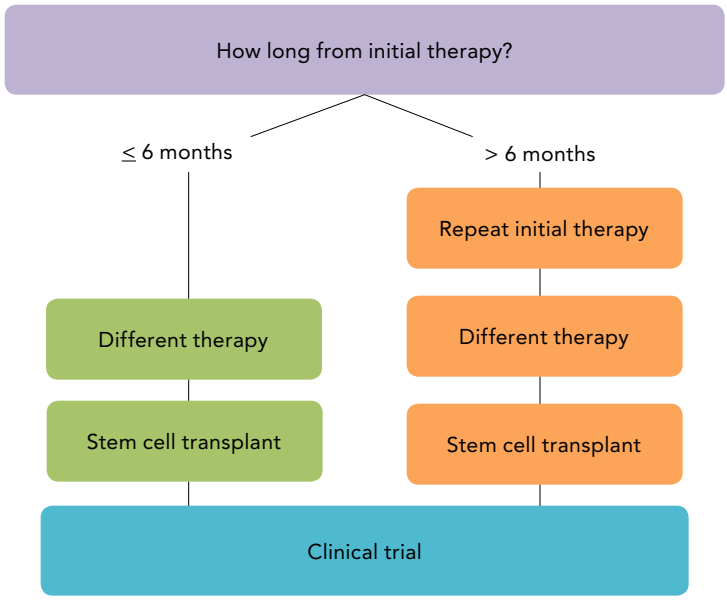
Novel agents for treatment of MM include immunomodulators [lenalidomide (Revlimid®), pomalidomide (Pomalyst®), daratumumab (Darzalex®), elotuzumab (Empliciti®), panobinostat (Farydak®)] and proteasome inhibitors [bortezomib (Velcade®), carfilzomib (Kyprolis®), ixazomib (Ninlaro®)]. The standard of care has been to give lenalidomide with dexamethasone (Rd) or bortezomib with dexamethasone (Vd). Dexamethasone has some anti-MM properties. Trials done and published in recent years have tried to improve upon these two standard regimens. One regimen investigated was adding carfilzomib to lenalidomide/dexamethasone (KRd), which increased progression-free survival (PFS) by about nine months and an improvement in median overall survival (mOS) compared with Rd. Most MM regimens for the relapsed/refractory setting are approved based on PFS and not overall survival.

Ixazomib was the first oral proteasome inhibitor approved for MM. It has been studied in combination with lenalidomide/dexamethasone and has shown to improve PFS by 5.9 months over the two-agent regimen.[3] Elotuzumab was the first monoclonal antibody to be approved for MM. It is an immunomodulator and has been studied in combination with lenalidomide/dexamethasone. Like the other newer agents, it improves PFS by 4.5 months.[4] Elotuzumab does not have single-agent activity. Traditionally, agents lacking single-agent activity have not been considered to be effective. This agent proved this theory wrong because it is effective when given in combination with other agents. Overall, these two new agents have led to about a 30 percent increase in progression-free survival when combined with lenalidomide/dexamethasone.

Daratumumab was approved just after elotuzumab and has also been evaluated in combination with lenalidomide/dexamethasone and appears to be more effective than elotuzumab and ixazomib.[5] This three-drug regimen has become first line because of efficacy. The regimen with ixazomib is an all oral therapy regimen and is sometimes chosen by patients because it is more convenient. Unfortunately, depending on a patient's pharmacy benefits, they may not be able to afford ixazomib. If they have better medical coverage than pharmacy coverage, they may have to have the intravenous regimens.

The other standard regimen has been bortezomib/dexamethasone. Panobinostat and daratumumab have been studied in combination with this regimen.[6,7] Panobinostat is another agent with no monotherapy activity. Unfortunately, this agent causes substantial gastrointestinal toxicity and thus has not been widely adopted by clinicians. The dosing intervals can be prolonged to lower adverse effects. Combining daratumumab with bortezomib/dexamethasone is very effective and doubles PFS. This regimen is beginning to be used but combining daratumumab with lenalidomide/dexamethasone is more popular and appears to be a more rational combination.

Exhibit 2: Options or Relapsed/Refractory Disease



A second transplant is also an option at the time of first progression. At least one study has shown improvement in PFS with this approach. Most MM centers look for 18 to 24 months duration of effect with the first transplant before considering a second transplant. The second transplant only has about 50 percent of the durability of the first one.

Several more therapies are under investigation for MM. Venetoclax (Venclexta®), which is already approved for chronic lymphocytic leukemia, may become the first biomarker (p19 deletion) driven treatment for MM. Selinexor is the first drug in a new class of agents known as selective inhibitor of nuclear export compounds and works by inhibiting XPO1, a protein found in the nucleus of cancer cells, which activates tumor suppressors by retaining them in the nucleus of cancer cells. This results in apoptosis of cancer cells, while largely sparing normal cells. It has shown activity in patients who have failed multiple lines of therapy and is likely the next agent to be FDA approved for MM. Various immunotherapies including check point inhibitors (pembrolizumab, nivolumab), antibody drug conjugates, bispecific T-cell engager (BiTE), and CAR-T cells are also under investigation.

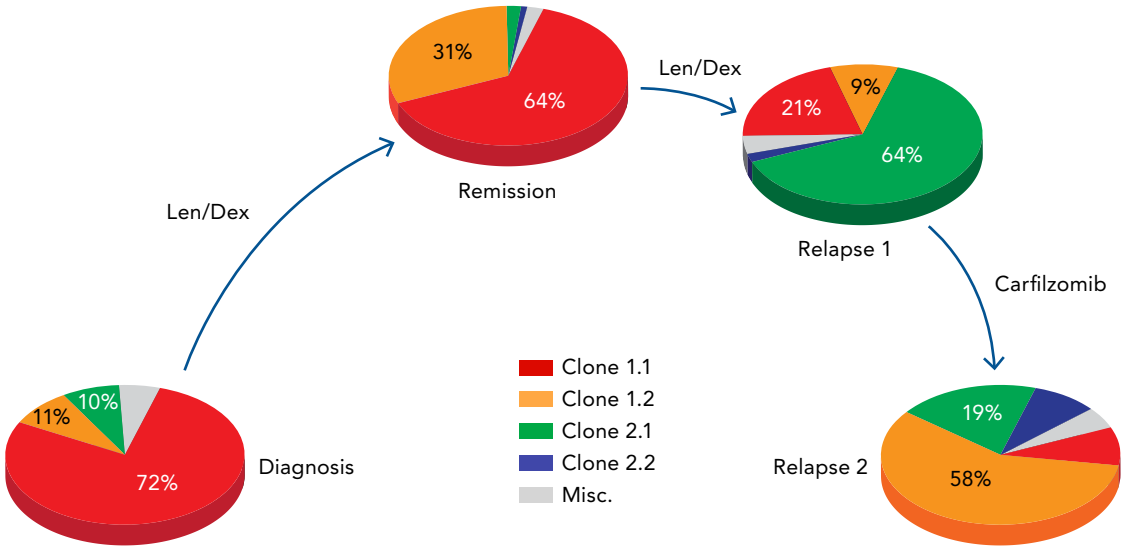
In terms of treatment, the research in MM is heading toward using combinations of agents with no single-agent activity and another compound to work synergistically together. Another issue with MM is that a number of agents can kill MM cells in the lab but do not work in vivo because of issues in the microenvironment of the bone marrow. A large number of strategies to target this microenvironment are being investigated.

Value-based care is also becoming an issue. MM was one of the first cancers investigated for value-based care because lenalidomide was the second most costly agent for Medicare. Companies working in this area are tuned into this issue and are using registries to try to determine the ideal patient populations for individual products.

Most of the agents for MM have been developed through the empirical method typical for pharmaceuticals - Phase I through Phase III trials with increasing patient enrollment at each stage. For agents such as lenalidomide, even though it has been available for 20 years, we still do not know how it actually works in MM. Genetics do matter in MM, so efforts are underway to develop personalized treatments Patients can be divided into high, intermediate, and low risk groups based on cytogenetic markers. Additionally, these genetic abnormalities can be picked up years before MM is an active disease during the monoclonal gammopathy of unknown significance [MUGUS] phase of the disease. These abnormalities are not what triggers the change to active/symptomatic disease. A great deal of research is ongoing trying to identify the genetic abnormalities or microenvironment issues which are leading to transition to active disease.

Many experts think it is time to abandon therapies with broad action for therapies with narrow

Exhibit 3: Changing Genetics Over Time[9]



specific targets relevant to MM.[8] Previously, tumor cells were thought of as monoclonal (i.e., all carried the same genetic abnormalities that caused the cancer) at the time of diagnosis but developed other genetic mutations in response to treatment. It is now known that all cancers, even at the time of diagnosis, are multi-clonal. Thus, many different genetic profiles can be found in the tumor cells. At the time of therapy resistance, one of the minor clones takes over the tumor and the original clone is suppressed by the prior treatment (Exhibit 3).[9]

Precision medicine is somewhat different from personalized medicine. Precision medicine ignores what type of cancer is present but defines the cancer by genetic mutations only. So far the FDA has not approved any drugs just based on the mutations present. Drugs have been approved for specific cancers which may have certain mutations. Trials are now ongoing that are looking at patients with specific mutations irrespective of the type of cancer. Hopefully, in the future, drugs will be approved based on mutations. For example, there are 30,000 new cases of MM annually, but maybe only 5 percent have a particular mutation. It is difficult to get a drug company to develop a drug for 5 percent of MM. Some drugs have failed in development because enough patients did not respond, but some did. It is important to go back and determine why those particular patients responded. Approving drugs based on mutations is one way to move therapy forward.

The current molecular profiles that are obtained are still in the elementary state. The MMRF CoMMpass trial is sequencing the DNA and RNA of over 1,000 patients at diagnosis and at each relapse to attempt to identify patient segments based on molecular profiling. Companies are using computer modeling to develop avatars to predict what drug may work in a patient with particular mutations. Others are looking at 3D modeling of the patient's tumor to figure out which drugs would work. The fruits of these big data projects are probably 10 to 20 years down the road.

Conclusion

Most advances in treatment of myeloma to date have targeted normal plasma cell biology and have been the result of an empirical paradigm of drug development. However, the future of advances in myeloma therapy lies in precision/personalized medicine. Tools to make this possible are starting to emerge. This will also require novel clinical trial designs.

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Evolving Considerations in the Individualization of Treatment in Metastatic Colorectal Cancer (mCRC): What do Targeted Therapies Have to Offer?

Minsig Choi, MD

For a CME/CNE version of this article, please go to http://namcp.org/home/education, and then click the activity title.
Supported by educational grants from Bayer, Merck and Taiho.

Summary

Targeted therapies offer significant benefits in managing metastatic colorectal cancer (mCRC). Unlike other cancers, a large portion of mCRC tumors have targetable genetic mutations._Survival continues to improve, but there is still work to be done to continue to advance care.

Key Points

- Biomarkers are used to individualize treatment in mCRC.
- Anti-VEGF, anti-EGFR, and multikinase therapies have modestly improved clinical outcome in mCRC patients.
- Patients whose tumors have RAS mutations should not receive anti-EGFR therapies.

MORE THAN 1.2 MILLION CASES OF COLORECTAL cancer (CRC) occur in the world annually, with 608,000 deaths. It was estimated that 135,430 cases would occur in the United States (U.S.) in 2017 and 50,260 deaths.[1] CRC is increasing in incidence in several developing countries as opposed to a decline in the U.S. and in several Western countries. Most cases still present in later stages because of suboptimal or absence of screening techniques.[2]

Most human CRCs arise from large-bowel adenomas (adenomatous polyps) that are dysplastic but nonmalignant. Adenomatous polyps form in the colon when normal mechanisms regulating epithelial renewal are disrupted. As a result of apoptosis and exfoliation, surface cells lining the intestine are continuously lost into the bowel lumen and must be continuously replaced. Typically, proliferation occurs at the crypt base. As cells move toward the luminal surface, they cease proliferating and terminally differentiate. This ordered process is disrupted as adenomas increase in size, become dysplastic, and attain invasive potential. CRCs develop from intermediate precancerous precursors. Early carcinomas are seen within large adenomatous polyps. It takes 10 to 15 years for adenomas to become cancerous in both sporadic and familial CRC.[3]

Specific genetic changes are believed to drive the transformation from normal colonic epithelium to invasive cancer. The molecular basis for CRC is a multistep process in which each accumulated genetic event confers a selective growth advantage to the colonic epithelial cell. Germline mutations underlie the common inherited syndromes (e.g., familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer or Lynch syndrome), whereas sporadic cancers result from the stepwise accumulation of multiple somatic mutations. Mutations in the adenomatous polyposis coli (APC) gene, a feature com-

Exhibit 1: Genes and Growth Factors in Colorectal Cancer Development[5]

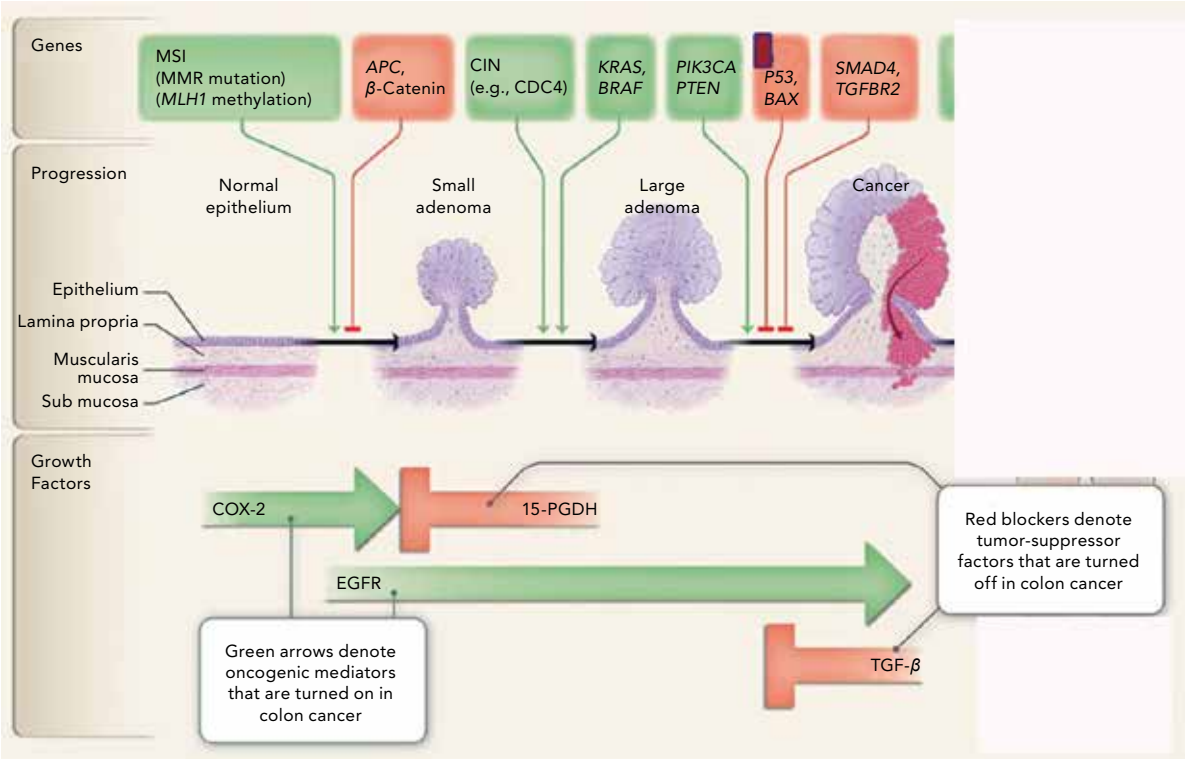
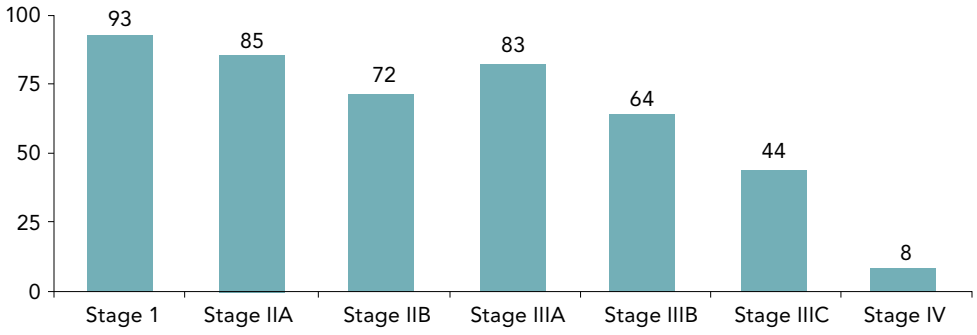


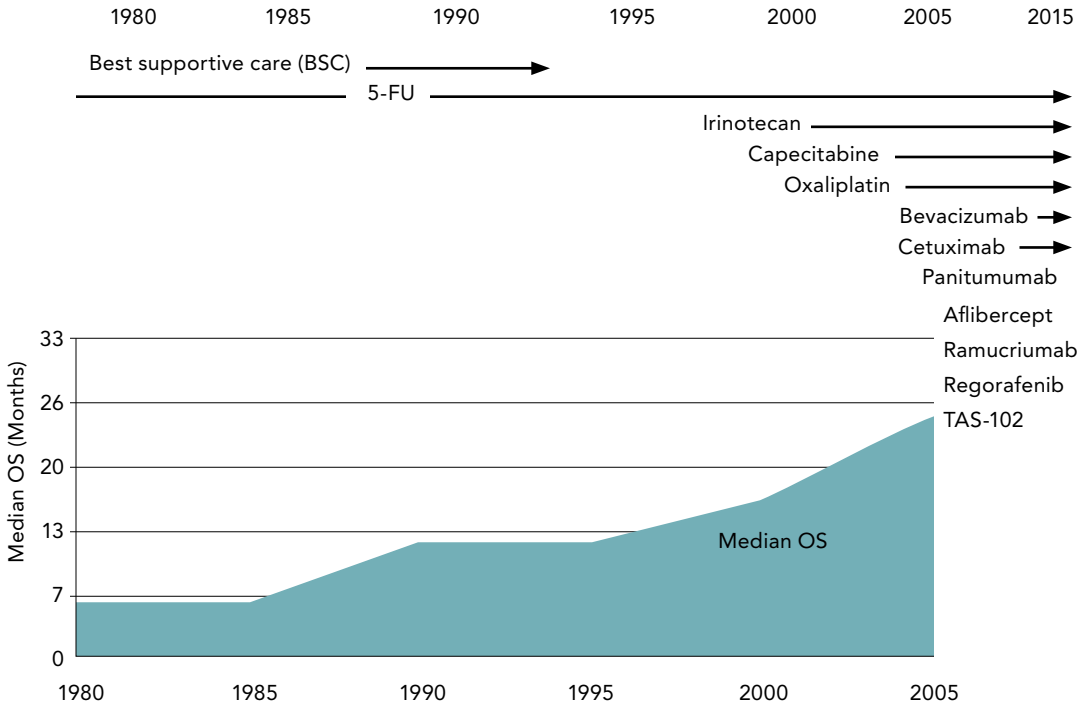
Exhibit 2: Five-year Survival by Stage for Patients with Colon Cancer[2]



mon to both inherited and sporadic tumors, occur early in the process; mutations of the p53 suppressor gene generally occur late.[4] Exhibit 1 illustrates some of the genes and growth factors that have been shown to be related to the development of CRC.[5]

There are several options for preventing CRC. One is screening, which is very effective. Screening has reduced the overall rate of CRC in the U.S. by approximately 10 percent. In addition to screening, individuals can make lifestyle changes to reduce their risk. For men, maintaining a normal body mass index, getting at least 15 metabolic equivalent task (MET) hours per week of physical activity, taking a daily folate-containing multivitamin, consuming less than 15 g/day of alcohol, not smoking, and consuming two or fewer servings of red meat weekly

Exhibit 3: Advances in the Treatment of mCRC



have all been shown to reduce risk. Instituting all of these would eliminate 71 percent of all CRC in men but unfortunately only 3.1 percent of all men are able to do all these.

Five-year survival for those diagnosed with CRC depends on the stage at diagnosis (Exhibit 2).[2] Unfortunately, only 38 percent of patients are diagnosed at Stages I and IIa, which have the best survival. Metastatic CRC (mCRC) is present in 20 percent of patients at presentation. Median survival of an untreated patient with mCRC is six months, and it is two years with chemotherapy. In patients who have KRAS wild-type disease, median survival is 30 months.

Exhibit 3 shows how the median OS in mCRC has improved with advances in treatment. Multidrug chemotherapy regimens are the standard of care for most patients with mCRC. These include FOLFOX (5-FU, leucovorin and oxaliplatin), CapOX (capecitabine and oxaliplatin), and FOLFIRI (5-FU, leucovorin, irinotecan). These are used in sequence if the patient relapses after one regimen.

Adding targeted biologics to chemotherapy has modestly improved survival outcomes in mCRC. Targeted therapies approved for Stage IV disease include vascular endothelial growth factor receptor [VEGF-R] inhibitors (bevacizumab, aflibercept, regorafenib), anti-epidermal growth factor receptor [EGFR] monoclonal antibodies (cetuximab, panitumumab), and a multikinase inhibitor (ramucirumab). Bevacizumab, cetuximab, or panitumumab are used in combination with chemotherapy as first-line treatment for patients with KRAS wild-type mCRC. Patients with KRAS mutations do worse when cetuximab or panitumumab are added to chemotherapy. The KRAS mutations allow the cancer cells to continue to grow despite EGFR blockade. For those with KRAS mutations, anti-VEGF agents are the only choice. The best sequence of therapies (VEGFi vs EGFRi) is still to be established. Exhibit 4 compares the strengths and weakness of these two classes.

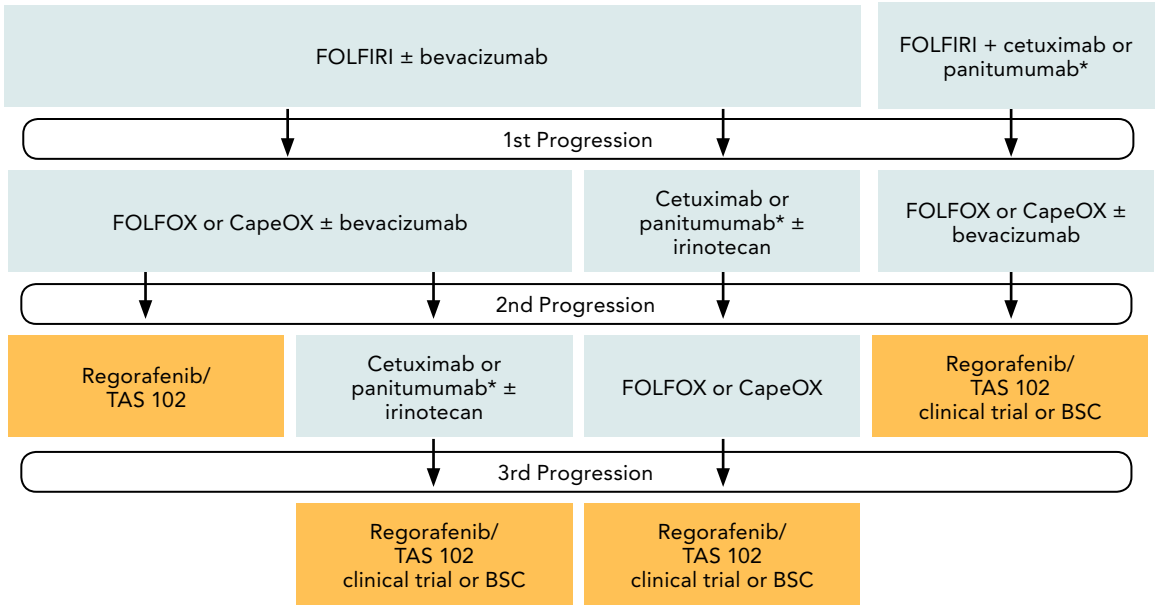
Bevacizumab is an anti-VEGF agent that reduces angiogenesis. Beyond hypertension, this is a relatively well-tolerated agent. This is not an appropriate agent for those who have cardiovascular disease. EGFR inhibitors prevent cancer cell growth. They typically cause problematic rashes that can be very severe, itching, and dry skin. Studies have shown that the patients who develop the rash typically do better. Aflibercept and ramucirumab are two newer oral agents which are FDA approved for second-line therapy.

Regorafenib is an option for patients who have failed multiple lines of therapy and do not have ac-

Exhibit 4: Anti-VEGF vs Anti-EGFR Antibodies in Advanced CRC

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

Exhibit 5: NCCN Guidelines – Chemotherapy for Advanced or Metastatic Disease



*KRAS/NRAS wild-type only. **STIVARGA is a treatment option for patients who have progressed through all available regimens (e.g., KRAS/NRAS mutant or KRAS/NRAS wild-type with previous exposure to an anti-EGFR inhibitor).

cess to a clinical trial. This agent is a multikinase inhibitor which has been shown to inhibit the activity of VEGFR1, VEGFR2, VEGFR3, BRAF, BRAFV600E, and numerous other kinases. Regorafenib is indicated for the treatment of patients with metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. A drawback of this agent is the development of hand and foot skin reactions and mucositis. It improves survival about 23 percent.[6,7] Another salvage therapy is TAS-102, which is an oral combination of trifluridine and a thymidine phosphorylase inhibitor. This agent is FDA approved for metastatic CRC previously treated with chemotherapy, an anti-VEGF biologic product, and an anti-EGFR therapy, if RAS wild-type. Hematologic toxicities are the most common adverse effects. Treatment with this agent improves median OS by 1.8 months.[8]

Forty percent of patients with mCRC have KRAS mutations, 5 to 10 percent have NRAS, 5 percent have BRAF, and 15 percent have PIK3CA. BRAF and RAS mutations are mutually exclusive and KRAS and NRAS mutations are mutually exclu-

sive. Patients with any RAS mutants do not benefit from anti-EGFR therapy. Testing for additional RAS mutations could help screen 10 to 20 percent more patients with mCRC who would not benefit from expensive EGFR inhibitors. The NCCN guidelines now recommend testing for all RAS mutations in mCRC.

Conclusion

Biomarkers tell us about an individual patient's tumor. Anti-VEGF, anti-EGFR, and multi-kinase therapies have modestly improved clinical outcome in mCRC patients. We are just at the beginning of this era of treatment options for patients using molecular markers. Individualizing risk and adverse events to patients are potential challenges to our patients. Large data and clinical trials in elderly and patients with comorbidity are really needed.

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Preventing Acute Exacerbations through Novel Insights in the Treatment Strategies for COPD

James F. Donohue, MD

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

Optimal COPD management to prevent exacerbations requires an individualized plan and appropriate device selection based on lung function, exacerbation risk, mental and physical attributes, comorbid conditions, and personal preferences. Combining beta agonists and antimuscarinic bronchodilators are a better option for reducing exacerbations than a bronchodilator combined with inhaled corticosteroids.

Key Points

- Clinicians have to assess symptoms, degree of airflow limitation by spirometry, exacerbation risk, and comorbidities to accurately treat COPD.
- Treatment choices are expanding and evolving and clinicians must be aware.
- Treatment selection should be based on evidence-based guidelines.
- Based on recent data, combinations of LABAs/LAMAs may be a better choice than a LABA/ICS combination.

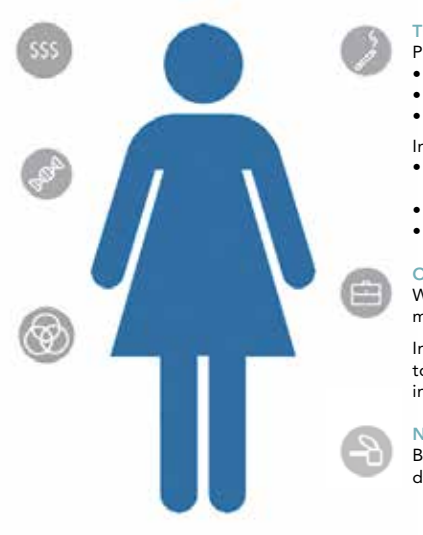
CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) is the third leading cause of death in the United States (U.S.)[1] Approximately 15 million Americans are diagnosed with the disease and an estimated 10 million are undiagnosed.[2] It is also associated with significant economic burden estimated at $50 billion in 2010. The burden of COPD is projected to increase in coming decades due to continued exposure to COPD risk factors and the aging of the world's population.

COPD affects both men and women, but women are impacted differently. Exhibit 1 summarizes some of the differences. There is significant clinician bias in diagnosing COPD in women; they tend to be diagnosed as having asthma. Although death rates from COPD declined among U.S. men between 1999 and 2010, there has been no significant change among death rates in women.[3] Death rates have declined because of public health efforts to reduce smoking.

This disease has a major impact on the lives of those who have it. Those with COPD have high susceptibility to disability and low physical and mental health related quality of life (HRQOL).[4]

COPD is triggered by cigarette smoking in about 80 percent of cases in the U.S. Biomass fuel is an important cause worldwide in women because of cooking duties. Heating fuels also cause issues. Other risk factors include viruses, bacteria, and occupational dust and chemicals.[5] These triggers lead to inflammation and oxidative stress, which leads to pathologic changes in the lungs (bronchoconstriction, edema, and mucus), causing airflow limitation.[6,7] Hyperinflation is also a significant component of this disease and leads to dyspnea. Systemic inflammation, secondary to lung inflammation, increases the risk of cardiovascular disease. Heart disease is major cause of mortality in COPD; one-third of patients die from heart disease, one-third from COPD itself, and one-third from lung cancer.

Exhibit 1: The Impact of Female Gender on COPD



SOCIOECONOMIC STATUS
Women with COPD are likely to be of lower socioeconomic status than men

COPD DISEASE PRESENTATION
Women are generally younger, smoke less and have lower BMI than men

COPD COMORBIDITIES
Higher burden of comorbidities in women vs. men

More asthma, osteoporosis and depression vs. men

TOBACCO USE
Prevalence:
- Varies by location
- Equal to men in some countries
- Increasing in many developing countries

In women with COPD there is evidence of:
- Greater harm vs. men for same level of tobacco smoke exposure
- Greater benefits of smoking cessation vs. men
- More difficulty with smoking cessation than men

OCCUPATIONAL EXPOSURES
Women now work more frequently in traditionally male occupations

In some locations, women are more likely than men to be exposed to risks from unregulated 'cottage' industries, such as fish smoking and textile working

NON-OCCUPATIONAL EXPOSURES
Biomass fuel exposure greater as a result of more domestic responsibilities

COPD should be considered if any of these indicators are present in patients aged 40 years and older: progressive and persistent dyspnea that characteristically worsens with exercise, chronic cough which may be intermittent and may be unproductive, chronic sputum production, family history of COPD, and exposure to known risk factors.[5] COPD should be diagnosed with spirometry. The goals of COPD assessment are to determine disease severity (i.e., degree of airflow limitation by spirometry), its impact on patient health status, and the risk of future events (e.g., exacerbations, hospital admissions, death) in order to guide therapy. Symptoms of the disease can be assessed with standardized questionnaires, such as the COPD assessment test (CAT), the clinical COPD questionnaire (CCQ), and the modified Medical Research Council Dyspnea Scale (mMRC). The CAT has eight questions rated on a scale of 0-5 and provides a unidimensional measure of health status impairment in COPD, correlates closely with health status using the St. George's Respiratory Questionnaire (SGRQ), and is reliable and responsive.[5] The CCQ has 10 questions rated on a scale of 0-6, is specifically developed to measure clinical control in patients with COPD, and is valid, reliable, and responsive.[5] The mMRC provides assessment of breathlessness (grade 0-4), relates well to other measures of health status, and predicts future mortality risk.[5]

The severity classification based on spirometry from the Global Obstructive Lung Disease (GOLD) guidelines is shown in Exhibit 2.[5] Spirometry classification also has implications for other risks, such as exacerbations, which are more likely with increased disease severity.

Exacerbations are a major driver of health care costs in COPD. An exacerbation is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.[5] A mild exacerbation will require a temporary adjustment of current medications, such as extra use of a short-acting bronchodilator. A moderate exacerbation is one that requires treatment with systemic corticosteroids or antibiotics. Severe exacerbations are associated with poor prognosis and increased risk of death and require hospitalization or evaluation in the emergency department. Predictors for having frequent exacerbations (≥2/year) include a history of previous treated events (best predictor) and worsening airflow limitation. Preventing exacerbations is important in COPD for preventing disease progression and reducing health care costs. Those with frequent exacerbations have lower QOL, increased inflammation, increased mortality, increased rates of hospitalization, faster disease progression, and increased risk of recurrent exacerbations.[8] Salmeterol, tiotropium, fluticasone furoate/vilanterol (Breo Ellipta®), roflumilast (Daliresp®) are the four treatments that have an FDA indication for preventing exacerbations. Azithromycin three times a week can also be used but is off-label. This works particularly well in those with the chronic bronchitis form of COPD.

Comorbidities are common in COPD and affect management because they influence mortality and hospitalizations. The common comorbidities are

Exhibit 2: GOLD Spirometric Classification of Severity of Airflow Limitation in COPD[5]

Classification	In Patients with FEV_1/FVC <0.70
GOLD 1: Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted

Based on Post-Bronchodilator FEV1
FEV_1 = forced expiratory volume in one second
FVC = forced vital capacity

lung cancer, anxiety, depression, pulmonary hypertension, anemia, diabetes/metabolic syndrome, cachexia, cardiovascular disease, muscle dysfunction/wasting, osteoporosis, and peptic ulcers.[9] These have to be considered in the treatment plan. Managing these can also help improve COPD management.

There are numerous treatment options for COPD including inhaled corticosteroids (ICSs), long-acting β2-agonists (LABAs), long-acting muscarinic antagonists (LABAs), phosphodiesterase 4 inhibitors (PDE4is); short-acting β2-agonists (SABAs), short-acting muscarinic antagonists (SAMAs), and various combinations of these agents.

Bronchodilators (LABA, LAMA, SABA, SAMA) increase forced expiratory volume in one second (FEV1) by altering airway smooth muscle tone. Improvements in expiratory flow reflect widening of the airways rather than changes in elastic recoil.[10] Bronchodilators also act on peripheral airways to reduce air trapping and improve emptying of the lungs, thereby reducing lung volumes and improving symptoms and exercise capacity.[10,11] Bronchodilators with a sustained 24-hour duration of action maintain airway patency, which is likely to be desirable in COPD.[12] Additional non-bronchodilator effects such as improvements in skeletal muscle function and mucociliary clearance have also been documented for long-acting ß2-agonists.[13] The combination of a LABA and a LAMA has complementary mechanisms of action, leading to the best lung function..

Inhaled LABAs and LAMAs are the mainstay of pharmacologic treatment of stable COPD. The long-acting agents are preferred over short-acting and inhaled is preferred over oral, based on efficacy and adverse effects. Combinations may be considered if symptoms are not improved with single agents.

Currently, available LABAs include formoterol, arformoterol, indacaterol, olodaterol, salmeterol, and vilanterol. Indacaterol, olodaterol, and vilanterol are the newest options and have longer durations of action than previous agents.[14,15] Lung function duration of indacaterol is significantly greater than that of formoterol, salmeterol, and arformoterol and similar to tiotropium, an antimuscarinic agent.[14] Formoterol and salmeterol have been shown to significantly improve FEV1 and lung volumes, dyspnea, health-related QOL, and exacerbation rate, but have no effect on mortality and rate of decline of lung function.[5] Salmeterol reduces the rate of hospitalization related to COPD.[5] Several studies have shown that LABAs are more beneficial than repetitive use of SABAs.[16] Unlike with asthma, a LABA can be used alone in COPD and does not have to be combined with an ICS for safety reasons.

LABA/ICS combinations are also available, including formoterol/budesonide, salmeterol/fluticasone, and vilanterol/fluticasone. This combination is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD, but it may be associated with a small increased risk of pneumonia.[5] The LABA/ICS combination really should be reserved for the more severe population.

The LAMAs are the other class of mainstay therapy in COPD. Tiotropium has been the hallmark of COPD treatment and has been the only LAMA available in an inhaler until recently. Four years of tiotropium treatment in those with moderate to severe disease is associated with reduced risk of exacerbations, related hospitalizations, and respiratory failure.[17] Aclidinium and umeclidinium are the newer LAMAs. In those with moderate to severe COPD, aclidinium improved FEV1 and delayed the time to the first exacerbation.[18] It also led to a clinically significant increase in trough and peak FEV1

and improvement in SGRQ and dyspnea scores.[19] Umeclidinium significantly improved trough FEV1 and led to significant improvements in least squares mean dyspnea scores.[20] Glycopyrrolate or glycopyrronium is an older agent that has been used as an injectable to reduce salivation during surgery. It has been introduced in inhaler form as monotherapy (Seebri Neohaler® – dry powder inhaler) and in combination with formoterol (Bevespi Aerosphere®) and indacaterol (Utibron Neohaler®). A nebulized formulation is scheduled to be marketed in spring 2018 (Lonhala Magnair®). Glycopyrrolate leads to significant and clinically meaningful improvements in FEV1 compared to placebo and to improvements in COPD symptoms, QOL, and rescue medication use in patients with moderate to severe airflow limitation.[21,22]

Various combination LABA/LAMA products are available. One combination is umeclidinium/vilanterol inhalation powder, which was FDA approved in 2013 as a long-term maintenance treatment in COPD. In a systematic review of 11 published studies, the combination led to improvements in mean trough FEV1 when compared to umeclidinium, vilanterol, tiotropium, and fluticasone/salmeterol.[23] This combination was not significantly different from tiotropium in terms of risk of exacerbations and likelihood of a minimal clinically important difference on a dyspnea score. Adverse effects were similar for all the agents.

The newest LABA/LAMA combination therapy is indacaterol-glycopyrrolate. In a trial comparing indacaterol/glycopyrrolate with salmeterol/formoterol, the LABA/LAMA combination was more effective than LABA/ICS in preventing COPD exacerbations in patients with a history of exacerbations during the previous year.[24] There was also a lower pneumonia rate in the LABA/LAMA group (3.2% vs 4.8%). Based on the results of this trial, a LABA/LAMA combination may be preferred over LABA/ICS.[25] A Cochrane review also found that treatment of chronic stable COPD with a LABA/LAMA combination results in fewer exacerbations, a larger improvement of FEV1, a lower risk of pneumonia, and more frequent improvement in quality of life than use of LABA/ICS.[26]

Triple therapy with LAMA/LABA/ICS is broadly used but may not be necessary in the majority of patients. Products containing all three will be coming to market soon. Additionally, more products containing glycopyrrolate derivatives will be coming to market.

Adherence with COPD medications and inhaler technique are typically suboptimal. Depending on the inhaler type and assessment method, a large percentage of patients fail to use their inhalers correctly.[27] In a study of 5,812 people with COPD from the Copenhagen General Population study, medication adherence varied from 29 to 68 percent .[28]

Inhalers are the most commonly recommended dosage formulation, but there are some clinical scenarios where nebulized therapy may be preferred. These include if the patient cannot generate adequate inspiratory flow required by dry powder inhalers (DPIs), cannot use pressurized metered dose inhalers (pMDIs) or DPIs appropriately despite adequate education and training, debilitation after hospitalization and cannot coordinate breathing with device requirements, inadequate symptom relief with appropriate use of inhalers, nonadherence with inhalers, and preference for nebulization.[29] Many small women and those with severe disease do not have adequate inspiratory flow for a DPI. There is a trend now to do measurements to make sure patients have adequate inspiratory flow before prescribing a DPI. Others clinical scenarios where nebulized therapy may be preferred include cognitive impairment (e.g., Alzheimer's, altered consciousness), impaired manual dexterity (e.g., arthritis, Parkinson's, or stroke), pain or weakness from neuromuscular disease (e.g., multiple sclerosis), need for higher bronchodilator or corticosteroid doses to control disease, or cannot afford therapy with pMDIs or DPIs.

Conclusion

Overall, optimal COPD management requires an individualized plan and appropriate device selection, based on lung function, exacerbation risk, mental and physical attributes, comorbid conditions, and personal preferences. The treatment armamentarium is continuously expanding and evolving to include new treatments and delivery systems, of which clinicians must be aware. Treatment selection should be based on evidence-based guidelines, comorbidities, and patient preference. By working through each of these factors, clinicians can offer patients with COPD great opportunities to improve acute and long-term outcomes.

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Coverage Trends for Two Lifestyle Medicine Programs Addressing Chronic Disease

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Summary

The prevalence and cost of diabetes mellitus and cardiovascular disease make these diagnoses among the most common for the managed care community to address. Historically, the focus of managed care has been on the pharmacologic and surgical treatment of these disease states. However, with growing evidence of the effectiveness and safety of lifestyle medicine programs, such as Intensive Cardiac Rehabilitation (ICR) and the Diabetes Prevention Program (DPP), some managed care companies are starting to add these benefits to their portfolios. This study looks at the trend of coverage for ICR and DPP in the Medicare, Medicaid and Commercial insurance marketplaces.

Key Points

While the availability of coverage policies varies, many insurers have begun covering ICR and DPP as evidence supporting their efficacy and cost-effectiveness grew.

- The expanding coverage for ICR and DPP may reflect a trend among managed care leaders to utilize lifestyle medicine therapies to address the increasing burden of cardiovascular disease and diabetes.
- The lack of easily accessible state Medicaid policies regarding ICR makes it difficult to draw conclusions about Medicaid ICR coverage.

Introduction

SINCE ITS INCEPTION, HEALTH INSURANCE in the United States (U.S.) has evolved dramatically in name (i.e., managed care) and in practice, with the expansion of services accompanied by rising costs. In 2015, health expenditures comprised 17.8 percent of the gross domestic product (GDP), totaling $3.2 trillion.[1] Two conditions in particular, diabetes mellitus and cardiovascular disease, have captured attention with their morbidity, mortality, and economic impact of $176 billion[2] and $318 billion[3] in direct medical costs, respectively. Furthermore, the American Heart Association and American Stroke Association project the total cost of cardiovascular disease alone to be $1.1 trillion by 2035.[3]

The financial burden of expensive solutions and an unyielding disease burden are insurmountable in our current approach. While many attempts to address diabetes and cardiovascular disease rely on pharmaceuticals and technology, these approaches are not without their shortcomings. Pharmacologic agents, for example, carry the risks of adherence issues, side effects, and prescription errors, which contribute to overall medical errors in claiming more than 250,000 lives annually in the U.S.[4] Pharmacologic agents and procedures also fail to address the underlying issue, given that both conditions are highly linked to lifestyle.[5]

As our health care system increasingly emphasizes value-based care, practitioners, administrators, and insurers are considering lifestyle modification to improve health and decrease the financial burden.

Beyond covering grades "A" and "B" U.S. Preventive Services Task Force recommendations such as diabetes screening and dietary and physical activity counseling, as mandated by the Affordable Care Act, managed care decision-makers have started covering lifestyle medicine programs. Lifestyle medicine involves "evidence-based lifestyle therapeutic approaches, such as a predominantly whole food, plant-based diet, exercise, stress management, tobacco and alcohol cessation, and other non-drug modalities, to prevent, treat, and […] reverse [...] chronic disease."[6]

Two notable lifestyle medicine programs are intensive cardiac rehabilitation (ICR) and the Diabetes Prevention Program (DPP). Unlike traditional cardiac rehabilitation (TCR), which focuses almost exclusively on exercise, ICR also incorporates other lifestyle medicine modalities such as diet, stress reduction, and group support. Dr. Ornish's Program for Reversing Heart Disease, also called the Multicenter Lifestyle Demonstration Project, is an ICR program that has enabled patients to avoid coronary revascularization, reduce angina and biomarkers such as body mass index (BMI), low-density lipoprotein (LDL), and hemoglobin A1c, and improve diet, exercise, stress management, and psychosocial wellness across socioeconomically diverse sites.[7-9] Other ICR programs are the Pritikin Program[10,11] and the Benson-Henry Institute Cardiac Wellness Program,[12] which have been associated with improved biomarkers and symptoms, lower hospitalization rates, and even lower mortality rates.[13] Despite critiques of these programs' restrictiveness, they have demonstrated excellent adherence.[14]

The DPP, another lifestyle medicine program incorporating diet, fitness, and stress management, is the nation's longest clinical trial on diabetes prevention through lifestyle modification. The original study, published in 2002, was a 27-center randomized control trial comparing lifestyle modification to metformin (and a control arm) in more than 3,000 individuals with impaired glucose tolerance.[15] The investigators found a 58 percent reduction in diabetes onset in the lifestyle group compared to controls, with the metformin group showing a 31 percent reduction compared to control. Follow-up at 10 and 15 years illustrated a 34 percent and 27 percent reduction in diabetes incidence, respectively, in the lifestyle group, versus 18 percent in the metformin group.[16] Subsequent research has shown the DPP's association with decreased inpatient admissions, emergency visits, and overall medical costs.[17]

Although research establishing the efficacy and cost-effectiveness of these programs is abundant, less is known about their coverage patterns among managed care insurers. We focus on coverage for DPP and ICR because both programs involve multiple modalities of lifestyle medicine and are becoming more commonly accepted interventions within the medical community. By looking at the coverage trend for DPP and ICR, managed care leaders might be swayed for or against further coverage evaluation for their own health plan.

Methods

We searched the Centers for Medicare and Medicaid Services (CMS) website for Medicare policies addressing ICR and DPP. To identify state Medicaid policies, we searched the Internet using keywords such as "diabetes prevention program," "intensive cardiac rehabilitation," "Medicaid," and "coverage."

We identified the 20 largest U.S.-based commercial payers in terms of membership size.[18] and searched their websites for policies addressing ICR and DPP. We included only commercial plans and not Medicare Advantage or Medicaid plans. We used HCPCS codes G0422 and G0423, and CPT code 0403T, to verify that the policies addressed ICR and DPP, respectively. For payers that did not have publicly available policies addressing ICR or DPP, we searched for other evidence of coverage, such as press releases. To illustrate the trend of coverage over time, we determined the approval date, announcement date, effective date, or date of last review, as appropriate, if available. Included policies were current as of August 2017.

Results

Intensive Cardiac Rehabilitation

Coverage by Medicare

In order to gain CMS approval, an ICR program must illustrate with peer-reviewed, published research that it positively affects the progression of coronary heart disease or reduces the need for coronary bypass or percutaneous coronary interventions, as well as reduces at least five of six biomarkers.[19] Since August 2010, Medicare has approved coverage for three programs through the national coverage determination (NCD) process: Dr. Ornish's Program for Reversing Heart Disease, the Pritikin Program, and the Benson-Henry Institute Cardiac Wellness Program.[19]

Coverage by Medicaid

Based on our methodology, we were unable to find state Medicaid policies regarding coverage for ICR.

Coverage by Commercial Payers

Of the 20 largest commercial payers, 13 have medical policies for ICR or address ICR through its

HCPCS codes. Of these 13 payers, eight cover ICR, two consider ICR investigational, and three do not cover ICR (Table 1).

Diabetes Prevention Program

Coverage by Medicare

Following the CMS Chief Actuary's certification of DPP as a cost-saving program that improved quality of care, CMS announced in July 2016 that it would expand coverage to Medicare starting January 2018.[20] This landmark decision made DPP the first preventive service model from the CMS Innovation Center successful enough to be expanded from a demonstration into the Medicare program.

Coverage by Medicaid

Seven state Medicaid programs currently offer or will soon offer DPP as a covered benefit, through a Section 1115 waiver, or through a demonstration project. Montana was the first to cover DPP in August 2012, followed by Minnesota in January 2016. Texas and New York received Section 1115 waivers from CMS in 2011 and April 2014, respectively, to demonstrate the feasibility, health impact, and cost-saving potential of offering DPP under Medicaid. In June 2016, Maryland and Oregon received funding for a two-year project to demonstrate ways of offering DPP to the Medicaid population through managed care and accountable care organizations, respectively. Most recently, in July 2017, California approved a $5 million annual allocation to cover DPP under Medi-Cal, starting in July 2018 (Appendix).

Coverage by Commercial Payers

In fall 2012, the CDC awarded $6.7 million to six national organizations to increase access to and utilization of DPP.[21] Among the six organizations was the American Health Insurance Plans, which worked with six member plans - Anthem, Cigna Corporation, Denver Health, EmblemHealth, Florida Blue, and Molina Healthcare - to implement DPP.[22]

To facilitate coverage by commercial payers, the American Medical Association created a CPT code to bill for DPP services in January 2016.[23] Since then, the number of payers covering DPP has increased significantly: 30 private insurers as of January 2016[24] and over 70 as of September 2016.[25] Of the 20 largest commercial payers, ten list policies or press releases addressing DPP. Of these ten, nine cover DPP while one considers DPP investigational (Table 2).

Discussion

As the U.S. shifts toward value-based care, managed care leaders, practitioners, and stakeholders are leveraging lifestyle medicine programs against chronic conditions such as cardiovascular disease and diabetes. While literature on these programs has focused on health outcomes, an overview of coverage trends is also valuable to managed care decision-makers hoping to improve care while decreasing costs.

Although research supporting ICR[7-14] and DPP[15-17] spans multiple decades, coverage for these programs only began to proliferate after 2010, when the CMS approved the Ornish and Pritikin Programs as ICR therapies[19] and the CDC announced the National DPP public-private initiative,[21] shortly followed by UnitedHealthcare establishing the Diabetes Prevention & Control Alliance and offering DPP in collaboration with the YMCA. Since then, another ICR program has been approved by the CMS, and eight of 13 commercial payers among the largest 20, whose policies regarding ICR were discovered, have begun covering the program. Likewise, the CMS, seven state Medicaid programs, and nine of 10 commercial players among the largest 20, whose policies regarding DPP were discovered, have decided to cover DPP. Coverage for DPP has also expanded among employers and states, with over three million public employees and their dependents in 12 states enjoying coverage.[25] Given these patterns, we anticipate a growing number of insurers covering lifestyle medicine therapies in a national shift toward high-value care.

Beyond their health impact, ICR and DPP have demonstrated reduced spending for insurers offering coverage. Highmark Blue Cross Blue Shield, for example, reported significant savings following patient enrollment into the Ornish Program, citing an 89 percent reduction in hospital admissions related to chest pain and angina within two years and a projected $17,687 saving per patient at risk for medical intervention over three years.[26] Additionally, studies have found the Ornish and Benson-Henry Institute Programs cost-effective,[13] and a meta-analysis in 2000 described the Ornish Program as "highly likely to be cost saving, and [...] highly unlikely to be cost-increasing."[26] Similarly, multiple studies have found DPP cost-effective or cost-saving, with program costs offset by reduced indirect medical costs and improved quality of life, even if uptake is as low as 10 percent.[27]

To increase uptake of TCR and ICR programs, the CMS introduced the Cardiac Rehabilitation Incentive Payment Model in December 2016 to encourage practitioners and hospitals to refer eligible patients, using a payment system based on the number of services attended by the beneficiary.[28] Similarly, the CDC has awarded thousands of grants to raise awareness, increase enrollment, promote

Table 1: Coverage Policies for Intensive Cardiac Rehabilitation

Payer	Policy Available	Coverage, Comments and Policy Availability	Date Approved, Announced, Effective, or Last Reviewed
CMS - Medicare	Yes	Covered Dr. Ornish's Program for Reversing Heart Disease Pritikin Program Benson-Henry Institute Cardiac Wellness Program	Effective 8/12/2010 Effective 8/12/2010 Effective 5/6/2014
CMS - Medicaid	No		
Commercial Payers (number in parenthesis indicates rank in terms of membership size)			
Aetna (3)	Yes	Covered[1]	Last reviewed 3/3/2017[a]
Anthem, Inc. (2)	Yes	Covered[2]	Announced 2/11/2014
BlueCross BlueShield of Tennessee (17)	No		
BlueCross BlueShield of Alabama (20)	No		
BlueCross BlueShield of Florida, Inc. (19)	No		
BlueCross BlueShield of Illinois (6)	Yes	Covered[3]	Last reviewed 7/15/2017[a]
BlueCross BlueShield of Michigan (11)	No		
BlueCross BlueShield of Texas (9)	Yes	Covered[4]	Last reviewed 7/15/2017[a]
BlueShield of California (16)	Yes	Covered[5]	Approved 11/26/2014
CareFirst BlueCross BlueShield (18)	Yes	Not Covered[6]	Last reviewed 8/22/2016[a]
Centene Corporation (10)	No		
Cigna Corporation (4)	Yes	Not Covered[7]	Effective 3/15/2017
Coventry Health & Life Insurance Company (13)	No		
Health Net, Inc. (8)	Yes	ICR considered investigational[8]	Effective April 2014 Last reviewed January 2017[a]
Highmark BlueCross BlueShield (15)	Yes	Covered[9]	Effective 1997[10]
Horizon BlueCross BlueShield (14)	Yes	ICR considered investigational[11]	Last reviewed 7/11/2017[a]
Humana, Inc. (5)	Yes	Not covered[12]	Last reviewed 7/28/2016
Kaiser Permanente (7)	No		
Molina Healthcare, Inc. (12)	Yes	Covered with prior authorization[13]	Effective 2/1/2017
United Healthcare, Inc. (1)	Yes	Covered[14]	Last reviewed 1/1/2017[a]

ICR = Intensive Cardiac rehabilitation
CMS = Centers for Medicare and Medicaid Services
[a]Last reviewed dates were used when the date of approval, date of announcement, or effective date were not available. The date of first approval for the program was likely earlier than the last reviewed dates.

Table 2: Coverage Policies for Diabetes Prevention Program

Payer	Policy Available	Coverage, Comments and Policy Availability	Date Approved, Announced, Effective, or Last Reviewed
CMS - Medicare	Yes	All CDC-recognized programs will be covered starting 1/1/2018	Announced 7/7/2016 Effective 1/1/2018
CMS - Medicaid	Yes[1,2]	Seven states currently offer or will soon offer DPP: • Montana and Minnesota currently cover DPP as a benefit • California will soon cover DPP as a benefit • Maryland and Oregon offer DPP through the National DPP Demonstration Project • New York and Texas offer DPP through a Section 1115 Waiver	**California:** Approved 7/10/2017 Effective 7/1/2017 **Maryland and Oregon:** Announced 6/21/2016 Effective 7/1/2016 - 6/30/2018 **Minnesota:** Approved 1/1/2016 **Montana:** Approved August 2012 **New York:** Approved April 2014 **Texas:** Approved 2011
Commercial Payers (number in parenthesis indicates rank in terms of membership size)			
Aetna (3)	Yes	Covered.[3] Offers programs such as Newtopia's program for metabolic syndrome prevention[4]	Last reviewed 7/17/2017 Received award from CDC via AHIP in October 2012[5]
Anthem, Inc. (2)	No, but coverage information available in press release	Covered in California[6] and Colorado.[7,a] Offers a variety of programs in partnership with Solera Health, Inc.	California: August 2016 Colorado: April 2015
BlueCross BlueShield of Tennessee (17)	No		
BlueCross BlueShield of Alabama (20)	No		
BlueCross BlueShield of Florida, Inc. (19)	No, but coverage information available in press release and issue brief	Covered. Offers a variety of programs in partnership with Solera Health, Inc.[8]	Began offering DPP to employees in 2013 and to members in 2014[9] Received award from CDC via AHIP in October 2012[10]
BlueCross BlueShield of Illinois (6)	No		
BlueCross BlueShield of Michigan (11)	No		
BlueCross BlueShield of Texas (9)	No		
BlueShield of California (16)	Yes	Covered.[11] Offers a variety of programs in partnership with Solera Health, Inc.[12]	Approved 3/1/2016
CareFirst BlueCross BlueShield (18)	No		
Centene Corporation (10)	No		
Cigna Corporation (4)	Yes	Covered.[13] Offers Omada's program[14]	Effective 7/1/2017
Coventry Health & Life Insurance Company (13)	No		
Health Net, Inc. (8)	No, but coverage information available in issue brief	Covered for large emploer groups and PPO members.[15] Offers Omada's program[16]	Unable to determine date
Highmark BlueCross BlueShield (15)	Yes	DPP considered experimental and investigational[17]	Last updated October 2016
Horizon BlueCross BlueShield (14)	No		
Humana, Inc. (5)	No		
Kaiser Permanente (7)	No, but coverage information available on payer's website	Covered in Colorado[18,19] and Georgia.[20] In Colorado, a mixed in-person and digital program is offered. In Georgia, an in-person program is offered.	Colorado: started by 2011 Last reviewed 11/29/2016 Georgia: Last reviewed 7/20/2017
Molina Healthcare, Inc. (12)	Yes	Covered.[21] Partners with community organizations to deliver DPP in English and Spanish	Received award from CDC via AHIP in Oct 2012
United Healthcare, Inc. (1)	Yes	Covered.[22] Offers programs delivered by the YMCA, among others	Diabetes Prevention & Control Alliance launched in April 2010

CMS = Centers for Medicare and Medicaid Services
CDC = Center for Disease Control and Prevention
DPP = Diabetes Prevention Program
AHIP = American Health Insurance Plans
YMCA = Young Men's Christian Association.
[a]A national policy was not found for these commercial payers; only press releases addressing specific states, or information about specific states on the payers' websites, were found.

coverage, and expand the number of organizations offering DPP.[21] To facilitate this expansion while maintaining evidenced-based standards, the CDC created the Diabetes Prevention Recognition Program, which includes a publicly available curriculum and requirements to gain CDC recognition.[29]

Limitations

We were unable find the coverage policies of state Medicaid programs for ICR based on our methodology. This may be due to a lack of publicly available information, or due to ICR not being covered by state Medicaid programs. While searching for state Medicaid programs, we found several commercially sponsored Medicaid plans that cover ICR. Since we did not systematically search for these plans, however, we did not include them in the results.

Because our methodology relies on publicly available information, we may have been unable to find some commercial payers' policies regarding ICR and DPP. This limitation would have led to an underreporting of coverage, with actual coverage higher than represented in the study. Possible explanations for not sharing policies publicly include the administrative burden of updating policies and the desire to retain flexibility in coverage decisions.

Conclusion

As health expenditures continue to rise, it is imperative for managed care leaders to consider all options for addressing the chronic disease burden. ICR and DPP, two lifestyle medicine therapies notable for their efficacy and cost-effectiveness, are increasingly being covered by public and private insurers. The positive trend of coverage for ICR and DPP indicates a growing belief in the managed care community that these health care services are effective and safe. The rest of the managed care industry should take note so that they can benefit from offering these programs to their membership as well.

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Intensive Cardiac Rehabilitation

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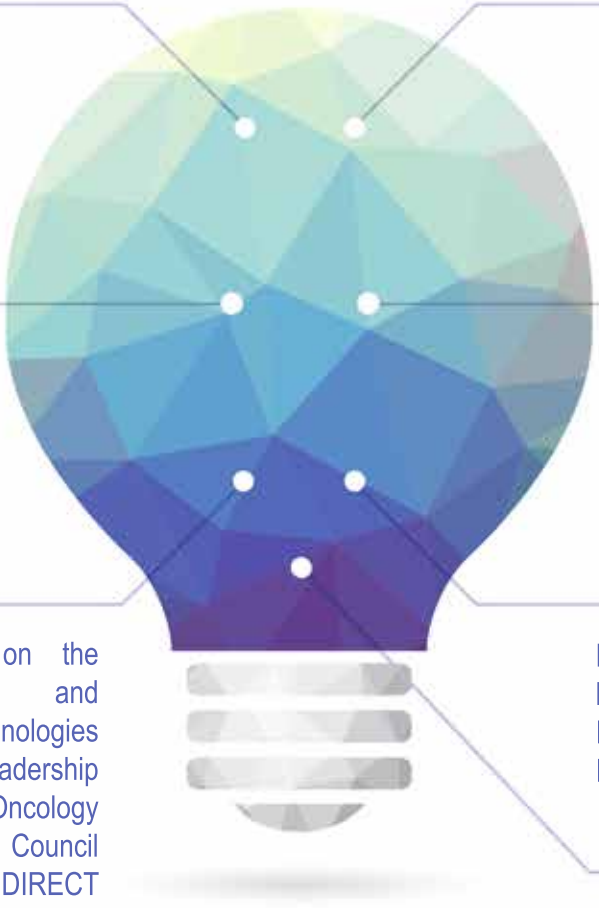

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