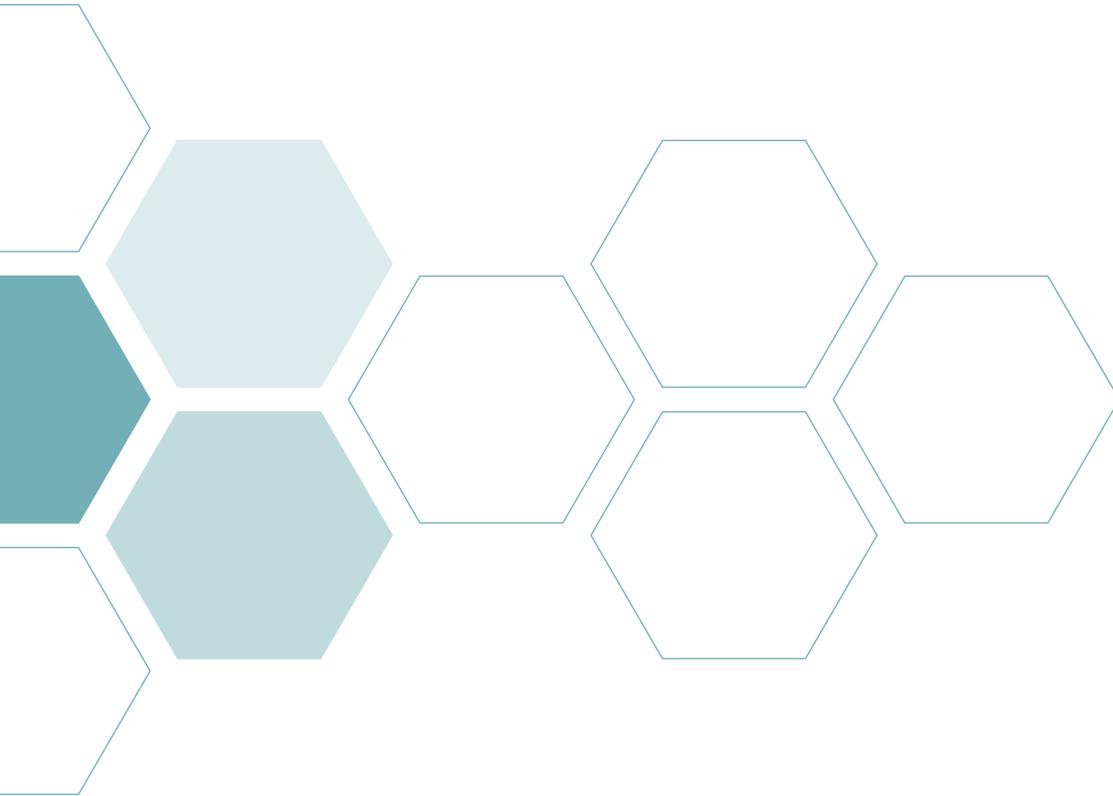


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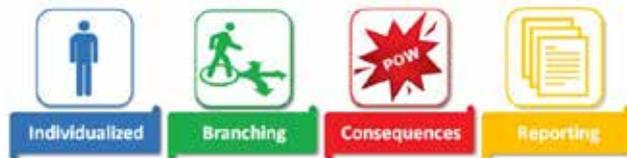


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Clinical Advances in Atopic Dermatitis: Novel Therapies for Improved Patient Outcomes

Lawrence F. Eichenfield, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Atopic dermatitis is a common disease and is costly in terms of quality of life. Until now, there has been a great deal of undertreatment and uncontrolled moderate to severe disease because of lack of safe and effective FDA approved treatment options. The treatment landscape is changing dramatically with the approval of a new topical for mild to moderate disease and the first targeted biologic for moderate to severe disease. Many more new treatment options are on the horizon.

Key Points

- Good skin care is important for all patients with atopic dermatitis.
- Mild to moderate disease can be managed with topical therapy.
- Moderate to severe disease requires more aggressive treatment which may include targeted systemic therapy.
- A targeted therapy is now available which attacks an underlying pathologic mechanism of inflammation in atopic dermatitis.

ATOPIC DERMATITIS (AD) IS THE TERM FOR the most common type of eczema. It is a chronic inflammatory skin disease, often starting in childhood, with a chronic, intermittent or persistent course. It manifests as eczematous rashes, severe itch, staph aureus skin colonization and secondary infections. There is thickening and crusting of the skin and pigmentary changes.

AD prevalence varies across the United States (U.S.), but it affects 9 to 14 percent of the population.¹ AD is a worldwide problem; rates vary between industrialized and rural, non-industrialized regions. In industrialized countries, 10 to 15 percent of children in the first few years of life are affected compared with 4 to 5 percent in non-industrialized areas. Rates flip with “westernization” or emigration to industrialized areas.² For cases that begin in childhood, AD persists in 3 to 5 percent of adults.

Medical consequences of AD include chronic

rashes; sleep disturbance; bacterial and viral infections; sepsis, bone, and tissue infection, which is rare; and atopic and non-atopic comorbidities. Sleep disturbance secondary to itching has a significant impact on quality of life. Other associated atopic conditions are asthma, allergic rhinitis and conjunctivitis, food allergy and contact allergy (“occupational dermatitis”). For example, the children who have severe AD during the first year of life are the group with the highest risk of developing a peanut allergy. In a cross-sectional study of 2,270 children with AD, nearly 80 percent reported another form of allergy (asthma, allergic rhinitis, animal allergies, food allergies, or medication allergies).³ Thirty-eight percent had both asthma and allergic rhinitis. The associated atopic comorbidities are tremendous “cost multipliers” in disease impact over a lifetime.

The progression from AD to food allergies, allergic rhinitis, and asthma is called the atopic or al-

Exhibit 1: Two Major Hypotheses on Atopic Dermatitis Inflammation⁸

Outside-Inside View



Inside-Outside View



lergic march. There is a question whether early AD control will prevent development of asthma and the other complicating comorbidities.

Mental health issues are the common non-atopic comorbidities of AD. Attention deficit hyperactivity disorder (ADHD) in younger children has a “dose-dependent” relationship between severity prevalence of AD.^{4,5} Depression is common in teens and adults with AD with an additional large burden of sleep disturbance and fatigue. People with moderate to severe AD have impaired sleep and are compromised in their ability to perform certain activities of daily living. Approximately one in five adults with AD meet “diagnostic criteria” for major depression.⁶

Simplified, AD is a disease of barrier dysfunction and T helper cell two (Th2) driven inflammation. The skin of someone with AD is leaky with breaks in the skin barrier which allows water out, leading to dryness and allergens in to activate the immune system. Immunologic “priming” of naïve Th2 cells is part of the early pathogenesis of AD.⁷ Th2 cytokines downregulate expression of proteins of epidermal differentiation (including filaggrin) and lipids. There is a question whether the skin barrier dysfunction or a primary dysfunction in the immune system is the initiating factor (Exhibit 1).

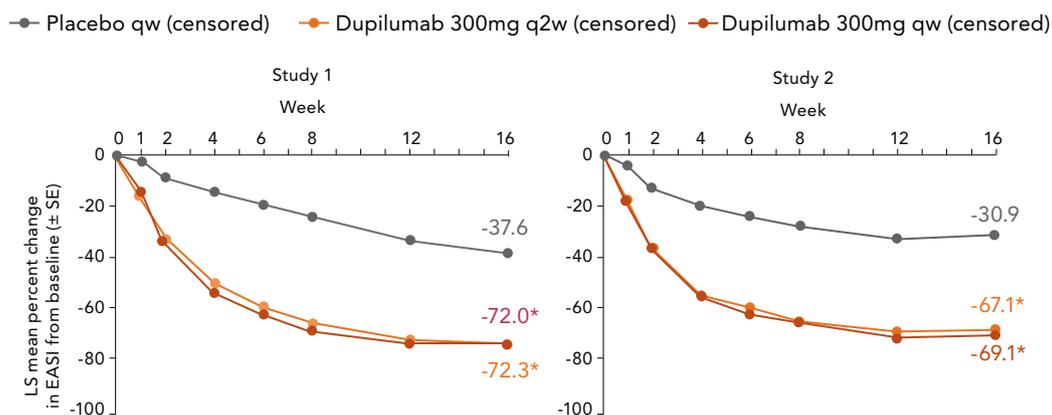
Treatment of AD includes short-term treatment of disease flares and a long-term maintenance approach to skin care designed to prevent or minimize flares. The American Academy of Dermatology (AAD) publishes clinical care guidelines for AD which address use of nonpharmacologic, topical, and systemic therapies.^{9,10}

The first-line treatment is good skin care to improve barrier function. Bathing is suggested for patients with AD as part of treatment and maintenance; however, there is no standard for the frequency or duration of bathing appropriate for those with AD.⁹ The addition of oils, emollients, and most other additives to bath water, and the use of acidic spring water are not recommended. Moisturizing after bathing with liberal application of emollients is part of maintenance care and the primary intervention for mild AD in infants. Some individuals have easily controlled disease for which good skin care is all they need, whereas others have difficulty to control disease.

Targeted barrier repair products/devices may have a role for targeting specific defects in the skin barrier occurring in AD. These typically have lipids added, including glycyrrhetic acid or ceramides. Some are prescription products and quite expensive and others are over the counter. In a head-to-head trial in 39 subjects, petroleum jelly or one of two different barrier repair products had comparable efficacy, but petroleum jelly was over 40 times more cost-effective.¹¹ Current AAD guidelines recommend the choice of an emollient or barrier repair product based on patient preference.⁹

Beyond good skin care, topical prescription corticosteroids are the mainstay of therapy for AD. As anti-inflammatories, they are used for acute flare management and intermittently for maintenance therapy to prevent flares. There are seven classes from mild to superpotent (hydrocortisone > desonide > mometasone > triamcinolone > fluocinonide > betamethasone > clobetasol).

Exhibit 2: Effect of Dupilumab on EASI % Change from Baseline²⁶



*P < 0.0001 vs placebo

The mid-potency agents are the most commonly used. Delicate skin areas (face, genitals, and skin folds) should be treated with low-potency agents and super-potent agents should be reserved for refractory lesions and tough-to-treat areas (hands and feet). Although most are available generically, the cost of generic topical steroids has skyrocketed in the past decade. Patients often have high copays and may not be able to get the preferred topical steroid.

Adverse effects with topical corticosteroids are a concern with long-term use and use of high-potency agents. Local adverse effects include skin atrophy, telangiectasia, steroid-induced acne/perioral dermatitis and striae (stretch marks). Striae are an irreversible complication. Hypothalamic-pituitary-adrenal axis suppression effects from systemic absorption are a concern with the highest potency agents.

There is significant fear of topical corticosteroids. Parents worry about using steroids on their child's skin; 24 percent in one trial admitted to not using medicines because of the worries.¹² Patient and caregiver education is very important in order to teach them how to properly use steroids and to educate them in regard to the benefits and risks of use.

Topical calcineurin inhibitors [tacrolimus (Protopic[®]) and pimecrolimus (Elidel[®])] are anti-inflammatory agents that were considered breakthrough products when initially introduced because they did not have steroid adverse effects. Clinicians quickly moved away from steroids to these. They inhibit calcineurin dependent T-cell activation, blocking the production of pro-inflammatory cytokines in AD. Extensive clinical trials have shown fair to good efficacy for mild, moderate, and severe AD.

Calcineurin inhibitors have a black box warning

about possible malignancy risk. Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors. Thus, continuous long-term use of topical calcineurin inhibitors, in any age group, should be avoided, and application limited to areas of involvement with AD.⁹ When the black box warning was added to the product labeling for this class, there was a 70 percent reduction in the use of these agents and a move back to topical corticosteroids.

Phosphodiesterase (PDE) inhibitors are a new class of medication for treating AD. There is increased phosphodiesterase type 4 PDE4 activity and decreased intracellular cyclic adenosine monophosphate (cAMP) levels in peripheral blood leukocytes of patients with AD.¹³ PDE4 is localized in macrophages, lymphocytes, and neutrophils. PDE4 inhibitors increase intracellular cAMP levels and reduce cytokine and mediator release.^{14,15} Crisaborole (Eucrisa[®]), a topical PDE4 inhibitor, is indicated to treat mild to moderate AD in adults and children 2 years of age and older.

Crisaborole has a boron ring integrated in its cyclic structure which provides stability and effective target-binding capacity and selectivity. This agent's low molecular weight facilitates penetration through human skin and access to target cells. There is little systemic absorption in either adults or children.

Studies have shown that crisaborole reduces inflammation and itching and repairs the skin barrier.¹⁶⁻¹⁷ This agent results in a 7.4 to 13.4 percent improvement in Investigator Static Global Assessment of clear or almost clear (≥ 2 grade improvement) over vehicle at 29 days of treatment.¹⁶ A statistically

significant increase in QOL in all age population was also found with crisaborole treatment.^{18,19}

The most common adverse effects with crisaborole are AD flares and application site pain and infections. These occur in less than 5 percent of patients. The rates of topical adverse effects remained very low over two years of treatment.¹⁶ Steroid-like adverse reactions did not occur during the crisaborole studies.

There are a few issues which need to be resolved with this class. There are no comparative efficacy studies with topical corticosteroids or calcineurin inhibitors. The cost-effectiveness, effect on sensitive skin regions, efficacy and adverse effects in those under age 2, nor long-term safety with this agent are known. Oral PDE4 inhibitors (apremilast (Otezla[®]) for psoriasis and roflumilast (Daliresp[®]) for chronic obstructive pulmonary disease) have been used long term without major adverse effects. Other oral and topical PDE4 inhibitors are under investigation for AD.

When topical therapy is insufficient, systemic therapy is an option. Prednisone is an FDA approved systemic agent, but its use is not recommended beyond short term to treat a severe flare because of adverse effects. In addition to adverse effects, prednisone is not a very good choice because rebound flares tend to occur with discontinuation. Various other broad-spectrum immunosuppressants have been used to treat AD, but none are FDA approved for AD. Cyclosporine, oral tacrolimus, azathioprine, methotrexate, and mycophenolate mofetil have been used, but all have issues with safety or efficacy. Cyclosporine, oral corticosteroids, and azathioprine have been the most commonly used prescribed systemic agents for AD.²⁰ In pediatrics, cyclosporine and methotrexate are the most commonly used.²¹ In the general scheme, systemic agents have not been used extensively because of lack of data.

The main barriers to use of broad-spectrum systemic agents are adverse effects and long-term toxicity. Doctors fear prescribing systemic therapy and patients are reluctant to take these agents.

Phototherapy, another systemic therapy, has a slower onset of efficacy, but has robust responses when dosed appropriately. It is likely the safest long-term option, but inconvenient and inaccessible for many patients.

The area of systemic immune therapy for AD is getting ready to explode. The first biologic targeted at specific components causing inflammation in AD treatment was recently approved by the FDA. Many more agents are in Phase II and III trials. Biologic agents in later stage trials for AD include nemolizumab (interleukin-31 (IL-31) inhibitor), tofacitinib and baricitinib (Janus kinase inhibitors), tralokinumab (IL-13 inhibitor), antileukotriene

agents, and liver X receptor antagonists.

Dupilumab (Dupixent[®]), a fully human monoclonal antibody targeted therapy, was FDA approved March 28, 2017, with an indication for adult patients with moderate to severe AD whose disease is not well controlled with topical prescription therapies or who cannot use topical therapies. It is an IL-4 α receptor antagonist which inhibits signaling of IL-4 and IL-13, two Th2-derived cytokines that are important drivers of inflammation in AD. After a loading dose of 600 mg, dupilumab is given as a 300 mg subcutaneous injection every other week.

In trials, dupilumab significantly improved measures of skin clearing (Eczema Area and Severity Index [EASI] and Investigator Global Assessment [IGA]) and severity of disease.²²⁻²⁶

In the two placebo controlled phase III trials, there was a clearing or near clearing of skin lesions among 37.9 percent and 36.1 percent who received injections every two weeks compared with 8.5 and 10.3 percent in the placebo groups.²⁶ Exhibit 2 compares the percent reductions in EASI in the two treatment groups.²⁶ The dupilumab treatment groups had an average 35 percent more patients achieve EASI-75 (75 percent improvement in rash area and eczema severity) compared with placebo.²⁶ In AD poorly controlled with topicals, dupilumab reduced peak itch at 16 weeks relative to placebo, improved sleep and health-related quality of life, and reduced anxiety and depression symptoms.^{25,26}

Dupilumab appears to be well tolerated. Compared with placebo, it caused similar rates of treatment-emergent adverse effects (AEs). Equally low numbers of infectious AEs occurred in two treatment groups.²⁶ Herpes infections and conjunctivitis are the two AEs of interest; etiology of the conjunctivitis is unknown. Eight percent of the dupilumab patients compared with 2 percent in the placebo group developed herpes infections.²⁶ Pediatric studies with dupilumab are underway in Europe and will be starting in the U.S. shortly.

Overall, for mild to moderate disease, topicals will be sufficient for controlling disease in most patients. The PDE4 inhibitor class is a welcome addition. Recommended regimens are evolving to the minimize disease symptoms with proactive plus reactive therapy. There still is a high burden of care and much room for improved care in this population.

There has been much undertreatment in moderate to severe AD, primarily because the older systemic agents have poor benefit to risk ratios. Corticosteroids can be used, but with negative health effects. The new biologics and additional agents under investigation may be tremendously important in minimizing disease impact.

There are some issues which need to be resolved in integrating the new treatments into care. To best define which patients should receive biologic therapy, definitions of severity need to be refined and a definition of topical therapy failure needs to be developed. Duration of biologic therapy and whether biologics will work in pediatric AD need to be determined.

Conclusion

AD is a common condition with variable severity. It is hugely impactful to the patient and their family. There has been significant undertreatment and clinical need, but it is an exciting time with new innovations in therapy.

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Recent Advances in the Management of Rheumatoid Arthritis: A Closer Look at Emerging Therapies

Gary M. Owens, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Biologic and newer nonbiologic therapies have revolutionized the treatment of rheumatoid arthritis, but they also present many management issues for managed care. Because of the expense of these therapies, managed care needs to determine how to get the most value for their members. The treat-to-target approach is one way to do this.

Key Points

- 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.
- Current treatment often is suboptimal.
- Payers are challenged to get the most value from RA treatments.

RHEUMATOID ARTHRITIS (RA) IS A CHRONIC, progressive, inflammatory, autoimmune disease of unknown etiology which causes major physical and financial burden. It affects approximately 1.3 million Americans (0.6% of the U.S. population).¹ Because of RA-related disability, many patients are unable to work within 10 years of onset. In the pre-biologic era, this occurred in 50 percent of patients; in the biologic era, this still happens in 35 percent (2008 data).^{2,3}

In addition to disability, those with RA have higher cardiovascular disease and mortality rates from the chronic inflammatory process. There is a five times higher cardiovascular event rate in those with RA compared with the general population.⁴ The mortality rate for those with RA is 1.5 to 1.6-fold higher than for the general population.⁵

RA is also a costly disease in terms of finances. The annual per patient direct medical cost is estimated at \$13,012 compared with \$4,950 for controls.⁶ The total annual excess direct cost of RA compared

to a control population is \$22.3 billion.⁶ Managed care spending on specialty drugs has been growing dramatically and is projected to outpace traditional medication spending in 2018.⁷ RA biologics are one of the major drivers of specialty drug spend. 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 category.⁸ In a 2015 paper, Curtis and colleagues used a claims-based algorithm to estimate the mean one-year biologic cost per effectively treated patient. The authors reported the following costs: etanercept (\$43,935), golimumab (\$49,589), adalimumab (\$52,752), abatacept (\$62,300), and infliximab (\$101,402).⁹

There are several management challenges in RA care. There are no standardized outcome measures used in clinical practice. There are a growing number of biologic agents for the treatment of RA and not every biologic agent works for every RA patient. Clinicians have little understanding of the

Exhibit 1: ACR Recommended Tools to Meet Treat-to-Target Goals¹⁸

Patient data

- Patient activity scale (PAS or PAS-II)
- Routine assessment of patient index data 3 (RAPID-3)

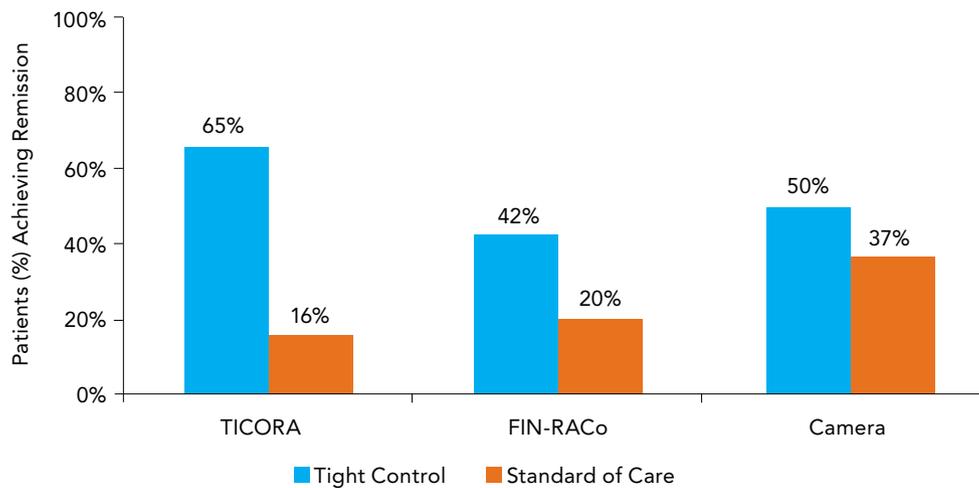
Patient and provider data

- Clinical disease activity index (CDAI)

Patient, provider, and lab data

- Disease activity score-28 erythrocyte sedimentation rate (DAS-28 ESR) or DAS 28 C reactive protein (DAS-28 CRP)
- Simplified disease activity index (SDAI)

Exhibit 2: Treat-to-Target Approach Versus Standard of Care¹⁹⁻²¹



cause of variation of drug efficacy between patients. Additionally, the clinical guidelines on how biologics should be compared to optimize RA treatment outcomes are lacking; however, it is very important to understand the optimal use of these agents given their high cost. Physicians, patients, and plan managers need better data to compare the effectiveness of the different biologics, but all need to use caution when comparing drugs across studies. Payers must use caution when comparing drugs across studies—but it is often the only method available.

Practice in treating RA has not been optimal, especially when provided by non-rheumatologists. A “start low, go slow” approach has been relatively common in RA management, despite guideline recommendations for more aggressive treatment.¹⁰ Delayed treatment or prolonged undertreatment contributes to uncontrolled inflammation and irreversible tissue damage.¹¹ Patients not referred to a rheumatologist are less likely to receive disease-

modifying anti-rheumatic drug (DMARD)-based therapy within 12 months of symptom onset.¹² Additionally, patients frequently receive irregular follow-up and minimal therapeutic adjustment.¹³

The RA management paradigms are changing to treat early and aggressively and use standardized measurements to measure efficacy. There is a therapeutic window of opportunity in early RA for preventing joint damage, which is the primary cause of disability. Fifty to 70 percent of patients have radiographic damage within the first two years after onset of symptoms.^{14,15} The historical approach to treating RA was to start with traditional DMARDs such as methotrexate. In 2012 the American College of Rheumatology guidelines began advocating early aggressive treatment with biologics in combination with methotrexate.¹⁴ The approach was treat-to-target (T2T), which continued in the 2015 update of the guidelines.¹⁶ The goal with T2T is to achieve disease remission; however, low disease activity is

Exhibit 3: Characteristics of RA Biologics

	Etanercept (Enbrel)	Infliximab (Remicade)	Certolizumab (Cimzea)	Adalimumab (Humira)	Tocilizumab (Actemra)	Abatacept (Orencia)	Rituximab (Rituxan)	Tofacitinib (Xeljanz)
Target	TNF	TNF	TNF	TNF	IL-6	T-Cell	B-Cell	JAK1 JAK3
Dosing	Once Biweekly - weekly	Once every 4 - 8 weeks	Once every 4 weeks	Once every 1 - 2 weeks	Once every 4 - 6 weeks	Once monthly	Twice every 6 - 12 months	Once or twice daily
Route	SQ	IV	SQ	SQ	IV	IV	IV	Oral

SQ = subcutaneous
 IV = intravenous
 TNF = tumor necrosis factor
 IL = interleukin
 JAK = janus kinase

an acceptable alternative goal. Key elements of this strategy are to aim at a predefined target and adjust therapy regularly until the target is achieved. Disease activity is monitored every one to three months until the target is reached; then it is monitored every three to six months.¹⁷ The ACR recommends several tools be used to monitor disease activity to meet T2T goals. These are patient data, patient and provider data, and patient/provider/lab data tools (Exhibit 1).¹⁸

As shown in Exhibit 2, the T2T approach leads to higher rates of disease remission.¹⁹⁻²¹ For DMARD-naïve patients with established disease, DMARD monotherapy, usually methotrexate, is recommended first-line treatment for those with low, moderate, or high disease activity.¹² After DMARD monotherapy failure, a combination of traditional DMARDs are used. The recommended combination options include a TNF inhibitor with or without methotrexate, a non-TNF-inhibitor biologic with or without methotrexate, or tofacitinib plus methotrexate.¹⁶ Overall, RA treatment can be summarized as detect early, start treatment immediately, treat-to-target, maintain tight disease control, aim for remission, individualize treatment, and adjust treatment if the target is not achieved.

In addition to methotrexate, the anti-tumor necrosis factor (TNF) biologics are the mainstay of RA treatment. Exhibit 3 provides some of the characteristics of biologics used for managing RA. Newer agents include tofacitinib, which is an inhibitor of the Janus kinase 1 (JAK1) and Janus kinase 3 (JAK

3). Tofacitinib is FDA approved for the treatment of adults with moderately to severely active RA who have had an inadequate response to, or who are intolerant of, MTX.

One-third of patients with rheumatoid arthritis have an inadequate response to TNF inhibitors, but there has been little guidance or comparative data on choosing the next treatment. One 52-week multicenter, pragmatic, open-label, randomized clinical trial of 300 patients with insufficient response to anti-TNF therapy has been published.²² Patients were randomly assigned (1:1) to receive a non-TNF-targeted biologic agent or an anti-TNF that differed from their previous treatment. The choice of the biologic prescribed within each randomized group was left to the treating clinician. Those who received a non-TNF biologic agent had lower disease activity scores but similar health assessment scores. Sixty-nine percent of patients achieved an effective clinical response with a non-TNF biologic compared with 52 percent of patients who took a second anti-TNF drug. Thus, for patients with RA and an insufficient response to anti-TNF therapy, a non-TNF biologic agent may be more effective than switching to a second anti-TNF agent.

Rheumatologists are trying to meet aggressive treatment approaches to achieve early remission. Various combinations are being used and biologics are being used more frequently in early RA. Additionally, with a T2T approach, treatments are frequently switched due to inadequate response or intolerance. All these factors can make managing spending on

RA therapies challenging for managed care.

As discussed previously, drug costs in RA are a payer challenge. Drug acquisition cost is high for the biologics for RA but also price increases have been another driver of costs. The pipeline in RA is robust and new entrants may drive additional costs. Importantly, RA is a chronic disease and drug costs continue over many years.

High budget impact and lack of clear clinical superiority among biologic alternatives makes RA care an attractive target for cost-effectiveness research. Unfortunately, total cost of care is difficult to assess for an individual payer, so it can be difficult to determine if a specific therapy or approach is cost effective. 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 costs year over year. The medical claims system often does not have granular information to allow care costs to be accurately tracked.

The Agency on Healthcare Research and Quality (AHRQ) published a cost-effectiveness review of RA therapies in 2012. This review concluded that comparisons of synthetic DMARDs revealed no significant differences in long-term clinical and radiographic outcomes, functional capacity, health-related quality of life, or rates of adverse events.²³ For a biologic combined with methotrexate, combination therapies were generally associated with better clinical response rates and outcomes. It is important to note that this review is out of date because tofacitinib is not included. Additional cost-effectiveness studies are needed.

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 have moving toward earlier and more aggressive treatment. Yet, current treatment often is suboptimal. Clinicians need to be educated on T2T and encouraged to adopt this to optimize the cost effectiveness of biologic therapy in RA. Payers are challenged to get the most value from RA treatments.

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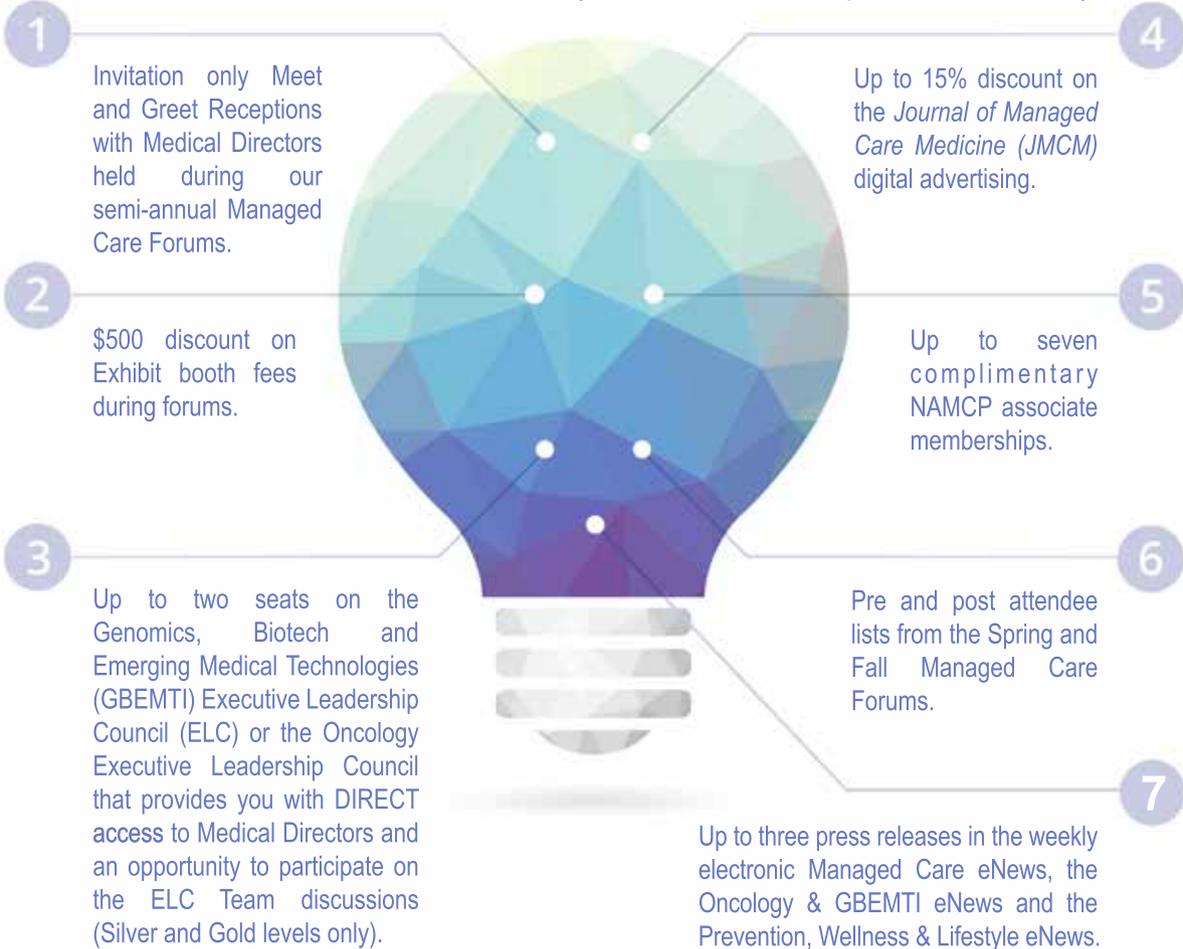
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Advances in the Management of Cystic Fibrosis: A Closer Look at the Roles of CFTR Modulation Therapy

Susanna A. McColley, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Cystic fibrosis (CF) is caused by abnormalities in the CF transmembrane conductance regulator (CFTR) gene. Therapies are now available to restore function of the problem protein and have been shown to slow the progression of CF-related lung disease. Although the medications are expensive, they have major potential to reduce the long-term complications of CF and allow patients to live a more normal life.

Key Points

- Nutritional and pulmonary abnormalities occur very early in life with CF.
- Lung disease is present even when standard lung function tests are normal.
- Genetic testing is important in diagnosis and, increasingly, to guide therapy.
- CFTR modulation therapy has an increasing role in treatment and management of cystic fibrosis.
- Modulator therapy may reduce morbidity and mortality over time.
- Multidisciplinary care is essential.

CYSTIC FIBROSIS (CF) IS AN AUTOSOMAL recessive disorder that occurs in about one in 4,400 births in the United States (U.S.).¹ It is much more common in non-Hispanic Caucasians than in other groups. There is multi-organ expression and manifestations of this disease, but lung-related disease is the primary reason for morbidity and mortality. The median survival for a CF patient in the U.S. is 40 years of age, but the median age of death is still in the mid to late 20s.

Under normal circumstances, mucus in the airways is thinned by water and cleared by the lungs. In CF, there is defective ion transport through the CF transmembrane conductance regulator (CFTR). There is resulting airway surface liquid depletion and modified mucociliary clearance. These lead to thick mucus that obstructs the airways, leading to a viscous cycle of obstruction, inflammation, and infection.

Most infants born with CF are healthy at birth. The lungs in infants with CF are nearly normal at

birth, but small airway disease begins to occur during the first months of life.³ The silent damage to the lungs in the CF process is illustrated in Exhibit 1. Malnutrition also starts in the first weeks to months after birth. Without pancreatic enzyme replacement therapy, severe forms of CF are fatal early in life, primarily because of malnutrition and vitamin deficiency. Early growth in those with CF has been shown to predict childhood survival.²

Although the majority of cases are diagnosed in childhood, people can be diagnosed with CF as adults. Most CF patients diagnosed during adulthood have mild CF mutations associated primarily with pancreatic sufficiency. CF may also present in the second or later decade of life with predominately sinopulmonary disease as illustrated in Exhibit 2. Adults with CF are at risk of infertility (men), reduced fertility (women), recurrent acute pancreatitis, CF-related diabetes and pulmonary complications are prevalent in CF (allergic bronchopulmonary aspergillosis and mycobacterial infections).

Exhibit 1: CF Disease Process

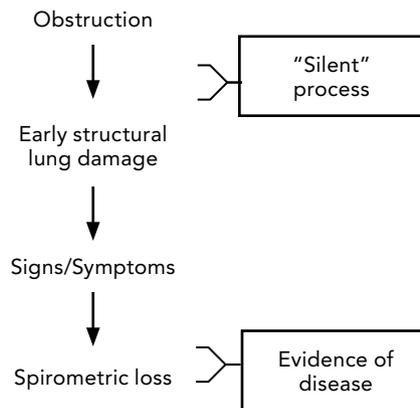


Exhibit 2: Case Study

- Ellen became ill with dyspnea and cough at age 28 during her second pregnancy. She continued to have cough and sputum production after giving birth but denied significant respiratory symptoms as a child.
- Evaluation
 - Spirometry showed an obstructive defect.
 - Forced expiratory volume in one second (FEV₁) was 50% of predicted.
 - CT scan showed bronchiectasis.
 - Sweat chloride value was 40 mEq/L (intermediate, not diagnostic for CF).
 - CFTR gene mutation panel: F508del and R117H/7T.
- In spite of having all recommended pulmonary treatments, her FEV₁ decreased 10 percent by age 40.

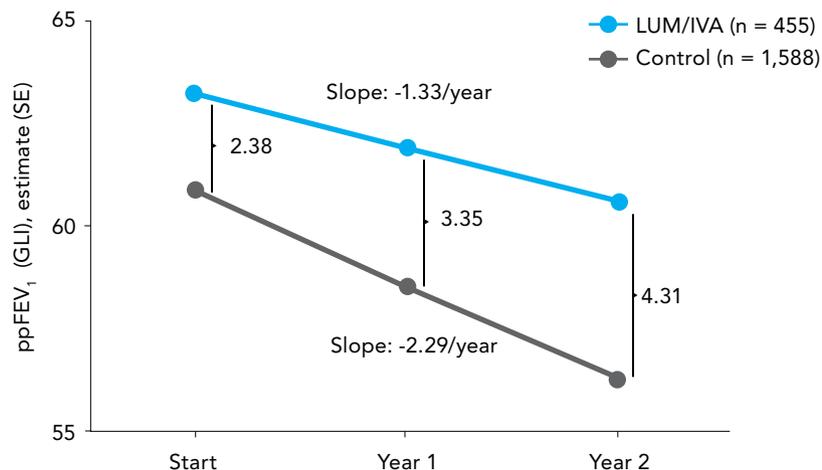
In the U.S., advances have been in care of the CF population. The body mass index (BMI) and heights of U.S. patients have improved, but those with CF are still shorter than those without CF. BMI is directly correlated with survival; the higher the BMI, the better the survival. With improved treatment, population measures of lung function [forced expiratory volume in one second (FEV₁)] have been improving but are not yet normal. It is important to note that FEV₁ is insensitive to early structural lung disease but is a good measure for monitoring lung function over time. The lung clearance index, a gas washout procedure, is a better measure of early disease.⁴

CF is caused by abnormalities in the CF transmembrane conductance regulator (CFTR) gene. More than 2,000 genetic sequence variants of the CFTR gene have been identified, but the disease li-

ability of most of these genetic alterations is unclear. CFTR gene mutations lead to production of a malfunctioning CFTR protein. The CFTR protein can be completely nonfunctional or have limited functional ability. The most common mutation is F508del, with 80 percent of CF patients in the U.S. having at least one copy. Other pathogenic mutations occur in 5 percent or fewer. These include G551D and R117H.

The CFTR protein functions as a channel across the cell membrane in cells that produce mucus, sweat, saliva, tears, and digestive enzymes. CFTR mutations reduce the amount or function of the protein at the cell surface. Class I mutations result in no production of the protein. Class II mutations (e.g., F508del) result in an improperly folded protein that is destroyed by the cell and never makes it to the luminal surface. Class III mutations (e.g., G551D)

Exhibit 3: LUM/IVA Associated with a Slower Annual Rate of Lung Function Decline than Matched Controls¹⁴



result in a protein that is folded almost right, but it cannot be unfolded correctly to work. In Class IV mutations, the protein opens on the luminal surface but is not available long enough or large enough for chloride to pass through. Lastly, Class V mutations produce a completely normal protein but in insufficient quantities. R117H is an example of a Class V mutation. Class IV and V mutations typically produce milder disease than the other mutations.

CFTR mutation testing aids in the diagnosis of CF and is important for therapy selection. Increasingly, it helps with therapeutic decision making. CFTR mutation panels may test from 23 (American College of Gynecology recommended panel done at birth) to hundreds of mutations. These panels will miss rare gene mutations, deletions, or duplications. Currently, panels are less costly than gene sequencing.

CFTR gene sequencing finds any sequence variant in the CFTR gene. Sequencing still misses deletions and duplications; tests for these need to be ordered separately. Sequencing will find disease causing mutations, but also mutations of variable or unknown disease liability. Disease liability of rare mutations is being analyzed in an ongoing project.

Once genetic testing is conducted, it is essential that people get appropriate genetic counseling. False negatives, identification of mutations of unknown significance, consequences for family members, and notification of possible carrier status should be covered in the counseling. Counseling is best provided by a certified genetic counselor, when available.

Interventions in CF are targeted at the underlying lung obstruction and damage, managing signs and symptoms, and dealing with the lung damage. Management guidelines for CF are available from the Cystic Fibrosis Foundation (www.CFF.org). To effectively make a difference in preventing the development of lung disease, therapy probably should be initiated during the early silent phase before damage has occurred. The newest therapies in CF are either correctors or potentiators of CFTR and are the only therapies reviewed here.

Ivacaftor (Kalydeco[®]) is a potentiator of CFTR. It was initially approved for those with G551D mutation but is now FDA approved for patients age 2 and older who have at least one mutation in their CF gene that is responsive to ivacaftor. Because the mutation list is frequently changing, the package labeling should be consulted at www.kalydeco.com.

In patients with moderate to severe homozygous G551D CF, those who received ivacaftor had a 10 percent increase in lung function, improvement in symptoms scores, reduced exacerbations requiring antibiotics, and weight gain (3–3.5 kg).⁵ Decreased weight is associated with worsened lung function and prognosis, so weight gain is typically a desired endpoint in those with CF. Similar results have been seen in patients with only one copy of the defective gene and less severe disease.^{6–10} The benefits of ivacaftor have been shown to persist out to three years.

Overall, ivacaftor is a disease-modifying treatment in those with relevant CFTR mutations because it has been shown to slow the decline in lung disease.¹¹

Even in patients with the “mild” mutations, there is evidence of disease modification and symptom benefits. The CF lung disease management guidelines strongly recommend the chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations for individuals with CF, 6 years of age and older, with at least one G551D CFTR mutation.¹² These guidelines have not been updated since additional mutations were added to the FDA approved indications and the age limit was lowered to 2 years of age. Ivacaftor is generally well tolerated, but is expensive in terms of drug costs. It is indicated for approximately 6 percent of the population with CF.

Nearly half of U.S. CF patients are homozygous for the F508del mutation. In those with the Class II F508del mutation, correction of the protein being transported to the luminal surface and potentiation of its effect are both needed. Lumacaftor / ivacaftor (Orkambi[®]) is a combination of corrector and potentiator for patients homozygous for F508del who are age 6 and older. In a 24- week study, the combination improves FEV₁ modestly (~2-3%) and increases the time to pulmonary exacerbation (hospitalization requiring intravenous antibiotics) in this population. Importantly in the studies, FEV₁ improvement was not required for exacerbation reduction. Benefits have been shown out to 120 weeks of therapy. Another exciting finding has been a steady improvement in BMI over 120 weeks of treatment. This is important given the relationship between BMI and survival.

This combination has been shown to be disease modifying in the homozygous F508del population (Exhibit 3).¹³ The difference of 0.97 percentage points per year represents a 42 percent reduction in the rate of decline (P<0.001). Over the course of a single year in an individual patient this reduction may not appear to make a large difference; where this change is important is in improving health over the long term. It is important to note that even with lumacaftor/ivacaftor therapy there is still a decline in pulmonary function; the rate of decline is slowed but not stopped.

Adverse effects with the combination include frequent chest tightness/shortness of breath and elevated transaminases. Pulmonary symptoms occur most commonly at the beginning of therapy, usually resolve, and rarely lead to discontinuation of therapy. The mechanism of this adverse event is unknown. Elevated transaminases are more common than with ivacaftor alone.

Patients taking ivacaftor or lumacaftor-ivacaftor should have transaminases monitored every three months for 12 months after initiating therapy. Dose

reductions are recommended for moderate to severe liver disease. Children less than 12 years old should have an eye exam prior to starting therapy, due to the occurrence of cataracts in exposed rat pups. A human ocular safety study has been recently completed but has not yet been reported. Monitoring efficacy should include FEV₁ and the number of exacerbations requiring antibiotics; it can be difficult in patients with milder disease.

CF care should be multidisciplinary. Multidisciplinary care teams support good nutrition in children and adults with CF. Good nutrition and normal body weight is important because it directly correlates with lung function and exacerbations. A dietician conducts a dietary assessment and provides counseling and recommendations for supplemental tube feeding. The nurse provides family counseling and support on dietary matters and other issues. Physicians provide support of diet plans, prescription of adequate pancreatic enzymes, and diagnosis of comorbidities attributing to poor nutrition. Multidisciplinary care is also good for achieving the desired pulmonary outcomes. Respiratory and physical therapists evaluate posture, teach airway clearance techniques and use of inhalational medications, and they collaborate with patients and physicians in making treatment decisions on maintenance therapies. Social workers and psychologists screen for depression and anxiety and offer referrals, in accordance with recent practice guidelines. Social workers provide family counseling and support and referral to resources for food insecure families and to programs to offset high medication co-pays.

Conclusion

Onset of CF-related lung disease is an early post-natal event. Nutritional abnormalities also occur very early in life. Genetic testing is important in diagnosis of CF and, increasingly, to guide therapy. Genetic counseling and multidisciplinary care are essential for CF management. CFTR modulation therapy has an increasing disease-modifying role in treatment. Ultimately, modulator therapy may reduce morbidity and mortality related to CF.

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New Management Strategies for Patients with Chronic Pain

Melissa Cheng, MD, MOH, MSPH

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Summary

There is an enormous opioid crisis in America. To prevent further loss of life from these agents, clinicians need to work to get patients off opioids and avoid prescribing them for patients with risk factors for addiction. Selecting appropriate patients for chronic opioid therapy requires understanding the biopsychosocial model of pain and intensive screening.

Key Points

- Clinicians need to adopt the biopsychosocial model in understanding chronic pain and teach this to patients.
- The goal is not to eliminate pain; the focus should be on functional restoration.
- Interdisciplinary team management is needed for chronic pain patients.
- Clinicians need to recognize and treat comorbidities, especially psychosocial issues and barriers to returning to work.
- In a managing chronic pain, low-dose opioids are appropriate in conjunction with other analgesics, pain medications, and exercise in a very carefully selected population.

CHRONIC PAIN AND OPIOID THERAPY ARE very hot topics currently. There is a much attention in regard to this issue. Numerous professional associations have issued statements or guidelines in treating chronic pain. The American College of Occupational and Environmental Medicine and Centers for Disease Control management guidelines are the basis for this article.^{1,2}

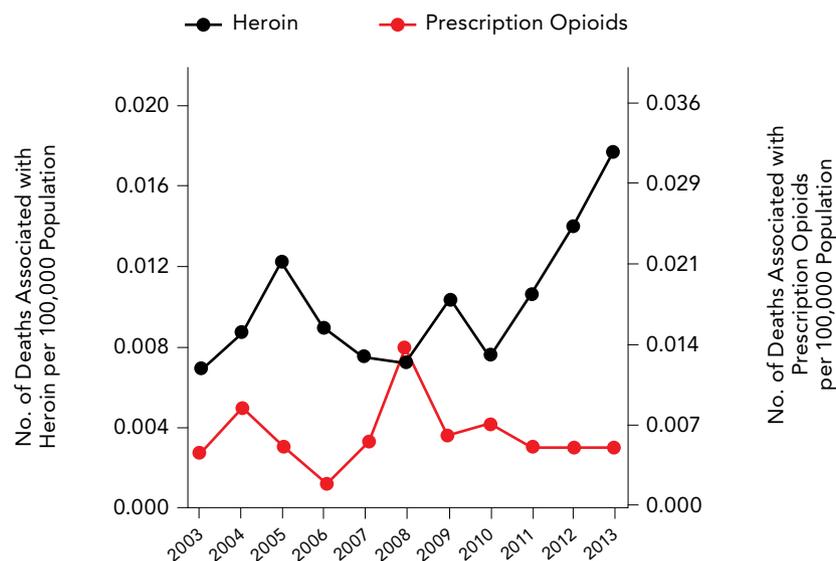
Chronic pain is an unpleasant sensory and subjective emotional experience associated with actual or potential tissue damage, or described in terms of such damage.³ It is pain that persists beyond the anticipated time of tissue healing and is of at least three months duration. Chronic pain is both a symptom and a disease; it is a psychological disorder. In the DSM-V, it is considered a somatic symptom disorder. The severity of the disorder is based on how much it interferes with a patient's daily life.

Chronic pain is the most prevalent health condition found among the United States (U.S.) work-

force and the most costly in terms of lost productivity. An estimated \$64 billion in lost productivity costs occur yearly due to pain limitations reducing job performance. Forty- three percent of adults are in pain and 64 percent of adults will have chronic pain by the age of 80. Health care expenditures for back and neck pain alone have risen to more than \$80 billion a year in the U.S., increasing 50 percent in eight years without evidence of improved health status.

Many clinicians practicing today learned about pain as a biomedical model. In this model, persistent pain is considered a result of some injury or illness or some etiologic factor resulting in the painful condition, but this assumes there is a causal relationship between a specific pathophysiology and the presence or extent of a particular symptom. This is the common paradigm used by many patients and physicians and leads to the drive to pursue diagnostic and therapeutic pathways at great expense to identify the

Exhibit 1: Rates of Death Associated with Heroin and Prescription Opioids, 2002–2013¹⁰



anatomic reason for the pain. Because chronic pain frequently does not always have an underlying anatomic reason, the lack of answers for why the patient has pain leads to dissatisfaction with conservative care and the health care system.

The biopsychosocial model recognizes that pain is ultimately the sum of the individual's biology, psychological history and state, belief system about pain, along with interactions with the environment (workplace, home, disability system, and health care providers). Environmental factors strongly influence symptom severity and how quickly the individual can be returned to a more functional state. This model is better for use in understanding and managing chronic pain. Clinicians need to educate their patients about this model.

Despite the knowledge about the safety issues related to opioid therapy, opioids are used to treat an estimated 20 percent of all pain complaints.^{2,4} Opioid use in the acute setting has been found to increase risk for chronic opioid use, increase risk for dose escalation, and increase medical costs. Low back pain (LBP) is the most common diagnosis for opioids in those under Workman's Compensation. In the early 2000s, about 60 percent of LBP cases were treated with opioids.⁵ Acute opioid use for LBP has been shown to lead to chronic opioid use and an increase risk for back surgery.⁶

The use of opioids in the Workman's Compensation (WC) system is very expensive. Ten percent of WC clients have chronic pain but account for 80

percent of the \$60 billion WC budget.⁷ Opioid use among workers is associated with reduced productivity, increased presenteeism, increased medical claims, and increased risk for long-term disability due to decreased functional outcomes.⁷⁻⁹ About a third of the people on long-term disability have LBP and this has increased from 20 percent since the mid-1990s. Approximately 40 percent of people on long-term disability are on chronic opioid therapy.

The adverse effects of opioids which can affect job performance include sedation, cognitive dysfunction, and impaired alertness, attention, concentration reaction time, and judgment. These effects especially pose a danger in safety sensitive jobs such as commercial truck drivers, miners, factory workers, and construction workers.

Opioids cause dependence in everyone. This dependence takes place within seven days of continuous therapy. Addiction, a pathologic process that interferes with interpersonal relationships, does not occur in every opioid user but does occur in a significant number.

Opioid abuse kills 40 people per day in the U.S. The rate of opioid-related deaths increased from 2002 to 2006, plateaued from 2006 through 2008, then decreased slightly from 2009 through 2013 (Exhibit 1).¹⁰

The U.S. spends approximately \$72 billion annually on opioid abuse. Opioid abusers spend more time in the emergency room and hospital. The average annual per-patient health care cost for abusers is

Exhibit 2: Factors to Screen for Prior to Opioid Initiation

Depression	Substance(s) Abuse History	Sleep Disorders
PTSD	Benzodiazepine Use	COPD
Anxiety	Sedating Medication Use	Alcohol Abuse
Personality Disorder	Anti-histamines	Tobacco Use
Other Psychiatric Disorder	Opioid Dependence	Balance Problems/Fall Risk
Cognitive Impairment	Osteoporosis	Renal/Liver Disease

\$20,000 compared with non-abusers, with matching baseline characteristics costing \$9,000. Five billion dollars annually are spent on law enforcement, the court system and on correctional facilities dealing with this issue.

Opioids are the second most commonly used recreational drug. An estimated 20 percent of Americans report using pain relievers for nonmedical reasons.¹¹ Unfortunately, when opioids are not available, many abusers turn to heroin. The U.S. is currently in a heroin and fentanyl overdose crisis. Fentanyl and U-47770 (Pink, a synthetic opioid being imported from China) are incredibly inexpensive and potent.

Despite all the issues with opioid medications, there are some patients with noncancer pain who may benefit functionally from chronic opioid use. This is very controversial; some providers have strong beliefs in efficacy, which is mostly among pain specialty providers. Many primary care providers and occupational medicine physicians have strong beliefs in the problems with opioid therapy. In unselected patients with chronic pain, there is no quality evidence to support the beliefs of long-term efficacy or safety. Pain has not been shown to be eliminated by long-term use, function does not go up, and quality of life does not go up.

With chronic use, patients become hyperalgesic – more sensitive to pain rather than less. There is also decreased testosterone levels and sex drives. Long-term use also increases risk for depression. Opioid treatment may be prescribed to reduce pain and improve function, but the treatment may actually result in just the opposite

Routine use of opioids for treatment of chronic nonmalignant pain conditions and for myofascial pain, fibromyalgia, tender points, and trigger points is not recommended.^{1,2} Opioids are not recommended for those with a “chronic pain syndrome” or “pain disorder” characterized by behavioral and emotional issues, poor coping, dysfunctional pain behaviors, life disruption, history of substance abuse

and delayed recovery with subjective-objective mismatch.² Opioids may be used for a very narrow selection of patients. Criteria for initiation include a clear medical diagnosis associated with objective evidence of anatomical or physiologic abnormalities that are ordinarily associated with pain and measurable functional physical or medical limitations are expected to improve if pain is reduced. Also the use of opioids should not be initiated unless non-opioids, adjuvants, and alternative pain control modalities have been tried and either were not tolerated or were inadequate despite patient compliance.

Before initiating therapy, all patients need to be screened for addiction potential. Exhibit 2 lists the conditions/concomitant factors of major concern which should be screened for before initiating opioids. There are also numerous minor concerns which can impact the decision to initiate opioid therapy (Exhibit 3). Several screening tools are available for clinician use, including the opioid risk tool (ORT), the opioid abuse and risk screen (OARS), and the drug abuse screening tool (DAST). The guidelines note that psychological evaluation and, if warranted, referral for appropriate psychological, behavioral, and/or rehabilitative interventions should be initiated before any opioid prescribing is done in the chronic noncancer pain population. Clinicians also need to check the Prescription Drug Monitoring Database in relevant states.

The “ideal” candidate for opioid therapy is someone who meets all the previous criteria discussed and is willing to sign an opioid treatment agreement or plan. This agreement states they will only get opioid prescriptions from one provider, will not share their medications, and will only take as directed. Use of a treatment agreement, routine use of urine drug screening for patients on chronic opioids, and attempts to wean patients on opioids to the lowest clinically effective dose or completely from opioids every six months must be done.^{1,2}

A urine drug screen should be conducted before

Exhibit 3: Additional Cautions for Opioid Prescribing

Chronic Hepatitis and/or Cirrhosis	Coronary Artery Disease	Dysrhythmias
Cerebrovascular Disease	Orthostatic Hypotension	Thermoregulatory Problems
Osteopenia	Fluid Retention	Gastroparesis
Testosterone Deficiency	Erectile Dysfunction	Abdominal Pain
BPH	Oligomenorrhea	Constipation
Pregnancy	Herpes	HIV
Ineffective Birth Control	Allodynia	Dementia
Gait Problems	Concentration Problems	Cognitive Dysfunction
Insomnia	Coordination Problems	Slow Reaction Time
Tremor	Suicidal Risk	Impulse Control
ADHD	Asthma	Recurrent Pneumonia

prescribing and then continued randomly two to four times per year. More frequent screening should be done if the patient is in an opioid treatment program or receiving more than 50 mg morphine equivalent dose (MED) per day. Screening for cause can also be done and this includes suspicion of misuse, motor vehicle crash, other accidents and injuries, driving while intoxicated, premature prescription renewals, self-directed dose changes, lost or stolen prescriptions, more than one provider for prescriptions, non-pain use of medication, using alcohol for pain treatment, excessive alcohol use, missed appointments, hoarding, or selling medications.

A trial of opioids in the appropriately screened patients should be done at the lowest dose of a single medication to ascertain whether functional improvement occurs. Objective functional gains to measure can include ability to work, specific occupational tasks, walking ability, physical therapy/exercise participation, aerobic capacity, strength, and ability to complete household chores. Lower doses are preferable as there is a better safety profile, less dose escalation risk, less work loss, and faster return to work.

There are numerous opioid formulations available, including immediate-release (IR, Lortab[®], Percocet[®], oxycodone, hydrocodone), extended-release/ long-acting (ER/LA), methadone, and abuse deterrent formulations. Research has shown there is no difference between IR and ER formulations for pain outcomes. There is an increased risk of death with ER/LA and methadone. Additionally, no difference in pain outcomes has been shown with dose escalation compared with a stable dose over 12 months. Thus, IR formulations should be used for acute pain management. ER

formulations have a role for cancer pain and possibly for chronic noncancer pain.

The goal is to keep patients at less than 50 mg MED per day to minimize risk of overdose. If the patient is receiving greater than 50 mg MED, the recommended monitoring is more than if they are receiving lower doses. Patients should be seen for monthly appointments. Attempts to wean to less than 50 mg MED should be made every six months. Persistence of functional benefit and review of medications, particularly to assure there is no sedating medication use, should also be done every six months.

Concomitant treatments with chronic opioid use should be an active exercise program and nonopioid medications. An active exercise program is the most effective treatment ongoing and should be part of a multi-modal treatment plan. Nonopioid prescriptions (e.g., nonsteroidal anti-inflammatories (NSAIDs), acetaminophen, gabapentin, or antidepressants) should nearly always be the primary pain medication and accompany an opioid prescription. Opioids should be prescribed to take at night or for use when the patient is not at work and used by the patient as little as possible. There has to be ongoing monitoring of efficacy, adverse effects, compliance and surreptitious medication use. Shorter, rather than longer duration opioid prescriptions, should be written. Opioids should be discontinued if there is no functional benefit, resolution of pain, intolerance, adverse effects, noncompliance, aberrant drug screening results, or if the patient is using sedating medications, alcohol, or benzodiazepines.

Different types of chronic pain require slightly different approaches. Neuropathic pain includes

complex regional pain syndrome, radiculopathies, toxic neuropathies, and nerve entrapments. Nociceptive pain (end organ pain receptors) includes spine pain, crush injuries, fractures, chronic tendinopathies, and osteoarthritis. Fibromyalgia is the third type of chronic pain, but its treatment is not addressed in this article. Neuropathic pain should be treated with NSAIDs and acetaminophen. Tricyclic antidepressants, duloxetine, gabapentin, and pregabalin are also treatment options. Nociceptive pain is best treated with NSAIDs and exercise. Patients need to move their way out of pain. Trigger point injections (either topical anesthetic or dry needling) and acupuncture are also options. Selective serotonin reuptake inhibitors (SSRIs) are only recommended for treating the combination of depression and chronic pain.

In response to the opioid crisis, abuse deterrent formulations were developed to prevent injection, inhalation (smoking), and insufflation (snorting). FDA guidance describes seven categories of abuse-deterrent technologies — physical/chemical barriers, agonist/antagonist combinations, aversion, delivery system, new molecular entities (NMEs) and prodrugs, combinations, and novel approaches. There are currently no new molecular entities (NMEs) and prodrugs, combinations, or novel approaches marketed. An example of physical/chemical barriers include capsules or tablets designed to prevent chewing, biting, dissolving or melting [oxycodone ER (Remoxy[®]), morphine (Morphabond[®])]. An agonist/antagonist combination example is an opioid with naloxone which is not absorbed from the gastrointestinal tract [Oxynal[®] and Embeda[®]]. If crushed and injected or snorted, the naloxone blocks the effects of the opioid in the formulation. Whether the naloxone combination products are effective in deterring abuse is controversial because patients are likely to turn to heroin or fentanyl instead of using these. An altered delivery system example is ER/LA formulations [OROS hydromorphone ER (Exalgo[®])]. There are currently no immediate-release or generic opioids with FDA approved abuse-deterrent labeling.

Mental health and behavioral interventions are important in managing patients with chronic pain. Treatment has to involve a multidisciplinary team. Depression, anxiety, and other factors which make pain worse and perpetuate it have to be treated or chronic pain will never be managed. Patients need to learn healthy coping skills.

Occupational concerns are a major issue in chronic pain patients. Patients should be encouraged to return to work as soon as possible through modified duty programs and participatory ergonomics

programs where available. It has been shown that the longer someone is out of work, the more likely they are to become chronically disabled and have more pain. Nonphysical factors such as job satisfaction and interaction with co-workers and supervisors will have to be addressed because they impact return to work. Patients must be encouraged to accept responsibility for managing their recovery.

The focus of chronic pain management should be on function and not pain. Rest and disuse of body parts is not recommended. Functional restoration emphasizes physical activity (“reanimation”). Clinicians should use an active therapy approach with objective measure of physical function and intensive graded exercise. There should be judicious use of diagnostic and interventional procedures.

Conclusion

Clinicians need to adopt the biopsychosocial model in understanding chronic pain. In managing chronic pain, the goal is not to eliminate pain; the focus should be on functional restoration. Interdisciplinary evaluation including mental health evaluation is needed. Clinicians need to recognize and treat comorbidities; especially psychosocial issues and barriers to return to work. Treatment should be educational and patient centered with early return to work and minimal, appropriate use of opioids.

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Improving Patient Outcomes with Individualized Therapy in the Management of Type 2 Diabetes

Timothy S. Reid, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

It is an exciting time to be managing type 2 diabetes mellitus (T2DM). Combining classes of therapy in new ways is producing effective reduction in blood glucose with minimal adverse effects. Combination therapy, patient education on self-management, and clinician skills in working with the patient to achieve mutually agreed upon goals all work together to achieve appropriate outcomes.

Key Points

- T2DM prevalence has grown to epidemic proportions.
- The landscape of diabetes medications continues to expand.
- Opportunities for improved control of the disease state with fewer side effects, and the potential for reduction of CV risk are growing.
- Combination therapy with newer agents provides powerful synergy.

OVER 29 MILLION AMERICANS HAVE DIABETES, which is about 9.3 percent of the population. More importantly, 86 million Americans age 20 and older have prediabetes and will be the next wave of patients. Over eight million Americans with diabetes are undiagnosed. Overall, diabetes is the seventh leading cause of death in the United States (U.S.).

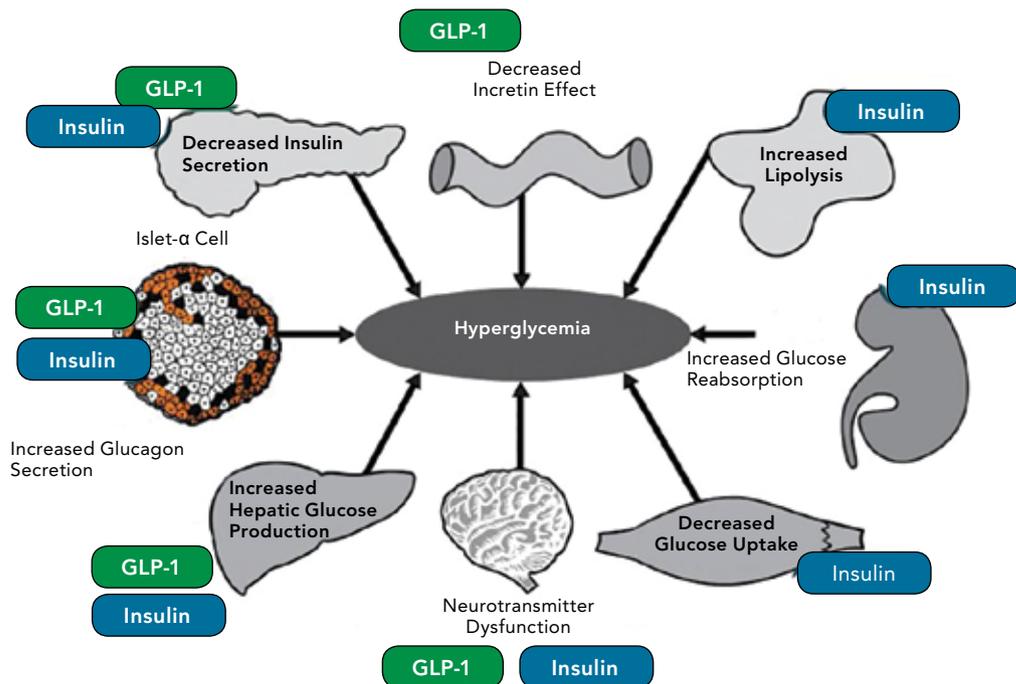
Patients worry about low blood glucose, weight, economics, their kidneys, and their heart. They have fears and concerns. Clinicians cannot lose sight of the fact that each patient is a real person. When patients come to a health care visit, the words clinicians use can have a mighty impact and their body language tells more than words. Clinicians need to leave some hope with the patient and work with the patient's priorities. Clinicians can be there to support the patient and help move them toward mutually agreed upon goals.

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinolo-

gists (AACE) both publish clinical management guidelines for T2DM.^{1,2} Both the ADA and AACE guidelines emphasize the comprehensive nature of diabetes management through lifestyle modifications, dietary recommendations, medication initiation and combination therapy, appropriate specialist referrals, and screenings. Diabetes self-management education is a key part of T2DM management. It improves diabetes knowledge, self-care behavior, clinical outcomes, A1C, self-reported weight, quality of life, and healthy coping, while also resulting in lower costs.

The number of diabetes medications available for use continues to grow. There are now nine classes of oral anti-diabetic medications, four classes of subcutaneous medications, new concentrated insulins, and insulin/glucagon-like peptide-1 (GLP-1) combinations which can be confusing for clinicians. Most of these agents have come to market since 1990. Each medication class targets different metabolic defects

Exhibit 1: Effects of GLP-1 and Insulin in Type 2 Diabetes Mellitus



that contribute to hyperglycemia in T2DM. To take advantage of the differing but complementary mechanisms of action, various classes are available in preset combinations or individual agents can be combined. In addition to hemoglobin A1C (A1C) reduction, prevention of the long-term consequences of the disease also needs to be considered in selecting therapy. Kidney, stroke, and cardiovascular disease prevention are especially important.

Pharmacological therapy for T2DM begins with metformin. It is the preferred choice if tolerated and not contraindicated because of efficacy, long-term clinical experience, low risk of hypoglycemia, no weight gain, and low cost. Insulin should be considered if the patient is symptomatic or has A1C greater than 9%.² Combination therapy should be considered from the beginning for A1C greater than 7.5%.² Therapy should be advanced using a patient-centered approach every three months until the goal A1C is reached. It is important to note that T2DM is progressive; insulin therapy will eventually be needed in most cases. If metformin is not enough to reach goal, a second or third agent can be added. The focus of the rest of this article will be on the addition of GLP-1 targeting agents and basal insulin to metformin because that is where the most of the recent changes in T2DM therapy have been.

GLP-1 is a hormone that stimulates insulin secretion in response to oral carbohydrate intake. This action impacts multiple sites of glucose regulation, including suppression of glucagon at the pancreatic alpha cell, stimulation of insulin release at the pancreatic beta cell, and promotion of satiety and reduced appetite in the central nervous system. Dipeptidyl peptidase-4 (DPP-4) rapidly inactivates native GLP-1. In T2DM, there is substantial impairment in GLP-1 secretion in response to a meal or oral glucose load. Two ways to enhance GLP-1 are to slow down DPP-4 with inhibitors (gliptins) or give agents which act like GLP-1 [GLP-1 receptor agonists (GLP-1 RAs)]. Exhibit 1 shows where the GLP-1 agents have effects.

GLP-1 RAs include exenatide twice daily (Byetta[®]), exenatide once weekly (Bydureon[®]), lixisenatide (Adlyxin[®]), liraglutide (Victoza[®], Saxenda[®]), albiglutide (Tanzeum[®]), and dulaglutide (Trulicity[®]). Exhibit 2 shows the dosing schedules and expected A1C reductions for each agent. Semaglutide, injected once weekly, and ITCA 650, an implanted osmotic mini-pump of exenatide changed every six months, have been submitted to the FDA for approval.

In terms of adverse effects, nausea, vomiting, and diarrhea are relatively common when therapy is started with a GLP-1 RA; these effects tend to be

Exhibit 2: Current Stable of GLP-1 Agonists

Generic Name	Dosage	Expected A1c Reduction	Fasting BGM Reduction	% Patients Reaching < 7% A1c
Albiglutide (Tanzeum)	30 mg/week	-0.7%	-16 mg/dl	
	50 mg/week	-0.9%	-25 mg/dl	
Exenatide IR (Byetta)	5 mcg BID	-0.7%	-17 mg/dl	48%
	10 mcg BID	-0.9%	-19 mg/dl	53%
Exenatide LAR (Bydureon)	2 mg subQ weekly	-1.6%	-25 mg/dl	58%
Dulaglutide (Trulicity)	0.75 mg/week	-0.7%	-26 mg/dl	
	1.5 mg/week	-0.8%	-29 mg/dl	
Liraglutide (Victoza)	1.2 mg/d	-0.8%	-15 mg/dl	
	1.8 mg/d	-1.1%	-26 mg/dl	
Lixisenatide (Adlyxin)	10 mcg/d	Transition Dose		
	20 mcg/d	-0.83%	-15.84 mg/dl	44%

A1C = hemoglobin A1C
BGM = blood glucose monitoring

mild and improve with continued therapy. Patient education on these adverse effects is important to promote tolerance. Hypersensitivity, renal impairment, and pancreatitis can also occur. Medullary thyroid carcinoma nodules have been seen in rat and mice studies but have not been reported in humans. Rats and mice have many GLP receptors in their thyroids which humans do not have. Hypoglycemia typically only occurs when a GLP-1 RA is used in combination with insulin or sulfonylureas.

Exclusions to using GLP-1 RAs include personal history of pancreatitis or high risk of developing pancreatitis (high triglycerides, alcoholism), gastroparesis, severe renal disease, personal or family history of medullary thyroid carcinoma, or personal or family history of multiple endocrine neoplasia two (MEN-2, thyroid, parathyroid and adrenal tumors).

As shown in Exhibit 1, insulin has multiple effects and is the most effective way to reduce blood glucose. Unfortunately, insulin is a four-letter word to many patients. They fear injections, worry about losing control of their life and scheduling, and think that insulin therapy is the end of the road in terms of therapy. Clinicians have to use all of their resources, including certified diabetes educators and nurses, to educate patients on the benefits of insulin. Pen

delivery devices have made a huge difference in patient acceptance.

Because of their long half-lives, once-daily basal insulins are typically used in T2DM (Exhibit 3). Insulin produces robust A1C reductions with little toxicity. Hypoglycemia is a concern, especially if used with secretagogues (sulfonylureas, glinides), and requires monitoring and management. Weight gain is also an issue with insulin. Other possible adverse effects include hypersensitivities (typically related to excipients), lipodystrophy, and edema (when used in combination with thiazolidinediones).

The newer basal insulins have flatter action curves, prolonged insulin activity (24-28 hrs.), smaller insulin depot with the concentrated forms, and a possibility of improved nocturnal hypoglycemia.

The latest trend in T2DM management is to combine a GLP-1 RA, basal insulin, and metformin. The triple combination provides a balanced approach to fasting and prandial glucose coverage without the need for multiple injections of meal time insulin. The basal insulin replaces insulin overnight for fasting and underlying glycemic control. Up-regulating native gut metabolism to glucose stimulation by the GLP-1 RA covers mealtime glucose surges. The combination is easier for the patient than multiple daily doses of insulin.

Exhibit 3: Current Basal Insulins

Generic Name	Concentration	Expected A1c Reduction	Fasting BGM Reduction
Degludec (Tresiba)	U-100	-0.7%	-16 mg/dl
	U-200	-0.9%	-25 mg/dl
Detemir (Levemir)	U-100	-2.0%	-69 mg/dl
Glargine (Lantus, Toujeo)	U-100	-0.46%	-49 mg/dl
	U-300	-0.9%	-29 mg/dl

A1C = hemoglobin A1C
BGM = blood glucose monitoring

In patients with uncontrolled T2DM, insulin degludec and liraglutide compared with insulin glargine alone results in better reduction of A1C, less weight gain, and lower rates of hypoglycemia.⁴ The combination of insulin degludec and liraglutide is now available in a pen- based product (Xultophy® 100/3.6) containing 100 units of degludec and 3.6 mg of liraglutide in each milliliter. This is given as a single injection once daily.

Insulin glargine, insulin glulisine (short acting), and metformin have been compared to insulin glargine, lixisenatide, and metformin.⁵ The intensive regimen including three times a day mealtime glulisine produced the most A1C reduction (7% vs 7.2%) but with a much higher rate of hypoglycemia. Insulin glargine and dulaglutide have also been studied in combination and produces better A1C reduction than glargine alone.⁶ Lastly, albiglutide, a weekly GLP-1 treatment, produced better A1C and fasting blood glucose reduction with less weight gain compared with thrice-daily prandial insulin lispro in patients already on metformin, pioglitazone, and insulin glargine.⁷

The combination of metformin, basal insulin, and a GLP-1 RA is a powerful new approach to patients with T2DM that provides effective A1C reduction, less hypoglycemia exposure, and even potential for weight loss. Patients are seeing good results and feel better so now they are able to exercise and eat less, which leads to some weight loss. This triple combination is good for the patient who has tried a number of oral agents or basal insulin without any exclusions to GLP-1 RA therapy.

Conclusion

T2DM prevalence has grown to epidemic propor-

tions. The landscape of diabetes medications continues to expand, which can be confusing for clinicians. Opportunities for improved control of the disease state with fewer side effects and the potential for reduction of CV risk are growing. Combination therapy with newer agents provides powerful synergy for patients and has the potential to change the landscape of T2DM management.

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Key Advances in the Treatment and Management of Asthma

David M. Lang, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Uncontrolled asthma is a significant cost driver for managed care. Achieving asthma control is key to reducing morbidity, mortality, and costs. With a better understanding of the different types of asthma, clinicians can better select appropriate therapies which may include biologics.

Key Points

- Asthma disease control is key.
- Biomarkers for disease control and for identifying phenotypes are becoming more important.
- Biologics are indicated for severe allergic asthma.
- In the future, phenotypes and endotypes will be used to select therapy.

IN 2017, THERE ARE 26 MILLION PEOPLE estimated to have asthma in the United States (U.S.), compared with 20 million in 2001.^{1,2} Rates are higher in African Americans compared with the Caucasian population. Each person with asthma has about \$3,300 in medical expenses each year for a total of \$56 billion in annual costs, including medical costs, lost school/work, and early deaths. Asthma can also be deadly, with 3,630 deaths in 2013.¹ Asthma mortality has been declining because of increased prescribing of controller medications; however, morbidity has not changed.

The goals of treatment and measuring those goals in asthma are different from and are less clear than with other chronic diseases. For example with hypertension, the goal is to achieve a particular blood pressure which can be measured easily. For asthma, there are numerous goals, including preventing hospitalizations, preventing exacerbations, preventing decline in lung function, and symptom control. There is no one simple test that can be done to say the treatment goal has been achieved. Asthma tends to be complicated to manage because of all the goals.

The goal of asthma management can be simpli-

fied into asthma control. Disease control correlates closely with health care resource utilization. In a multicenter, prospective, observational study of severe or difficult to treat asthma in the U.S., the mean costs to provide care are significantly higher in those whose disease is uncontrolled (Exhibit 1).³ Controlled patients also have fewer work/school absences. Overall, those with controlled disease are less likely to have hospitalizations, exacerbations, declining lung function, or symptoms.

In another study where everyone in a primary care practice was asked to take the Asthma Control Test regardless of the reason for their visit, almost half of the patients visiting for a nonrespiratory complaint had not well-controlled or poorly controlled asthma (48%). Patients with poorly controlled asthma are not going to be identified unless someone is asking the right questions.

From a public health standpoint, if patients who have uncontrolled asthma can be identified and moved to better control, there will be improved outcomes and reduced health care costs. From a managed care perspective, the payoff in achieving asthma disease control will occur much sooner

Exhibit 1: Burden of Uncontrolled Asthma³

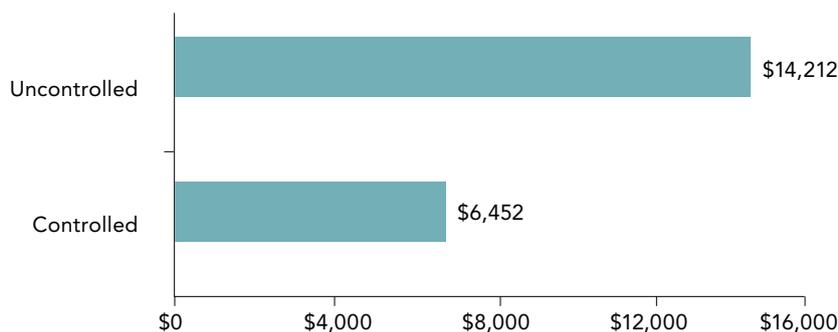


Exhibit 2: Assessing Asthma Control in Children ≥ 12 Years of Age and Adults: NAEPP Guidelines⁴

Components of Control		Well Controlled	Not Well Controlled	Poorly Controlled
Impairment	Symptoms	≤ 2 days per week	> 2 days per week	Throughout the day
	Nighttime awakenings	≤ 2 per month	1 - 3 per month	4 per week
	Interference with normal activity	None	Some limitation	Extremely limited
	SABA use for symptoms (not prevention of EIB)	≤ 2 days per week	> 2 days per week	Several times per day
	FEV ₁ or peak flow	$\geq 80\%$ predicted or personal best	60% - 80% predicted or personal best	$< 60\%$ predicted or personal best
	Validated Questionnaires ATAQ ACQ ACT	0 ≤ 0.75 ≥ 20	1 - 2 > 1.5 16 - 19	3 - 4 N/A < 15
Risk	Exacerbations	0 - 1 per year	2 - 3 per year	> 3 per year
	Positive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

ACQ = Asthma Control Questionnaire
 ACT = Asthma Control Test
 ATAQ = Asthma Therapy Assessment Questionnaire

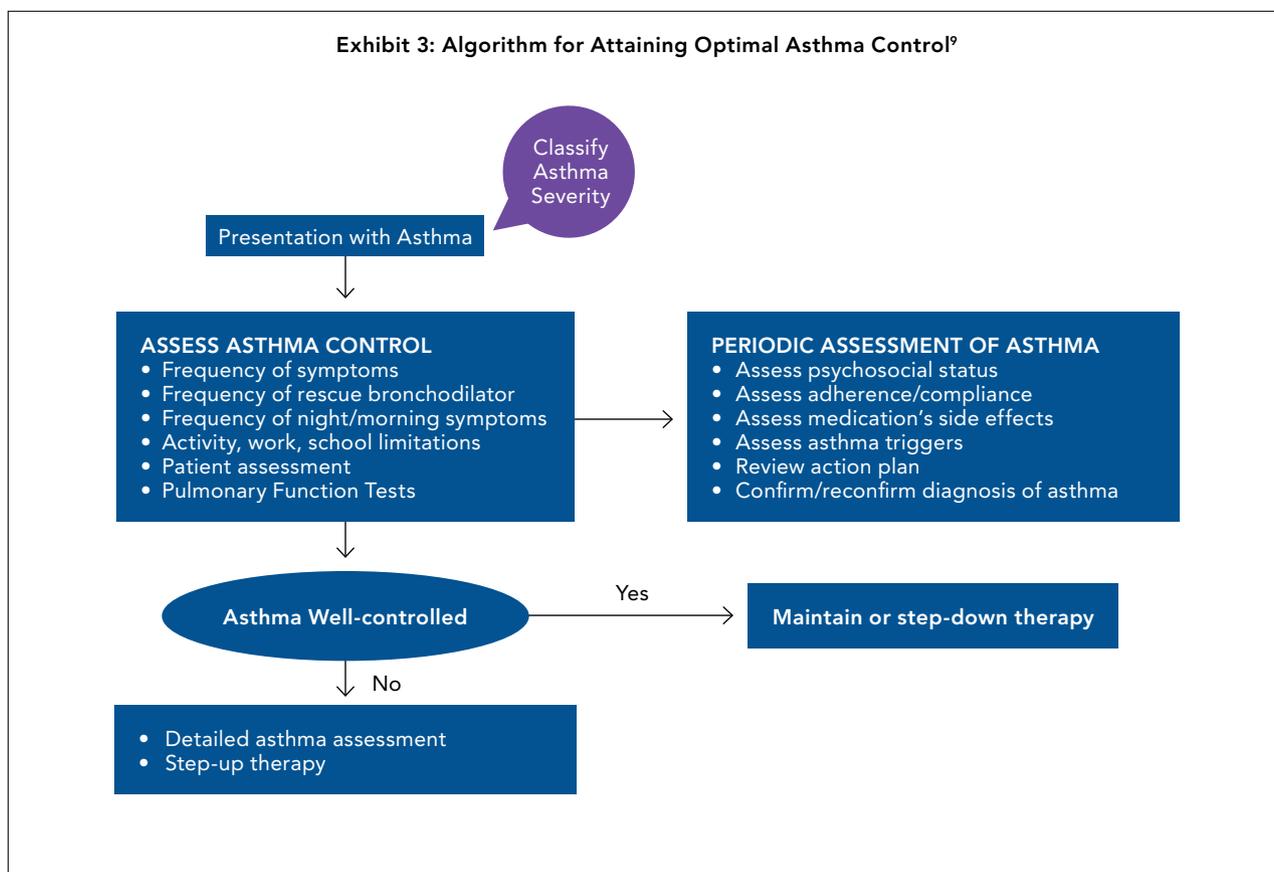
EIB = exercise-induced bronchospasm
 FEV₁ = forced expiratory volume in 1 second
 N/A = not applicable.

compared with the cost benefits of controlling diseases with long-term outcomes like hypertension or diabetes.

Before discussing how to achieve asthma control, it is important to have some definitions. In asthma, severity is the intrinsic intensity of the disease process. It is measured most easily and directly in

a patient not receiving long-term control therapy. Control is the degree to which manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met.⁴ Exhibit 2 outlines how well-controlled, not well-controlled, and poor control are defined specifically using impairment and

Exhibit 3: Algorithm for Attaining Optimal Asthma Control⁹



risk domains in the National Asthma Education and Prevention Program guidelines.⁴ The impairment domain includes symptoms and lung function measures. The risk domain is the frequency of exacerbations. To still be considered controlled, these guidelines allow patients to have one exacerbation per year that requires an emergency room visit. The Global Initiative for Asthma (GINA) guidelines do not allow any exacerbations.⁵

Patient questionnaires are one component of assessing asthma control. There are three validated instruments for evaluating control - Asthma Control Questionnaire (ACQ), Asthma Control Test (ACT), and Asthma Therapy Assessment Questionnaire (ATAQ).⁶⁻⁸ Scores for a given questionnaire can be tracked over time; showing the patient how their score has changed with improved control can be a powerful reinforcer of adherence behavior. Exhibit 3 presents an algorithm for getting asthma control.⁹

Risk factors for future exacerbations include poorly or not well-controlled asthma, a history of recent exacerbations especially requiring steroids in the last year, inhaled beta agonist overuse (> two containers/month), controller medication underuse, and certain biomarkers.⁴ One biomarker of increasing importance is peripheral eosinophil counts (EOS). An elevated count means the patient has active in-

flammation. An EOS of 400 cells/mm³ or more is predictive of asthma exacerbation and an emergency room or hospital visit compared with lower values.¹⁰

In the early 19th century, asthma was regarded as a syndrome of episodic shortness of breath that covered a range of conditions rather than a single disease. That understanding was lost during the 20th century when asthma was considered a single disease. Asthma is now viewed as heterogeneous; it is not a single disease entity. It is a syndrome characterized by multiple phenotypes which can be identified by various characteristics including age, gender, race/ethnicity, disease pattern, remission/relapse, and persistence. Examples of these phenotypes include early-onset mild allergic asthma, later-onset asthma associated with obesity, and severe non-atopic asthma with frequent exacerbations. Endotypes are mechanistically different subgroups of asthma. Aspirin-exacerbated respiratory disease (AERD) and cold air exposure asthma are two examples. Better tools for identifying the various phenotypes and endotypes are needed. In the future, there will likely be a series of biomarkers that will be measured to either identify a given subtype of asthma and/or predict favorable medication response.

Exhibit 4 shows how two patients with asthma can vary in presentation and treatment. Barbara 2 has

Exhibit 4: Two Barbaras

Barbara 1

- 48 year old African American woman with 15 year history of asthma – poorly controlled.
- 2 - 3 exacerbations per year.
- Frequent reliance on oral steroid
- Co-morbid conditions
 - GE reflux
 - Obesity
- PE:
 - Chest: clear
 - Otherwise unremarkable
- Skin testing: wheal/flare reactions to tree/grass/ragweed/weed pollen, dust mites, cockroach, cat dander.
- ACT = 5 (poorly controlled)
- Disposition:
 - Aeroallergen avoidance measures
 - Maintain current asthma regimen with high dose ICS/LABA, antileukotriene, and optimize regimen for GE reflux.
 - Therapeutic trial of anti-IgE.
 - Dramatic improvement in course of asthma

Barbara 2

- 48-year-old Caucasian woman with 15 year history of rhinosinusitis, requiring 3 sinus surgeries.
- 12 year course of asthma
- Frequent reliance on oral steroid
- 3 episodes of respiratory reaction to ASA/NSAID, one requiring ICU management
- PE:
 - Chest: End expiratory wheeze in all lung fields.
 - HEENT: Nasal polyps
- Skin testing: no wheal/flare reactions at prick or intradermal level.
- CT scan: pansinusitis
- ACT = 5
- Disposition:
 - Avoid ASA/NSAIDs
 - Maintain current regimen for asthma with high dose ICS/LABA, antileukotriene.
 - Aspirin desensitization
 - Sinus surgery

ICS = inhaled corticosteroid
LABA = long acting beta agonist
ASA = aspirin
NSAID = non steroidal antiinflammatory
GE = gastroesophageal

AERD. This subtype of asthma has an onset in one's 30s and 40s with vasomotor rhinosinusitis, asthma, and an aspirin/nonsteroidal respiratory reaction.¹¹ Nasal polyposis and eosinophilia are seen with aspirin-induced disease. Aspirin desensitization is one option for AERD and is done with intranasal ketorolac. Indications for ASA desensitization include unacceptably high doses of systemic corticosteroids required for control of AERD, refractory rhinosinusitis mandating repeated polypectomies and sinus surgery procedures, and ASA/NSAID needed for cardiovascular or musculo-rheumatic conditions.¹² Once desensitized, the patient has to take a 1300 mg of aspirin daily to prevent the reaction. For patients who are successfully desensitized and who remain on aspirin, 87 percent will have reduced symptoms.¹³

Cold exposure asthma is another endotype. It responds to montelukast but not inhaled steroids. T helper type 2 cell (TH2)-low and TH2-high asthma are additional endotypes. TH2-high asthma re-

sponds best to biologics, which are discussed later, when EOS counts are high.

Barbara 1, in Exhibit 4, is African American, which is another phenotypic characteristic of asthma. In 2011, the asthma prevalence rate for African Americans was 47 percent higher than for Caucasians.¹⁴ Overall, one in six African American children have asthma. For African Americans, the rate of emergency department visits is 330 percent higher and the rate of hospitalizations is 220 percent higher compared to Caucasians. Additionally, African Americans are three times more likely to die from asthma. There are likely numerous reasons for these differences, including racial/ethnic differences in asthma prevalence. Other reasons include living in poverty, urban air quality, exposure to indoor allergens, and inadequate medical care.

Medication response is another phenotype. Patients have been shown to have varying responses to different medications. Patients with atopy are also

a phenotype. These patients tend to have multiple allergies (asthma, allergic rhinitis, food and medication allergies).¹⁵

Beyond work on phenotypes and endotypes, there have been some other advances in medical therapy of asthma. There are several biologic agents which are available or under investigation for asthma. Omalizumab is an FDA approved anti-IgE agent; mepolizumab and reslizumab are anti-interleukin-5 (IL-5) agents. Benralizumab (anti-IL-5), tralokinumab (anti-IL-4/anti-IL-13), and dupilumab (anti-IL-4/anti-IL-13) are investigational agents.

Omalizumab is indicated for moderate to severe persistent asthma that is poorly or not well-controlled on combination controller therapy. Patients should have an IgE level between 30-700 IU/ml and a positive skin or in vitro test to perennial aero-allergen. Treatment with this agent results in a 25 percent relative rate of reduction in exacerbations.¹⁶ Those with high exhaled nitrous oxide levels and/or eosinophil levels are more likely to respond to omalizumab.¹⁷

In patients with high eosinophils, mepolizumab reduces the rate of exacerbations by 53 percent compared with placebo.¹⁸ Reslizumab reduced exacerbations 41 to 50 percent.¹⁹

Conclusion

Asthma control should be the goal of treatment; achieving this goal will reduce exacerbations, health care resource utilization, and overall costs. One way to achieve control is to identify the phenotype or endotype and ensure the appropriate therapy is prescribed. The future of asthma therapy is new biologics and corresponding biomarkers for identifying the subtypes more likely to respond to these agents.

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Evolving Treatment Options and Strategies in Relapsing Multiple Sclerosis

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For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Numerous effective disease-modifying therapies are available for the relapsing/remitting subtype of multiple sclerosis (RRMS), and now there is an FDA approved agent for primary/progressive MS. Each of the RRMS therapies has advantages and disadvantages, but disease control is an attainable goal for most patients.

Key Points

- MS is unpredictable.
- A large number of disease modifying-therapies are available for RRMS and one for primary/ progressive MS.
- No evidence of disease activity (NEDA) is the goal of MS therapy for relapsing/remitting disease.

MULTIPLE SCLEROSIS (MS) IS AN UNPREDICTABLE, inflammatory, autoimmune disease which attacks the central nervous system (CNS). Several subtypes of MS are recognized. Clinically isolated syndrome (CIS) is the first MS attack experienced by a patient. CIS can be optic neuritis, transverse myelitis, or isolated brain stem cerebellar syndrome. There is also relapsing/ remitting MS (RRMS), primary/progressive, and secondary/progressive. In addition to identifying the subtype, new MS phenotype definitions divide the disease into active and progressive disease (Exhibit 1).¹ Those with active disease are having relapses and those with progressive disease are experiencing functional decline. Patients can have active or inactive disease and progressive or not progressive disease.

Management of MS attempts to address symptoms and disease sequelae, shorten relapses, and improve recovery. Disease-modifying therapy (DMT) is

aimed at reducing the number and severity of relapses, preventing the accumulation of disability, and eventually reversing disability. Wellness and comorbidities also have to be addressed.

Clinicians today are well equipped to treat and monitor the inflammatory component of RRMS with 14 approved therapies. These therapies represent a range of mechanisms of action which interrupt the immune system attack on the nervous system (Exhibit 2). The DMTs are variably effective in individuals. Currently, there is no biomarker to prospectively predict efficacy of specific treatments in individual patients. Therapy ends up being trial and error to find an effective therapy. Monitoring therapy efficacy, clinically and with MRI scans, is common, though there are no standards or defined targets in the clinic.

The general approach to MS disease management is shown in Exhibit 3. If the patient has active dis-

Exhibit 1: New MS Phenotype Definitions¹

Active Disease
Clinical: relapses, acute or subacute episodes of new or increasing neurologic dysfunction followed by full or partial recovery, in the absence of fever or infection.
and/or
Imaging (MRI): occurrence of contrast-enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions.
Progressive Disease
Clinical: steadily increasing objectively documented neurologic dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur)
Imaging (MRI): imaging measures of progression are not established or standardized and not (yet) useful as phenotype descriptors for individual patients. Under consideration are an increasing number and volume of T1-hypointense lesions, brain volume loss, and changes in magnetic transfer imaging and diffusion tensor imaging.

Exhibit 2: RRMS Therapeutic Landscape

Mechanism	Examples
Immunomodulation	Interferon-beta, glatiramer acetate, dimethyl fumarate, daclizumab
Inhibition of cell replication	teriflunomide
Cell depletion	alemtuzumab, ocrelizumab
Altered cell trafficking	natalizumab, fingolimod

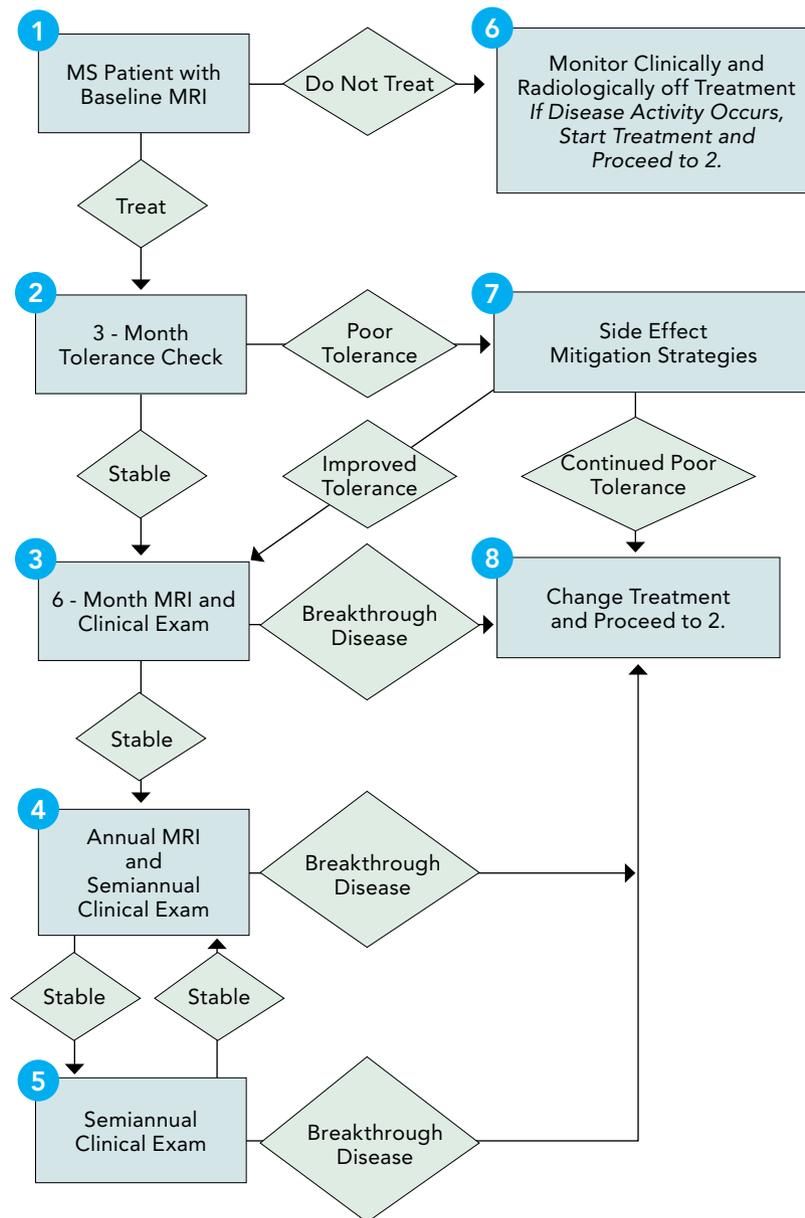
ease, DMT should be initiated. MRI scans are done at least yearly to make sure that the expensive DMT therapy is actually working.

There is significant rationale for treating MS early rather than waiting. The damage to the brain and nervous system starts long before the first clinical symptoms are seen. Additionally, clinical features correlate poorly with the ongoing inflammation and resultant irreversible tissue destruction in early RRMS. The ability to predict prognosis in individual patients is limited. With time, most patients ultimately evolve into a secondary/progressive course with some degree of permanent disability. All but one of the DMTs are effective in RRMS but not in progressive disease and do not restore damaged tissue. All of these factors contribute to the need to start DMT therapy early in active disease to prevent

irreversible damage and conversion to progressive disease.

Treat-to-target (TTT) in MS is a concept borrowed from rheumatoid arthritis. With TTT, the shared, explicit goal of therapy is to maximize long-term outcomes (neurologic function and health-related quality of life) through effective prevention of MS-related CNS tissue damage with selection and/or adjustment of therapy based on ongoing measurement of disease activity and severity to optimize treatment. No evidence of disease activity (NEDA) is increasingly reported in clinical trials and should be the goal of TTT. NEDA is the complete absence of detectable disease activity while on a disease therapy. The criteria include no MRI lesion activity (gadolinium-enhancing lesions, new/enlarged T2 lesions), clinical relapses, or disability worsening.

Exhibit 3: The Current Cleveland Clinic General Approach²



Interferon-beta (IFN β) was the first DMT approved for MS. Interferon leads to induction of a large number of genes in a sizable number of cells, including immune cells, inhibition of lymphocyte proliferation, immunomodulatory effects, altered cytokine production, decreased major histocompatibility complex (MHC) expression and decreased inflammatory cell migration across the blood-brain barrier. Early MRI activity occurring on IFN β predicts poor long-term outcome.³ Thus, if patients are having breakthrough disease (new MRI findings or clinical relapse) while on IFN β , therapy should be

changed. Because of adverse effects and lower efficacy compared to other agents, IFN β is not frequently being used as initial therapy.

Glatiramer acetate (Copaxone[®], generic) competitively binds to MHC on antigen-presenting cells in preference to myelin protein antigens, leading to T-cell suppression in both the periphery and CNS and expression of neurotrophic factors by glatiramer-specific T-cells. This is one of the safest DMTs, is pregnancy category B, and is available as a generic. Switching from a brand name to generic glatiramer acetate is treated as a change in therapy in some

Exhibit 4: Comparison of MS Treatments

Drug	Potency	Safety	Tolerability	Ease
IFNβ's	+	+++	++	++
GA	+	+++	+++	+++
Teriflunomide	+	++	+++	++
Fingolimod	++	++	+++	+
DMF	++	++	++	++
Mitoxantrone	++	+	++	+
Natalizumab	+++	+ or +++	+++	++
Alemtuzumab	+++	+	+++	+
Daclizumab	++	++	++	++
Ocrelizumab*	+++	++	+++	+++

Subjective ratings: + = low (worst), ++ = moderate, +++ = high (best)
 *Only one approved for primary progressive MS

practices, so monitoring is increased somewhat.

Interferon and glatiramer have good safety and extensive track records. These two agents have modest efficacy and many patients breakthrough treatment; but other patients do well on them. MRI lesion activity at six to 12 months after starting IFNβ predicts an inadequate treatment response long term. Selected patients benefit from switching between classes, but most clinicians do not favor switching among IFNβs. In most cases, clinicians should consider moving to a more potent agent when NEDA is not achieved on either agent. Patients dislike the frequent injections and bothersome side effects of both interferon and glatiramer.

Most clinicians do not routinely advise RRMS patients with effective disease control on IFNβ or glatiramer and good tolerability to change therapy. Both are sometimes used as initial therapy for RRMS patients. However, with postmarketing studies and use in clinical experience generally supporting better efficacy and good safety, routine use of newer agents is increasing. The newer agents are also more convenient for patients to use.

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. This is a novel mechanism of action. It reduces relapses by approximately 50 percent and provides significant benefit on MRI lesion activity and brain atrophy in the convenience

of a once daily tablet.⁴⁻⁶ This agent has to be initiated with six hours of monitoring due to potential for bradycardia and atrioventricular block. Other adverse effects of concern are macular edema and hypertension. Currently, this is the most common used DMT.

Dimethyl fumarate (Tecfidera®), a twice a day oral agent, activates the nuclear-factor E2-related factor-2 (Nrf2) transcription pathway and inhibits the NFκB transcription pathway. It has immunomodulatory and cytoprotective effects. This agent results in a 50 percent reduction in proportion of relapsing patients, a 34 to 38 percent reduction in confirmed disability worsening, reduced brain lesion formation, and reduced brain volume loss.⁷⁻⁸ Gastrointestinal adverse effects, flushing, and the need for lab monitoring for lymphopenia can be hurdles to patient acceptance of this agent.

Teriflunomide (Aubagio®) is an active metabolite of leflunomide used to treat rheumatoid arthritis. It inhibits T-cell and B-cell proliferation. Teriflunomide, a once daily oral agent, produces about a 30 percent reduction in ARR, 30 percent reduction in confirmed disability progression, MRI lesion reduction, and reduction in the risk of conversion to clinically definite MS in those with clinically isolated syndrome.⁹⁻¹² This agent is fairly well tolerated.

Teriflunomide is pregnancy category X based on experience with leflunomide and thus should be avoided in women of childbearing age. Slow elimination from the body is an issue in the case of an

unplanned pregnancy; it takes an average of eight months to reach a low plasma concentration. Elimination can be accelerated by administration of cholestyramine (8 g q8h) or activated charcoal (50 g q12h) for 11 days.

Natalizumab (Tysabri®) is an integrin $\alpha 4$ blocker that stops circulating lymphocytes from entering the CNS. Given as a monthly infusion, it provides effective relapse suppression (68% vs. placebo) and is the most effective agent for RRMS. Natalizumab is very well tolerated but does cause a rare serious adverse effect, progressive multifocal leukoencephalopathy (PML). This happens in 4.11 patients out of 1,000 treated with natalizumab. This potentially fatal 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. 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.¹³⁻¹⁴ Patients with prior immunosuppression are also at risk for PML from natalizumab. Risk of PML can be assessed with JC virus testing, which should occur prior to and during use. Those who are JCV positive can still receive natalizumab if there has been no prior immunosuppressive therapy. In the case of a JCV positive patient, use should be restricted to one to two years. Unique to natalizumab is a major rebound in disease activity with drug discontinuation.

Alemtuzumab (Lemtrada®) is a humanized monoclonal antibody (mAb) that targets the CD52 antigen, an anonymous surface protein expressed by T cells, B cells, monocytes, and eosinophils. It is given as five daily infusions and then given as three daily infusions one year later. It produces rapid, profound, and prolonged lymphocyte depletion with a gradual reconstitution with altered cell profile and function; it is like rebooting the immune system. It was previously approved for chronic lymphocytic leukemia and was approved for MS in 2014.

Alemtuzumab significantly reduces the annualized relapse rate (ARR) by 55 percent compared with IFN β -1a (ARR 0.18 vs. 0.39).¹⁵ It also reduces MRI lesions and brain atrophy compared with IFN β -1a. Alemtuzumab treatment results in a higher rate of relapse-free patients (78% vs 59%) and a higher rate of NEDA (39% vs 27%). Other trials have found similar benefits over interferon.¹⁶⁻¹⁷

Advantages are its potent efficacy and convenience of annual administration. A significant effect on brain atrophy and even a reduction of disability have been reported with this agent. The disadvantages include safety concerns related to development of new autoimmune conditions, a complicated start-up

process, and required monitoring for five years after completing treatment. Patients have to be premedicated with several medications to prevent infusion reactions before each infusion and have to take acyclovir for two years after receiving to prevent herpes infection. The principal indication for alemtuzumab is for patients with active RRMS who have failed other therapies.

Daclizumab (Zinbryta®) is a humanized mAb against the interleukin two receptor (IL-2Ra) which blocks IL-2 binding and signaling. This inhibits T-cell and B-cell activation by IL-2 and leads to expansion of CD56bright regulatory natural killer cells. It was approved for prevention of renal allograft rejection by the FDA (1997). It was approved for MS in 2016, is the first humanized mAb, and is the first mAb targeting a cytokine receptor. It decreases ARR by 50 to 54 percent, reduces MRI disease activity, and decreases disability worsening.^{18,19} Adverse effects of daclizumab include cutaneous events [pruritus, rash, dermatitis (eczema, atopic, allergic, seborrheic, exfoliative), acne, erythema nodosum, angioedema], increased infections, and increased liver function tests (usually mild). Because neurologists are not accustomed to managing the potential skin complications, the clinical use of daclizumab is limited.

Ocrelizumab (Ocrevus®) is the first agent to be FDA approved for primary/progressive MS. It is an anti-CD20 mAb that selectively depletes B cells via antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. This agent is similar to rituximab (Rituxan®), which has frequently been used off-label for MS treatment. Ocrelizumab is humanized instead of chimeric and has a different, though overlapping, antigen site. Ocrelizumab has more potent effect on ADCC and apoptosis, and less potent on CDC compared with rituximab.

Ocrelizumab is given as an every six month infusion. In PPMS, ocrelizumab was associated with lower rates of clinical and MRI progression than placebo.²⁰ The percentage of patients with 24-week confirmed disability progression was 29.6 percent with ocrelizumab versus 35.7 percent with placebo. Although not approved for RRMS, this agent results in a 46 to 47 percent reduction in ARR and a 40 reduction in disability progression when compared to interferon.²¹ The primary adverse effects are infusion reactions and oral herpes infection. Patients have to be premedicated with diphenhydramine and methylprednisolone to prevent infusion reactions. Exhibit 4 compares all the FDA approved DMTs based on potency, safety, tolerability, and ease of use.

Uncertainties in treating MS are numerous.

Knowledge on how best to use the available agents is continually evolving. The newest therapies (alemtuzumab, daclizumab, ocrelizumab) will have to be integrated with current therapies. The utility of “induction” therapy using the most potent efficacy agents and combination therapy is being explored. Restrictions imposed by insurance coverage, including the impact of generics, is another treatment uncertainty.

Conclusion

MS is unpredictable, but clinicians are learning to use available tools to control the disease. Overall, IFN and glatiramer acetate are safe but cause common, non-life-threatening adverse effects, have to be administered by frequent injection, and have modest efficacy.

The mAbs and oral agents are convenient, generally well tolerated, and have more potent efficacy. They cause rare, but potentially severe, adverse effects. The lack of biomarkers to monitor or predict efficacy is a major issue and all are expensive.

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Optimizing Outcomes in Advanced Non-Small Cell Lung Cancer: Integrating Novel Personalized Therapy into the Treatment Paradigm

Joel W. Neal, MD, PhD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

The treatment of advanced non-small cell lung cancer (NSCLC) continues to evolve rapidly with the development of immunotherapy, which turns on the body's own defenses to eliminate cancer. Additionally, the discovery of genetic mutations driving tumor growth and the subsequent development of therapy targeted at these growth factors is leading to improved survival.

Key Points

- In advanced NSCLC, therapy is selected based on histology and genetic biomarkers.
- Platinum-based doublet chemotherapy is the treatment of choice for the majority of cases.
- Pemetrexed is effective in nonsquamous disease and necitumumab is effective in squamous disease.
- Targeting angiogenesis improves survival in first and second-line treatment in nonsquamous disease.
- Immunotherapy is clearly effective in the second-line setting and is quickly moving into first-line therapy for selected patients.
- Molecularly targeted therapies offer longer time to progression in the first-line setting than conventional chemotherapy in those with selected genetic mutations.

LUNG CANCER IS THE LEADING CAUSE OF cancer-related mortality in the United States (U.S.). It accounts for more deaths than breast, prostate and colorectal cancers combined. Histologically and molecularly lung cancer is a very heterogeneous disease and includes non-small cell lung cancer (NSCLC) and small cell disease. Smoking remains the major risk factor for developing lung cancer; however, 25,000 to 30,000 never smoking Americans will develop lung cancer each year. Typically, this is a disease of aging, with the age of 70 being the median age of diagnosis.

Unfortunately, many patients with lung cancer have an unfavorable stage at the time of diagnosis. In NSCLC, 60 percent of patients already have advanced metastatic disease when diagnosed. Screen-

ing in active smokers or in those with significant smoking history with low-dose computed tomography (LDCT) is helpful in identifying disease earlier. There are some hurdles, especially in the Medicare population, in getting payment approval. Screening with LDCT reduces the risk of cancer by about 20 percent compared with chest x-ray based screening, but this screening is not for the general population.

NSCLC is treated with surgery, radiation, chemotherapy, and targeted therapies. Advanced disease is primarily treated with chemotherapy, targeted therapy, and immunotherapy. Over the past two decades, there have been major paradigm shifts in advanced NSCLC management. These shifts have included the recognition of the importance of histology in selecting therapy, addition of maintenance

Exhibit 1: Identification of Immune-Related AEs

Organ System	Signs/symptoms
Lung	Pneumonitis
Gastrointestinal	Diarrhea, colitis
Liver	Elevation in liver function tests <ul style="list-style-type: none"> • AST >2.5 x ULN • ALT >2.5 x ULN • Total bilirubin >1.5 x ULN
Skin	Pruritis, rash
Neurologic	Motor and sensory neuropathy <ul style="list-style-type: none"> • Unilateral and bilateral weakness • Sensory alterations • Paresthesia
Endocrine	Fatigue, headache, changes in mental status, abdominal pain, unusual bowel habits, hypotension, abnormal thyroid function tests and/or serum chemistry values (endocrinopathies)
Hematologic	Hemolytic anemia, thrombocytopenia
Cardiovascular	Myocarditis, pericarditis, vasculitis
Ocular	Blepharitis, conjunctivitis, iritis, uveitis
Renal	Nephritis

ALT = alanine aminotransferase
 AST = aspartate aminotransferase
 ULN = upper limit of normal

and second-line chemotherapy, introduction of anti-angiogenic therapy, emergence of immunotherapy, and discovery and targeting of oncogenic driver mutations. Therapy is now divided into histology-targeted and genotype-directed therapy.

Before any treatment decisions are made, the histology of the tumor must be determined. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the types of NSCLC. The histologic type determines whether molecular genetic testing is done and is used in selecting therapy.

In patients with squamous cell disease, platinum-based doublet chemotherapy is used. The platinum component will be either carboplatin or cisplatin. Carboplatin tends to be used most commonly because it has less effect on quality of life. The platinum agent will be combined with paclitaxel, gemcitabine, docetaxel, or nanoparticle albumin-bound (nab) paclitaxel.^{1,2} The nab paclitaxel can be given much quicker than paclitaxel and does not require premedication because it does not cause infusion reactions. In patients with nonsquamous NSCLC without genetic mutations, pemetrexed is an effective option for adding to platinum-based regimens.³ Twenty years ago

the main treatment decision for advanced NSCLC would be whether to start chemotherapy or palliative/supportive care. There are now multiple lines of chemotherapy that can be given. Choice of therapy for subsequent lines of therapy will depend on what the patient has received previously.

Before the development of maintenance regimens, several cycles of chemotherapy were given and then the patient was monitored for recurrence. Continuation of maintenance therapy, rather than stopping therapy, may be used depending on patient tolerance and tumor response. Maintenance aims to continue tumor suppression. Continuation of maintenance therapy with pemetrexed is the standard of care in nonsquamous NSCLC.⁴

Overall for NSCLC, cytotoxic chemotherapy is still the standard of care for about 70 percent of cases. It improves survival and palliates symptoms in first line, maintenance, and subsequent treatment settings.

In order for a tumor to grow beyond about one centimeter in size, it must have a blood supply. Angiogenesis is the process of developing a blood supply and is a function of multiple signals from multiple cell types. One signal is vascular endothelial growth

Exhibit 2: First-line Molecular Testing¹²

Who to test	All patients with advanced-stage lung adenocarcinoma or tumors with an adenocarcinoma component
What to test for	EGFR DNA mutation and ALK (IHC or FISH), or more
When to test	At the time of diagnosis (not just when treatment decision needed)
What specimen	Core needle biopsy (or multi-pass FNA), cytology cell block, surgical biopsy (bone biopsy problematic)
How to test	Concurrently (not sequentially test-by-test)
How long a turnaround time is acceptable	5 - 10 working days with ≤ 3 days transport time
When to re-biopsy	After a targeted therapy intervention (to assess for tumor evolution in the molecular profile)

factor (VEGF), which is targeted by bevacizumab. Bevacizumab improves survival in nonsquamous NSCLC but worsens survival in squamous disease because of pulmonary bleeding.⁵⁻⁷ It is given along with the platinum-doublet chemotherapy.

Necitumumab, another anti-angiogenesis agent which targets epidermal growth factor receptor (EGFR), is first-line therapy for chemo-naïve patients with advanced squamous NSCLC in combination with a platinum doublet.⁸ Addition of this agent to chemotherapy leads to about a 1.5-month median increase in overall survival (OS); the benefit in survival must be weighed against the cost of this agent before selecting this option.

Addition of ramucirumab, another VEGF agent, to chemotherapy also provides a 1.5-month improvement in median OS.⁹ Because it has more toxicities than some other agents, it is only appropriate for carefully selected patients. Overall, targeting angiogenesis in NSCLC improves survival in first- and second-line treatment.

Emergence of immunotherapy is one of the most exciting developments in the treatment of NSCLC. There may be cancers that develop in everyone that are not seen clinically because the immune system eliminates them. Immunotherapy for cancer is an attempt to get around tumor defenses to allow the innate immune system to kill cancer cells. One of the tumor defenses is a cell surface protein programmed death ligand 1 (PD-L1), which is like a shield on the tumor cell preventing recognition by the immune system. Approximately 30 percent of NSCLC tumors express PD-L1. Inhibiting interaction of the ligand with programmed death 1 (PD-1)

can restore antitumor T-cell activity, leading to an immune-mediated response. PD-1/PD-L1 antagonists are active in a wide variety of cancers but are currently only approved in a few cancers (melanoma, renal, Hodgkin's lymphoma, and NSCLC). There are three approved immunotherapies. Nivolumab and pembrolizumab bind PD-1 receptors on T cells and disrupt negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function. Atezolizumab binds PD-L1 receptors. Nivolumab, pembrolizumab, and atezolizumab are approved in second-line NSCLC. Nivolumab improved median OS by three months.¹⁰ Pembrolizumab is better than docetaxel chemotherapy in the first-line setting in those who have tumors that express PD-L1 greater than 50 percent.¹¹ The benefits of immunotherapy have pushed docetaxel to third-line therapy.

There are some long-term survivors (5 years) with immunotherapy. Tumors that do not have a lot of mutations seem to be less responsive to immunotherapy.

The toxicities of immunotherapy are very different from those seen with chemotherapy. Essentially this therapy is taking the brakes off the immune system, so the adverse effects are from an overactive immune system. The immune adverse effects can occur within hours of administration out to three months later (Exhibit 1). The average is six to 12 weeks after initiation of therapy. Patient complaints should be considered autoimmune and drug-related until proven otherwise because early recognition, evaluation, and treatment are critical due to the fact the adverse effects can be fatal. Primary management is corticosteroids and sometimes anti-tumor necrosis alpha medications. Grade 3 or 4 toxicities

Exhibit 3: Selected "Other" Mutations in NSCLC

Oncogene	Prevalence %	Available drugs with potential benefit**	Therapeutic pathways being targeted
KRAS mutations	25 - 30	Selumetinib, trametinib, cobimetinib	KRAS G12C inhibitors, MEK and PI3K inhibitors, JAK/TBK1/KK inhibitors
ROS1 rearrangements	1 - 3	Crizotinib** , ceritinib	ROS inhibitors, Hsp90 inhibitors
HER2 mutations	1 - 3	afatinib, trastuzumab, T-DM1	HER2 inhibitors, Hsp90 inhibitors
BRAF mutations	1 - 3	Vemurafenib, dabrafenib , selumetinib, trametinib	BRAF inhibitors, MEK inhibitors
RET rearrangements	1	Cabozantinib , vandetinib	RET inhibitors, Hsp90 inhibitors
MET amplification	1	Crizotinib , cabozantinib	Met inhibitors
MET exon 14 mutation	3	Crizotinib , cabozantinib	Met inhibitors
NTRK rearrangements	< 1	Crizotinib	TRK inhibitors

Evidence level: Bold typeface = Strong clinical evidence; Standard typeface = weak clinical evidence
 ** FDA approved

occur in less than 5 percent of those given immunotherapy.

Overall, immunotherapy is clearly effective in the second-line setting and is quickly moving into first-line therapy for selected patients. PD-L1 immunohistochemistry (IHC) testing is available and can be helpful clinically to estimate probability of response and to select the therapy. Education at all provider levels about the nature of immune-related adverse events is necessary to ensure safe use.

It is now known that NSCLC tumors have numerous genetic mutations. Tumor testing guidelines are given in Exhibit 2.¹² Testing and treating with the appropriate targeted therapy is important; the presence of EGFR mutations and anaplastic lymphoma kinase (ALK) rearrangement changes the choice of first-line therapy. Additionally, patients with an oncogenic driver mutation who receive targeted therapy live longer than those with the mutations who do not receive targeted therapy and the ones without the mutations.¹³

EGFR mutations occur in 15 percent of NSCLC cases and are most common in those with adenocarcinoma, female gender, never smokers, and Asian.¹⁴ In NSCLC with nonsquamous cell histology and with an EGFR-sensitizing mutation, first-line therapy is a tyrosine kinase inhibitor (TKI, erlotinib, afatinib, or gefitinib). Afatinib appears more effective but causes more diarrhea, stomatitis, and paronychia.

Second-line therapy, after progression on first-line TKI, includes combination chemotherapy, a switch to another EGFR TKI, or possibly immunotherapy.

Tumors evolve and have incredible genetic diversity within a given tumor. EGFR T790M is an acquired resistance mutation to EGFR TKI found in over 50 percent of patients with acquired resistance.¹⁵ Osimertinib is a third-generation EGFR TKI which is effective against tumors with the T790M mutation; a 61 percent response rate was seen in one trial.¹⁶

Four percent of NSCLC cases will have an ALK rearrangement. First-line treatment options for ALK-positive NSCLC are crizotinib and alectinib.^{17,18} Second-line treatment options for ALK-positive disease includes ceritinib and alectinib, if not used in the first line. Alectinib, a highly potent, selective ALK inhibitor, results in a significant reduction in metastatic brain tumors, which can be a particularly difficult area of metastases to treat.¹⁷

There are many other mutations which have been identified in NSCLC (Exhibit 3). There are not currently any FDA approved therapies, except for ROS rearrangement, but there are trials ongoing for most of these.

Overall, molecular genotyping is now the standard in advanced NSCLC with adenocarcinoma histology. A multidisciplinary approach is required to assure that adequate biopsy tissue for molecular testing is available. Selected molecular biomarkers (EGFR,

ALK, ROS1, others), in addition to histology, drive therapeutic choices. Other targetable drivers may also respond to “off label” use of available targeted therapies, which is reasonable following chemotherapy failure. Re-biopsy should be considered routinely after progression on targeted agents, and drugs to overcome initial resistance are available.

Conclusion

The treatment of advanced NSCLC continues to evolve toward personalized medicine. Histology and genetic biomarkers are used to select therapy. Immunotherapy is now a reality in the treatment of advanced NSCLC and is clearly effective in the second-line setting. It is quickly moving into first-line therapy for selected patients.

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Optimal Anticoagulation Strategies for Stroke Prevention in Atrial Fibrillation

R. Scott Wright, MD.

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Preventing stroke in patients with atrial fibrillation (AF) typically requires anticoagulation. In those with nonvalvular AF, the direct oral anticoagulants (DOACs) are becoming the treatment of choice over warfarin. In selecting among the available DOACs, several factors including patient comorbidities and clinical data on the agents can be used.

Key Points

- DOACs cause a lower rate of bleeding and higher efficacy in terms of stroke prevention.
- Depending on the patient situation, one DOAC may be preferred over another.
- Medication adherence with anticoagulation is a large problem.
- Anticoagulation clinics can improve adherence and outcomes.
- Overall costs of DOACs and warfarin are similar.

ATRIAL FIBRILLATION (AF) AFFECTS A LARGE percentage of the population, particularly the elderly. Approximately six million Americans have AF. Only 0.1 percent of those less than 50 years old have AF, whereas 10 percent of those greater than 80 years old have the condition.

Stroke and systemic emboli are the major complications of AF which should be prevented. Of those with AF, 72 to 95 percent should be anticoagulated to prevent stroke according to risk scales (CHADS₂, CHA₂DS₂-VASc).^{1,2} By the CHADS₂ scale, someone with AF alone and no other risk factors has a 1.9 percent annual stroke risk compared with an 18.2 percent risk for someone who scores 6, the highest score. CHA₂DS₂-VASc is a modification to the CHADS₂ scale which gives an extra point to those over 75 and includes points for vascular disease and for being female (Exhibit 1).² With a 1 point score, the stroke risk is less than 1 percent and 8.5 percent per year with a score of 4. CHA₂D₂-VASc is the preferred risk scoring tool.

There are two major guidelines for stroke prophylaxis in AF. This article addresses stroke prophylaxis in nonvalvular AF; the reader should consult the guidelines for managing risk in other types of AF.^{3,4} The 2012 European Society of Cardiology guidelines recommend anticoagulation (AC) for all nonvalvular AF patients except those with low risk (age <65 and lone AF in both men and women) or with contraindications.³ If the patient has greater than or equal to 2 points/risk factors, these guidelines recommend AC therapy with direct oral anticoagulants (DOACs) rather than adjusted-dose warfarin; antiplatelet therapy is recommended only if the patient refuses AC.

The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guideline recommendations are similar.⁴ For patients with AF and a CHA₂DS₂-VASc score of zero, the guidelines state it is reasonable not to AC. Anticoagulation can be considered in those with a score of 1 and is recommended for

Exhibit 1: CHA₂DS₂-VASc²

Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (MI, PVD or AAA)	1
Age 65 - 74 years	1
Female gender	1

LV = left ventricular
TIA = transient ischemic attack
TE = thromboembolism
MI = myocardial infarction
PVD = peripheral vascular disease
AAA = abdominal aortic aneurysm

a score of 2 or more. Warfarin, dose adjusted for international normalized ration (INR) 2.0 to 3.00, or a DOAC are the options.

The DOACs have gained significant market share in AF treatment. Fifty percent or more of patients with new onset AF are started on a DOAC. In AF patients who had chronically been on warfarin, about 25 percent get transitioned to a DOAC. Most patients do not like having to have frequent blood checks with warfarin. Introduction of DOACs in routine practice has been associated with improved rates of overall AC use for AF from 52.4 percent to 60.7 percent, but significant gaps remain.⁵

The DOACs target either factor Xa or IIa (Exhibit 2). There are some differences in the DOACs which can impact treatment selection. These agents are all eliminated from the body by the kidneys. Dabigatran is solely eliminated by the kidneys, but the others have some hepatic and, in the case of apixaban, enteric elimination.

In terms of ischemic stroke prevention efficacy, dabigatran has been shown to be superior to warfarin (0.9% versus 1.2%), whereas the other agents were noninferior in the published studies.⁶⁻⁹ Dabigatran offers an efficacy advantage for patients at elevated risk for ischemic stroke, but the absolute differences in efficacy between agents are modest.

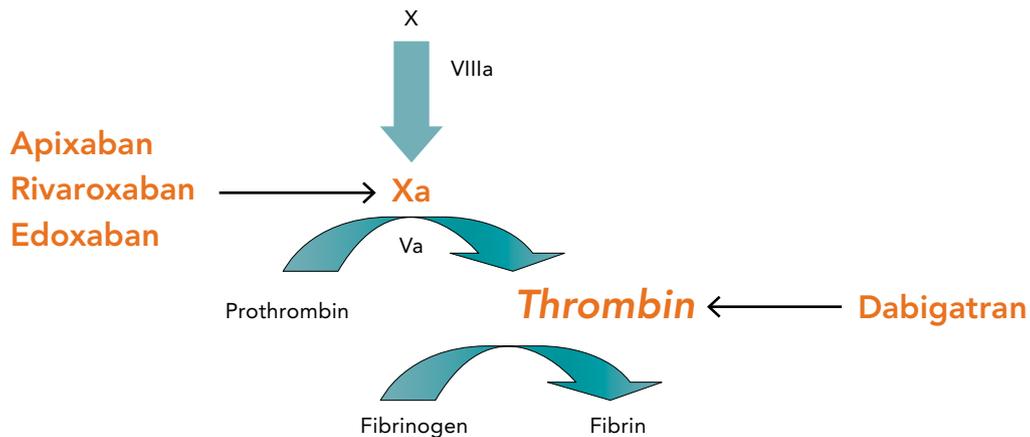
In addition to emboli causing a stroke, systemic embolism can occur secondary to AF. Ninety per-

cent of emboli from AF cause an ischemic stroke and 10 percent are systemic emboli.¹⁰ Hydrodynamic, anatomic, and physical factors play into where an emboli ends up. Anatomy and inertia cause a linear projection into the common carotid arteries. Larger thrombi sufficient to occlude iliac (1 cm), femoral (0.9 cm) or popliteal (0.8 cm) arteries pass by the carotid orifice merely as a function of size. Independent predictors of systemic emboli in AF are age greater than 75, severe left atrial enlargement, and high CHADS₂ score. Rivaroxaban is the only DOAC to offer a statistical efficacy advantage for patients at risk for recurrent systemic embolism.⁶⁻⁹

Bleeding is the adverse effect of AC that concerns patients and clinicians the most. For major bleeding, edoxaban and apixaban have been shown to cause statistically significant lower rates than warfarin.⁶⁻⁹ Rivaroxaban causes a slightly higher rate of intracranial hemorrhage (ICH) than the other DOAC, similar to the rate seen with warfarin.⁷

A patient history of falls is the most common reason cited for withholding anticoagulants in AF. Unfortunately, elderly patients are frequently at highest risk for thromboembolism from AF. In one trial, major bleeding rates with AC did not differ when comparing those with high versus low fall risk.¹¹ Overall there were 0.6 fall-related bleeds per 100 patient years. There were actually more fall-related bleeds and ICH in the low risk group. Most bleeds

Exhibit 2 : Direct Oral Anticoagulants



seen in this trial were from the gastrointestinal tract.

In a United States national registry of AF patients, different findings were seen. In the registry, patients with a high fall risk were two times more likely to fall, two times more likely to suffer a fracture, and had threefold higher ICH rates than those with lower risk.¹² Warfarin therapy did not impact ICH rates; those with high fall risk were seven times more likely to suffer ischemic stroke compared to ICH. Overall, patients with AF taking AC would have to fall 295 times a year before the risk of ICH outweighs the benefit of stroke prevention. Both apixaban and edoxaban offer superior bleeding rates compared to warfarin therapy and should be selected in those with fall risk.

In patients with a history of previous gastrointestinal (GI) bleed, low-dose edoxaban (30 mg) would be the best choice of a DOAC.⁹ Dabigatran, which is activated by colonic esterases, should be avoided in patients who have polyps which need to be removed. If a patient has a GI bleed from AC, therapy should be restarted once the bleed is resolved. Patients who have had an AC-induced GI bleed do have an increased risk of rebleeding, but the reduced risk of stroke and death outweighs the bleeding risk.¹³ Exhibit 3 provides AC options for various patient situations.

Clinicians will frequently consider switching patients from warfarin to a DOAC. Warfarin therapy comes with some well-known challenges, which is why many clinicians have moved away from its use. Frequent prothrombin time monitoring, drug interactions, and food interactions are just some of the issues. Providers and patients can develop exhaustion in dealing with the struggles.

Patients who are currently stable on warfarin therapy can remain on warfarin. Those with stable in therapeutic range INRs and no bleeding episodes

have a very low risk of stroke and bleeding. In the clinical trials comparing warfarin to the DOACs, patients were only in therapeutic range with warfarin 55 to 68 percent of the time.⁶⁻⁹ In clinical practice, with good monitoring, patients can stay within the therapeutic range.

In the clinical trials, the discontinuation rates were about the same with DOACs and warfarin (~35%).⁶⁻⁹ Real-world adherence with the DOACs is slightly better (57.1% vs 56.2%) than with warfarin, but it is still not very good.¹⁴

Adherence with AC can be improved with referral to an anticoagulation clinic. Anticoagulation clinic management has been shown to improve time in therapeutic range with warfarin, lower major bleeding rates, lower thromboembolism rates, and lower emergency department visits. If a clinic is not available, routine INR monitoring can identify poor adherence with warfarin and be used to encourage better adherence. Home INR monitors are very useful for improving adherence. Unfortunately, there is not a laboratory test for checking DOAC adherence comparable to the INR. For some patients the multiple daily dosing of the DOACs can be difficult to adhere with and warfarin, which is dosed once daily, would be the preferred option.

If a patient is noncompliant with warfarin, simply changing to a DOAC does not solve the problem. Careful follow up of patients receiving DOACs is required to improve compliance. The guidelines suggest that patients should be seen one month post AC initiation and then every three months.⁴

In terms of cost effectiveness, actual costs associated with warfarin and the DOACs are similar.¹⁵ DOACs have higher acquisition costs, but warfarin has substantially higher monitoring and therapy ad-

Exhibit 3: Choice of DOAC

Clinical Situation	First Choice	Second Choice	Avoid
High thromboembolic and low bleeding risk	dabigatran 150	apixaban, edoxaban 60, rivaroxaban, warfarin	edoxaban 30
Low thromboembolic and high bleeding risk	edoxaban 30 apixaban	edoxaban 60	warfarin, rivaroxaban, dabigatran 150
High-moderate thromboembolic and bleeding risk	apixaban edoxaban 60	dabigatran 150, warfarin, rivaroxaban	edoxaban 30
≥ 70 - 80 years or frail	apixaban	rivaroxaban, warfarin, edoxaban 60, 30	dabigatran 150
Compliance concerns	edoxaban 60 rivaroxaban	edoxaban 30 warfarin	apixaban dabigatran
CrCl 30 - 50 ml/min	apixaban warfarin	rivaroxaban 15 edoxaban 30	dabigatran 150 edoxaban 60
CrCl < 30 ml/min	warfarin	apixaban	dabigatran, edoxaban, rivaroxaban
Nasogastric tube - crushed form	apixaban, rivaroxaban, warfarin	edoxaban ???	dabigatran

justment costs. All are associated with bleeding, but the DOACs have lower rates than warfarin, which improves their cost effectiveness.

Conclusion

Anticoagulation of those with AF has been under-utilized in the past because of real or perceived issues with warfarin. Anticoagulation should be prescribed for those patients with AF at significant stroke risk. The newer anticoagulants are the most appropriate choice in many cases and are cost effective.

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Psoriasis: Shaping the Future through Advanced Therapeutic Strategies: The Payer's Perspective

Gary M. Owens, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Biologic and nonbiologic agents have revolutionized treatment for moderate to severe psoriasis, but these agents have high annual costs. Managed care payers are implementing different strategies to contain these costs. They will continue to be challenged as more new therapies reach the market.

Key Points

- Moderate to severe psoriasis requires more aggressive treatment than mild to moderate disease.
- Managed care uses many strategies to control costs for psoriasis treatment.
- Additional biologics are on the horizon.

PSORIASIS IS THE MOST COMMON AUTO-immune disease in the United States (U.S.), affecting 7.5 million people.¹ Although there are different types, plaque psoriasis represents about 80 to 90 percent of the cases (Exhibit 1). Two-thirds of patients with plaque psoriasis have mild to moderate disease and one-third have a more severe presentation. In a patient survey, 46 percent thought that the treatments were worse than the disease and 85 percent stated there was a need for better therapies.² Thus, there is significant unmet need in psoriasis treatment.

Psoriasis can present at virtually any age, but the most common age groups for development are 20 to 30 and 50 to 60 years. There is a genetic component to developing psoriasis. About 14 percent of those with one parent affected will have the disease and 41 percent with both parents affected. Plaque psoriasis is driven by inflammation and altered keratinocyte differentiation.

Plaque psoriasis can usually be diagnosed by physical exam of the skin, nails, and scalp. Rarely, a skin biopsy is needed. The differential diagnosis includes

lichen planus, pityriasis rosea, tinea corporis, and seborrheic dermatitis. Labs and other diagnostics are usually not required except as a prerequisite to biologic or immunosuppressive treatment.

Psoriasis is not just a skin disease, but is a systemic inflammatory disease. Because of its inflammatory state, psoriasis patients are more likely to have associated comorbidities, including cardiovascular disease, psoriatic arthritis, depression, obesity, diabetes, hypertension, and cancer. Someone with psoriasis is 58 percent more likely to have a major cardiac event and 43 percent more likely to have a cerebrovascular vascular accident.³

Goals of therapy include rapid initial disease control, maintenance of long-term remission, avoidance of adverse effects as much as possible, and improvement of the patient's quality of life. One of the challenges in managing psoriasis is that patients present with a broad spectrum of symptoms and severity. In general, psoriasis can be classified as mild (3% or less of skin surface area affected), moderate (3-10%), and severe (more than 10%). A variety of

Exhibit 1: Psoriasis Types

Types of Psoriasis

Scalp:

- Affects the scalp (other parts of the body may or may not be affected)
- Affects 50% of people with psoriasis

Inverse:

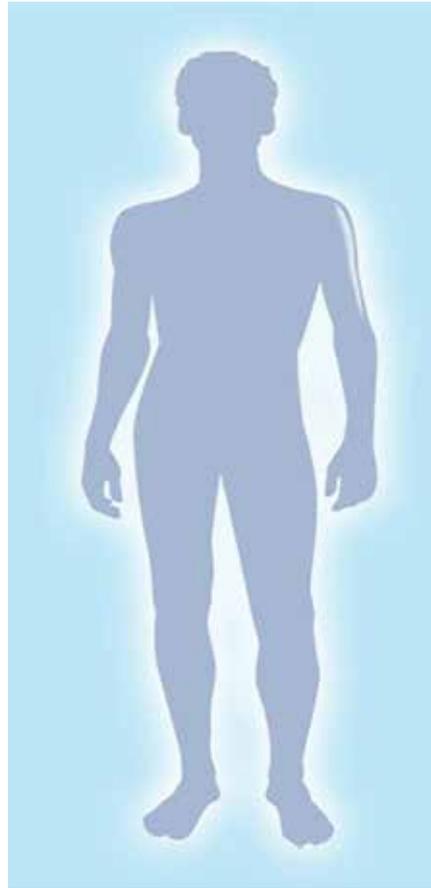
- Affects under the breast, groin, armpits i.e. where the skin folds
- Smooth, dry and well-defined salmon-colored patches
- Not known how many people it affects

Erythrodermic:

- Affects entire body surface
- Involves whole body surface, which scales and itches
- Affects 1 - 2% of people with psoriasis

Nails:

- Affects fingernails, toenails
- Nails may become pitted, discolored, thickened and loose
- Affects 10 - 50% of people with psoriasis



Gluttate:

- Affects trunk/torso, face
- Not as red or scaly as plaque psoriasis and looks like "droplets" on the skin
- Affects up to 18% of people with psoriasis

Pustular:

- Affects beneath the thumb and fingers on the palm, soles of feet
- Large fluid-filled blister-like areas (pustuloses) that can appear in specific places on the body or in a generalized form
- Affects less than 2% of people with psoriasis

Plaque:

- Affects knees, elbows, lower back, ears, scalp
- Red plaques surrounded by white silvery scales, which can be itchy and sore
- Affects 80 - 90% of people with psoriasis

treatment options are available and must be tailored to the needs of the patient.

A stepwise progression of treatments was used in the past to manage psoriasis. Patients had to fail the prior step of therapy before moving on to more aggressive therapy. Therapy has moved to severity-based treatment that starts with more aggressive treatment for more severe disease, with the goal of attaining disease control quickly.⁴

Several new agents for psoriasis have been approved in recent years. Apremilast (Otezla[®]), a phosphodiesterase-4 (PDE4) inhibitor which reduces inflammation, is an oral agent FDA approved for treatment of moderate to severe plaque psoriasis and active psoriatic arthritis. Thirty-three percent of patients achieve a 75 percent reduction in the Psoriasis Area and Severity Index score (PASI-75) with this agent compared with a 5 percent response with placebo.⁵

Biologics have revolutionized the treatment of

moderate to severe plaque psoriasis. Those approved include etanercept (Enbrel[®]), adalimumab (Humira[®]), infliximab (Remicade[®]), ustekinumab (Stelara[®]), secukinumab (Cosentyx[®]), and ixekizumab (Taltz[®]). All of the biologics significantly improve the PASI-75 score in short-term trials.⁶

Etanercept, adalimumab, infliximab are all anti-tumor necrosis factor (TNF) agents and are indicated for moderate to severe plaque psoriasis. Etanercept is given as a subcutaneous injection of 50 mg twice weekly for the initial three months of therapy, followed by a 50 mg injection once weekly for maintenance therapy. Adalimumab is given as an initial subcutaneous injection of 80 mg and then 40 mg every other week, beginning one week after the initial dose. Standard dosing for infliximab for adults is an intravenous infusion of 5 mg/kg at weeks 0, 2, and 6, followed by every eight weeks thereafter.

There are some important safety considerations

Exhibit 2: Payer Challenges

Increased Utilization

- Specialty drug pipeline continues to grow
- Increase in oral specialty drugs
- New indications for existing therapies
- Use of specialty drugs earlier in disease course

Clinical Guidelines

- Lack of widely accepted guidelines, resulting in variations in care
- Lack of data demonstrating best practices in managing diseases

Outcomes Data

- Lack of data analyzing specialty drug utilization
- Lack of comparative effectiveness data assessing efficacy, costs, outcomes and safety

with the anti-TNF biologics for psoriasis. Anti-TNF therapy should not be started or continued in patients with serious active infection and should be used with caution in those at high risk of infection. All patients have to be screened for mycobacteria, human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV) infection before starting anti-TNF therapy. Prophylactic vaccination for tuberculosis and HBV in high-risk patients should be considered before initiating anti-TNF therapy. In patients with HIV, HBV, or HCV, initiate anti-TNF therapy only in those with well-controlled disease. Anti-TNF treatment should be avoided in patients with a current or previous history of malignancy, unless there is a high likelihood of cure or the malignancy was diagnosed and treated more than 10 years ago. Patients need regular screening for skin cancers while on therapy. Anti-TNF therapy must be stopped prior to women getting pregnant. Anti-TNF treatment is restarted following the end of lactation or delivery if the mother is not breastfeeding.

Ustekinumab (Stelara[®]) is an anti-IL-12 and 23 agent indicated for moderate to severe plaque psoriasis. Standard dosing for ustekinumab for adults weighing less than 100 kg is 45 mg given at weeks 0, 4, and every 12 weeks thereafter. A 90 mg dose, given in the same regimen, is recommended for adults who weigh more than 100 kg.

Secukinumab (Cosentyx[®]), an anti-IL-17A agent, is one of the two newest agents indicated for moderate to severe plaque psoriasis. It is given as an initial 300 mg dose subcutaneously at weeks 0 through 4 and then a 300 mg monthly maintenance dose is started four weeks later. In trials, it has produced superior results to etanercept and ustekinumab.⁷ A second anti-IL-17A agent, ixekizumab (Taltz[®]), was approved in early 2016 and was also shown superior to etanercept.⁸ It is given as two 80 mg subcutaneous injections initially, then 80 mg every two weeks

for 12 weeks, and then 80 mg every four weeks.

In general, specialty drug management, which includes the biologics, is posing multiple challenges to managed care (Exhibit 2).⁹ Treatment of inflammatory conditions including psoriasis is the largest category of specialty spending. According to Express Scripts, in 2015, inflammatory conditions were the most expensive specialty therapy class for the seventh year in a row.¹⁰ The per-member-per-year (PMPY) spend was \$89.10 in 2015, up 14.7 percent from 2014.

In treating psoriasis today, it is still about the right therapy for the right patient while being fiscally responsible. Management strategies to control psoriasis costs include step therapy through nonbiological immune-modifiers before biologicals, prior authorization of biological agents, preferred biological agents, limiting prescribing of biologicals to appropriate specialists, guideline-based management, and managing site of service. Other payer strategies include newer benefit designs, multiple tiers of specialty benefit, consideration of the emerging biosimilar marketplace, specialty specific formularies, and alignment of patient incentives.

Managing psoriasis medication spending will get more complicated as more agents are approved. There are numerous additional biologic agents in the pipeline for psoriasis treatment. A few examples include briakinumab, IL-12/-23 blocker; brodalumab, IL-17 blocker; AMG 827, IL-17 blocker; guselkumab, anti-IL-23p19; tildrakizumab, anti-IL-23p19; and BI655066, anti-IL-23

Conclusion

Moderate to severe psoriasis is costly to manage. To cost-effectively treat those with significant disease, treatment selection should be based on disease severity rather than forcing patients through a stepped approach. Managed care has implemented many

strategies to control costs for psoriasis treatment and will continue to be challenged as additional biologics reach the market.

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Updated Treatment Strategies in the Management of Obesity

Holly Wyatt, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

Clinicians, especially primary care physicians, need to become more involved in diagnosing obesity and setting their patients on a path to weight loss and maintenance. Although lifestyle therapy is the main intervention, medications, devices, and surgery are all options which produce effective weight loss.

Key Points

- Obesity needs to be diagnosed and treated.
- Comprehensive lifestyle therapy is the cornerstone for the management of overweight and obesity.
- Medications, devices, and surgery should be considered in some patients.

THERE IS CURRENTLY AN OBESITY EPIDEMIC in the United States (U.S.). New ways of attacking this problem are needed. In an overweight patient with weight-related disease and prediabetes, under the old paradigm for weight loss, clinicians would start metformin to prevent diabetes development and give some recommendations to lose weight. The new paradigm is to diagnose the disease of obesity and pursue aggressive weight loss. This is because of the recognition that managing weight is the key to treating chronic diseases. The numerous chronic diseases caused by excessive weight are shown in Exhibit 1.

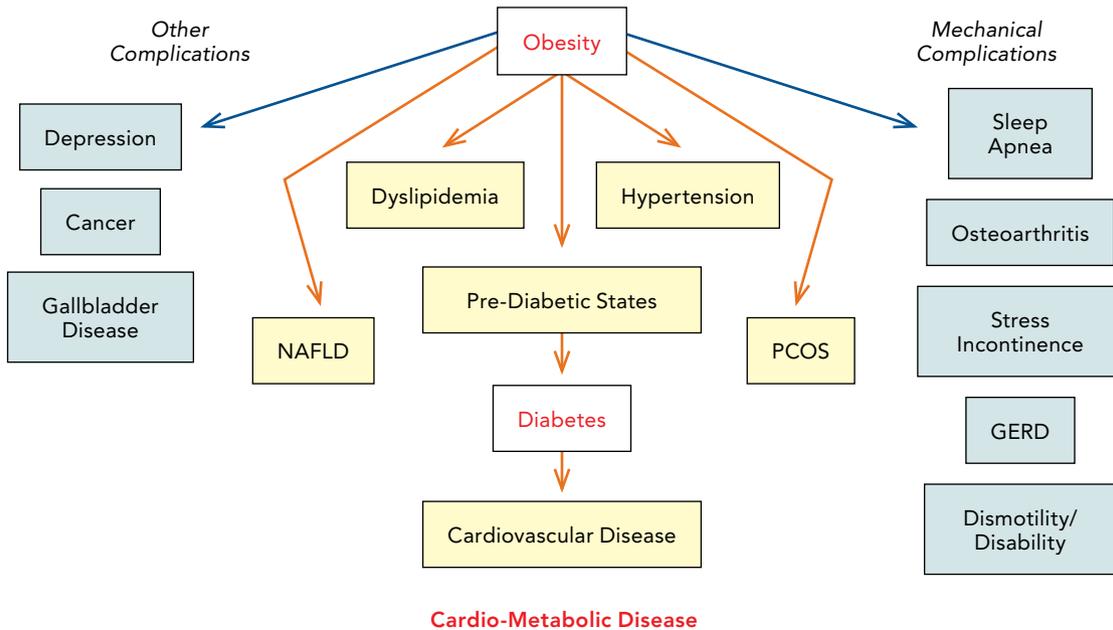
At the basic level, obesity is the result of energy intake being greater than energy expenditure in someone with a genetic propensity for the disease. There are many reasons for the obesity epidemic, including genetics and epigenetics, biology, environment, societal changes, personal responsibility, weight gaining medications, health care, economics, ecology, diet, physical inactivity, social networks, stress and emotion, and microbiota. Overall, there is not one reason why someone has obesity; therefore, there is not one solution for helping them lose weight. Both the genetic and physiologic fac-

tors and the environmental factors all have to be addressed for successful weight loss. Clinicians do not have to be obesity experts, but they need a plan for helping their overweight patients. They can identify the weight issue and refer the patient to a weight loss program or obesity specialist, or they can become educated about obesity treatment and treat the patient within their own practice.

There have been several advances in the obesity field which are leading to improvements in weight management. The American Medical Association recognized obesity as a disease in 2013, which gave legitimacy to treating it as a disease rather than a cosmetic issue. The Centers for Medicare and Medicaid Services (CMS) now reimburse primary care providers for intensive behavioral therapy for obesity. Four new medications have been approved by the FDA since 2012, and multiple new practice guidelines promote weight management as a path to chronic disease management. Additionally, another treatment option of endoscopic bariatric devices was approved by the FDA in 2015 and 2016. All of these advances have brought obesity and its management to the forefront.

Weight loss guidelines have been published by

Exhibit 1: Complications of Obesity



NAFLD = nonalcoholic fatty liver disease
 PCOS = polycystic ovary syndrome
 GERD = gastroesophageal reflux disease

the American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS), the American Association of Clinical Endocrinologists (AACE), the Obesity Medicine Association (OMA), the Endocrine Society, and the Society of Behavioral Medicine.¹⁻⁶ The AHA/ACC/TOS guidelines focus on lifestyle intervention with guidance on referral for surgery. The AACE guidelines provide a framework for diagnosis and an algorithm based on assessment of disease severity. A comprehensive and holistic approach is advocated by the OMA guidelines. The Endocrine Society guidelines are especially helpful in making pharmacological interventions. Lastly, the Society of Behavioral Medicine guidelines provide specific recommendations for using the 5A's (Ask, Assess, Advise, Agree, and Assist) in practice. The 5A's model, originally designed as a behavioral intervention strategy for smoking cessation, has been associated with increased patient motivation and behavioral change when used by health care providers in weight-management consultations with patients.⁷

Because obesity is a chronic disease, patients need a two phase approach – acute weight loss and then long-term weight loss management. The strategies that work best for weight loss are not the same as those that work for weight loss maintenance. Exhibit 2 presents the current approach to selecting acute

weight loss treatment based on disease risk.⁸ There is a role for weight loss medication because of their impact on physiologic pathways that impact food intake and weight. It is important to note that weight loss medications are an adjunct to lifestyle changes.

Evaluation of an obese patient begins with identifying correctable issues. Secondary causes of obesity do have to be ruled out. This includes hypothyroidism, Cushing's syndrome, congenital abnormalities (Prader-Willi syndrome, Down syndrome) and hypothalamic disorders secondary to trauma, tumor, or surgery. Hypothyroidism can result in modest weight gain and can also impede weight loss efforts. Medications that can cause weight gain should be eliminated if possible. Weight and lifestyle histories should be assessed to identify factors contributing to weight gain and barriers to weight loss. These histories can guide the approach to adjusting the weight loss regimen. A successful weight loss regimen will address contributing factors and barriers, utilize lifestyle/behavioral intervention (diet, physical activity, behavioral changes) and possibly adjunct weight loss medication.

Consuming fewer calories is key to weight loss; therefore, a structured eating plan is essential. There is not one diet for weight loss nor is there a magic composition of nutrients; what is most important is

Exhibit 2: Current Approach to Obesity Treatment⁸

TREATMENT OPTIONS	Current Patient Risk LOW		Patient Risk High			
	25 - 26.9	27 - 29.9	30 - 34.9	35 - 39.9	≥ 40	
Diet, Exercise and Behavioral Therapy	Potential Treatment Risk LOW ↓	+	+	+	+	+
Pharmacotherapy			with a comorbidity	+	+	+
Surgery	Treatment Risk HIGH				with a comorbidity	+

being adherent with the diet.⁹ Clinicians should prescribe a nutritional plan to reduce caloric intake that the patient can adhere with. Clinicians need to be familiar with several types of diet plans.

Physical activity is modestly helpful for weight loss, but it is most important for weight loss maintenance. Physical activity can help with maintaining muscle mass during weight loss. Clinicians should be prescribing a physical activity plan of at least 150 minutes or more per week of moderate activity or 75 minutes or more per week of vigorous aerobic activity during the weight loss phase. Resistance training to preserve lean mass should also be instituted. Activity should be stepped up to 200 to 300 minutes per week of moderate exercise or more than 150 minutes per week of vigorous aerobic activity for more robust weight loss and to prevent weight regain.^{1,4} There are currently numerous options, at a vast price range, for patients to use in order to track their activity.

Another important intervention is a behavioral support program. For weight loss, the ideal behavioral support program has high contact frequency, 14 or more group or individual sessions in six months, and an on-site, high-intensity program with behavioral strategies.^{1,4,10} Alternatives to the ideal program include telephone or electronic counseling (with personalized feedback) and commercial programs with evidence of safety and efficacy. Three examples of commercial programs include Weight Watchers, Nutrisystem, and Jenny Craig. Commer-

cial or local community programs should include self-monitoring; portion control; regular, moderate physical activity; social support through individual and group sessions; incremental steps to behavior change; and an option for long-term participation or weight maintenance support. During the weight loss maintenance phase, patients should still have ongoing contact for goal setting and self-monitoring once a month or more.

Additional resources and tools to facilitate self-monitoring and planning include pedometers and sports watches, personal-activity monitors (e.g., BodyMedia FIT, DirectLife, Fitbit One, Fitbit Zip, ActiGraph, Jawbone Up, Basis B1), smartphone applications (e.g., Calorie King, GoMeals, Fitter Fitness Calculator, SparkPeople, Strava Cycling, South Beach Diet, Charity Miles, LiveStrong, MyFitnessPal), and the Internet (e.g., ChooseMyPlate, www.choosemyplate.gov; SparkPeople, www.sparkpeople.com). When using these tools, patients need a plan of how to use the information to make changes.

Weight loss medications are going to need to be used long term. When the medicine is stopped, weight is regained. Exhibit 3 lists the FDA approved weight loss medications. It is important to note that phentermine is only approved for short-term use. There are many options and if one medication is not effective then the clinician can try another one.

Bariatric surgical procedures produce the most weight loss but have the disadvantages of cost and complications such as infection and need for revi-

Exhibit 3: Weight Loss Medications

	Mechanism of action	Available for chronic use	Mean percentage weight loss		Advantages	Disadvantages
			Placebo	Drug		
Phentermine: 15-30 mg orally	Sympathomimetic	For short-term use	Not stated in label	Not stated in label	Inexpensive	Side-effect profile: no long-term data
Orlistat: 120mg orally three times a day before meals.	Pancreatic lipase inhibitor	Yes	-2.6%	-6.1%	Not absorbed: long-term data	Modest weight loss: side-effect profile
Lorcaserin: 10 mg orally twice a day	5-HT _{2C} serotonin agonist with little affinity for other serotonergic receptors	Yes	-2.5%	-5.8%	Mild side-effects: long-term data	Expensive: modest weight loss
Phentermine/topiramate ER: 7.5 mg/46 mg of 15 mg/92 mg orally indicated as rescue (requires titration)	Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	Yes	-1.2%	-7.8% (mid-dose) -9.8% (full dose)	Robust weight loss: long-term data	Expensive: teratogen
Naltrexone SR/bupropion SR: 32 mg/360 mg orally (requires titration)	Opioid receptor antagonist: dopamine and noradrenaline reuptake inhibitor	Yes	-1.3%	-5.4%	Reduces food craving: long-term data	Moderately expensive: side-effect profile
Liraglutide: 3.0 mg injection (requires titration)	GLP-1 receptor agonist	Yes	-3%	-7.4% (full dose)	Side-effect profile: long-term data	Expensive: injectable

sion. Adjustable gastric banding, sleeve gastrectomy, and Roux-en-Y gastric bypass are the three most common procedures performed in the U.S. and are in order from lowest to highest efficacy for weight loss and type 2 diabetes remission. The adjustable gastric band procedures result in the lowest morbidity and mortality rate and the gastric bypass the most.

In addition to the adjustable gastric band, three additional FDA approved devices designed to treat obesity are now on the market. Electrical stimulation systems that are placed in the abdomen to block nerve activity between the brain and stomach were approved in 2015. Intra-gastric balloon systems are inflatable balloons placed in the stomach to take up space and were also first approved in 2015. The two approved are Obera[®] and ReShape[®] Integrated Dual Balloon System; both are indicated

for those with BMI between 30 and 40 kg/m² who have failed other nonsurgical weight loss programs. The most recent device approved (2016) is a gastric emptying system (AspireAssist[®]), which is a tube inserted between the stomach and outside of abdomen to drain food after eating into an external bag. This device is indicated for obese patients with a BMI of 35 to 55 kg/m², who are 22 years of age or older, and who failed to achieve weight loss using nonsurgical means.

Obesity treatment for most doctors is out of their comfort zone. It takes some effort to change practice patterns, but clinicians can have a strategy for patients with an elevated BMI just as they have a strategy for patients with elevated blood pressure. Clinicians can start small with the easier patients and work their way toward helping the more difficult patients.

If patients hear from a physician or other health care professionals that they are overweight, they are six times more likely to perceive themselves as overweight and about 2.5 times more likely to attempt weight loss. In one study, only 45.2 percent of individuals with BMI greater than or equal to 25 had been told they were overweight and 66.4 percent of individuals with BMI greater than or equal to 30 had been told they were overweight.¹¹

Moving the needle in improving obesity management requires setting the bar higher than in the past. Clinicians should be advocating more rapid initial weight loss. In the past, clinicians have advocated for slow, steady weight loss, but data show that the greater a patient's initial weight loss the better the long-term success in maintaining the loss.¹² Clinicians also need to begin with weight loss maintenance in mind when educating patients and designing weight loss programs. Many overweight people know what needs to be done to lose weight, but they need motivation from clinicians on why it is important to lose and how to accomplish this. Lastly, clinicians need to utilize the power of the mind through behavioral interventions to assist patients with long-term weight maintenance. Transformative weight loss is where the field is going. This is the process of creating and aligning a new, reduced body weight, a positive and emotionally resilient mindset and a bigger purpose/spirit with a new lifestyle and way of being. This approach links the what and the why. Clinicians have to provide the how – the bridge between the what and the why of weight loss.

Conclusion

Obesity is associated with increased morbidity and mortality, and the majority of patients are obese or overweight. Clinicians need to take an active role in treating obesity, but a one size approach does not fit all. Comprehensive lifestyle therapy that includes behavioral intervention, reduced calorie intake, and increased physical activity is the cornerstone for the

management of overweight and obesity. Medications, devices, and surgery should be considered in some patients. The new medical devices provide additional strategies in the management of obese patients.

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Integrating Emerging Therapies into the Treatment Paradigm in the Management of Advanced Renal Cell Carcinoma

Daniel M. Geynisman, MD

For a CME/CNE version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary

There has been significant developments in how renal cell carcinoma (RCC) is treated in the last decade. There are several new medications which have become preferred agents because they result in better overall survival.

Key Points

- Nivolumab, cabozantinib and lenvatinib/everolimus are the new standard of care for advanced RCC.
- Immunotherapy has and is changing the treatment paradigm for RCC.
- Many other stand alone or combination immunotherapies are being investigated.
- Patients with RCC will be living longer, but on chronic treatment with possibly chronic physical, emotional and financial toxicities.

APPROXIMATELY 64,000 CASES OF RENAL cell carcinoma (RCC) are diagnosed annually in the United States and more than 14,000 will die from the disease.¹ There are several subtypes of RCC, including clear cell, papillary I, papillary II, chromophobe, collecting duct, and medullary. Although numerous new therapies have come to market for RCC, almost all are for the clear cell subtype.

Exhibit 1 shows the staging of the RCC based on size and spread beyond kidney.² Unlike other cancers, the majority of patients are diagnosed with curable disease. Sixty-five percent of cases are localized (Stage I, II) to the kidney at the time of diagnosis.³ Another 16 percent have regional disease (Stage III) at diagnosis. The five-year survival rate for localized disease is 92.5 percent and 63.7 percent for regional disease. Those with Stage IV disease only have a five-year survival of 11.7 percent.

Treatment for Stages I to III is removal of the kidney. There is about a year survival benefit to adjuvant anti-vascular endothelial growth factor (VEGF) therapy (sunitinib or sorafenib) after tumor removal in select patients at high risk for recurrence.^{4,5} These agents do not yet have FDA approval for this indication. It is likely that these agents delay disease recurrence rather than produce a cure. Adjuvant treatment with immunotherapy is being studied with the hope of a cure.

Exhibit 2 outlines the general approach to Stage IV disease. Before 2006, the systemic therapy options for treating Stage IV disease were interleukin, high-dose interferon or standard chemotherapy. The chemotherapy was not effective in altering the course of the disease. Interleukin treatment produced a 5 to 7 percent complete response but had a 1 percent death rate and is highly toxic. Interferon

Exhibit 1: Staging of RCC²

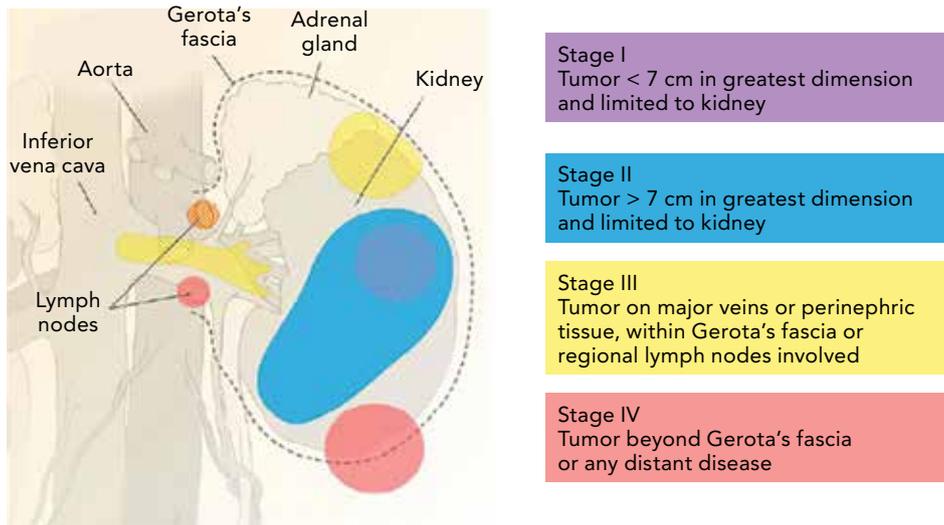


Exhibit 2: Stage IV Initial Treatment Paradigm

Extent of Tumor	Treatment
Surgically resectable renal mass with solitary metastatic site	Nephrectomy + metastasectomy OR Nephrectomy + systemic therapy
Potentially resectable primary with multiple metastatic sites	Cytoreductive nephrectomy in select patients prior to systemic therapy
Medically or surgically unresectable	Systemic therapy or observation in select patients

produced about a 15 percent response rate, but the response was not sustained.

The revolution of RCC treatment started in 2006 with the approval of sorafenib (an anti- VEGF tyrosine kinase inhibitor [TKI]). Sunitinib, temsirolimus, everolimus, bevacizumab, axitinib, and pazopanib followed. There was a lull in FDA approvals between 2010 and 2015. Starting in 2015, nivolumab, cabozantinib, and lenvatinib/everolimus were all approved.

In greater than 50 percent of clear cell RCC, there is an inactivated von Hippel–Lindau (VHL) tumor suppressor gene.⁶ Because of this inactivation, there is accumulation of hypoxia-inducible factor (HIFalpha) in the cell which leads to VEGF

secretion which leads to production of blood vessels. Several of the new medications for RCC affect VEGF or HIFalpha.

In the National Comprehensive Cancer Network (NCCN) guidelines, there are many treatment options for Stage IV RCC that are Category 1 recommendations (Exhibit 3).⁷ With the two Category 1 preferred agents, pazopanib and sunitinib, there is about a 30 percent partial response rate and no difference in overall survival (OS).⁸ Both of these agents cause significant adverse effects, including hand-foot syndrome, hypertension, hypothyroidism, fatigue, mouth sores, nausea/stomach upset/diarrhea, cytopenias, proteinuria, hyperlipidemia, hyperglycemia, and taste change/anorexia. Numerous

Exhibit 3: NCCN Guidelines for First-line Therapy⁷

FIRST-LINE THERAPY

(alphabetical by category and preference)

Clinical trial

or

Pazopanib (category 1, preferred)

or

Sunitinib (category 1 preferred)

or

Bevacizumab + IFN (category 1)

or

Temsirolimus (category 1 for poor-prognosis patients, category 2B for selected patients of other risk groups)

or

Axitinib

or

High-dose IL-2 for selected patients

or

Sorafenib for selected patients

and

Best supportive care

See NCCN Guidelines for Palliative Care

additional treatments are needed to manage these adverse effects.

Subsequent lines of therapy at disease progression are also recommended in the NCCN guidelines. Cabozantinib (preferred), nivolumab (preferred), axitinib, and lenvatinib/everolimus are all Category 1 recommended therapies.⁷

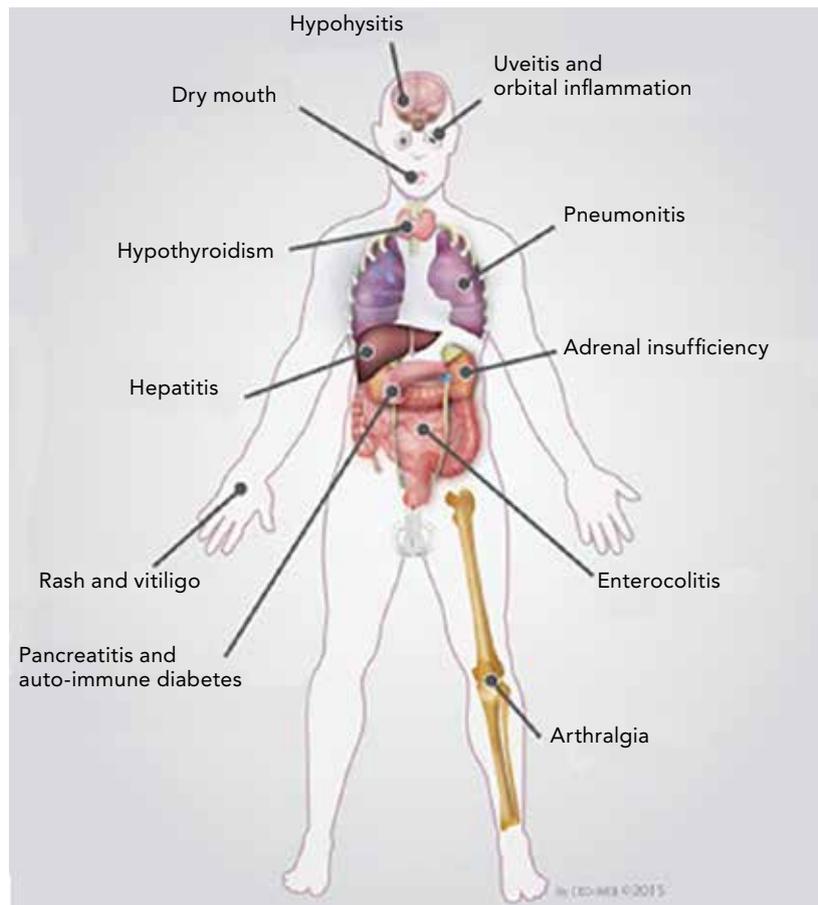
Nivolumab (Opdivo[®]) is the only agent for RCC with a radically different mechanism of action. It is an anti-programmed death 1 (PD-1) monoclonal antibody that works as a checkpoint inhibitor, blocking a signal that would have prevented activated T cells from attacking the cancer, thus allowing the immune system to clear the cancer. Essentially this agent takes the brakes off the immune system to allow it to attack tumor cells. Compared to everolimus as second-line treatment, nivolumab results in a 25 percent response rate compared with a 6 percent response for everolimus and a 25-month median survival compared with 19.6 months with everolimus.⁹ Patients on this agent also have better quality of life compared with everolimus. If a patient has a partial or complete response to nivolumab, they have a 96 percent chance of being alive 12 months later. This is very good given that these are patients who have already had prior therapy and have advanced disease. Unlike with other cancers, PD-L1 expression is not predictive of response to nivolumab. Thus, tumor tissue is not tested to decide whether to use this drug. With immuno-

therapy, there can be a long-lasting response after therapy is stopped.

Toxicity with immunotherapy is very different from classic adverse events from chemotherapy. The immune-related adverse events (irAEs) may be due to cytokine release by activated T cells and can affect many body systems (Exhibit 4). Twenty percent of patients or fewer will have grade 3 to 4 irAEs, but death from irAEs has occurred in approximately 2 percent of those treated with immunotherapy. Because they can be serious, managing these irAEs requires a multidisciplinary approach and requires prompt recognition and treatment. The irAEs are treated with high-dose corticosteroids. Patients and health care providers, especially those who do not typically deal with this therapy such as emergency room physicians and primary care providers, need education on recognizing these adverse events.

Cabozantinib (Cabometyx[®]) is a VEGF inhibitor as well as a MET inhibitor. Compared with everolimus in RCC patients who had previous VEGF therapy, the overall response rate was 17 percent with cabozantinib compared with 3 percent for everolimus.¹⁰ Overall survival was also better with cabozantinib at 21.4 months compared with 16.5 months. In patients with poor and intermediate risk, cabozantinib has been studied as first-line therapy against sunitinib. Cabozantinib therapy resulted in better response, progression-free survival,

Exhibit 4: Toxicity with Immunotherapy Agents



and response rate. The side effect profiles for the two agents were very similar. This may become a front-line option over sunitinib, especially in poor and intermediate risk patients.

The combination of lenvatinib (Lenvima[®]) and everolimus (Afinitor[®]) targets both VEGF and fibroblast growth factor receptor (FGFR) and was recently approved by the FDA for Stage IV RCC following prior anti-VEGF therapy. Compared with either agent alone, the combination results in higher OS (25.5 months vs 19.1 vs 15.4), objective response rate (43% vs 27% vs 6%), and progression-free survival.¹¹ Exhibit 5 compares the various options for second-line therapy.

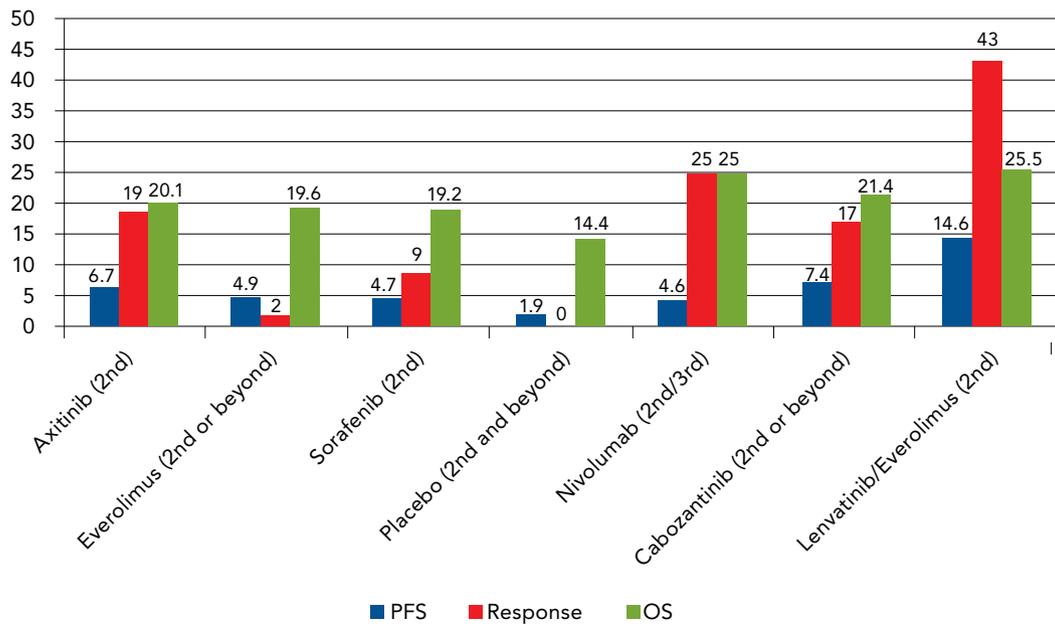
The new therapies have significant and sometimes life-threatening adverse effects. There are now more treatment options for advanced RCC, which is great, but there is also more uncertainty in how best to sequence the available agents. There are no clear answers on which therapy to use first. With immunotherapy, therapy can be stopped; yet,

the benefit continues but clinicians do not yet know when therapy should be stopped. These are all expensive treatments and many patients have problems affording them. The treatment of side effects of the therapies can also be expensive.

Because these newer therapies are allowing patients to live longer with RCC, there can be issues with the psychology of living with a deadly disease. Patients can live for years with end-stage disease. The costs physically, emotionally, and financially of living with a chronic but deadly disease have to be considered.

Multiple completed or ongoing trials are combining immunotherapy with VEGF inhibition for first-line therapy. There have been very high response rates in the early results from the trials (~70%). During the next couple of years, the standard of care will likely change to this combination for first-line therapy. There are also a great deal of other things being studied in this disease, including novel combinations, adoptive immunotherapy, autologous vac-

Exhibit 5: Second Line Therapy



PFS = progression free survival
OS = overall survival

cines, novel targeted antibodies, epigenetic therapy, chemokine receptor inhibition, HIF inhibition, and antisense oligonucleotides.

Conclusion

The landscape of options for advanced RCC has and continues to rapidly evolve. Nivolumab, cabozantinib and lenvatinib/everolimus are the new standard of care for advanced RCC. Immunotherapy has and is changing the treatment paradigm for RCC. Many other stand alone or combination immunotherapies are being investigated. Patients will be living longer, but the will be on chronic treatment, with possibly chronic physical, emotional and financial toxicities.

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