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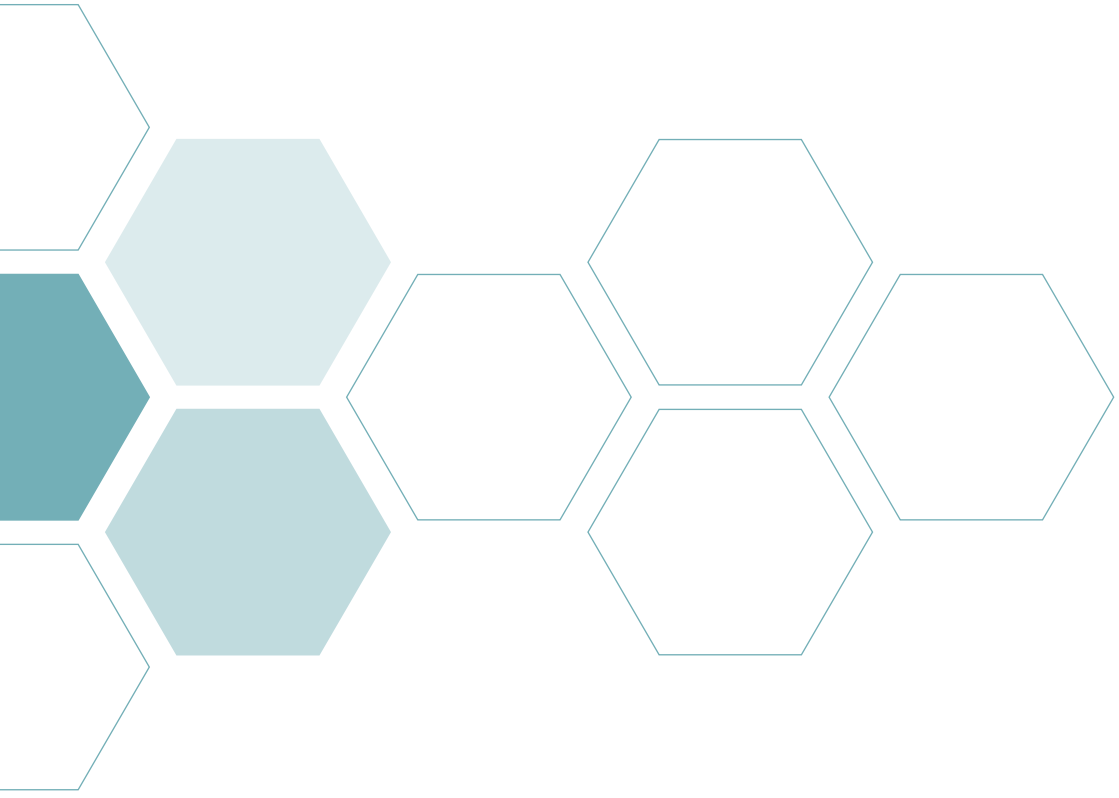

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EDITOR-IN-CHIEF
J. Ronald Hunt, MD

PUBLISHER
Jeremy Williams

ADVERTISING REPRESENTATIVE
Maria Sercia
American Medical Communications, Inc.
msercia@americanmedicalcomm.com
(267) 614-6809

JOURNAL MANAGEMENT
Douglas Murphy
Communications Inc.
P.O. Box 71895
Richmond, VA 23255-1895
(804) 387-7580

MANAGING EDITOR
Barry Barnum
barry.barnum@douglasmurphy.com

GRAPHIC DESIGN
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Editorial Review Board

New Horizons in the Treatment and Management of B-Cell Non-Hodgkin Lymphoma (NHL): A Closer Look at the Role of Emerging Therapies

Owen A. O'Connor, MD, PhD

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

Summary

Several breakthrough therapies are having a major impact on the natural history of both Hodgkin and non-Hodgkin lymphomas. These newer therapies are leading to significant improvements in survival, but the increased risk of adverse events has to also be considered.

Key Points

- Checkpoint immunotherapy is an option for Hodgkin lymphoma.
- BTK inhibitors and PI3K inhibitors are both now available for treating various non-Hodgkin lymphomas and leukemias.
- The adverse events of these newer agents and the continued risk of older treatments, such as chemotherapy, need to be balanced against the benefit.

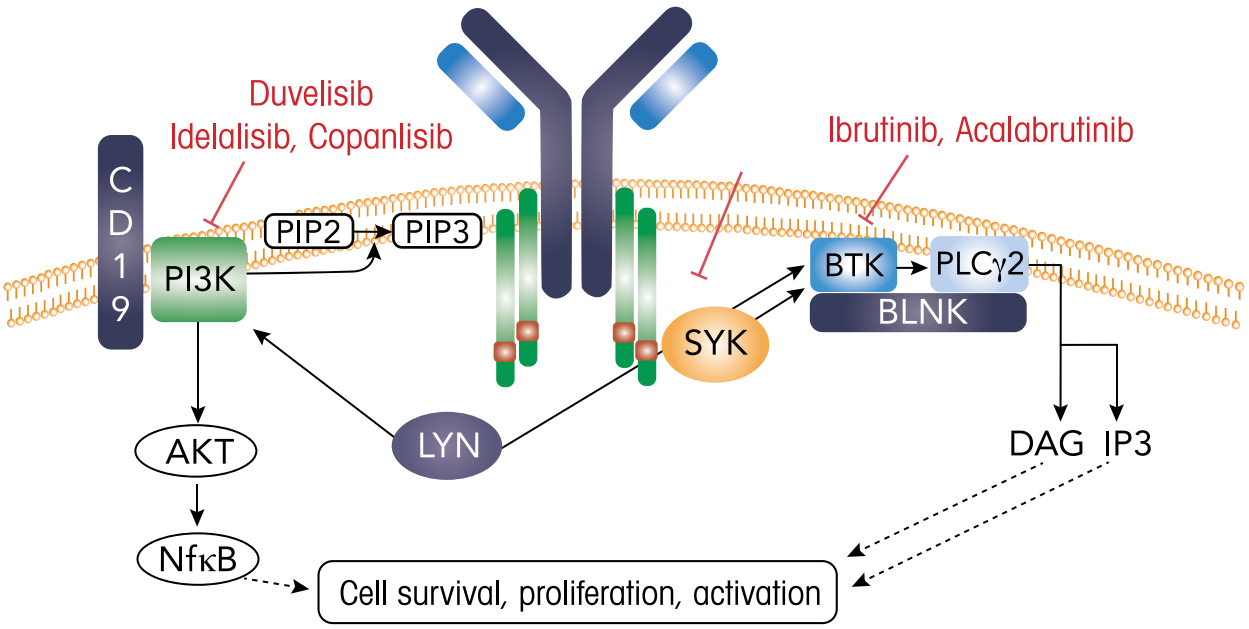
LYMPHOMA IS A CANCER OF THE LYMphocytes and is typically classified as either Hodgkin lymphoma or non-Hodgkin lymphoma of which there are more than 107 types. Most non-Hodgkin lymphoma arises from B cells (85%). Subtypes of non-Hodgkin lymphoma that involve B cells include diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and Burkitt lymphoma. Diffuse large B-cell lymphoma and follicular lymphoma are among the most common subtype. Hodgkin lymphoma is often diagnosed at an early stage and is therefore considered one of the most treatable cancers. Non-Hodgkin lymphoma is typically not diagnosed until it has reached a more advanced stage.

Three advances to discuss that are altering the natural history of lymphoma are targeting programmed death one (PD-1) in Hodgkin lymphoma with immune checkpoint inhibitors, Bruton's tyrosine kinase (BTK) inhibitors in non-Hodgkin lymphoma, and targeting the phosphatidylinositol 3-kinase (PI3K) pathway in non-Hodgkin lymphoma.

The immune checkpoint pathway is an elaborate series of cellular interactions that prevent excessive T-cell effector activity.[1] Inhibitory receptors, such as cytotoxic T-lymphocyte- associated protein-4 (CTLA-4) and programmed death receptor-1 (PD-1) downregulate T-cell activity. Checkpoint inhibitor monoclonal antibodies that block CTLA-4 or PD-1 pathway components essentially take the brakes off the immune system, allowing it to target and kill cancer cells. These agents are FDA approved for treating many different cancers. Hodgkin lymphoma cells express PD-1 on the surface as a survival mechanism.

Pembrolizumab (Keytruda®), an anti PD-1 agent, is FDA approved for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL) who have relapsed after three or more prior lines of therapy.[2] This indication received accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. In the trial leading to FDA approval, the study subjects had disease progression after autologous stem cell transplantation (SCT) and subsequent brentuximab vedotin (BV; cohort 1); salvage

Exhibit 1: Targeting BCR Signaling

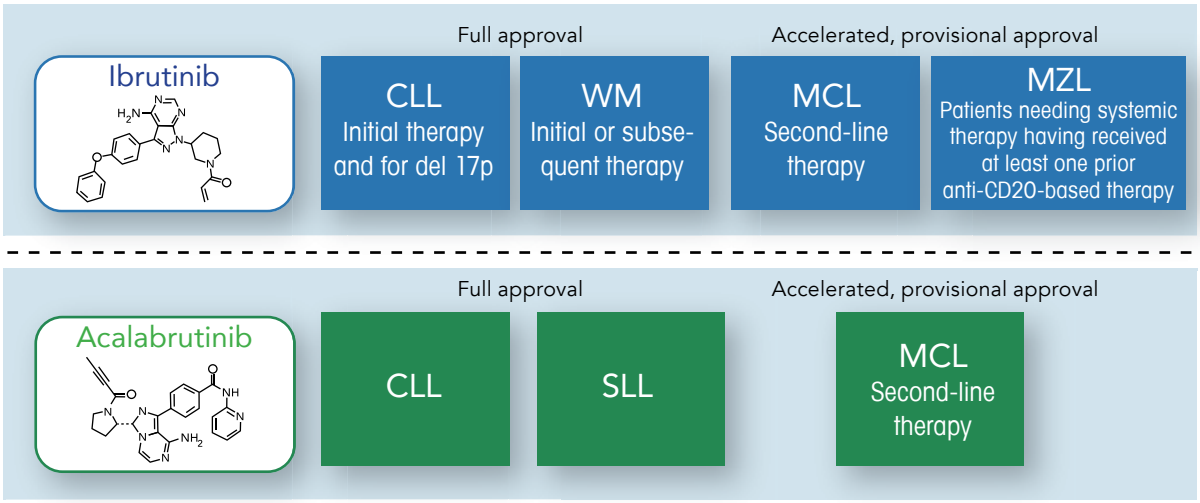


chemotherapy and BV, with ineligibility for SCT owing to chemorefractory disease (cohort 2); or progression after SCT without BV (cohort 3).[3] With a median follow-up of 27.6 months, the objective response rate (ORR) was 71.9 percent, the complete response (CR) rate was 27.6 percent, and the partial response (PR) rate was 44.3 percent. Median duration of response was 16.5 months in all patients, 22.1 months in cohort 1, 11.1 months in cohort 2, and 24.4 months in cohort 3. Median progression-free survival (PFS) was not reached in the patients with CR and was 13.8 months for patients with PR and 10.9 months for patients with stable disease. Median overall survival was not reached in all patients, or in any cohort. It did not appear to matter what previous treatment the patient had received to receive benefit from pembrolizumab. Treatment-related adverse events of any grade occurred in 153 (72.9%) patients; grades 3 and 4 occurred in 25 (12.0%) patients; none resulted in death. Nivolumab (Opdivo®), another anti-PD-1 agent, is also indicated for the treatment of adult patients with cHL that has relapsed or progressed after autologous SCT and brentuximab vedotin (BV), or after three or more lines of systemic therapy that includes autologous SCT and carries the same caveat that approval was done under the accelerated process and is based on ORR.[4] Nivolumab has been studied alone and in combination with ipilimumab (Yervoy®), a CTLA-4 inhibitor for cHL, but it does not currently appear that the addition of ipilimumab contributes significantly to efficacy in cHL.

Brentuximab vedotin (BV), an antibody/chemotherapy conjugate, plus nivolumab is being studied as salvage therapy for relapsed/refractory cHL. BV disrupts the microtubule network and triggers an immune response through the induction of endoplasmic reticulum stress. The CR rate (n = 61) was 61 percent, with an objective response rate of 82 percent.[5] BV plus nivolumab was an active and well-tolerated first salvage regimen, potentially providing patients an alternative to traditional chemotherapy. Immunotherapy is also being combined with lower toxicity chemotherapy regimens. The use of immunotherapy or immunotherapy in combination with lower toxicity chemotherapy are designed to be tailored to the biology of the disease to reduce reliance on very toxic chemotherapy regimens that have been traditionally used.

As noted previously, approximately 85 percent of non-Hodgkin lymphomas are of B-cell origin. The BTK pathway signaling is fundamental for the functionality and survival of B cells (Exhibit 1). In the B cell, immune responses to antigens are mediated through BTK interaction with B-cell receptors (BCR). When B cells recognize

Exhibit 2: BTK Inhibitor FDA Approvals[7,8]



CLL = chronic lymphocytic leukemia
MCL = mantle cell leukemia
MZL = marginal zone lymphoma
WM = Waldenström's macroglobulinemia
SLL = small lymphocytic lymphoma.

antigens through BCR, BTK interacts with BCR and initiates a signaling cascade critical to the production of antibodies, proinflammatory cytokines and chemokines, as well as influencing antigen presentation on B cells. BTK is also expressed to high levels in certain myeloid cells, such as macrophages and granulocytes. In these cells, receptor activation by immune complexes promotes BTK signaling and expression of proinflammatory cytokines and cell adhesion molecules. Dysregulated BCR signaling has been identified as a potent contributor to tumor survival in B-cell non-Hodgkin lymphomas (NHLs).[6] This pathway's emergence as a rational therapeutic target in NHL led to development of BCR-directed agents, including inhibitors of BTK and PI3K.

BTK receptors are permanently turned on in B-cell NHLs; essentially, BTK inhibitors turn off these receptors reducing cell proliferation and survival. Two oral BTK inhibitors are currently FDA approved—ibrutinib (Imbruvica®) and acalabrutinib (Calquence®) (Exhibit 2).[7,8] The BTK inhibitors have substantially different levels of selectivity. Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro and thus causes fewer adverse events. The most common adverse events with this class are anemia, neutropenia, headache, diarrhea, and thrombocytopenia. Ibrutinib also causes bleeding/ecchymosis, rash, blurred vision, and atrial fibrillation. In clinical trials, 4 percent of patients treated with ibrutinib developed grade 3 or 4 atrial fibrillation, whereas it only occurred in 1 percent of those treated with acalabrutinib. Acalabrutinib is replacing ibrutinib in diseases where it has FDA approval because of the lower rate of serious adverse events.

Ibrutinib has been shown to improve five-year survival in chronic lymphocytic leukemia (CLL). CLL and small lymphocytic lymphoma (SLL) are closely related diseases. The same type of cancer cell (small lymphocyte) is seen in both CLL and SLL. The only difference is where the cancer cells are found. In CLL, most of the cancer cells are in the blood and bone marrow. In SLL, the cancer cells are mainly in the lymph nodes and spleen. The important point about the BTK inhibitors is that they work in those patients who have a very poor prognosis and where chemotherapy never worked. This includes those with 17p or 11q deletion or mutated heavy chain CLL. In mantle cell lymphoma (MCL), the ORR is 67 percent with ibrutinib; it is also very effective when combined with venetoclax.[9,10] Two other diseases where BTK inhibitors are effective are Waldenström's macroglobulinemia, a lymphoma characterized by the presence of abnormally large numbers of B lymphocytes and excessive quantities of IgM, and

marginal zone lymphoma (MZL). These patients are being managed with long-term use of oral BTK inhibitors instead of requiring chemotherapy. BTK inhibitors do not appear to be effective in FL, even though this is also a B-cell disease.

The PI3K pathway is an intracellular signal transduction pathway that promotes metabolism, proliferation, cell survival, growth and angiogenesis in response to extracellular signals. The PI3K pathway is the most altered pathway in cancer and thus PI3K inhibitors were developed to target this pathway.The enthusiasm for this class of therapy was very high when these agents were first approved; however, that enthusiasm has been blunted by the toxicity, resulting primarily in severe diarrhea, making patients miserable.

Idelalisib (Zydelig®), duvelisib (Copiktra®), and copanlisib (Aliqopa®) are the three FDA approved PI3K inhibitors. Idelalisib is an inhibitor of PI3K-δ kinase, which is expressed in normal and malignant B cells. Idelalisib induced apoptosis and inhibited proliferation in cell lines derived from malignant B cells and in primary tumor cells. Idelalisib inhibits several cell signaling pathways, including BCR signaling and the CXCR4 and CXCR5 signaling, which are involved in trafficking and homing of B cells to the lymph nodes and bone marrow. Idelalisib is FDA approved for relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities; relapsed FL in patients who have received at least two prior systemic therapies; and relapsed SLL in patients who have received at least two prior systemic therapies. In FL, an indolent NHL, the response rate was 57 percent (71 of 125 patients), with only 6 percent meeting the criteria for a CR. The median time to a response was 1.9 months, median duration of response was 12.5 months, and median PFS was 11 months.[11]

Duvelisib is an inhibitor of PI3K with inhibitory activity predominantly against PI3K-δ and PI3K-γ isoforms expressed in normal and malignant B cells. Duvelisib induced growth inhibition and reduced viability in cell lines derived from malignant B cells and in primary CLL tumor cells. Duvelisib inhibits several key cell-signaling pathways, including BCR signaling and CXCR12-mediated chemotaxis of malignant B cells. Duvelisib has accelerated approval for relapsed or refractory CLL or SLL after at least two prior therapies and for relapsed or refractory FL after at least two prior systemic therapies and is given orally twice a day.[12] In FL treated with duvelisib, ORR was 42 percent with one patient having a CR, the median duration of response was 10 months, 17 percent of patients (n = 6/35) maintained a response at 12 months, and the median PFS was 8.3 months.[13]

Copanlisib has accelerated FDA approval for the treatment of adult patients with relapsed FL who have received at least two prior systemic therapies.[14] It has inhibitory activity predominantly against PI3K-α and PI3K-δ isoforms expressed in malignant B cells. Copanlisib has been shown to induce tumor cell death by apoptosis and inhibition of proliferation of primary malignant B cell lines. It inhibits several key cell-signaling pathways, including BCR signaling, CXCR12 mediated chemotaxis of malignant B cells, and NF-κB signaling in lymphoma cell lines. It is different from the other two PI3K inhibitors because it is given as a one-hour intravenous infusion on days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off), rather than as a daily oral agent. In relapsed FL, it produced a 59 percent ORR with 14 percent having a CR.[14] Overall, the PI3K inhibitors that have been approved so far produce reasonable but not great responses in FL, but they have a very high rate of adverse events, which limits their use.

Diarrhea is the most common adverse event of PI3K inhibitors. Severe diarrhea (grade 3 or higher adverse reaction) occurs in 16 to 42 percent of patients receiving idelalisib, in 23 percent receiving duvelisib, and in 5 percent receiving copanlisib.[12,14,15] Type 1 diarrhea generally occurs within the first eight weeks and is typically mild or moderate (grade 1 to 2) and is responsive to common antidiarrheal agents. Type 2 diarrhea tends to occur relatively late and is usually watery, without cramps, and devoid of blood or mucus. In general, cessation of the drug is recommended for severe diarrhea (including unresolved grade 2 and grade 3 colitis), and steroids (systemic or enteric budesonide) may also be administered, as they may result in a shorter time to resolution of symptoms. In the small intestine, celiac-like changes predominate, with increased intraepithelial lymphocytes and villous blunting. The colon shows a spectrum of changes including prominent apoptosis with acute cryptitis, crypt abscesses, increased intraepithelial lymphocytes and lamina propria expansion with mild architectural distortion. Idelalisib and duvelisib have boxed warnings about fatal and serious toxicities, including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis. These same reactions have been reported with copanlisib and

are noted in the package labeling, but it does not have the boxed warning and the rates appear lower probably due to the on-off dosing regimen.

Umbralisib is an investigational oral PI3K-δ inhibitor which also inhibits casein kinase 1(CK1) epsilon. It is chemically different from the other approved PI3K inhibitors and because of its selectivity should have lower rates of adverse events.[16] The incidence of serious diarrhea has been as low as 3 percent, and it does not cause colitis and pneumonitis. The other difference is that this agent appears to have activity in other diseases besides FL, which is probably because of its effect on CK1 epsilon. It is being studied in CLL/SLL and in combination trials for various leukemias and lymphomas, such as MCL. Twenty-four percent of patients with FL responded to this agent.[17] Umbralisib has been submitted to the FDA for approval in MZL and FL and will likely replace the other PI3K inhibitors once approved. Additionally, there are at least 10 more of these agents under investigation. It is hoped the newer agents will have better efficacy with minimal toxicity, which is the primary goal of treating lymphomas.

Conclusion

The idea of treating every patient with lymphoma the same is disappearing, and the newer agents are changing the natural history of this disease. It is still important to manage the risk versus benefit of treatment. For those patients with more aggressive forms of lymphoma, greater risk of adverse events may be acceptable, whereas those patients with a more indolent form, such as follicular lymphoma, who are going to have to take these medications for many years, are going to want medications with few adverse events.

Owen A. O'Connor, MD, PhD is the American Cancer Society Research Professor, Professor of Medicine and Experimental Therapeutics, and Director, Center for Lymphoid Malignancies in the Department of Medicine at Columbia University Medical Center—College of Physicians and Surgeons and The New York Presbyterian Hospital in New York, NY.

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Current and Novel Treatment Advances and Their Impact on the Management of Psoriasis

Junko Takeshita, MD, PhD, MSCE

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Summary

Biologics have become a mainstay of treatment for moderate- to-severe psoriasis. In addition to clearing skin lesions and reducing systemic inflammation with psoriasis-specific treatment, clinicians need to consider reducing the risk of cardiovascular disease by treating various comorbidities. Management of these patients can take a team approach.

Key Points

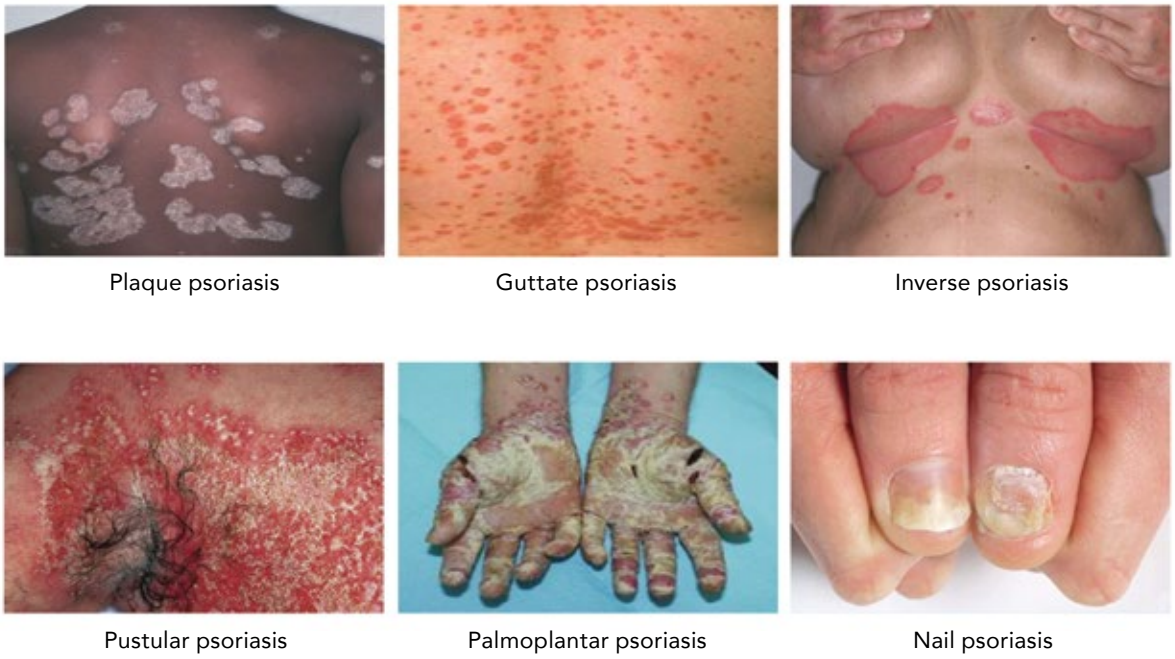
- Psoriasis is associated with major comorbidities (e.g., psoriatic arthritis, cardiometabolic disease), especially with more severe disease.
- Treatment options for moderate-to-severe psoriasis are phototherapy, biologics, and oral small molecule therapies.
- The management of moderate-to-severe psoriasis often requires a multidisciplinary team.
- Treatment selection is highly dependent on individual characteristics and preferences.

PSORIASIS AFFECTS 2 TO 4 PERCENT OF the adult population in the United States (U.S.) (> 7 million). It affects about 1.3 percent of African Americans, who are more likely to have moderate-to-severe disease.[1] It is estimated that 600,000 to 3,600,000 people have undiagnosed psoriasis.[2] Plaque psoriasis is the most common type which occurs in 80 to 90 percent of patients, and this is the type for which all the therapies discussed in this article are approved (Exhibit 1). A patient can have more than one type; for example, plaque and nail disease occur together commonly. Overall, 15 percent of patients have moderate disease [3% to 10% of body surface area (BSA) affected] and 5 percent have severe disease (> 10% BSA).

This disease has a chronic waxing and waning course. The typical onset occurs in one's 20s to 30s. There are rare cases of spontaneous remission. Psoriasis can affect any part of the skin; when the face, scalp, nails, and genitals are affected, the disease can be especially disabling. Psoriasis has a major negative impact on quality of life, similar to other serious chronic diseases.[3] In the past, most patients with more severe psoriasis remained poorly controlled for decades. Most psoriasis patients, especially those who just have the vulnerable areas discussed above affected, are undertreated. One study found that in patients who had greater than 10 lesions on their palms 37 percent were on no prescription treatment and 57 percent were on topicals only.[4] Uncontrolled psoriasis of the hands can make undertaking activities of daily living and working very difficult.

Psoriasis is a multifactorial disease (Exhibit 2). There are triggering events which activate dendritic cells to release cytokines, which begins the process and then perpetuates the disease. Involved cytokines include interleukin 17 (IL-17), IL-23, and tumor necrosis factor (TNF). Because it is a systemic inflammatory disease, there are significant increases in the risk for various comorbidities. Well-established comorbidities of psoriasis include psoriatic arthritis, myocardial infarction, stroke, cardiovascular death, metabolic syndrome (obesity, insulin resistance, cholesterol abnormalities, hypertension), type 2

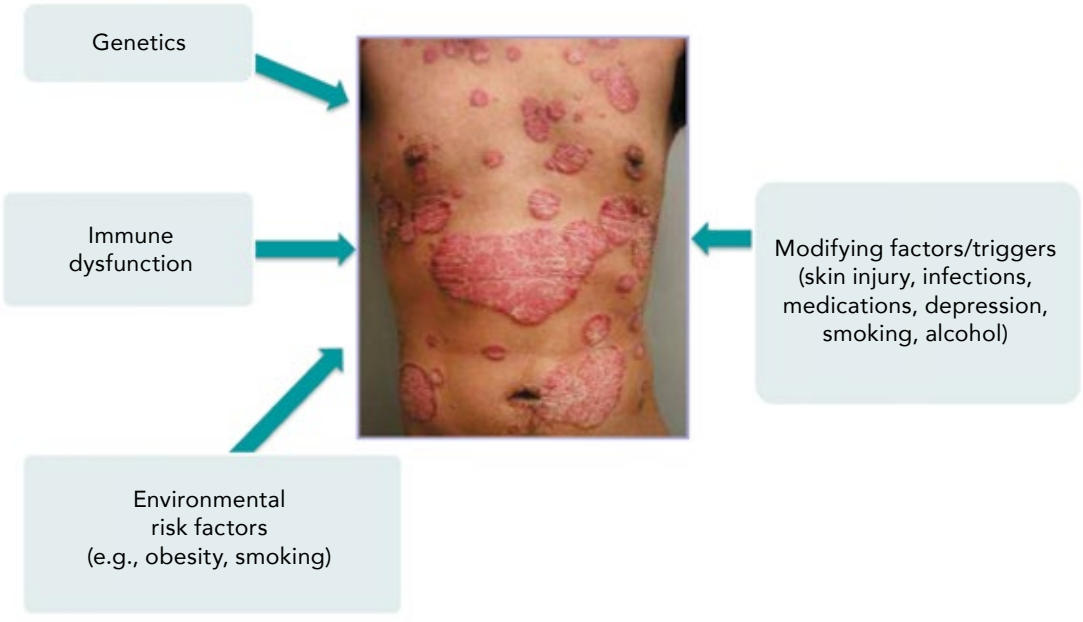
Exhibit 1: Clinical Manifestations of Psoriasis



Plaque psoriasis | Guttate psoriasis | Inverse psoriasis

Pustular psoriasis | Palmoplantar psoriasis | Nail psoriasis

Exhibit 2: Psoriasis is a Multifactorial Disease



diabetes, mood disorders (anxiety, depression, suicide), Crohn's disease, and T-cell lymphoma (rare).[5] Patients with severe psoriasis lose an average of five years of life because of cardiovascular complications. If greater than 10 percent of the body surface area is affected, there is an 80 percent higher risk of death over four years, independent of other risk factors.[6] The 2019 American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) guidelines recommend that cardiovascular risk score models should be adapted for patients with psoriasis by introducing a 1.5 multiplier if the patients has BSA > 10 percent affected or is a candidate for systemic or phototherapy.[7] The American College of Cardiology (ACC) and the American Heart Association (AHA) recommendations for primary cardiovascular disease prevention now include psoriasis as a risk modifier.[8]

Treatment of psoriasis with psoriasis-specific therapies may have an impact on cardiovascular disease risk. In one meta-analysis, TNF inhibitors were shown to be cardioprotective compared to phototherapy.[9] Another meta-analysis of psoriasis randomized clinical trials found that biologic treatment did not result in significant differences in cardiovascular events.[10] None of these trials were designed as cardiovascular disease prevention trials; several ongoing clinical trials are examining the impact of various biologics and apremilast on disease risk and lipid values. At this time, clinicians are not yet sure what effect psoriasis therapy has on cardiovascular risk.

Mild psoriasis (< 3% BSA) can be managed solely with topical therapies. Moderate-to-severe disease is managed with phototherapy, systemic therapies, and biologics. Many experts have suggested that mild, moderate, and severe classification should be replaced with candidates for localized therapy versus systemic or phototherapy. Candidates for systemic therapy may have one or more of the following features: more than 3 to 5 percent BSA involved; involvement of palms, soles, face, scalp, nails, and genitals; significant impact on quality of life; failure of localized therapy; and concomitant psoriatic arthritis.[11]

Phototherapy is a good option for moderate-to-severe disease, especially in patients who are leery of the biologic therapies. It does not have as much efficacy as biologics, but it results in clear skin in about 30 percent of cases. Managed care should provide coverage for this valuable therapy.

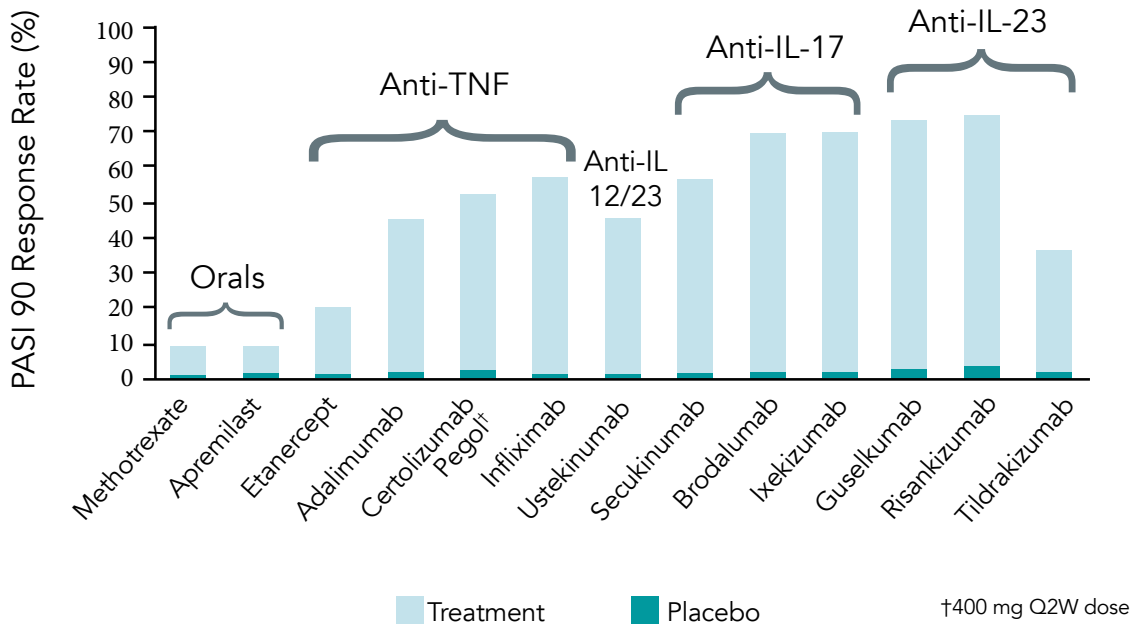
Trials of psoriasis therapies use the Psoriasis Area and Severity Index (PASI) as a primary efficacy measure. PASI 75, which is a 75 percent improvement in the disease from baseline, has been the target which therapies have had to meet to be considered efficacious. PASI 90 and PASI 100, 90 percent and 100 percent improvement from baseline, achievement is possible with the biologics.

Eleven injectable biologics, which target the pathologic cytokines in this disease, are now FDA approved for treating moderate-to-severe psoriasis. All are self-administered by subcutaneous injection except infliximab, which is given by intravenous infusion. Etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®) are all TNF inhibitor biologics. Ustekinumab (Stelara®) is an IL-23/IL-12 inhibitor while guselkumab (Tremfya®), tildrakizumab (Ilumya™), and risankizumab (Skyrizi™) are IL-23 inhibitors. Ixekizumab (Taltz®), secukinumab (Cosentyx®), and brodalumab (Siliq™) are IL-17 inhibitors. An oral therapy for moderate-to-severe psoriasis is apremilast (Otezla®), a phosphodiesterase (PDE) 4 inhibitor which reduces inflammatory cytokines (TNF, IL-2, IL-12, IL-23). It has moderate efficacy for psoriasis in Phase III trials, with 21 to 33 percent of patients achieving PASI 75.[12,13]

Exhibit 3 compares the PASI 90 responses for all the major oral and biologic agents for treating psoriasis.[12-22] It is important to note that this data is from the clinical trials with these agents and is not always from direct comparison studies. From this data, it appears that secukinumab, brodalumab, ixekizumab, guselkumab, and risankizumab are the most effective for skin clearing in psoriasis. This has been borne out in comparison trials between secukinumab, ixekizumab, higher dose brodalumab, guselkumab and risankizumab against ustekinumab.[20,23-25] The IL-17 agents (secukinumab, ixekizumab) also have a very quick onset of action.

Treatment selection for psoriasis can depend on the severity of the disease and current concomitant conditions, including obesity, psoriatic arthritis, heart failure, inflammatory bowel disease, and multiple sclerosis. For example, TNF inhibitors should be avoided in patients with heart failure or multiple sclerosis. The dosing regimen can also influence treatment selection. Needle phobic patients may prefer an agent given every eight to 12 weeks; guselkumab is given every eight weeks and ustekinumab and risankizumab are given every 12 weeks. Patients who are overweight have a lower response rate to certain biologics compared with those of normal weight. The 2019 AAD/NPF treatment guidelines support dose escalation for etanercept (2x/week), adalimumab (qweek), infliximab (up to 10mg/kg, q4 weeks), and ustekinumab (q8 weeks) in those who are overweight. Potential adverse events and drug interactions can also affect selection. The TNF inhibitors have a black box warning about serious infections and malignancy. The other classes do not

Exhibit 3: PASI 90 Response in Psoriasis Treatment[12-22]



have black box warnings for these issues. Apremilast has some drug interactions, whereas the biologics have none. An advantage of apremilast, apart from being an oral agent, is there is no required laboratory monitoring, where the biologics have required monitoring.

Goals of therapy are clearance of skin symptoms, enhanced quality of life, minimized day-to-day psoriasis burden, minimized adverse events through individualization of therapy, minimized comorbid disease burden, and maintenance of patient involvement. The National Psoriasis Foundation treatment targets are BSA < 1 percent at three months after treatment initiation and thereafter.[26] Although clear skin is a major objective measure of disease, other measures such as inflammatory biomarkers and quality of life are important. In one trial, nearly 20 percent of people with almost clear skin met Dermatology Life Quality Index (DLQI) criteria for treatment change.[27] A DLQI score of greater than 5 in a patient with a PASI 50 or 75 score would suggest a need for a therapy change.[28] A multidisciplinary approach to psoriatic disease management is necessary to optimally achieve these goals. It can require the dermatologist, a cardiologist, a rheumatologist if psoriatic arthritis presents, an endocrinologist for diabetes, a psychiatrist for mood issues, and a dietician for weight management.

The only dermatology outcome measure in the Centers for Medicare and Medicaid Services Merit-Based Incentive Payment System (MIPS) is clinical response to oral systemic or biologic medications in psoriasis. The outcome targets are physician global assessment (PGA) ≤ 2, BSA < 3 percent, PASI < 3, and DLQI ≤ 5. In 2017, the performance rate on these outcome targets was 60.3 percent, so there is significant room for improvement.[29]

Conclusion

Psoriasis is associated with major comorbidities (e.g., psoriatic arthritis, cardiometabolic disease), especially with more severe disease. Treatment options for moderate-to-severe psoriasis have rapidly expanded largely due to biologic therapies with increasing efficacy and possibly improved safety. The management of moderate-to-severe psoriasis often requires a multidisciplinary team and treatment selection is highly dependent on individual characteristics and preferences.

Junko Takeshita, MD, PhD, MSCE is an Assistant Professor of Dermatology and Epidemiology and Senior Scholar at the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania Perelman School of Medicine in Philadelphia, PA.

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Examining the Impact of Cardiovascular Safety in the Management of Type 2 Diabetes: Managed Care Considerations in an Evolving Treatment Paradigm

Gary M. Owens, MD

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

Summary

Because cardiovascular disease is such a common complication of type 2 diabetes and the most common cause of death in those patients, treatment is evolving to add agents which have been shown to modify cardiovascular risk. The SGLT2 inhibitors are one class which has been shown to provide cardiovascular benefit.

Key Points

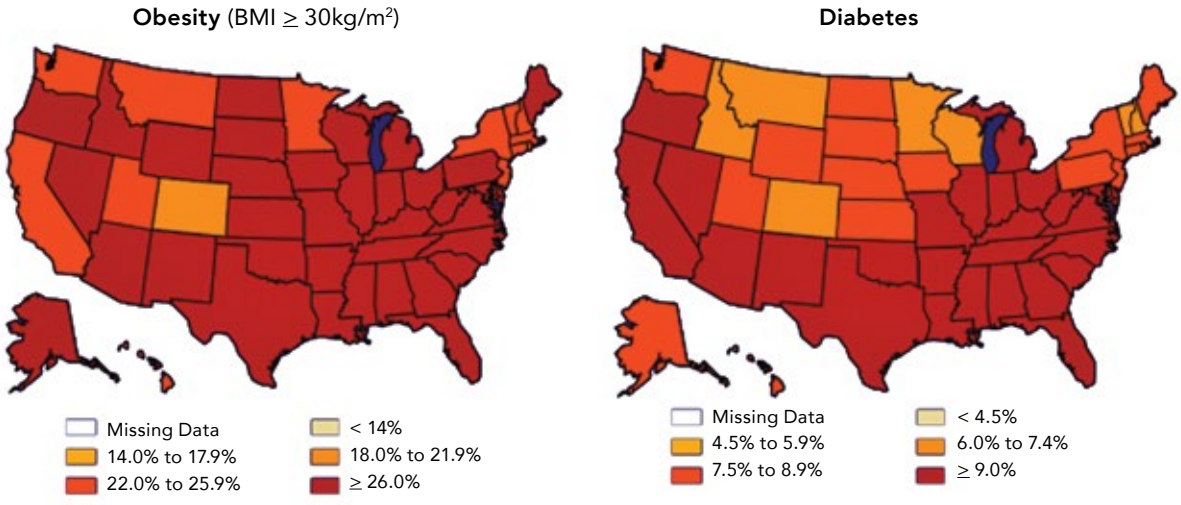
- Diabetes is a major risk factor for developing cardiovascular disease.
- The majority of diabetic deaths are due to cardiovascular disease.
- There is an increasing body of evidence that some agents have a positive impact on CV outcomes in diabetes.
- The evidence for the SGLT2 inhibitors is robust and continues to grow.
- Guidelines are evolving to direct appropriate selection of T2DM treatments based on CV risk.

THE RATES OF OVERWEIGHT, OBESITY, and type 2 diabetes mellitus (T2DM) have increased dramatically in the United States (U.S.) since 1994, to the point that the country has an epidemic of each (Exhibit 1).[1] In 2015, 30.3 million Americans, or 9.4 percent of the population, had diabetes, with about 7.1 million of those undiagnosed. T2DM is a costly disease to manage. The total cost of diagnosed diabetes in the U.S. in 2017 was estimated at $327 billion, with $237 billion for direct medical costs and $90 billion in reduced productivity.[2] After adjusting for population age and sex differences, the average medical expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures would be in the absence of diabetes.

T2DM is also a costly disease in terms of long-term consequences from micro and macro-vascular disease. Patients with diabetes have an increased risk for atherosclerosis due both to diabetes and to the frequent presence of other risk factors. At least 68 percent of people age 65 or older with diabetes die from some form of cardiovascular disease, and 16 percent die of stroke. Adults with diabetes are two to four times more likely to die from heart disease than adults without diabetes. Uncontrolled disease is especially a contributor to the development of complications and for every 1 percent increase in hemoglobin A1C, the risk of stroke, coronary heart disease (CHD), and death is increased 10 to 30 percent. The American Heart Association (AHA) considers diabetes to be one of the seven major controllable risk factors for cardiovascular disease (CVD).[3]

Diabetic patients with CHD are more likely to be asymptomatic or have atypical symptoms than nondiabetic patients with CHD. Despite the frequency of silent ischemia, it has not been proven that identifying asymptomatic disease or providing early intervention will improve outcomes in this population. CHD risk factors (dyslipidemia,

Exhibit 1: Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults[1]



hypertension, smoking, positive family history of early coronary disease, and presence of increased urinary albumin excretion) do not predict the likelihood of having ischemic findings on stress testing or coronary angiography.[4,5]

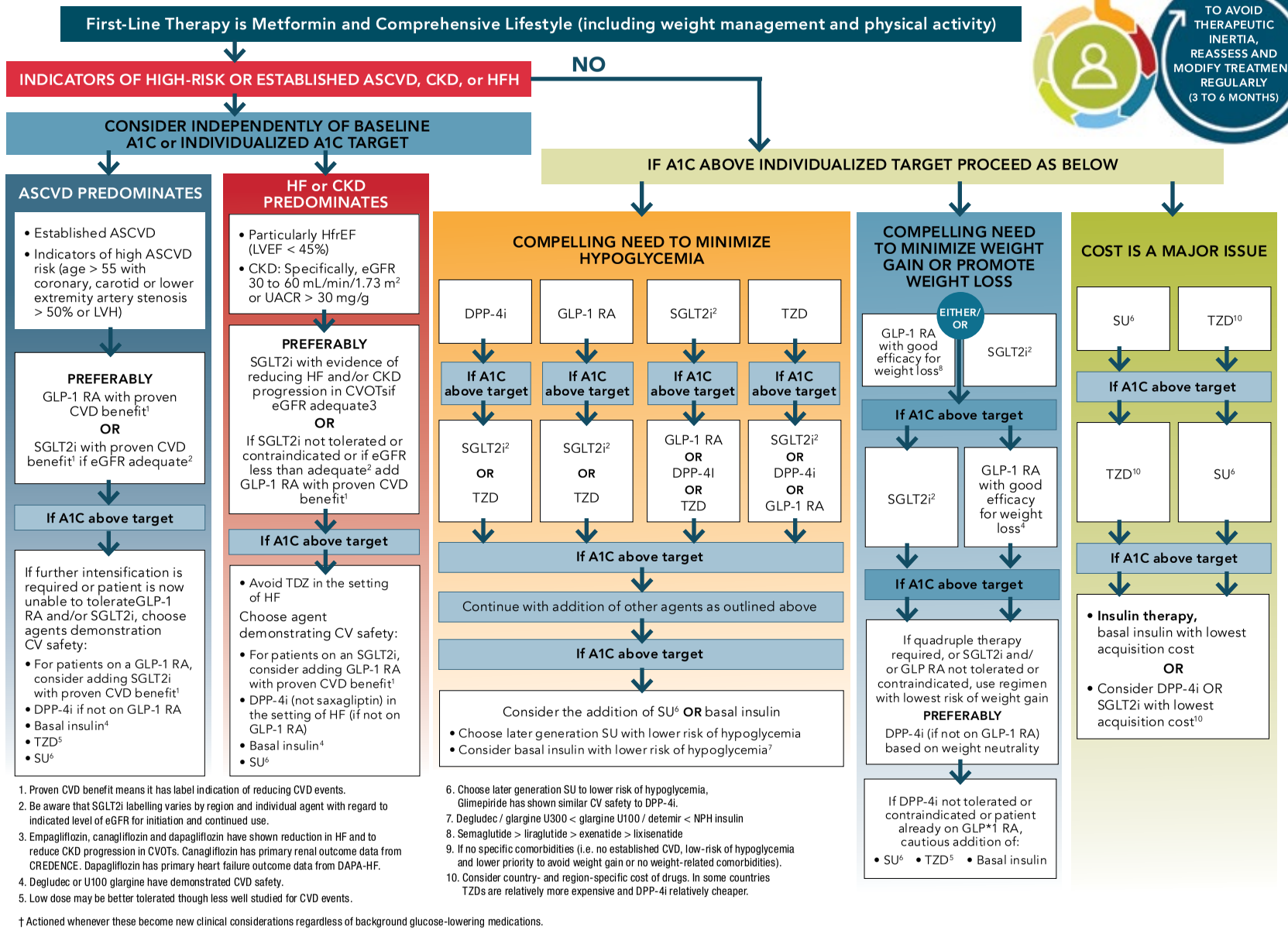
Given that most of these patients have obesity in conjunction with T2DM and CVD, the management strategies needed to reduce the myriad of risk factors and provide optimal care must consider the impact that treatment has on every organ in the body and not just on blood glucose levels. Current treatments have centered on increasing insulin availability (either through direct insulin administration or through agents that promote insulin secretion), improving sensitivity to insulin, delaying the delivery and absorption of carbohydrate from the gastrointestinal tract, or increasing urinary glucose excretion. Sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce blood glucose by increasing urinary glucose excretion.

The 2020 American Diabetes Association (ADA) management guidelines for managing T2DM still have metformin as the preferred initial pharmacologic agent in combination with lifestyle management.[6] Metformin is safe, effective, inexpensive, and may reduce the risk of cardiovascular events and death. Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy.

In patients with contraindications or intolerance to metformin, a patient-centered approach should be used to guide the choice of pharmacologic agents.[6] Considerations include the following comorbidities: atherosclerotic cardiovascular disease (ASCVD), heart failure, chronic kidney disease, hypoglycemia risk, impact on weight, cost, risk for adverse events, and patient preferences. The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. Clinicians should consider initiating dual therapy in patients with newly diagnosed T2DM who have A1C ≥1.5% (12.5 mmol/mol) above their glycemic target.

For patients with established ASCVD or indicators of high ASCVD risk (such as patients > 55 years of age with coronary, carotid, or lower-extremity artery stenosis > 50 percent or left ventricular hypertrophy), established kidney disease, or heart failure, a SGLT2 inhibitor or a glucagon-like peptide 1 receptor agonist (GLP-1 RA) with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors. Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart

Exhibit 2: ADA Guideline for Pharmacologic Management of Type 2 Diabetes Mellitus[6]



1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF.
4. Degludec or U100 glargine have demonstrated CVD safety.
5. Low dose may be better tolerated though less well studied for CVD events.
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i.
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low-risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities).
10. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; CVOTs = cardiovascular outcome trials; DPP4i = dipeptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HF = heart failure; SGLT2i = sodium-glucose cotransporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione

Exhibit 3: Current SGLT2 Inhibitors
Canagliflozin (Invokana®)
Canagliflozin and metformin (Invokamet®)
Canagliflozin and metformin extended release (Invokamet® XR)
Dapagliflozin (Farxiga®)
Dapagliflozin and metformin extended release (Xigduo® XR)
Dapagliflozin and saxagliptin (Qtern®)
Empagliflozin (Jardiance®)
Empagliflozin and linagliptin (Glyxambi®)
Empagliflozin and metformin (Synjardy®)
Empagliflozin and metformin Extended release (Synjardy® XR)
Ertugliflozin (Steglatro™)
Ertugliflozin and metformin (Segluromet™)
Ertugliflozin and sitagliptin (Steglujan™)

failure coexists, SGLT2 inhibitors are preferred. For patients with type 2 diabetes and chronic kidney disease, consider use of a SGLT2 inhibitor or GLP-1 RA shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. Exhibit 2 shows the treatment algorithm for T2DM from the ADA.[6]

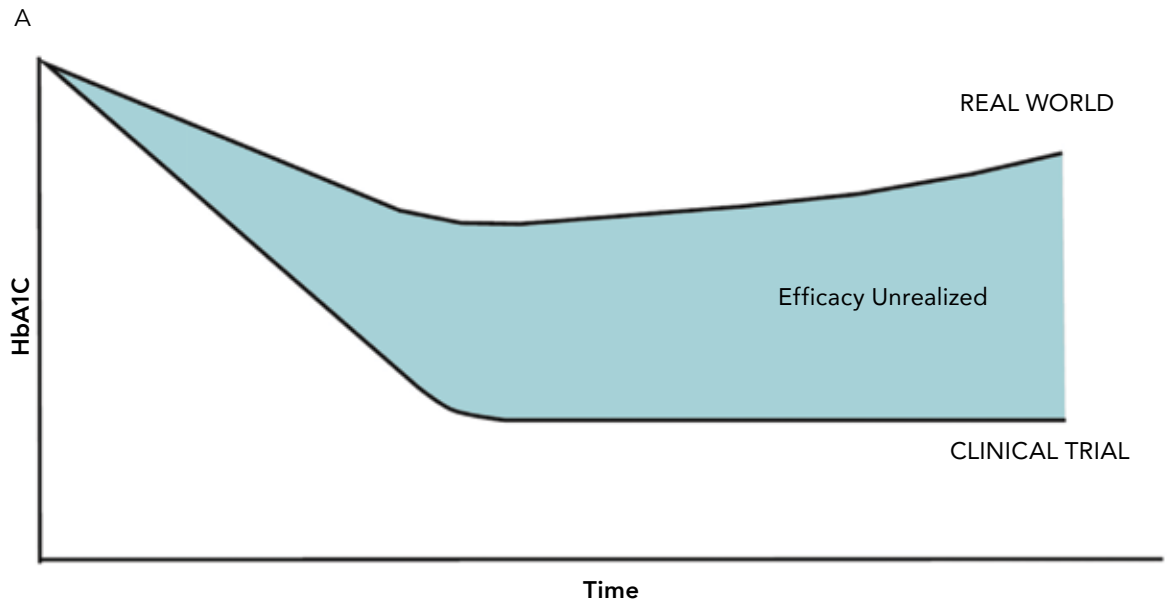
In healthy individuals, tubular glucose is absorbed, resulting in no urinary glucose excretion. Sodium-glucose co-transporters 1 and 2 contribute to the renal absorption of glucose. SGLT2 is responsible for 90 percent of the glucose reuptake in the first segment of the proximal tubule, while SGLT1 is accountable for the remaining 10 percent. Unlike other antidiabetic medications, which act by increasing insulin secretion or improving insulin sensitivity for the receptors, SGLT2 inhibitors prevent the reuptake of glucose into the bloodstream. This selective action spares the inhibition of SGLT1 present in other tissues, avoiding gastrointestinal effects.

SGLT2 inhibitors are relatively weak glucose-lowering agents, with mean reductions in A1C compared with placebo ranging between 0.4 to 1.1 percent depending on baseline level of hyperglycemia.[7] They have been studied as monotherapy and in combination with metformin, sulfonylureas, pioglitazone, sitagliptin, and insulin. In meta-analyses of clinical trials comparing SGLT2 inhibitors with placebo or active comparators (metformin, sulfonylurea, dipeptidyl peptidase-4 [DPP-4] inhibitors, insulin), SGLT2 inhibitors, compared with placebo, reduced A1C by approximately 0.5 to 0.7 percentage points.[8] In addition to A1C decreases, these agents decrease weight, increase HDL-C, decrease intestinal absorption of LDL-C, decrease albuminuria, and decrease blood pressure. The disadvantages are an increase in genitourinary infections and a risk of diabetic ketoacidosis, acute kidney injury, hypotension, and bone fractures. There are currently four SGLT2 inhibitors available which are also available in various combinations (Exhibit 3).

The most excitement with these agents is the CV benefits. There are now multiple large randomized controlled trials reporting statistically significant reductions in CV events in patients with T2DM treated with a SGLT2 inhibitor.[9] The empagliflozin trial evaluated CV morbidity and mortality in patients with T2DM and established CVD. Over 7,000 patients were randomly assigned to empagliflozin (10 or 25 mg) or placebo once daily. The majority of patients were taking metformin, antihypertensives, and lipid-lowering agents (equally distributed in both groups). Approximately 48 percent of patients in each group were taking insulin. The primary outcome (a composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in fewer patients assigned to empagliflozin than to placebo (10.5 versus 12.1 percent; hazard ratio [HR] pooled analysis 0.86, 95% CI 0.74 to 0.99).[10] The findings were driven by a significant reduction in risk of death from CV causes (3.7 versus 5.9 percent with placebo; HR 0.62, 95% CI 0.49 to 0.77). There was no significant difference in the occurrence of the individual components of nonfatal myocardial infarction (4.5 versus 5.2 percent with placebo) or nonfatal stroke (3.2 versus 2.6 percent).

The data for canagliflozin comes from two trials involving a total of 10,142 participants with T2DM and high CV risk (65.6% had a history of CV disease), where participants were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The rate of the primary outcome (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) was lower with canagliflozin than with placebo (occurring in 26.9 versus 31.5 participants per 1,000 patient-years; hazard ratio, 0.86; 95 percent confidence interval [CI], 0.75 to 0.97; $P < 0.001$ for noninferiority; $P = 0.02$ for superiority).[11] Although, on the basis of the prespecified hypothesis testing sequence, the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of

Exhibit 4: What Payers Often See



a sustained 40 percent reduction in the estimated glomerular filtration rate, the need for renal replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77). There was an increased risk of amputation (6.3 versus 3.4 participants per 1,000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal.

More than 17,160 patients with T2DM, who had or were at risk for CVD were randomly assigned to dapagliflozin (10 mg) or placebo once daily. The majority of patients were taking metformin, antihypertensives, and lipid-lowering agents (equally distributed in both groups). Approximately 40 percent of patients in each group were taking insulin. Two primary efficacy outcomes were measured. For one co-primary outcome, dapagliflozin did not result in a statistically different lower rate of major adverse cardiovascular events (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P = 0.17).[12] Dapagliflozin did result in a statistically significant lower rate of cardiovascular death or hospitalization for heart failure (4.9% versus 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P = 0.005), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88). There was no difference between the two groups in death from any cause (6.2 versus 6.6 percent in the placebo group, HR 0.93, 95% CI 0.82 to 1.04).

The newest approved SGLT2 inhibitor is ertugliflozin. The CV benefit trial with this agent (VERTIS-CV) is ongoing and studying the safety and efficacy of ertugliflozin in T2DM patients with established ASCVD.[13] This trial includes older patients, those with kidney disease, and those with heart failure. The VERTIS-CV trial has completed enrollment of over 8,200 patients. Publication of the results from this trial are keenly anticipated because it will provide data on the glycemic efficacy of ertugliflozin in patients receiving specific anti-hyperglycemic treatments, in patients with stage 3A chronic kidney disease, and additional data on the safety of SGLT2 inhibitors in a population at high CV risk with regard to events of special interest such as amputations, fractures, and diabetic ketoacidosis.

Overall, there are several completed and ongoing studies about CV risk modification and diabetes. The findings from these studies need to be kept in perspective. The large cardiovascular benefit of empagliflozin and canagliflozin, while impressive, was in a very high-risk population with established CVD at baseline. The benefit in patients taking canagliflozin, in particular, must be balanced with the increased risk of amputations. The CV benefits of dapagliflozin were a lower rate of cardiovascular death or hospitalization for heart failure. The difference in glycemia between the treatment groups

was minimal, suggesting that extra-glycemic effects of the drugs were responsible for the CVD outcome.

The CV safety of an investigational dual SGLT1/SGLT2 inhibitor (sotagliflozin) in T2DM is being tested in the SCORED trial. This trial is aiming to recruit 10,500 patients with moderate renal impairment and high CV risk, and is scheduled for completion in 2022. The FDA turned down a new drug application for sotagliflozin to treat type 1 DM in early 2019; it is already approved in the European Union for this indication. Several other SGLT2 inhibitors including ipragliflozin, luseogliflozin, and tofogliflozin are already in use in Japan and may make their way to the U.S.

Glycemic control can minimize risks for retinopathy, nephropathy, and neuropathy in both type 1 and type 2 diabetes and has been shown to decrease the risk for CVD. Payers often see a significant difference in glycemic benefit between clinical trial outcomes and real-world outcomes (Exhibit 4). Prevention of cardiovascular morbidity is a major priority for patients with diabetes, but many patients with diabetes are not receiving recommended levels of health care, and development of systems of care involving disease management principles may be important in delivering improved care. Payers are challenged to develop better systems of care to manage both diabetes and the associated CV risk.

Conclusion

Diabetes is a complex and costly disease state. Cardiovascular disease and diabetes are closely linked, with the majority of diabetes deaths being due to CV disease. There is an increasing body of evidence that some agents have a positive impact on CV outcomes in diabetes. That evidence for the SGLT2 inhibitors is robust and continues to grow. Guidelines are evolving to direct appropriate selection of T2DM treatments based on CV risk.

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

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Best Approaches for Diagnosing, Treating, and Managing Patients with Major Depressive Disorder

Charles L. Raison, MD

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

Summary

There has not been the progression in the treatment of depression as there has been with many other diseases. In the early days of blockbuster antidepressants such as fluoxetine, many clinicians thought a cure had been found; however, that is not true. Only about one-third of patients achieve remission of their symptoms on the first antidepressant, and the best method to manage the rest of the patients is not known.

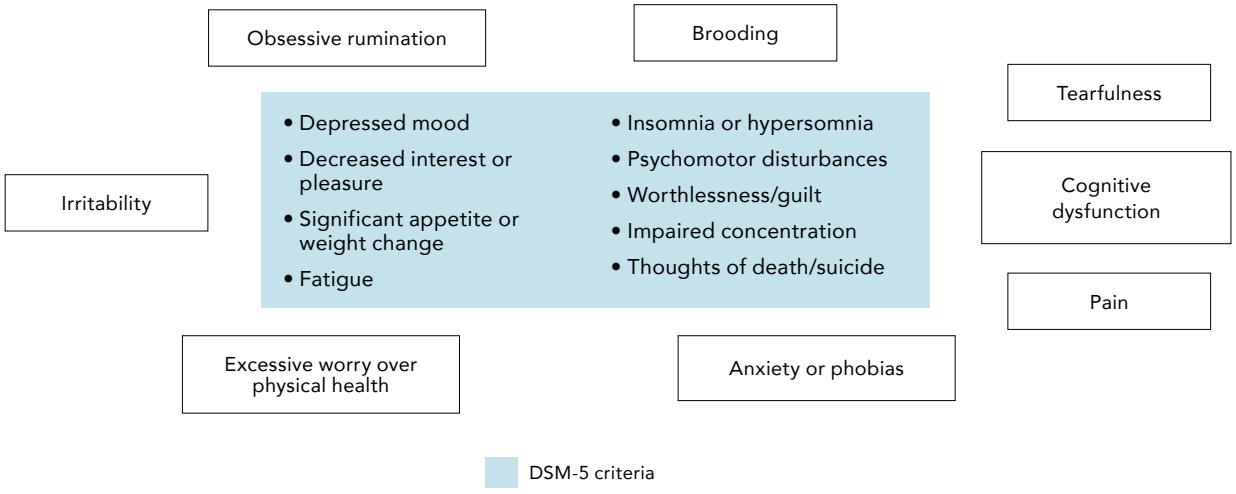
Key Points

- Approximately one-third of patients achieve remission on the first antidepressant.
- Response to antidepressants occurs early (~2 weeks).
- Non-improvement may actually reflect that the antidepressant is causing harm (compared to placebo).
- Non-response to one or two antidepressants is an ominous sign that treatment resistance will be likely.
- There are no clear best practice guidelines for treating patients who fail to respond to an antidepressant.
- Non-responders will receive at least some benefit from one of several strategies (more time on dose, augmenting, switching).
- Challenges with using currently available antidepressants include acute and chronic adverse events, tachyphylaxis, withdrawal syndromes, and withdrawal relapse.
- New agents are being approved, or are in development, that will provide options for patients not adequately treated with currently available antidepressants.

MAJOR DEPRESSIVE DISORDER (MDD) IS characterized by a persistently depressed mood and long-term loss of pleasure or interest in life, often with other symptoms such as disturbed sleep, feelings of guilt or inadequacy, and suicidal thoughts. It is one of the most common causes of medical morbidity.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for MDD were developed to capture the symptoms that best identify a patient with depression, but does not include all of the symptoms that can occur. As noted in Exhibit 1, many symptoms that clinicians may not associate with depression may be present.[1] Cognitive dysfunction with MDD is very impairing, but the criteria only ask about difficulty concentrating. Two fundamental types of cognitive dysfunction observed in MDD are cognitive biases, which include distorted information processing or attentional allocation toward negative stimuli, and cognitive deficits, which include impairments in attention, short-term memory and executive functioning.[2] Impaired executive functioning can lead to trouble making decisions. Most patients will also have some pain and anxiety, but neither is included in the criteria. Anxiety is a reliable predictor for poor

Exhibit 1: Major Depressive Disorder Diagnostic Criteria and Symptoms Outside the Criteria[1]



response to antidepressants. Antidepressants can also worsen the anxiety, especially the selective serotonin reuptake inhibitors (SSRIs).

One way to improve outcomes and clinician efficiency in this disease is to provide measurement-based care. This involves the systematic use of measurement tools to monitor progress and guide treatment choices and involves regularly scheduled visits. Clinicians should have patients fill out a measurement tool in the waiting room. Validated tools are helpful for both diagnosis and regularly monitoring symptom improvement, adverse events, and medication adherence. Also, the use of a flexible treatment algorithm with established critical decision points can improve outcomes.[3]

The current antidepressant effectiveness is not ideal. The Sequenced Treatment Alternatives to Relieve Depression (STAR-D) found that approximately one-third of patients have remission with a maximum dose first antidepressant at 12 weeks of therapy.[4] The majority of patients in this trial still had symptoms at 12 weeks of therapy; 16 percent had severe symptoms. A study using data submitted to the FDA for the licensing of four new-generation antidepressants found that drug-placebo differences increased as a function of initial severity, rising from virtually no difference at moderate levels of initial depression to a relatively small difference for patients with very severe depression.[5] Only at the upper end of the very severely depressed category did antidepressants provide clinically significant benefit over placebo. Another analysis found that all antidepressants beat placebo, and there was not one agent that was significantly more effective.[6]

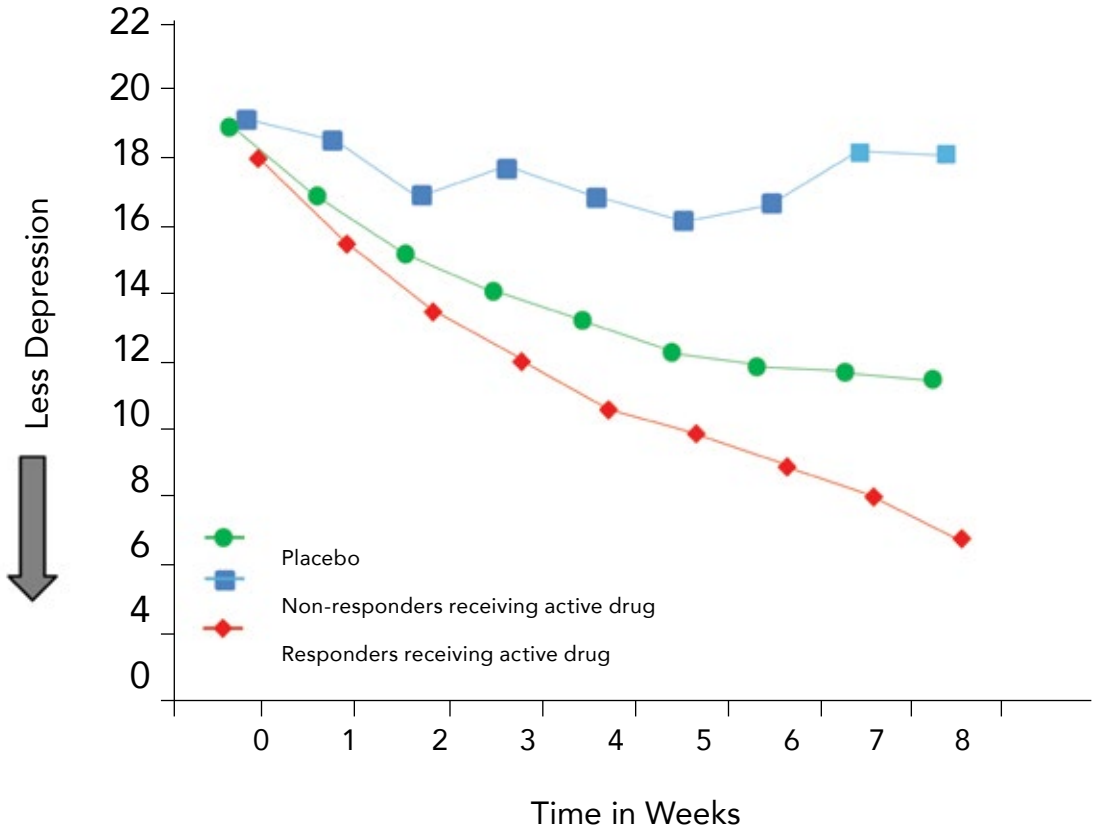
As shown in Exhibit 2, compared to placebo, antidepressants lower depression scores about three points more.[7] Three points on the Hamilton Depression Scale is considered to be the lowest possible significant difference between two agents. There are also a large number of non-responders which may not respond to the first antidepressant.

Unfortunately, the common practice today is to start the patient with depression on an antidepressant and have them return in eight weeks. The problem here is that optimal response requires much more frequent visits. The majority of effect is going to be seen in the first two weeks, which is contrary to the popular belief that it takes six to eight weeks to see efficacy. Optimally, the patient should be seen two weeks after starting medication. If they are not responding, therapy needs to be changed at that point. If they are responding, they probably need to be seen every two weeks for the first two months of therapy.

The options if the first antidepressant fails are increasing dose, antidepressant augmentation, or switching therapy. There are no clear best practice guidelines for which option to choose. The data on raising the dose is questionable because it has never been systematically studied. Currently, there is not a preference between augmentation and switching therapy. The STAR-D trial suggested that there was no difference in these two approaches.[8] If patients are achieving some response, many clinicians will choose augmentation.

Other challenges beyond efficacy are adverse events, withdrawal symptoms, and challenges in maintaining remission. An antidepressant is only as

Exhibit 2: Acute Antidepressant Effect versus Placebo Effect[7]



good as a patient's willingness to take it. The most common reasons for stopping an antidepressant are adverse events.[9] Sexual dysfunction and weight changes are two common adverse events which lead to discontinuation. Another significant reason is that people do not feel like themselves when they are taking antidepressants.

MDD is not typically an acute disease and, for the majority of patients, it is a chronic disorder. How to prevent it from becoming chronic is not yet known. When the first antidepressant does not work, the patient is typically going to have continued episodes of depression. Patients with multiple episodes of depression are more likely to have a chronic disease course. It is known that patients who reach true remission are less likely to relapse, and long-term antidepressant therapy appears to reduce recurrence in medication responders.[10]

Because MDD tends to be chronic, many patients are on antidepressants for many years. Unfortunately, data on the effectiveness and safety of long-term use of antidepressants and augmenting agents are lacking. There are no definitive guidelines on how long to continue therapy, whether it needs to be life-long, and what are the long-term adverse events. It is known that patients who stay on therapy are much less likely to relapse. Medication persistence during remission is also important for preventing relapse. There are some data suggesting that antidepressants cause some type of change in the brain that makes it more likely that relapse will occur if the medication is discontinued abruptly. Importantly, a few weeks of tapering should be done to prevent provoking a relapse if antidepressants are discontinued.

There is definitely room for improvement in treating MDD. Vortioxetine (Trintellix®) is one of the newer agents which has a better adverse event profile compared with older agents and results in the lowest rate of sexual dysfunction adverse events. It has the best data revealing that it might actually help with the cognitive symptoms of depression that have been very difficult to treat. Exhibit 3 shows which agents have some data on improving cognitive dysfunction.[11,12] The cognitive benefits may be related to the mechanism of action where there is post-receptor antagonism of the 5HT-7 receptor.

Ketamine and esketamine are other advances in treating MDD. In past decades, an important

Exhibit 3: Evidence for Direct Impact on Cognitive Symptoms in MDD[11,12]

	Learning/ Memory	Attention/ Concentration	Executive Function	Processing Speed
Vortioxetine	1	1	1	1
Duloxetine	1		2	
Lisdexamfetamine				
Other (e.g., SSRI, SNRI, and bupropion)	3	3	3	3
Modafinil	3	3	3	3

Independent effect indicated by a priori specification, cognition as primary; pathoanalysis; subgroup analysis in non-responders and non-remitters.

Level 1 replicated placebo-controlled trial evidence with demonstration of independent effect.

Level 2 single placebo-controlled trial evidence with demonstration of independent effect.

Level 3 uncontrolled evidence (e.g., lacking placebo and case-series) with lack of demonstration of independent effect.

SSRI = selective serotonin reuptake inhibitor; SNR = selective norepinephrine reuptake inhibitor

role of glutamate in mood modulation has been hypothesized and ketamine, a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptors, has been demonstrated to be effective in both MDD and treatment-resistant depression. Patients can have an antidepressant response within hours of ketamine infusion which lasts about a week.[13] Additionally, it has a very rapid effect on suicidal ideation.[14] Multiple doses over time result in sustained resolution of depressive symptoms. It is typically given twice a week for six doses, then weekly, and then periodically, if symptoms return. In one study, 66 percent of patients achieved remission and 91.6 percent had at least some response as measured by depression scales.[13] Typically, the antidepressant that the patient was previously taking is continued during and after ketamine treatment.

Ketamine is usually a racemic mixture consisting of two enantiomers, (R)- and (S)- ketamine, and it is mostly metabolized in norketamine, an active metabolite. (S)-ketamine has been reported as approximately four times more active, having better pharmacokinetic properties and being more tolerable than (R)-enantiomer.[15] Also, (S)-ketamine has been found to induce less psychotomimetic adverse events (e.g., dissociation and hallucinations). Esketamine (Spravato™), a nasal formulation of (S)-ketamine, was recently FDA approved, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression. In clinical trials of esketamine, treatment-resistant depression was defined as adults who were currently struggling with major depressive disorder and who had not responded adequately to at least two different antidepressants of adequate dose and duration in the current episode. Esketamine has to be given under medical supervision, the patient has to be monitored for two hours after the dose, and it is a Schedule III controlled substance. Approximately 70 percent of patients experience dissociative events during or immediately after administration. It is given twice a week for the first four weeks, then once a week for a month, and then either once a week or once every two weeks.

Esketamine costs approximately $590 to $885 per treatment session, depending on dosing. The initial month of therapy can cost from $4,720 to $6,785, while subsequent treatment can cost $2,360 to $3,540 per month. Ketamine infusion for depression usually costs $400 to $800 per treatment, and most ketamine clinics perform a series of six treatments over two to three weeks. Some providers offer four treatments over one to two weeks. It is important to note that ketamine is not FDA approved for depression. With both forms of ketamine, patients have to be observed for a period of time after administration and should not drive or operate machinery for at least 24 hours after dosing. Ketamine and esketamine are not a miracle cure for depression but have a unique mechanism of action and are an option for those not responding to current treatment.

A unique agent, brexanolone (Zulresso™), is available for treating postpartum depression. It is a neuroactive steroid gamma-aminobutyric acid (GABA), a receptor positive modulator. A 60-hour infusion of brexanolone produces significant antidepressant effect 30 days post-treatment.[16] The manufacturer is currently developing an oral version. This is the first treatment which is given once and appears to set in motion a compensatory effect in the brain. This would avoid possible harmful brain dependence that may occur with traditional antidepressants.

Psychedelics are also being investigated to treat MDD. Single-dose psilocybin produced high rates of response (~70%) and remission six months post-dosing.[17] Even ketamine has some of this long-term effect where antidepressants may not need to be continued. The promise of the next 10 years is to have a treatment that is given once, which resets the brain to treat MDD for a sustained period of time.

Conclusion

Outcomes in MDD can be improved by using measurement-based care and seeing patients frequently early in the treatment process. Unfortunately, many patients will not remit with any given treatment. Non-improvement may actually reflect that antidepressants are causing harm compared to placebo. Non-response to one or two antidepressants is an ominous sign that treatment resistance will be likely. There are no clear best practice guidelines for treating patients who fail to respond to an antidepressant. Many will get at least some benefit from one of several strategies (more time on dose, augmenting, or switching). Challenges with using currently available antidepressants include acute and chronic adverse events, tachyphylaxis, withdrawal syndromes, and withdrawal relapse. New agents are being approved or are in development that will provide options for patients not adequately treated with currently available antidepressants.

Charles L. Raison, MD is the Mary Sue and Mike Shannon Chair for Healthy Minds, Children, and Families, Professor in the School of Human Ecology and Professor in the Department of Psychiatry at the School of Medicine and Public Health at the University of Wisconsin-Madison, in Madison, WI.

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Improving Patient Outcomes in the Treatment and Management of Cystic Fibrosis: What's New in CFTR Modulator Therapy

Gregory S. Sawicki, MD, MPH

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

Summary

Cystic fibrosis (CF) management is a story of true medical progress. The advances have been in targeting both the symptoms and downstream effects of the disease; however, the real change has been in the development of agents targeted at the underlying genetic defect of the disease. These agents are not a cure, but they are changing the course of the disease.

Key Points

- Therapies targeting specific pathologic genetic mutations are available for approximately 90 percent of CF patients in the United States.
- Precision medicine for CF needs to focus beyond genetic therapies to include individual and health system determinants of outcomes.
- Many more therapies for CF are on the way.

MUCH SUCCESS HAS BEEN ACHIEVED IN managing cystic fibrosis (CF) since the 1950s and especially in recent decades. The median survival age has increased from about 28 years of age in 1990 to 41 years of age in 2015.[1] The majority of this advance in survival is not from the new therapies; the expectation today is for someone with CF to live a normal lifespan. It is now a disease of both childhood and adulthood; as of 2014, more patients are now over 18 years of age (52.7%) than are under. There are actually patients over the age of 70 in the CF Foundation Patient Registry. Additionally, the death rate from CF has been declining. In 2016, there were 373 deaths; the median age at death was 29.6 years. The number of adults with CF has an impact on the health care system because many clinicians who encounter adult patients do not have CF training.

The major measure of health in CF is lung function measured by forced expiratory volume in one second (FEV_1). Lung function outcomes in CF are improving (Exhibit 1).[2] Spirometry cannot accurately be done until about the age of five, but the FEV_1 at first test in those with newly diagnosed CF has improved about 100 percent with advances in care. Outcomes in CF have improved because of earlier diagnosis through newborn screening in every state, new therapies, and improved care delivery systems. The majority of cases in the United States (U.S.) are diagnosed based on positive newborn screening. Early diagnosis allows for early intervention, which prevents lung damage from occurring. Before widespread newborn screening, patients presented with symptoms and already had inflammation and damage to their lungs. CF-specific medications were approved by the FDA starting in the mid-1990s. Quality improvement programs, team-based care, treatment guidelines, sharing of best practices, and Cystic Fibrosis Foundation-accredited care centers have substantially improved care delivery for patients with CF. There are evidence-based guidelines for all aspects of CF care, including treatment of children and adults, managing bone disease, pulmonary complications, infection control, and many more.

CF is a genetic disorder of dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR), which results in altered ion transport

Exhibit 1: Lung Function Outcomes Have Improved[2]

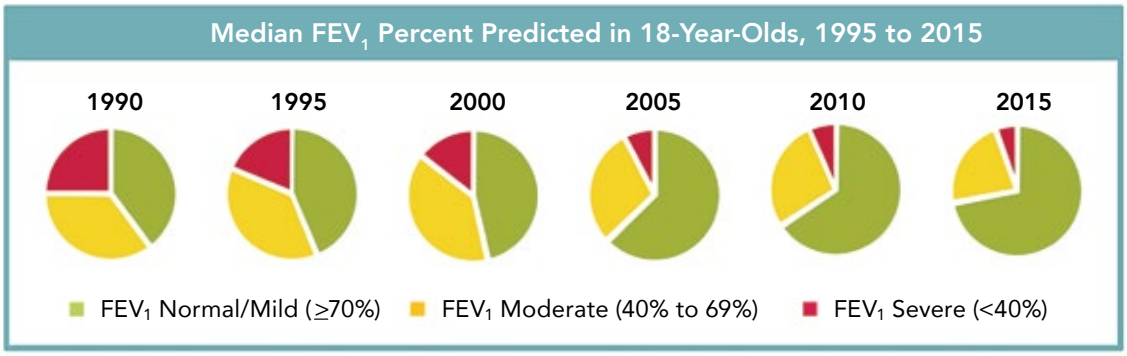
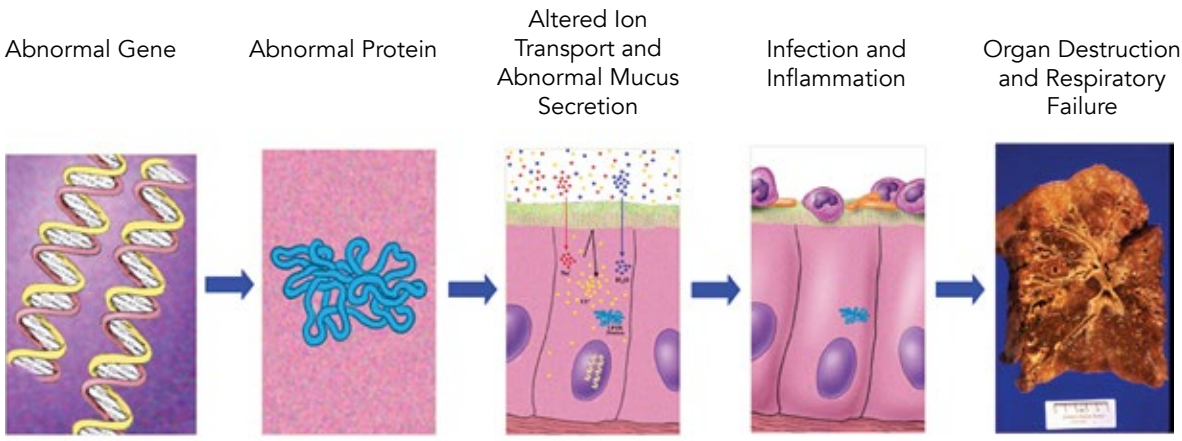


Exhibit 2: CF Pathophysiology



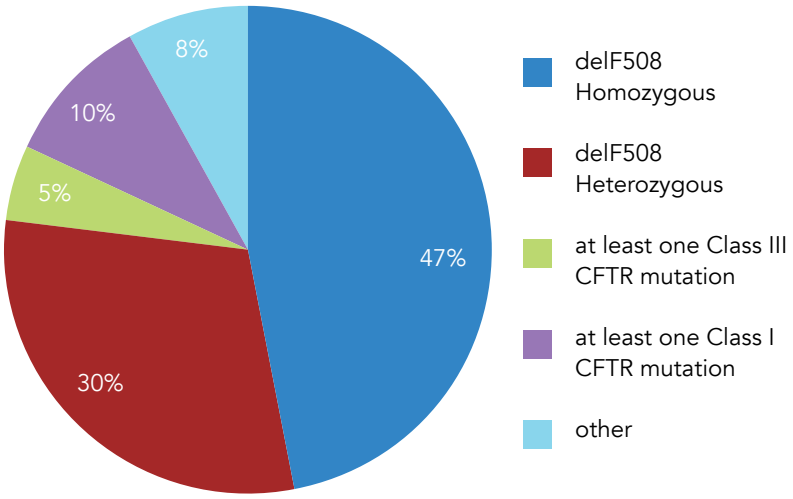
and abnormal mucus secretion (Exhibit 2). The resulting thick mucus in the airways is difficult to clear and leads to infections, inflammation, and ultimately end-organ damage of the lungs. The disease also affects the pancreas and gastrointestinal tract. There are five CFTR mutation classes that lead to differences in CFTR function, and more than 2,000 different mutations have been identified. Class I mutations result in no functional CFTR protein being made, Class II in misfolded CFTR protein that cannot make it to the cell surface, Class III in dysfunctional CFTR, Class IV in faulty opening of the CFTR protein, and Class V in insufficient quantity of functional CFTR. The majority of patients are either delF508 homozygous or heterozygous (Exhibit 3); delF508 is a Class II mutation. Class IV and V mutations result in less severe disease because the CFTR protein is partially functional or sufficient; these are the patients who get diagnosed as adults because they had chronic sinusitis, chronic pancreatitis, or male infertility.

Early lung disease in CF is a reality; therefore, aggressive treatment needs to be initiated as soon as possible. Approximately 60 percent of patients will have bronchiectasis by age three, and it has been detected in infants as young as three months old.[3] Inflammatory markers are also high in young children with CF.[4] The goal of CF therapy is to interrupt the cycle of thick mucus, lung infection, and inflammation to avoid the need for lung transplantation.

The therapeutic approaches in CF include mucolytics, airway hydrators, percussion devices, and chest physiotherapy to help remove mucus; oral and inhaled antibiotics to treat and prevent infection; anti-inflammatories to help remove obstruction and inflammation; and therapies that work to correct CFTR function. Lung transplant is a salvage treatment option.

The treatment burdens placed on patients with CF and their families are numerous and the burden is significant, regardless of age or disease severity. Every

Exhibit 3: Worldwide Distribution of CFTR Mutations



day, patients must coordinate medical treatments, chest physiotherapy, dietary supplementation, and pancreatic enzyme replacement. In addition, multiple respiratory medications must be administered, both oral and aerosolized.[5,6] Each additional CF-related therapy adds to the overall treatment burden in this patient population. In one study of adults with CF, the median number of therapies taken per day was seven, and the median number of minutes needed to complete therapy per day was 108 minutes.[7] Treatment burden is the most significant barrier to proper adherence.

The CFTR-specific therapies are either potentiators, correctors, or amplifiers. Potentiators help chloride flow through the CFTR protein channel at the cell surface. Correctors help the CFTR protein traffic to the cell surface and amplifiers increase the amount of CFTR protein that the cell makes. Amplifiers are still under investigation, but there are correctors and a potentiator available.

Ivacaftor (Kalydeco®) was the first CFTR-targeted therapy approved by the FDA. It is a CFTR potentiator that was first studied in those with G551D mutations. Since FDA approval in 2012, the indications for this agent have expanded to several Class III gating mutations, residual function, and splice mutations. It is now FDA approved for treating patients age six months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. Some of the CF mutations are so rare that a clinical trial to prove efficacy is not possible, so in vitro assay data have to be used. In those with responsive mutations, ivacaftor significantly lowers sweat chloride, improves lung function about 10 percent, reduces respiratory symptoms, helps the patient gain weight, and reduces exacerbations. It reduces the rate of decline in lung function over time.[8] The CF-specific therapies are not a cure for the disease, but they are disease modifying. Reductions in inflammation in the lungs and a significant reduction in hospitalizations has also been seen.[9]

Combining ivacaftor with lumacaftor (Orkambi®) was the next innovation in therapy. Lumacaftor is a CFTR corrector. Treatment of those who are delF508 homozygous results in a 61 percent reduction in exacerbations and a 56 percent reduction in the need for intravenous antibiotic therapy.[10] This combination more modestly improves FEV_1 by approximately 3 percent initially; it also reduces the rate of lung function decline over time.[11]

The next evolution in therapy was the introduction of tezacaftor in combination with ivacaftor (Symdeko®), which is indicated for the treatment of patients with CF age six years and older who are homozygous for the F508del mutation, or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. Tezacaftor is a CFTR corrector which is better tolerated than lumacaftor and has fewer drug interactions. About one-third of patients have to stop lumacaftor because of respiratory adverse events; this is not as much of an issue with tezacaftor. Many clinicians have switched to this combination from ivacaftor/lumacaftor. Similar to other therapies, there is significant improvement

in all aspects of the disease with this agent.[12] It is effective in those with residual function mutations (Class IV and V).[13]

The first triple combination therapy elexacaftor/ivacaftor/tezacaftor (Trikafta™) was FDA approved in October of 2019. It is approved for patients 12 years and older with CF who have at least one F508del mutation. Elexacaftor is a CFTR corrector which binds to a different site than tezacaftor and has an additive effect in improving cellular processing and trafficking of F508del-CFTR proteins. As with the other agents, it increases FEV_1 (10% to 13%), improves sweat chloride, reduces exacerbations, and improves body mass index (weight-to-height ratio) compared to placebo.[14,15]

With the available agents, precision medicine is available for over 90 percent of patients with CF in the U.S., based on their genetic mutations. To have true precision personalized medicine for patients with CF, therapeutic regimens will need to incorporate individual and health system factors which impact outcomes in this disease.

The CFTR-targeting therapies have a significant acquisition cost (~$300,000 annually). Ideally, these agents would be started in infants at the time of diagnosis and would be used for a lifetime. Pharmacy-related costs for CF patients have risen significantly since the availability of CFTR targeting therapies, whereas inpatient costs have been relatively stable based on MarketScan Commercial Data from 2010 to 2016.[16] Cost-effectiveness analyses have not shown enough cost offsets in the traditional sense for these agents to be considered cost-effective. It will be interesting to see the long-term impact of these therapies on longer-term outcomes such as the need for lung transplant and the death rate with CF.

The new CF therapy pipeline is very robust. In addition to numerous CFTR-targeting agents, there are mucociliary clearance agents, anti-inflammatories, pancreatic therapies, antibiotics, and gene therapy under investigation.

Conclusion

Health outcomes in CF have been improving for decades, in part due to advances in diagnosis, treatment, and care delivery. Novel therapeutics targeting the genetic basis of CF hold great promise; however, they are not a cure. How such therapies modify disease progression is still unclear and how these therapies will be incorporated into the complex CF treatment regimen is a work in progress. Precision medicine for CF needs to focus beyond genetic therapies. Individual and health system determinants of outcomes need to be evaluated.

Gregory S. Sawicki, MD, MPH is Director of the Cystic Fibrosis Center in the Division of Respiratory Diseases at Boston Children's Hospital and is Associate Professor of Pediatrics at the Harvard Medical School in Boston, MA.

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Optimal Management Strategies for Reducing the Cardiovascular Risk in Patients with Hypertriglyceridemia

Michael Miller, MD, FACC, FAHA

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

Summary

Until recently, the value of lowering triglycerides (TGs) with medications did not have proven benefits on cardiovascular outcomes despite the known atherogenic role for triglycerides. With the publication of a large well-designed study of a purified form of eicosapentaenoic acid, there is now evidence to support using this agent to reduce cardiovascular events in those who are on statin therapy who still have elevated triglycerides.

Key Points

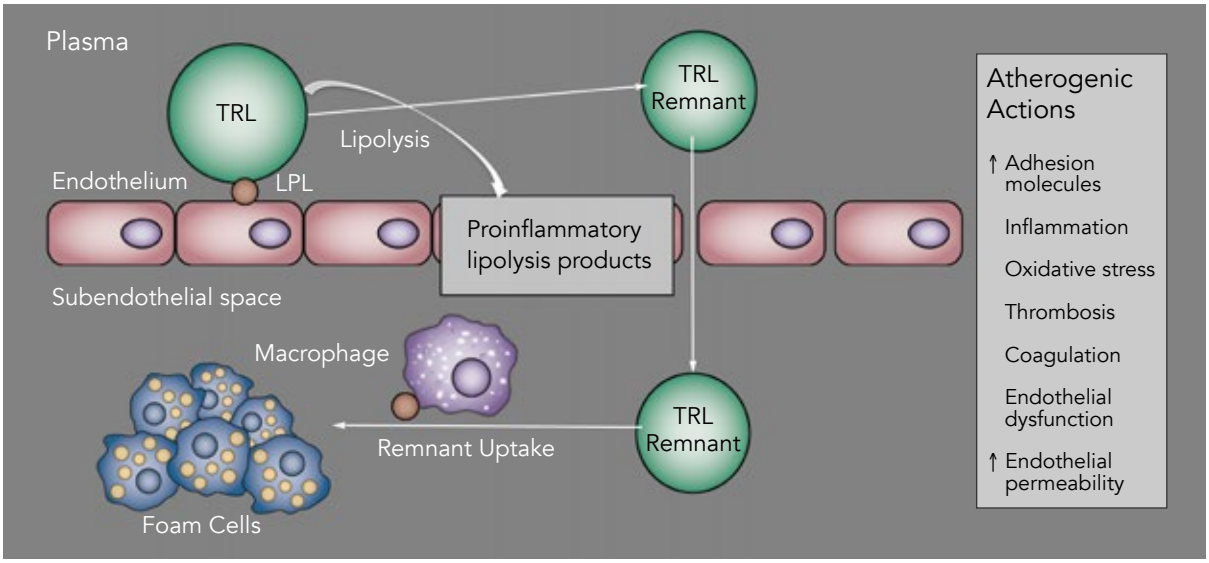
- Patients with high triglycerides remain at increased cardiovascular disease risk even when LDL-C is well controlled.
- REDUCE-IT is the first randomized controlled trial to evaluate primary and secondary prevention in patients with high triglycerides with controlled LDL-C.
- Icosapent ethyl significantly reduces cardiovascular events.
- Patients who fit the REDUCE-IT profile should be considered for this therapy.

ELEVATED TRIGLYCERIDES (TGS) ARE a significant atherosclerotic cardiovascular disease (ASCVD) risk factor.[1] A meta-analysis of 29 studies showed a strong and highly significant association between TGs level and coronary heart disease (CHD) risk.[2] Triglyceride-rich lipoproteins are lipolyzed and their remnants can enter the arterial wall where they interact with macrophages to form foam cells. This process induces a number of atherogenic processes shown in Exhibit 1.[3-5] Triglyceride-rich remnants are considered to be more atherogenic than LDL-C because these remnant particles do not need to be oxidized to be taken up by macrophages as LDL-C does.

High TGs are associated with residual risk, even when LDL-C is decreased below 70 mg/dL by statin therapy. In the PROVE IT-TIMI 22 trial, the combination of low on-treatment TG (< 200 mg/dL) and low on-treatment LDL-C (< 70 mg/dL) was associated with a 40 percent reduced risk for CHD endpoints (P = 0.001) compared with higher levels of on-treatment TG and low on-treatment LDL-C in adjusted analysis.[6]

Exhibit 2 shows the classification of fasting TG levels.[7,8] Less than 100 mg/dl is considered an optimal level. The 2018 American Heart Association AHA/American College of Cardiology (ACC) cholesterol guidelines recommend for adults 20 years of age or older with moderate hypertriglyceridemia (fasting or non-fasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.[9] In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5 percent or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin

Exhibit 1: Proposed Mechanisms for the Atherogenicity of TG-Rich Lipoproteins[3-5]



LPL = lipoprotein lipase; TRL = TG-rich lipoprotein

Exhibit 2: Classification of Triglyceride Levels[7,8]

Fasting Triglycerides (mg/dL)	
< 100	Optimal
< 150	Normal
150 to 199	Borderline high
200 to 499	High
≥ 500	Very high

Exhibit 3: Treatment Effect by Drug Class for Lowering TG Levels[8]

Drug Class	TG Reduction
Fibrates	30% to 50%
Immediate-release niacin	20% to 50%
Omega-3 fatty acids	20% to 50%
Extended-release niacin	10% to 30%
Statins	10% to 30%
Ezetimibe	5% to 10%

therapy. There are numerous secondary causes of hypertriglyceridemia such as diabetes, alcohol, obesity, pregnancy and several medications including estrogens, beta blockers, corticosteroids, retinoic acid, protease inhibitors, and antipsychotic medications.

Lifestyle interventions for lowering TGs include weight loss of 5 to 10 percent, a Mediterranean-style diet, and exercise of moderate intensity (e.g., brisk walking 4 to 5 mph, 30 m/d). These three interventions combined can reduce TGs by 50 percent. If lifestyle is not enough, then medication is considered. Exhibit 3 shows the impact of various classes on TGs.[8]

Although it is known that various classes of medications can reduce TGs, trials have not shown consistent cardiovascular (CV) outcome benefits for fenofibrate or niacin despite appreciable reductions in TGs.[10-14] A post hoc analysis for the fenofibrate studies did find a statistically significant benefit in the subgroup of patients with TGs greater than or equal to 204 mg/dL and HDL-C less than or equal to 34 md/dL.[12]

Fish oil dietary supplements are widely used; estimates suggest 7.8 percent of the population in the United Sates (19 million people) take fish oil supplements. Many people are using these supplements for their supposed cardiovascular benefit. In a meta-analyses of 10 studies, omega-3 fatty acids primarily as eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] given as supplements had no significant association with fatal or nonfatal coronary heart disease or any

Exhibit 4: Reduction in CV Events for Every 1,000 Patients Treated for Five Years with Icosapent Ethyl[18]

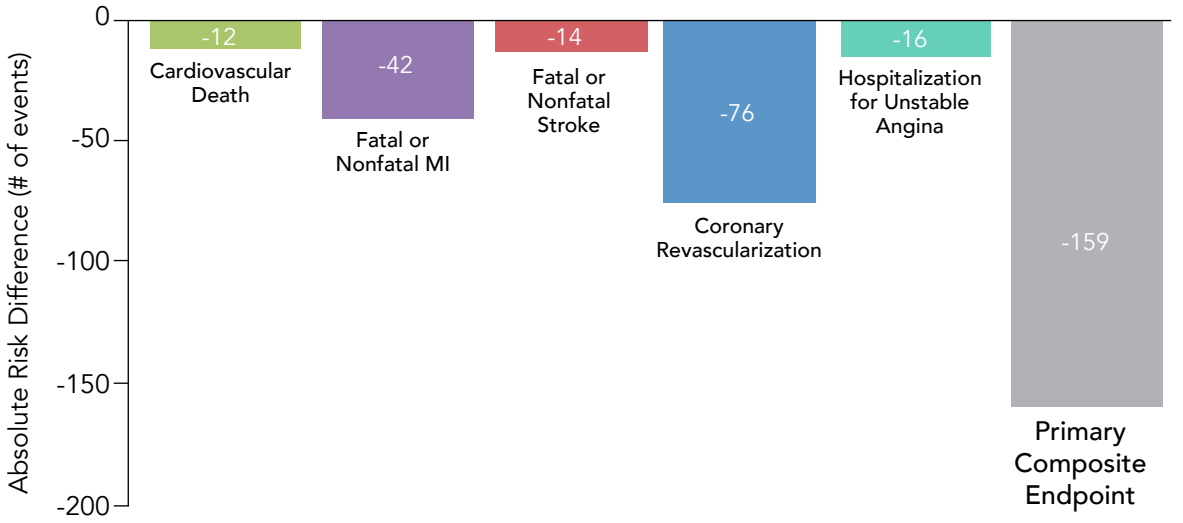


Exhibit 5: Candidates for Icosapent Ethyl Based on REDUCE-IT Inclusion Criteria and FDA Indication[17,19]

Study Inclusion Criteria	FDA Approved Indications
• Age ≥ 45 years with established CVD or ≥ 50 years with diabetes with ≥ 2 additional risk factors for CVD	• As an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and established cardiovascular disease or diabetes mellitus and two or more additional risk factors for cardiovascular disease.
• Fasting TG levels ≥150 mg/dL and < 500 mg/dL	
• LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥ 4 weeks	• As an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

major vascular events.[15] The lack of apparent effect of omega-3 fatty acids on ASCVD may be due to low doses (1 gram/day), use of dietary supplements, use of EPA/DHA products, and/or the lack of high triglyceride subjects. Overall, dietary supplement fish oils have not been proven useful for ASCVD prevention.

The choice of omega-3 fatty acid used for prevention may be important. The JELIS trial suggested a 20 percent CVD risk reduction with a purified form of EPA 1.8 gm/day in addition to a statin in Japanese hypercholesterolemic patients.[16]

This led to studies of purified EPA products including icosapent ethyl (Vascepa®), a highly purified EPA ethyl ester. In the REDUCE-IT trial published in 2019, icosapent ethyl 4 gm/day reduced CV events by 25 percent, including a 20 percent relative reduction in death due to cardiovascular causes, a 31 percent reduction in heart attack, and a 28 percent reduction in stroke.[17] The actual risk reduction (ARR) was 4.8 percent. This was a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting TG level of 135 to 499 mg per deciliter and LDL-C levels of 41 to 100 mg per deciliter. A total of 8,179 patients were enrolled (70.7% for secondary prevention of CV events) and were followed for a median of 4.9 years. As is

common in long-term trials, study drug adherence waned over time (from 80% down to 68%). Despite this, there was strong sustained treatment effect on total events. The only adverse event of icosapent ethyl that was more common in the icosapent ethyl group than in the placebo group was hospitalization for atrial fibrillation or flutter (3.1% versus 2.1%, P = 0.004); most clinicians do not think that this is a clinically significant issue because the rate of stroke was actually lower in the icosapent ethyl group. Serious bleeding events occurred in 2.7 percent of the patients in the icosapent ethyl group and in 2.1 percent in the placebo group (P = 0.06).

The number needed to treat (NNT) for icosapent ethyl based on the REDUCE-IT trial is 21; Exhibit 4 illustrates the reduction in various CV events with five years of treatment.[18] In a time to first event analysis of data from this study, icosapent ethyl substantially reduced the burden of first, subsequent, and total ischemic events.[18] Thus taking a medication which modifies risk for many years continues to provide benefits over time. Icosapent ethyl therapy should be considered for patients who fit the inclusion criteria for the REDUCE-IT trial and the FDA approved labeling (Exhibit 5).[17,19]

Conclusion

Patients with elevated TGs remain at increased CVD risk even when LDL-C is well controlled. The REDUCE-IT trial is the first randomized controlled trial to evaluate the effect of an omega-3 fatty acid on patients with high triglycerides and controlled LDL-C. Icosapent ethyl 4g/day was shown to significantly reduce CV events. Patients who fit the REDUCE-IT profile should be considered for this therapy.

Michael Miller, MD, FACC, FAHA is a Professor of Cardiovascular Medicine, Epidemiology and Public Health at the University of Maryland School of Medicine in Baltimore, MD.

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New Frontiers in the Treatment and Management of Relapsed/Refractory Multiple Myeloma: A Closer Look at the Role of Emerging Therapies

Ravi Vij, MD, MBA

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

Summary

The treatment of relapsed/refractory multiple myeloma (RRMM) has improved dramatically over the last decade, but the disease remains incurable for most patients. Potential cures are on the horizon with such treatments as CAR-T and BiTE cell therapies and genetically selected treatments.

Key Points

- A better understanding of disease biology, new agents, and use of combinations of agents are improving survival in MM.
- At relapse, multidrug combinations incorporating new agents are further improving outcomes.
- BCMA-targeted therapies (CAR-T, BiTEs) will likely provide the next major advance in MM therapy.
- Personalized medicine using genetic analysis for treatment selection is on the horizon.

MULTIPLE MYELOMA (MM) IS THE SECOND most common hematologic malignancy in the United States. There are approximately 10,000 new cases diagnosed annually. Because of improvements in therapy, patients are living longer with this disease. There are an estimated 100,000 to 125,000 people living with MM in the U.S. It is a disease of older individuals, with the median age at diagnosis being 70 years. MM is for the most part incurable, with a median survival of 10 years.

Initial treatment is a bone marrow transplant if eligible (~30% of patients), or combination chemotherapy. Patients receive treatment with maintenance treatments until disease progression occurs (relapsed or refractory multiple myeloma, RRMM). Current therapeutic strategies include combination and sequential treatments with corticosteroids, alkylating agents, proteasome inhibitors, immunomodulators, and monoclonal antibodies. These drugs prolong survival, but ultimately become ineffective.

Not every patient whose disease progresses needs treatment. Indications for treatment of RRMM include a clinical relapse or a significant biochemical relapse (Exhibit 1).[1] Patient-related factors, disease-related factors (especially high-risk features), previous treatment responses and toxicities will determine which treatment route is selected. The three options include retreatment with prior therapy, treatment with a new therapy, or enrollment in a clinical trial. Prior therapy can be selected in patients with relapse greater than six months after initial exposure, previous response to the treatment, and acceptable tolerance to the treatment.[2-4] When selecting a new therapy, triplet (or doublet) regimens are preferred over monotherapy. Immunomodulatory drug-based regimens are recommended if previously

Exhibit 1: Indications for Treatment at Relapse in MM[1]

Clinical Relapse

- Development of new soft tissue plasmacytomas or bone lesions
- Definite increase (≥ 50%) in size of existing plasmacytomas or bone lesions
- Hypercalcemia (≥11.5 mg/dL)
- Decrease in hemoglobin of ≥ 2 g/dL or to < 10 g/dL due to myeloma
- Risk in serum creatinine by ≥2 mg/dL due to myeloma
- Hyperviscosity requiring therapeutic intervention

Significant Biochemical Relapse without Clinical Relapse

- Doubling of M-component in two consecutive measurements separated by two months with the reference value of 5 g/L

  or
- In two consecutive measurements, any of the following increases:
  - Absolute levels of serum M protein by ≥ 10 g/L
  - Urine M protein by ≥ 500 mg/24 h
  - Involved FLC level by ≥20 mg/dL plus abnormal FLC ratio or by 25%, whichever is greater

treated with proteasome inhibitor-based therapy and vice versa.

There are many agents for treating relapsed MM (Exhibit 2). These agents are combined into various regimens, with triple therapy being the most common. The future is likely for drug class regimens which include the monoclonal antibodies to increase duration and depth of response. In addition to the medications listed in Exhibit 2, stem cell transplant is also an option at relapse. For patients who responded to an initial transplant, a second autologous transplant is an option.[5] The normal response for a standard risk patient who has had a first transplant is four to five years, with the second transplant typically lasting about half as long.

Treatment of MM is heading toward a possible cure. There are very long, deep remissions in some patients; among those receiving an autologous stem cell transplant (ASCT), the six-year probability of survival is 50 percent. Allogeneic SCT cures 10 to 20 percent of patients. Allogeneic transplantation for MM is reserved for patients with high-risk disease, and the majority are performed after an autologous transplant with reduced-intensity or nonmyeloablative conditioning regimens. Unfortunately, as many as 30 percent of patients will die within a year of allogeneic transplant.

Once MM is relapsed or refractory to immunomodulatory drugs and proteasome inhibitors, the probably of survival falls off dramatically.[6] Daratumumab (Darzalex®), as a salvage therapy, is helping with survival after immunomodulatory drugs and proteasome inhibitors have failed. This is an anti-CD38 monoclonal antibody that binds to MM cells that express CD38. Median OS for those treated with daratumumab who are non-refractory is 11.2 months; 9.2 months in those who are refractory to three or four lines of therapy; and 5.6 months in those who are pan-refractory.[7] It is also now FDA approved for use in combination with bortezomib, melphalan and prednisone for treatment of patients with newly diagnosed MM who are ineligible for ASCT.

Selinexor (Xpovio®) is the first-in-class exportin 1 inhibitor for treating MM. Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins that put the brakes on MM growth. This agent induces apoptosis in cancer cells through nuclear retention of tumor suppressor proteins and the glucocorticoid receptor, along with inhibition of translation of oncoprotein mRNAs. In combination with dexamethasone 20 mg daily in heavily pretreated RRMM, the overall response rate (ORR) was 21 percent and was similar for patients with quad-refractory (21%) and penta-refractory (20%) disease.[8] Among patients with high-risk cytogenetics, including t(4;14), t(14;16), and del(17p), the ORR was 35 percent (6 of 17 patients). The median duration of response was five months,

Exhibit 2: Available Anti-Myeloma Agents

IMiDs	Proteasome Inhibitors	Chemotherapy Anthracyclines	Chemotherapy Alkylators	Steroids	HDAC Inhibitors	mAbs
Thalomid® (thalidomide)	Velcade® (bortezomib)	Adriamycin	Cytoxan® (cyclophosphamide)	Dexamethasone	Farydak® (panobinostat)	Empliciti® (elotuzumab)
Revlimid® (lenalidomide)	Kyprolis® (carfilzomib)	Doxil® (liposomal doxorubicin)	Bendamustine	Prednisone	Zolinza® (vorinostat)	Darzalex® (daratumumab)
Pomalyst® (pomalidomide)	Ninlaro® (ixazomib)		Melphalan			

Exhibit 3: Investigational Agents in Myeloma Therapy

Oral Proteasome Inhibitors	Immunomodulatory	Histone Deacetylase Inhibitor	Kinase Inhibitors	Monoclonal Antibodies	Novel Mechanism	Immunotherapies
Oprozomib Marizomib	Avadomide Iberdomide	Ricolinostat	Afuresertib Ibrutinib (Imbruvica®) Trametinib (Mekinist®) Dabrafenib (Tafinlar®) JNJ-42756493 Sotatercept CV-5082 Vemurafenib (Zelboraf®)	Isatuximab Idasanutlin Belantamab mafodotin	Venetoclax (Venclexta®) Filanesib	Immune cell therapy CAR-T BiTEs MILs

Agents with brand names are already FDA approved for some other indication.
CAR-T = chimeric antigen receptor T cells; BiTEs = bispecific T-cell engager; MILs = marrow-infiltrating lymphocytes

and 65 percent of responding patients were alive at 12 months. It is FDA approved in combination with dexamethasone for the treatment of adult patients with RRMM who have received at least four prior therapies (penta-refractory) and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. Selinexor is an oral agent given twice a week. This agent is currently being studied for earlier line therapy (refractory to 1-3 lines of therapy) and in combination with lenalidomide for newly diagnosed disease.

Some of the numerous agents under investigation for RRMM are shown in Exhibit 3; many of these are likely to make it to market in the next few years. For example, isatuximab, an anti-CD38 monoclonal antibody, has been studied in heavily pretreated RRMM as monotherapy and in combination with other agents. It has been submitted to the FDA for review. Venetoclax (Venclexta®), a B-cell lymphoma 2 (BCL2) inhibitor, which is already approved for use in several types of leukemia, is being evaluated in patients who have t(11;14) abnormality and those with favorable BCL2 family profile (high BCL2:BCL2L1).

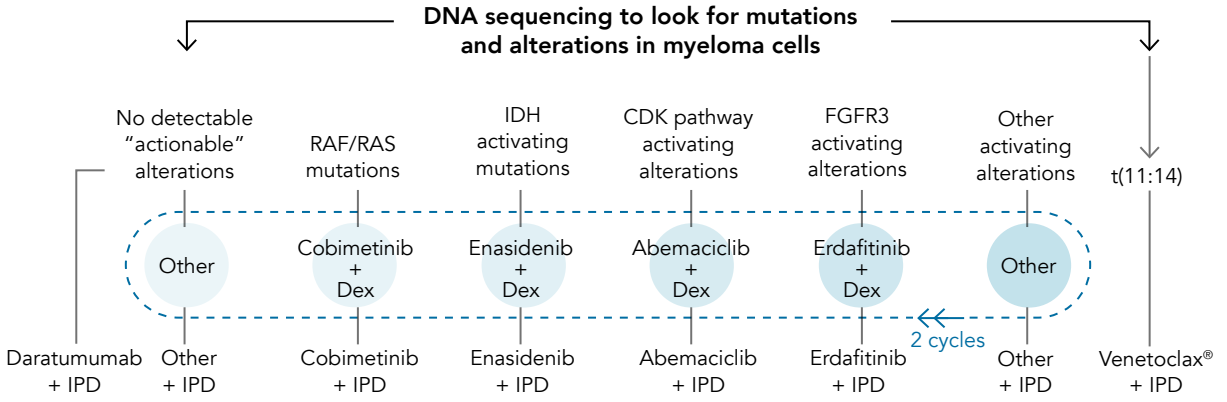
Checkpoint inhibitors (pembrolizumab, nivolumab) have been studied in MM treatment, but have essentially been eliminated as an option. They had no activity as a single agent; however, in combination with other agents, they did have activity but also produced excessive toxicity and deaths.The future and excitement in managing MM and other hematologic malignancies is in various cell-based therapies, which include chimeric antigen receptor T cells (CAR-T), bispecific T-cell engagers (BiTEs), and marrow-infiltrating lymphocytes (MILs).

Chimeric antigen receptors (CARs) are synthetic fusion proteins consisting of the variable portion of an antibody, known as a single-chain variable fragment (scFv) that can target an antigen displayed on the surface of a tumor cell. These receptors are attached to a patient's T cells in a laboratory and then reinfused into the patient. CAR-T cells do not rely on endogenous activation and co-stimulation, but receive supra-physiologic stimulatory signals through the CAR. CAR-T cell therapies targeting CD19, CD138, B-cell maturation antigen (BCMA), and others are being studied in RRMM.[9,10] In B-cell lymphomas, CAR-T infusions are producing a 30 percent rate of long-term remission. In MM the

Exhibit 4: MMRF MyDrug Trial (NCT03732703)

Relapsed refractory multiple myeloma, who have:

- received at least one prior but no more than three prior therapies
- exposed to both a PI and an IMiD
- had early relapse after initial treatment (within three years post-ASCT on maintenance or 18 months if unmaintained OR within 18 months of initial non-ASCT based therapy)



PI = proteasome inhibitors
iMID = immunomodulator
ASCT = autologous stem cell transplantation
IPD = ixazomib/pomalidomide/dexamethasone

data are not as robust. For example, the ORR in a BCMA CAR-T trial was 85 percent, including 15 patients (45%) with complete responses.[10] Six of the 15 patients who had a complete response have had a relapse. The median progression-free survival was 11.8 months (6.2 to 17.8). All 16 patients who had a response (partial response or better) and who could be evaluated for minimal residual disease (MRD) had MRD-negative status (≤10-4 nucleated cells). CAR-T therapy costs $350,000 to $500,000 for an infusion, plus hospitalization costs. It also takes at least two months from the start of the process (payer approval, plasmapheresis, and manufacturing of cell product) to infusion, which may mean this therapy is not an option for very ill patients.

MILs for myeloma have been in development for more than 10 years, with the first clinical trial published in 2015. Like CAR-T therapy, MILs are developed from T cells recovered from MM patients, expanded in a laboratory, and then reinfused as a cellular therapy. Conceptually related to tumor-infiltrating lymphocytes (TILs), which have demonstrated durable clinical remissions in melanoma, MILs are administered after a myeloablative therapy such as melphalan. Their activity in the bone marrow microenvironment creates the potential for a low relative risk of off-target effects.

BiTEs are also under development. The antigen recognition part of an antibody that identifies BCMA on the surface of myeloma cells and an antibody recognizing CD3 on a T cell are combined. Through this recognition, the two antibodies hook together, which allows the T cell to be brought to the myeloma cell. In a Phase I study evaluating AMG 420, seven of 10 patients with heavily pretreated RRMM, who were administered a 400-µg/day dose, responded to the therapy; four patients achieved a complete response (CR).[11] Moreover, the four patients with CRs and one patient who achieved a partial response had no minimal residual disease.

Personalized medicine strategies based on specific genetic markers in MM are also on the horizon. Widespread genetic heterogeneity has been shown for this disease, which has implications for targeted therapies. Frequent mutations in KRAS (particularly in previously treated patients), NRAS, BRAF, FAM46C, TP53, and DIS3 (particularly in nonhyperdiploid MM) are seen.[12] Mutations were often present in subclonal populations, and multiple mutations within the same pathway (e.g., KRAS,

NRAS, and BRAF) have been seen in the same patient. Genetic analysis-based treatment selection is being evaluated in the Multiple Myeloma Research Consortium Myeloma-Developing Regimens Using Genomics (MyDRUG) study (Exhibit 4).

Conclusion

Treatment of myeloma has evolved quickly over the past decade, due to better understanding of disease biology and new agents and the use of combinations that gives rise to deep responses. At relapse, multidrug combinations incorporating new agents are further improving outcomes. BCMA-targeted therapies (CAR-T, BiTEs) will likely provide the next major advance in MM therapy. In the future, personalized medicine strategies based on specific genetic markers are likely to evolve.

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

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Overcoming Challenges with a Patient-Centered Approach in the Management of HIV: Emerging Treatment Strategies for Improved Outcomes

Ian D. Frank, MD

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

Summary

Human immunodeficiency virus (HIV) infection is no longer a death sentence, but is now a chronic disease. The modern era of HIV therapy that started in 1986 has brought about these dramatic changes in longevity. Many patients can manage on a single-tablet once-a-day regimen.

Key Points

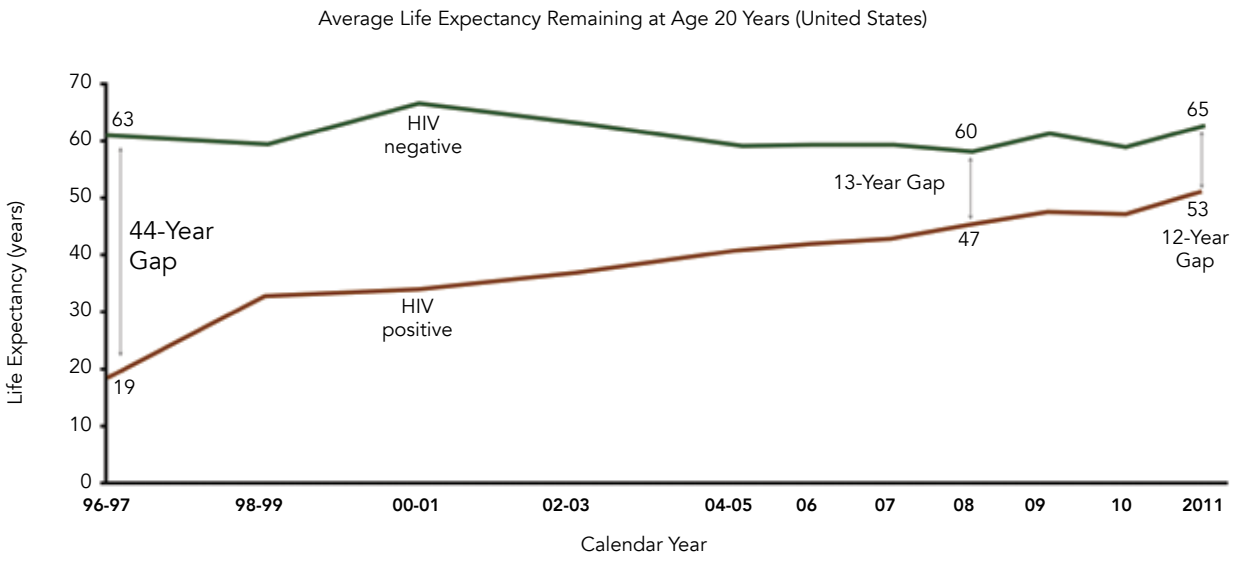
- People with HIV infection are living longer, and aging with HIV infection is associated with an increased risk of common comorbidities.
- Currently recommended therapies are highly effective with low rates of treatment failure.
- Effective therapy reduces costs, no matter what regimen is used.
- Generics and less expensive combinations might be able to replace more expensive agents in some situations.

LIFE EXPECTANCY FOR THOSE WHO ARE HIV-positive has improved dramatically, to the point where those with the infection can live an almost normal lifespan with adequate antiretroviral therapy. As of 2011, there was still a 13-year gap between those HIV-positive and uninfected persons (Exhibit 1).[1] When individuals who have a hepatitis C co-infection, a history of intravenous drug use, or who smoke, the gap is only about five years.

Many factors have contributed to the increase in life expectancy, and one of these contributing factors is there are now effective, one-pill, once-a-day regimens that are better tolerated and easier with which to be adherent than the multiple pills per day regimens of the past. Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality and to prevent the transmission of HIV to others.[2] The treatment guidelines recommend initiating ART immediately (or as soon as possible) after a HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV. When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence.

The regimens in Exhibit 2 are the recommended initial regimens for most people with HIV.[2,3] All but one of the recommended regimens contains an integrase inhibitor and two nucleoside reverse transcriptase inhibitors (NRTIs). Exhibit 3 shows some of the advantages and disadvantages of selecting a particular integrase inhibitor. Given the many options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions, access, and cost. Because patients must stay on therapy for

Exhibit 1: Life Expectancy Between HIV-Positive and Uninfected Persons (1996-2011)[1]



Kaiser Permanente Northern California (1996 to 2011): HIV-positive (n = 25,768) and matched non-HIV-infected adults (n = 257,600). Males (91%) and MSM (75%).

Exhibit 2: Recommended Regimens for First-Line ART in most Patients with HIV Infection[2,3]

Department of Health and Human Services	International Antiviral Society-USA
• Bictegravir/tenofovir alafenamide/emtricitabine (Biktarvy®)	• Bictegravir/tenofovir alafenamide/emtricitabine
• Dolutegravir/abacavir/lamivudine (Triumeq®)*	• Dolutegravir/abacavir/lamivudine
• Dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate)	• Dolutegravir plus /emtricitabine
• Dolutegravir/lamivudine (Dovato®) **	
• Raltegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate)	

Brand names note single tablet regimens
* Only for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection
** Except for individuals with HIV RNA >500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

their lifetime and inadequate adherence can lead to resistant virus, regimens must be as convenient as possible. Thus, most clinicians try to choose the one-pill, once-a-day regimen. To address individual patient characteristics and needs, the guidelines provide a list of recommended initial regimens in certain clinical situations and guidance on choosing a regimen based on selected clinical case scenarios. As shown in Exhibit 4, comorbidities are common in patients with HIV.[4] This is especially the case in the over 65 years of age population, where the number of comorbidities are significantly higher in those infected, compared to a non-infected cohort.[5] Clinicians are cautioned to always consult the online version of the Department of Health and Human Services (DHHS) guidelines because the guidelines are constantly being updated.

One exciting innovation has been the use of

Exhibit 3: Choosing Among Integrase Inhibitors for First-Line Therapy

Agent	Advantages	Disadvantages
Bictegravir	• Single tablet regimen (STR) once daily with TAF/FTC	• Least amount of data
	• Few drug or food interactions	• Only available as an STR
	• High barrier to resistance	• No safety data in pregnancy
Dolutegravir	• Single agent or STR once daily with ABC/3TC	• Increases metformin levels
	• High barrier to resistance • Few drug or food interactions • A preferred option in pregnancy guidelines during second and third trimester	• Recent concerns regarding conception/early pregnancy safety
Elvitegravir	• STR once daily with cobicistat plus TAF/FTC	• Numerous drug–drug interactions
		• Do not use during pregnancy
Raltegravir	• Longest experience	• Multiple pills
	• Few drug or food interactions	• No STR
	• A preferred option in pregnancy guidelines	• Limited safety data at conception

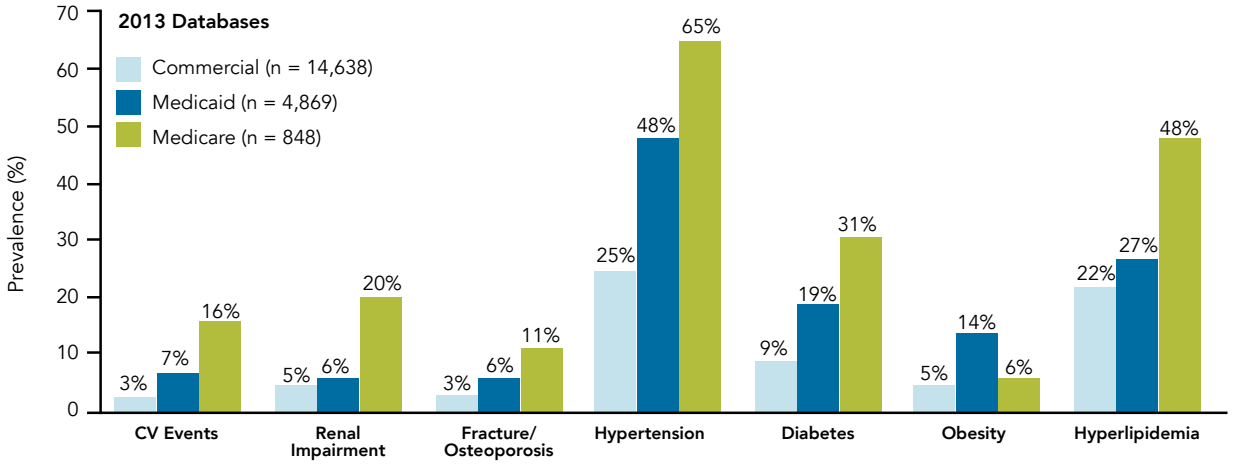
only two agents in an ART regimen. For several years, three agents have been used. There are now data with dolutegravir/lamivudine (Dovato) showing it has equivalent efficacy to a three-drug regimen.[6] This combination is not recommended for individuals with HIV RNA > 500,000 copies/mL, hepatitis B coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or hepatitis B testing are available. This combination is available as a single-drug regimen, has no protein pump inhibitor interaction, is safer for kidney and bone than a regimen containing tenofovir disoproxil fumarate (TDF), has adequate barrier to resistance, avoids most drug-drug interactions, and has a price advantage over some of the three drug regimens. This two-drug regimen is now one of the recommended regimens for initial therapy.

Clinicians will occasionally have to consider switching therapy in patients with good virologic suppression. Switching is primarily to get a better, safer regimen than the one the patient is currently on. One reason is a switch to a single-tablet regimen is for convenience, which aids in improving adherence. Development of a new comorbidity may also lead to the need to make a switch. Low bone density can be an example; switching from TDF to tenofovir alafenamide (TAF) can improve bone density.[7,8] Drug-drug interactions are another reason for changing therapy. For example, patients requiring proton pump inhibitors need to avoid rilpivirine and atazanavir. A woman contemplating pregnancy should be taken off dolutegravir, if currently receiving it.

Patients with HIV have an increased risk of developing heart disease. Thus it is important to note that traditional cardiovascular disease (CVD) risk calculators (Framingham, ACC/AHA) underestimate CVD outcomes in HIV-positive patients.[9] The risk for chronic kidney disease is also elevated for those with HIV infection who are treated with ART and the five-year risk rises with increasing age.[10] Because of the risk for heart and kidney disease, antiretrovirals, which impact this risk, need to be avoided. Exhibit 5 presents some considerations when switching therapies. Some patients are reluctant to change effective therapy, even if they are having significant adverse events.

One therapy on the horizon is a long-acting injectable given intramuscularly. GS-6207 is the first HIV capsid inhibitor being investigated. HIV capsid is essential at multiple stages in the viral life cycle. This agent appears to be comparable to an effective oral regimen for viral suppression and is given every 12 weeks. Injectable cabotegravir and rilpivirine given every four or eight weeks is also under investigation.

Exhibit 4: Comorbidities of Newly Diagnosed HIV Patients in the U.S.: A Longitudinal Analysis of Prevalent HIV Patients[4]



≥ 1 outpatient claim, ≥ 6 months of continuous care, and contributed data for 2003 – 2013 (continuous enrollment during the entire year). Baseline Commercial/Medicaid/Medicare: mean age 42/41/71 years; male: 78%/51%/64%.

Exhibit 5: Considerations When Switching Regimens in Virologically Suppressed Patients

Drug Resistance:

- Review ART history for possible viral failure
- Review all available resistance test results
- If earlier resistance uncertain, only consider switch if new regimen likely to maintain suppression of resistant virus
- Caution when switching from boosted PI to another class if full treatment/resistance history not known
- Consult an expert when switching if resistance to ≥1 class
- Within-class switches usually maintain virologic suppression if no resistance to drugs in that class are present

Safety:

- Review ART history for intolerance
- Must be HLA-B*5701 negative if considering ABC
- Consider drug–drug interactions with comedications

Comorbidity:

- HBV coinfection
- Cardiovascular disease or risk
- Renal function
- Bone mineral density
- Pregnancy
- Other coinfections

ART = antiretroviral therapy; PI = protease inhibitor; ABC = abacavir; HBV = hepatitis B virus

All data indicate that everyone with HIV infection should be on antiretroviral therapy and that achieving a viral load < 200 copies/mL prevents ongoing transmission. Patients with viral loads < 200 copies/mL rarely get HIV-related complications that require hospitalization. Avoiding hospitalization and complications of therapy are the major opportunities to save costs in this disease. Failure to link and retain people in care in the United States is the main obstacle to successful outcomes of HIV. For many, social support is critical for treatment success. Missing doses leads to resistance as well as loss of immunologic benefit. The typical HIV regimen costs more than $2,000 per month (wholesale acquisition cost). Even the generic medications approach this monthly cost. The newer regimens approach $3,000 or more monthly. Effective therapy reduces costs, no matter what regimen is used. Generics and less expensive combinations might be able to replace more expensive agents in some situations.

Conclusion

People with HIV infection are living longer. Aging with HIV infection is associated with an increased risk of common comorbidities. Currently recommended therapies are highly effective with low rates of treatment failure. Switching therapy can be important to simplify regimens and avoid toxicities and drug-drug interactions. New treatment strategies and new drugs continue to be developed.

Ian D. Frank, MD is a Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, PA.

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Optimizing Treatment Strategies in the Management of Pulmonary Arterial Hypertension to Improve Patient Outcomes

Robert P. Frantz, MD, FACC

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

Summary

Pulmonary arterial hypertension (PAH) is a rare, severe disease characterized by worsening right-sided heart failure, decreasing functional status, and poor survival. Multiple therapies are required to improve survival and keep these patients out of the hospital. Diagnosis and management of this disease is complex and typically requires a PAH specialist.

Key Points

- Early identification of PAH is important.
- Screening for PAH is important for people and family members who are at risk for developing the disease.
- Parenteral prostanoids are a key therapy for advanced disease.
- Double or triple combination therapy is becoming standard of care for most patients.

PULMONARY ARTERIAL HYPERTENSION (PAH), a rare type of pulmonary hypertension, is a panvasculopathy of small pulmonary arteries where there is increased cellular proliferation and decreased apoptosis. This leads to intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, inflammation, and vasoconstriction in the pulmonary vasculature. It is a progressive disease that can be roughly classified into three phases or categories (Exhibit 1):

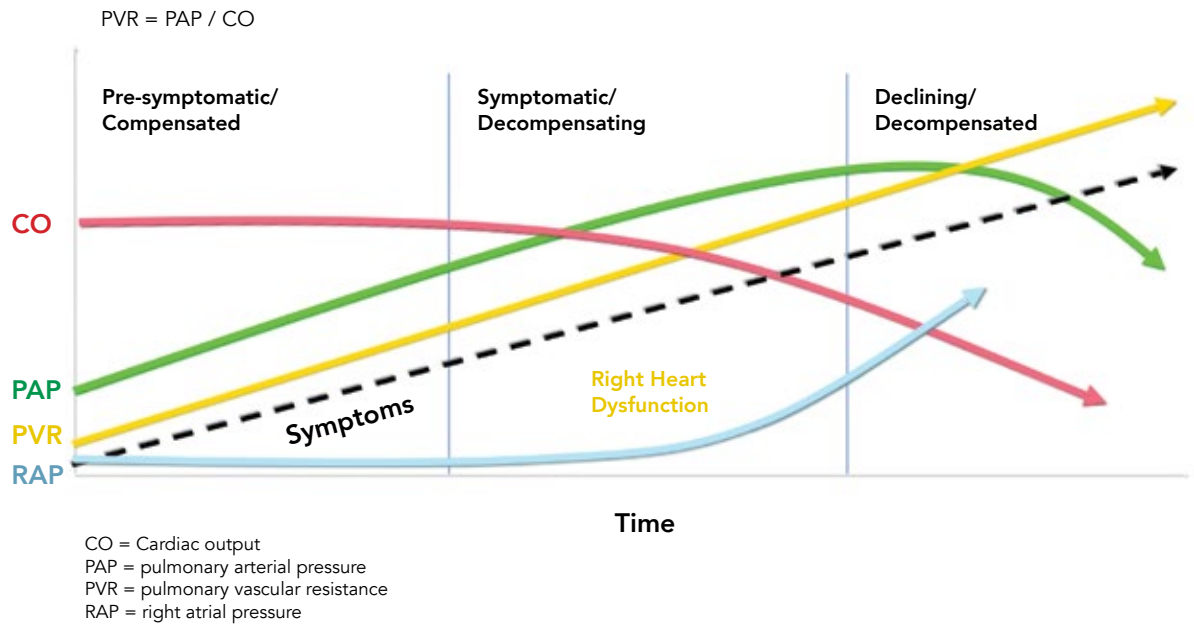
1. Pre-symptomatic or compensated
2. Symptomatic or decompensating
3. Declining or decompensated

Hemodynamically, a steady rise is seen in peripheral vascular resistance (PVR) and pulmonary arterial pressure (PAP) in order to sustain cardiac output (CO) as the vascular disease worsens. As long as the right ventricle is able to compensate for the resistance, pressure continues to increase as PVR increases. The increased right ventricle workload causes it to hypertrophy and its efficiency falls, right heart failure ensues, and PAP will fall as the patient decompensates. Failure to maintain CO leads to the symptoms of the disease, which include shortness of breath, chest tightness, dizziness, and syncope, especially with activity. The updated hemodynamic definition of PAH is a mean PAP > 20 mmHg, pulmonary artery wedge pressure (PAWP) ≤ 15, and PVR > 3.[1]

Because of residual lung and heart capacity, PAH gets diagnosed later in the disease process; there has to be a large amount of damage before major symptoms are present that will cause someone to seek care. Forty to 60 percent of the pulmonary vasculature can be compromised before symptoms occur.

PAH has to be distinguished from other forms of pulmonary hypertension. It is important to have a proper diagnosis because the therapies for PAH

Exhibit 1: PAH is a Progressive Disease



can cause problems for those with other types of PH; diagnosis probably requires referral to a PAH specialist. Chronic thromboembolic pulmonary hypertension (CTEPH) especially should be ruled out because it can be effectively treated with surgical thromboendarterectomy, balloon pulmonary angioplasty, and riociguat. A ventilation/perfusion lung scan should be done to rule out CTEPH.[2] Right heart catheterization is required for diagnosis of PAH and patients should not be started on PAH-specific therapy without results from this test.

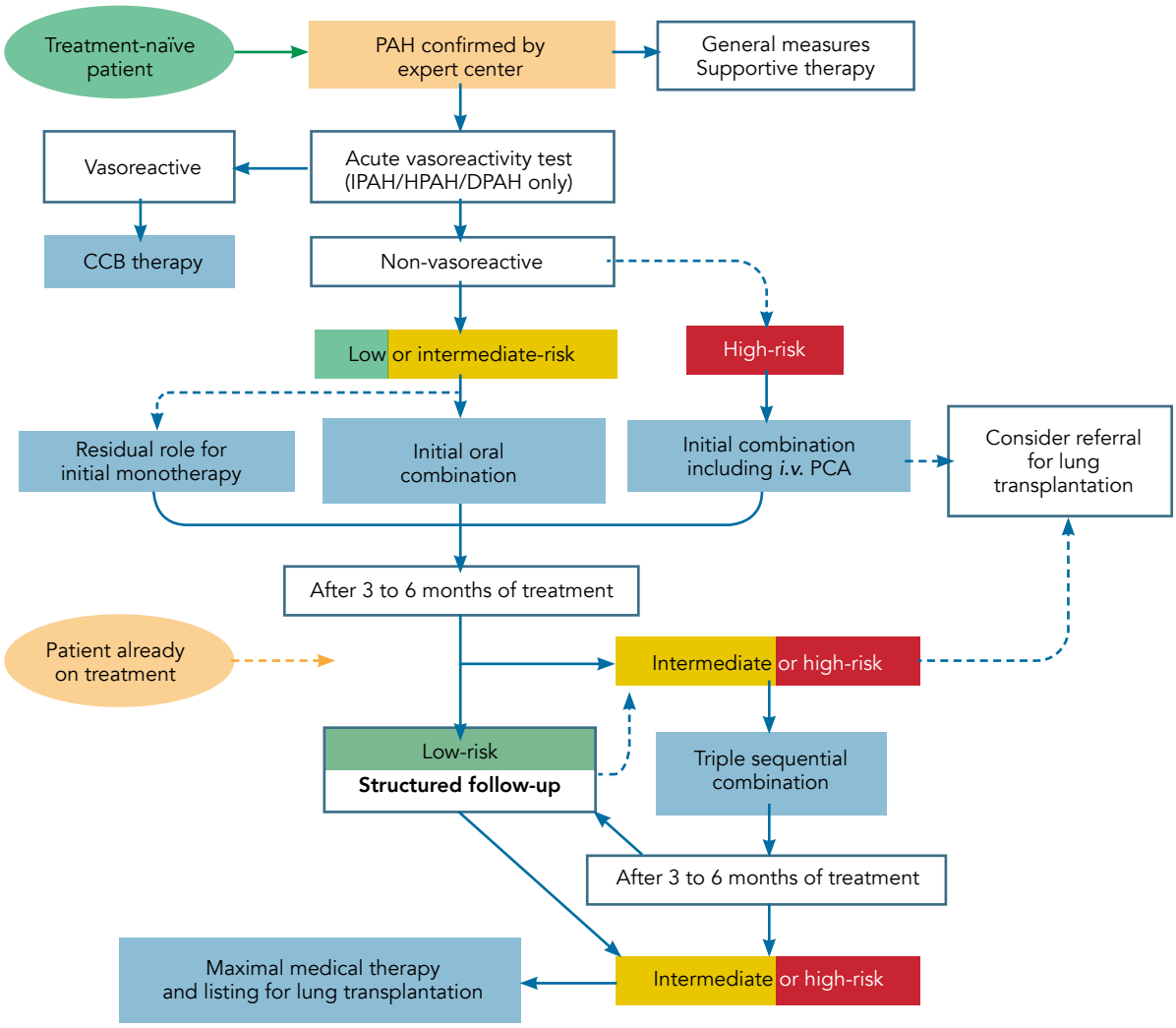
PAH can be idiopathic, familial, or associated with various conditions/medications. These include connective tissue disorders (scleroderma), congenital heart disease, portal hypertension, HIV infection, schistosomiasis, hereditary hemorrhagic telangiectasia, drugs such as methamphetamine, and toxins. Patients with these predisposing factors should routinely be screened for PAH. Siblings and children of women with PAH should be screened for familial PAH. Screening can help identify the disease earlier in the process so that outcomes may be able to be altered.

The goals in treating PAH are to normalize cardiovascular function and laboratory values as much as possible, reduce hospitalizations, allow patients to maintain function, and improve overall survival.[3] One aspect to treatment which can make a significant difference for patients is detecting and treating hypoxemia, which is a potent vasoconstrictor. This is done with an overnight oximetry and a six-minute walk test. Exercise training improves peak oxygen consumption and hemodynamics in patients with pulmonary hypertension, but PAH is not typically an insurer approved indication for pulmonary rehabilitation programs.

Anticoagulation can be a treatment option for some patients with PAH. There is conflicting evidence on whether patients with idiopathic, familial, or associated with drug or toxin PAH should be treated with warfarin because there has never been a prospective, randomized trial assessing this. One retrospective trial in idiopathic PAH found a survival benefit, whereas a study using the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) data found no benefit.[4,5] Warfarin should not be used in PAH associated with scleroderma because these patients tend to telangiectasia in the gastrointestinal tract which increased risk of bleeding. Factors favoring anticoagulation are an indwelling central line for treatment infusion and more advanced disease. The use of anticoagulation in PAH is now an individualized decision.

The PAH-specific treatments primarily target vasoconstriction and some proliferation in the pulmonary vasculature by the prostacyclin, nitric oxide, or endothelin pathway. Exhibit 2 shows a

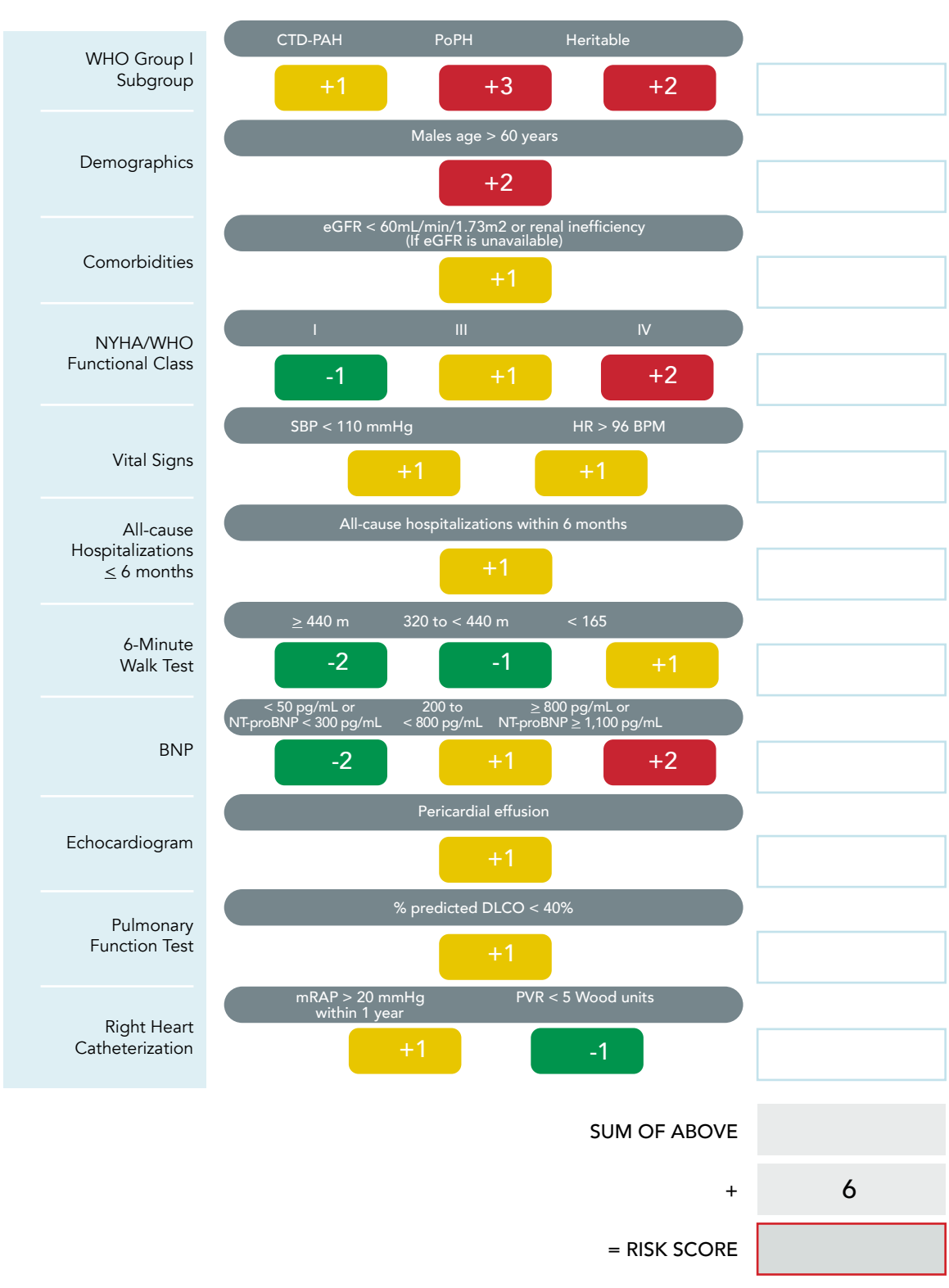
Exhibit 2: General Management Algorithm[6]



general treatment algorithm for a naïve patient.[6] Patients who respond to an acute vasoreactivity test during the right heart catheterization can be managed on inexpensive vasodilator calcium channel blockers (verapamil, diltiazem). Patients who are at low risk for disease progression can sometimes be managed on PAH-specific monotherapy, but patients who are intermediate risk should be started on combination therapy initially. High-risk patients should also be on combination therapy initially, and the regimen should include an intravenous prostacyclin agent. Patients who remain intermediate or high risk even with combination therapy will need triple therapy. There is also a move toward initial triple therapy in those with highest risk disease because the mortality is so great in this group. Exhibit 3 shows a risk assessment tool which can be used in the clinic to help clinicians make treatment decisions and to monitor patients over time.[7]

Endothelin receptor antagonists (ERAs) include bosentan (Tracleer®), ambrisentan (Letairis®), and macitentan (Opsumit®). These agents improve functional capacity and the six-minute walk distance. ERAs are teratogen, so monthly pregnancy tests are required as long a female is receiving one. There is also a drug interaction with oral contraceptives and this class of therapy; given the teratogenic nature of this class, women of child bearing age must use an alternative form of contraception. Anemia is more common with macitentan and fluid retention with ambrisentan. Bosentan is not used very much because of a higher rate of hepatotoxicity and

Exhibit 3: REVEAL PAH Score



the requirement for monthly liver function test monitoring, even though it is available generically. Ambrisentan is also available generically.

Phosphodiesterase-5 inhibitors (PDE5i) include sildenafil (Revatio®, generic) and tadalafil (Adcirca®, generic) and, as do the ERAs, these agents also improve functional capacity and exercise endurance. With sildenafil, there is a challenge in getting patients to be adherent with three times a day dosing. Tadalafil is given as a single daily 40 mg dose. Upfront combination therapy with ambrisentan results in a significantly lower risk of clinical-failure events than the risk with ambrisentan or tadalafil monotherapy, which is why combination upfront therapy has become the standard of care for most patients.[8] PDE5i should be not be used together with nitroglycerin and should be used with caution with alpha blockers because of the risk of excessive peripheral vasodilation.

Riociguat (Adempas®) is a soluble guanylate cyclase stimulator which also works on the endothelin pathway and is approved for PAH and CTEPH. Currently, riociguat is not usually used first-line in PAH because of the expense. Typical use is in patients already on both a PDE5i and an ERA needing additional therapy; clinicians can consider replacing the PDE5i rather than adding a third agent, but randomized evidence for this is not yet available. A nonrandomized study of conversion from a PDE5i to riociguat in PAH found an improved six-minute walk, improved N-terminal pro b-type natriuretic peptide (NT-proBNP) levels, and improved PVR.[9] A randomized study is ongoing whose results may lead to riociguat being used earlier in therapy.

Prostanoids are agents which act in the prostacyclin pathway and include epoprostenol (Flolan®, Veletri®), treprostinil, and selexipag (Uptravi®). Treprostinil is available in intravenous (Remodulin®, generic), subcutaneous (Remodulin®), inhaled (Tyvaso®), and oral (Orenitram®) formulations. Dry powder inhaled versions of treprostinil are under study. Selexipag, an oral prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin, is FDA approved to delay disease progression and reduce the risk of hospitalization for PAH. The prostanoids are the most effective vasodilators in PAH but the formulations, other than oral, are difficult and time consuming for patients to use. They also cause significant adverse events. The oral agents do not appear to be quite as effective as intravenous/subcutaneous prostanoids.

Patient-centered medicine considers improving survival and hospitalization outcomes in PAH, while choosing therapy that is safe and tolerable. It is often a battle, as the typical PAH patient is a young woman with young children who needs a great deal of support to be adherent and persistent with therapy. Because a subset of patients will have an aggressive disease course, end-of-life discussions and palliative care are both important. Because of the complexity and expense of managing this disease, therapy should be managed by a PAH specialist.

Conclusion

Early identification of PAH is important. Screening for PAH is important for people and family members who are at risk for developing the disease. Parenteral prostanoids are a key therapy for advanced disease. Double or triple combination therapy is becoming standard of care for most patients.

Robert P. Frantz, MD, FACC is a Professor of Medicine at the Mayo Clinic College of Medicine and is Director of the Mayo Pulmonary Hypertension Clinic in Rochester, MN.

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Utilizing Immunoglobulin Replacement Therapy to Improve Clinical and Economic Outcomes in the Management of Primary Immunodeficiency Diseases (PIDD)

Jennifer W. Leiding, MD

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

Summary

Individuals with primary immunodeficiency diseases have recurrent, chronic, and serious infections because of defects in the immune system. In addition, they can have other complications, including autoimmune disorders. Treatment is replacement of immunoglobulin, which reduces healthcare resource utilization and infection rates.

Key Points

- Immunoglobulin replacement therapy is the treatment for primary immunodeficiency diseases.
- Despite effective therapy, there are many barriers to good care of these patients.
- Individualized biologic threshold for immunoglobulin levels must be established for each patient.

PRIMARY IMMUNODEFICIENCY DISEASES (PIDD) are a group of more than 300 diseases with defects in the immune system.[1] PIDD are associated with acute or recurrent infections, depending on the portion of the immune system affected. Exhibit 1 shows the warning signs of a potential immunodeficiency.[2]

The immune system recognizes pathogens (non-self), organizes a defense response, and facilitates pathogen destruction and elimination. The innate immune system is present from birth and its specificity is "pre-programmed." It uses toll-like receptors for pattern recognition and includes non-immunological cells (e.g., skin and cilia). The adaptive immune system develops during life with exposure to infection (memory) and increases affinity with experience (specificity). There are two compartments to the adaptive immune system: cellular and humoral. Cellular immunity is mediated by T cells and humoral by antibodies. Memory and specificity are key features of the adaptive immune system.

Most PIDD are inherited and are present at birth; however, they often do not become apparent or diagnosed until late in childhood, or even in adult life. The incidence of PIDD is 1 in 1,200 to 1 in 20,000. There is a two to one incidence of males over females. Humoral or B-cell deficiencies are the most common (Exhibit 2).

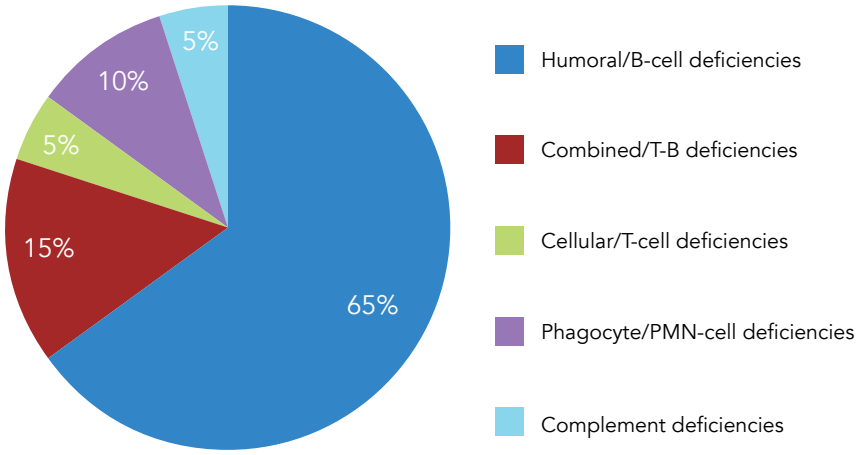
Evaluating a patient for potential PIDD requires identifying the medical history of recurrent infections (organisms, cultures, biopsies, frequency, site, therapy required). The type of infection may suggest a particular defect in immune system. Family history with attention to early deaths and recurrent infections, physical examination, and laboratory evaluation are also important components of the evaluation.

Diagnosis of PIDD can be significantly delayed. The average time from symptom onset to diagnosis has been 12.4 years, and an estimated 70 percent of patients remain undiagnosed.[3,4] Interestingly,

Exhibit 1: Ten Warning Signs of Immunodeficiency[2]

1	Eight or more new ear infections within one year.	Recurrent, deep skin or organ abscesses.	6
2	Two or more serious sinus infections within one year.	Persistent thrush in mouth or elsewhere on skin, after age 1.	7
3	Two or more months on antibiotics with little effect.	Need for intravenous antibiotics to clear infections.	8
4	Two or more pneumonias within one year.	Two or more deep-seated infections.	9
5	Failure of an infant to gain weight or grow normally.	A family history of primary immunodeficiency.	10

Exhibit 2: Distribution of Primary Immunodeficiencies



patients are more likely to be preschoolers or mature adults at first diagnosis. The most severe tend to get diagnosed in the first one to two years of life. Those with less severe disease, but who have had problems for many years, finally get diagnosed later in life. Patients in the 45 to 64-year-old age group represent the largest patient segment (35%) in the United States.[4]

Clinical characteristics of humoral/B-cell immunodeficiencies include sinopulmonary infections with encapsulated bacteria, otitis media, meningitis, sepsis, and osteomyelitis. The infecting agents are typically bacterial pathogens with few problems with fungus and viruses. The exception is enterovirus, which causes meningitis in these patients. The onset of infections is delayed until seven to nine months of age when maternal IgG levels wane, if the mother was healthy and the baby was full term. There is no growth failure in infants with humoral immunodeficiencies but there is increased incidence of allergy and autoimmunity. Patients also get gastrointestinal malabsorption and chronic diarrhea.

Besides recurrent and possibly deadly infections, complications of PIDD vary, depending on what type of deficiency the patient has. Complications

Exhibit 3: Immunogloblin Replacement Products[5]

PRODUCT NAME	Bivigam	Cutaquig	Cuvitru	Flebogamma DIF		Gammagard Liquid		Gammagard S/D		Gammaked		Gammaplex		Gamunex - C		Hizentra	HYQVIA[3]	Octagam		Privigen
MANUFACTURER	Biotest Pharmaceuticals Corporation[2]	Octapharma	Takeda	Grifols		Takeda		Takeda		Kedrion		Bio Products Laboratory		Grifols		CSL Behring	Takeda	Octapharma		CSL Behring
METHOD OF PRODUCTION (Including Viral Inactivation)	Cohn-Oncley fractionation, Anion exchange chromatography; Precipitation and removal of fraction III of the cold ethanol process, solvent/detergent treatment, 35 nm nanofiltration.	Cohn-Oncley cold ethanol fractionation, ultrafiltration, chromatography, solvent/ detergent treatment, low pH incubation	Cohn-Oncley fractionation, ion-exhange chromatograph solvent/ detergent treatment, 35nm nanofiltration, low pH/elevated temperature incubation.	Cold alcohol fractionation, polyethylene glycol precipitation, ion exchange chromatography, pH 4 treatment, pasteurization, solvent detergent treatment, and double sequential nanofiltration through 35 and 20 nm filters.		Cohn-Oncley fractionation, ion-exhange chromatography solvent/ detergent treatment, 35nm nanofiltration, low pH/elevated temperature incubation.		Cohn-Oncley fractionation, ion-exchange chromatography, solvent detergent treatment.		Cohn-Oncley fractionation, caprylate/chromatography purification, cloth and depth filtration, final container low pH incubation.		Kistler & Nitschmann fractionation, DEAE-Sephadex chromatography, Solvent/detergent, CM-Sepharose chromatography, Virus Filtration (20 nm) Terminal low pH incubation.		Cohn-Oncley fractionation, caprylate/chromatography purification, cloth and depth filtration, final container low pH incubation.		Cold alcohol fractionation, octanoic acid fractionation, anion exchange chromatography; pH 4 incubation, depth filtration, nanofiltration; TSE reduction steps include octanoic acid fractionation, depth filtration, and virus filtration.	IG 10% (Human) of HYQVIA: Cohn-Oncley fractionation, ion-exhange chromatography solvent/detergent treatment, 35nm nanofiltration, low pH/elevated temperature incubation recombinant human hyaluronidase: produced from genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase PH20.	Cohn-Oncley cold ethanol fractionation, ultra-filtration, chromatography, solvent detergent treatment.		Octanoic Acid Fractionation, CH9 Filtration, pH 4.0 incubation, Depth filtration, Chromatography, Nanofiltration, TSE Reduction Steps.
FORM	Liquid	Liquid	Liquid	Liquid		Liquid		Lyophilized		Liquid		Liquid		Liquid		Liquid	Liquid	Liquid		Liquid
SHELF-LIFE/ STORAGE REQUIREMENT	24 Months (refrigerated)	24 Months (refrigerated) 6 Months (room temperature up to 25°C or 77°F)	12 Months (room temperature storage not to exceed 25°C or 77°F)	24 Months (room temperature storage)		36 Months (refrigerated) 24 Months (room temperature storage not to exceed 25°C or 77°F)		24 Months (room temperature storage)		36 Months		36 months (room temperature storage)		36 Months		30 Months (room temperature storage)	36 Months (refrigerated) 3 Months[4] (room temperature storage not to exceed 25°C or 77°F)	24 Months		36 Months (room temperature storage)
RECONSTITUTION TIME	N/A	None (Liquid solution)	None (Liquid solution)	None (Liquid solution)		None (Liquid solution)		N/A		None (Liquid solution)		None (Liquid solution)		None (Liquid solution)		None (Ready-to-use liquid solution)	None (Liquid solution)	None (Liquid solution)		None (Liquid solution)
AVAILABLE CONCENTRATIONS	10%	16.50%	20%	5%	10%	10%		5%	10%	10%		5%	10%	10%		20% (200 mg/mL)	10%	5%	10%	10%
MAXIMUM RECOMMENDED INFUSION RATE	3.5 mL/kg/hour	Up to 100 mL/hr/ all sites combined. First 6 infusions: ≤ 20 mL/hr/site (30 mL/hr/all sites combined). Subsequent infusions: 25 mL/hr/site (Up to 100 mL/hr/all sites combined) Subsequent infusions may gradually increase to 50 mL, then to 80 mL; if well tolerated, use a max of 100 mL/hr/all sites combined	First 2 Infusions: 10 - 20 mL/hr/site Subsequent Infusions: ≤60 mL/hr/site	6.0 mL/kg/ hour	4.8 mL/kg/ hour	5 mL/kg/hr (IV)	≥40 kg BW: 30 mL/site at 20-30mL/hour site <40 kg BW: 20 mL/site at 15-20 mL/ hour/site (SC)	4 mL/ kg/hour	8 mL/ kg/hour	4.8 mL/kg/ hour (IV)	20 mL per hour (SC)	4.8 mL/kg/hour		4.8 mL/kg/ hour (IV)	20 mL per hour (SC)	Up to 25 mL/hr/injection site (50 mL/hr for all sites combined)	< 40kg BW: maximum 160 mL/site > 40kg BW: maximum 300 mL/site	<4.2 mL/kg/ hour	<7.2 mL/kg/ hour	4.8mL/kg/hour
TIME TO INFUSE 35 gms1	Time will vary based upon patient tolerability; 146.5 min based on recommended infusion rates.	Time will vary based upon patient tolerability	Time will vary based upon patient tolerability.	1.6 hours	1 hour	Time will vary based on tolerability and route of administration.		Time will vary based on concentration and tolerability.		Time will vary depending on route of administration.		35 grams for 70kg person, 2 hrs 40 minutes if infused according to PI	For 70 kg person, 1 hr 53 minutes if infused according to PI	Time will vary depending on route of administration.		Time will vary depending upon volume and tolerability.	Time will vary based on patient tolerability.	2.5 hours Time can vary based on patient tolerability.	1.44 hours Time can vary based on patient tolerability.	Variable based on patient tolerability.
SUGAR CONTENT	No added sugars	79 mg/mL Maltose	No added sugars	None		No added sugars		20 mg/ml glucose	40 mg/ml glucose	None		5% D-sorbitol (polyol)	None	None		None	No added sugars	100 mg/mL maltose	90 mg/mL maltose	None
SODIUM CONTENT	0.100-0.140 M sodium chloride	≤30 mmol/L	No added sodium	Trace amounts		No added sodium		8.5 mg/mL sodium chloride	17 mg mL sodium chloride	Trace amounts		30 - 50 mmol/L	< 30 mM	Trace amounts		Trace amounts (≤10 mmol/L)	8.5 mg/mL sodium chloride in recombinant human hyaluronidase, no added sodium in IG 10%	≤30 mmol/L		Trace amounts
OSMOLARITY/ OSMOLALITY	≤ 510 mOsm/kg	310-380 mOsm/kg	280-292 mOsm/kg	240-370 mOsm/kg		240- 300 mOsm/kg		636 mOsm/kg	1250 mOsm/L	258 mOsm/kg		460 - 500 mOsm/kg	Typically, 280 mOsmol/kg	258 mOsm/kg		380 mOsmol/kg	240 - 300 mOsm/kg	310 - 380 mOsm/kg		Isotonic (320 mOsmol/kg)
PH	4.0 - 4.6	5.0 - 5.5	4.6 - 5.1	5.0 – 6.0		4.6 – 5.1		6.8 ± 0.4		4.0 – 4.5		4.6 – 5.1	4.9 – 5.2	4.0 – 4.5		4.6 – 5.2	4.6 - 5.1	5.1 – 6.0	4.5 – 5.0	4.8
IgA CONTENT	≤ 200 µg/mL	≤0.6 mg/mL of IgA	80 µg/mL	Average: < 3 mcg/mL	Average: < 3 mcg/mL (Specification value: < 100 mcg/mL)	37 µg/mL		≤ 1 µg/mL ≤ 2.2 µg/mL	N/A	46 µg/mL		Average: <4 mcg/mL	Specification value: < 20 mcg/ml	46 µg/mL		≤50 mcg/mL	37 µg/mL	<100 µg/mL	Average of 106 µg/mL of IgA	< or = 25mcg/mL
APPROVED METHOD OF ADMINISTRATION	Intravenous	Subcutaneous	Subcutaneous	Intravenous		Intravenous	Subcutaneous	Intravenous		Intravenous	Subcutaneous	Intravenous		Intravenous	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous		Intravenous

Exhibit 4: IVIG versus SCIG versus Facilitated SCIG

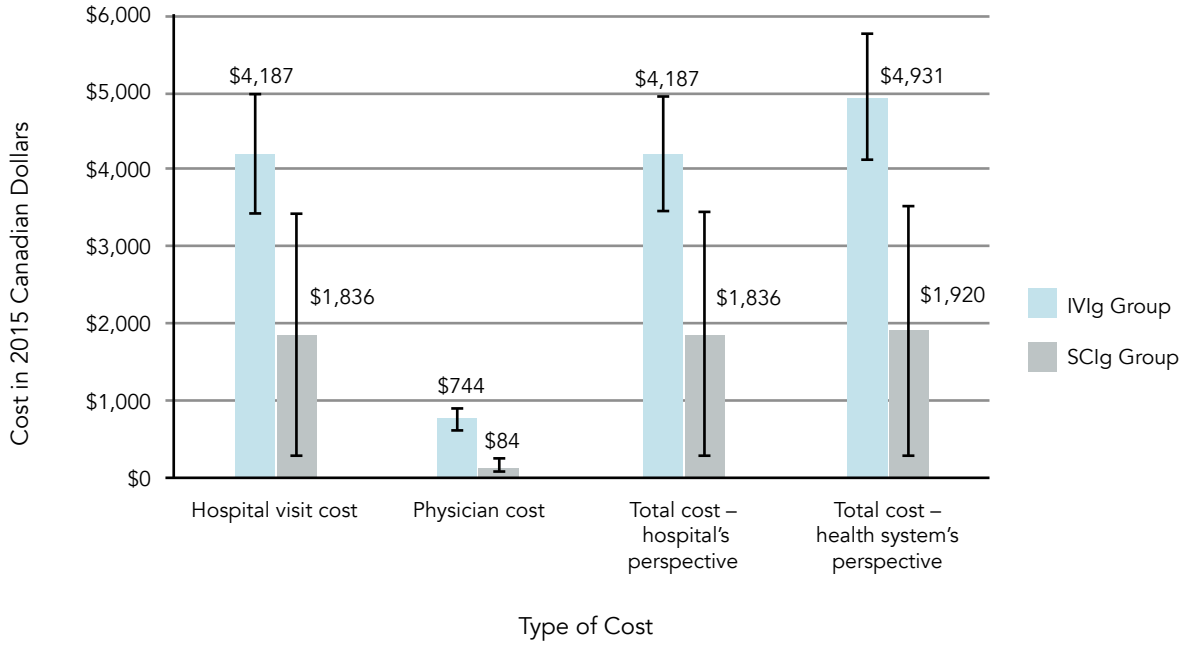
	Intravenous Immunoglobulin (IVIG)	Subcutaneous Immunoglobulin (SCIG)	Hyaluronidase Facilitated Immunoglobulin (fSCIG)
Who?	Indicated for adult and pediatric patients with PI.	Indicated for adult and pediatric patients with PI.	Indicated for adult and pediatric patients (two years and up)
How?	Usually administered by a nurse.	Self-administered.	Either self-administered or given by a nurse.
Where does it go?	Infused directly into the bloodstream through a vein.	Infused or injected under the skin into the subcutaneous tissues of the arms, belly, outer buttock or the thighs.	Infused under the skin into the subcutaneous tissues of the belly, outer buttock or the thighs.
When?	Usually given every 3 to 4 weeks	Can be given on a flexible schedule from daily to every 2 weeks.	Can be given every 3 to 4 weeks.
How long?	Can take 2 to 6 hours to infuse.	Can take 5 minutes to 2 hours to infuse or inject.	Can take 1 to 2 hours to infuse.
Where is it given?	Can be infused at home, in a hospital or an outpatient infusion center depending on insurance and patient preference.	Usually administered in a home setting after the patient is trained to be independent.	Can be infused at home or in an outpatient infusion center depending on insurance and patient preference.
Adverse events?	Patients can have side effects that are often related to the rate of infusion and can be treated and prevented with other medications, given before or after the treatment.	Injection side reactions, often improves with each injection.	Injection side reactions, often improves with each injection. The volume per injection is larger than standard subcutaneous injection, so the volume is more visible under the skin, and may take 48 to 72 hours to totally absorb.

include autoimmune disorders (hematopoietic cytopenias, endocrinopathies, inflammatory bowel disease). Damage to the heart, lungs, nervous system or digestive tract, slowed growth in children, and increased risk of cancer, especially lymphoid, can all occur. Clinicians who care for patients with inflammatory bowel disease that is not responsive to treatment should consider referring these patients to an immunologist for evaluation.

When patients are evaluated for PIDD, several laboratory tests are required. These include quantitative immunoglobulins (IgG, IgA, IgM, IgE), vaccine titers (diphtheria, tetanus, pneumococcal), lymphocyte enumeration (T, B, NK cell quantities), and genetic testing. When assessing serum immunoglobulin levels, age-related differences are significant and must be considered for each evaluation. Imaging (high resolution CT) and pulmonary function tests are also done because these patients are predisposed to chronic pneumonias and lung damage.

Immunoglobulin (IG) replacement therapy is the treatment of choice for PIDD. The IG products are derived from donor pools which can range from 2,000 to 60,000 donors, depending on the product. The products are composed of monomeric IgG (> 95%) with small amounts of dimeric and polymeric IgG. Small amounts of IgM and IgA are also present with the amount varying by product. One gram of IG contains 4 x 10^{18} molecules of antibody. These antibodies have greater than 10^{7} specificities to a broad range of bacterial and viral pathogens. For patients who have a specific predisposition for certain infections such as varicella, the specificity of a particular product may be important. The products are stabilized with sugars or amino acids (Carimune® NF-sucrose, Flebogamma®—sorbitol, Octagam—maltose, Gamunex®-C—glycine, Privigen®—proline,

Exhibit 5: Cost of IVIG versus SCIG[12]



and Gammagard Liquid—glycine) and patient comorbidities can impact which product may be preferred based on the stabilizer.

IG products were first approved by the FDA in 1981 for PIDD. The products have been improved over the years to prevent transmission of cytomegalovirus (CMV). There has been one case of Creutzfeldt-Jakob disease (CJD) being transmitted by an IG replacement product. Cases of renal failure were reported with sucrose-containing products in 1999, and most clinicians no longer use the one sucrose-containing product because of this issue. Thrombotic events related to IG administration were first reported in 2002, and it was subsequently discovered that factor XIa, a procoagulant found in the products, was the cause. The products are now microfiltered to remove factor XIa and potential prion diseases such as CJD.

IG products are not generic nor interchangeable, and they vary widely for various characteristics (Exhibit 3).[5] Replacement products are available for intravenous (IVIG) or subcutaneous (SCIG) infusion. Advantages of IVIG for treating PIDD include data on clinical use for over 30 years and the ability to give large volumes per infusion, which allows intermittent dosing (every 21 to 28 days). Disadvantages of IVIG are that it requires venous access and trained personnel in most situations, requires a longer time to infuse (4 to 6 hours) than subcutaneous, and the large shift in IgG levels during dosing may cause adverse events at or just after peak and during low troughs.[6] IVIG given in an infusion center requires a one day per month commitment from the patient for the infusion but some patients, particularly the elderly, use that time as a social visit. For working patients or parents of children with PIDD, IVIG given in an infusion center can be too time-consuming. Home infusion is possible, but it is more technically demanding than subcutaneous administration. Advantages of SCIG are data on clinical use for over 20 years internationally, it is done as self- or home-infusion, venous access is not required, and gradual absorption maintains more consistent IgG levels. Disadvantages include the ability to self-infuse, it requires a reliable and adherent patient, requires more frequent dosing than IVIG, and multiple infusion sites may be needed. Hyaluronidase-facilitated immunoglobulin (fSCIG, Hizentra®), the newest IG product, solves some of the issues with IVIG and SCIG (Exhibit 4). It takes a similar amount of time to infuse as SCIG, but it can be given less frequently (monthly). It has also been shown to provide more consistent steady-state IG levels than IVIG.[7] Hyaluronidase is injected before the IG to dissolve subcutaneous fat tissue to allow space for a larger volume than is possible with a normal subcutaneous infusion. This product is now approved for those ages two

and older. IVIG and SCIG also differ in adverse events. IVIG causes headache, nausea, muscle aches, rigors, and, rarely, aseptic meningitis. SCIG causes infusion site reactions (erythema, swelling), nausea, and headache.

Overall, there are many considerations in selecting a replacement product. This includes product characteristics, patient comorbidities, and patient lifestyle issues. For example, an 18-year-old patient who is going off to college may not have access to an infusion center nor a reliable refrigerator in which to store the product; therefore, he/she would need a product that could be self-infused that does not require refrigeration.

There are many barriers to optimal care of patients with PIDD. The prior authorization processes implemented by many health plans create barriers to IG product coverage and physician reimbursement. These barriers are exacerbated by specific factors associated with the treatment of PIDD, including inadequate ICD-9 codes, inadequate information from the physician in claims submission, and many others. The new ICD-10 codes are more comprehensive, and the various organizations dedicated to immunodeficiency research and support are working to make the codes even more specific. Omission of immunization responses to vaccines during the diagnostic process may delay approval. A big problem is that when a patient switches their insurer the new insurer sometimes asks that the patient be taken off replacement to prove they need it, which is inappropriate. Inadequate or outdated medical records for these patients may delay approval when a switch in insurer occurs. All of these barriers have the potential to compromise patient care if a patient has to discontinue therapy due to coverage issues.

The nuances of IG replacement therapy dosing may result in barriers related to appropriate and adequate dosing. Specialty pharmacists may dictate dosing without a full appreciation of the clinical course of the patient. An apparent fixation on trough levels of 500 mg/dL has the potential to limit the appropriate dosing of patients, even if it has been shown through various studies that IG levels should be individually optimized. Infection prevention requires identifying and maintaining individual biological IgG levels, which can be dramatically different from mandated trough levels of 500 mg/dL and varies widely among patients.[8] The risk of pneumonia can be proportionally reduced by higher trough IgG levels, up to at least 1,000 mg/dL.[9] Most insurers still ask why doses need to be increased and require a prior authorization.

Product switching because of insurer or formulary changes is another barrier. Switching products after tolerability has been demonstrated with a given product can result in adverse events and reduced efficacy. Formulary restrictions may mandate selection of a 5 percent IVIG product over a 10 percent IVIG product, regardless of clinical appropriateness. Beyond appropriate dosing and administration, patient satisfaction and resultant adherence with therapy are crucial for treatment success. In a recent survey of individuals with PIDD, most respondents (76%) were satisfied with their current treatment.[10] However, patients remained below the physical and mental well-being norms for health-related quality of life as determined by the questionnaire. All respondents expressed a desire for once-monthly infusions, the ability to administer these at home, self-administration, shorter duration of administration, and fewer needle sticks. Patient choice in route of administration has been shown to be a viable means of promoting treatment satisfaction and adherence. SCIG is generally preferred by patients due to matters of convenience related to self-administration, poor venous access, and adverse events. IVIG is generally preferred when the patient has difficulties self-administering SCIG, pain from multiple injections, and associated adherence issues.

The cost of managing PIDD is of concern to managed care; however, there are substantial costs of not treating PIDD. Healthcare resource utilization and costs have been shown to be significantly reduced by instituting IG replacement.[11] Hospital admissions (0.2 versus 1.8, $p < 0.01$), serious infections (3.3 versus 10.9, $p < 0.01$) and antibiotic prescriptions (3.0 versus 7.1; $p < 0.01$) decreased significantly overall. One possible way to save on costs of IG is to switch patients to home-based SCIG instead of hospital or infusion-based IVIG (Exhibit 5).[12]

Conclusion

Primary immunodeficiencies are a major cause of infection susceptibility, with antibody deficiency being most common. Immunoglobulin replacement therapy is a mainstay of therapy for PIDD patients and should be individualized to the needs of the patients. SCIG is a newer form of immunoglobulin replacement therapy, it is well tolerated, and cost efficient.

Jennifer W. Leiding, MD is an Associate Professor in the Division of Allergy and Immunology, Department of Pediatrics at the University of South Florida and Director of the Multidisciplinary Immunology Service at Johns Hopkins-All Children's Hospital Children's Research Institute in St. Petersburg, FL.

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New Treatment Paradigms in Castration-Resistant Prostate Cancer: Enhancing Care through Emerging Diagnostics and Novel Therapies

Daniel P. Petrylak, MD

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

Summary

It is relatively common for prostate cancer to become resistant and progress, despite castrate levels of testosterone. Once resistant, the disease is no longer curable, but there are several treatment options. Each of these therapies provides modest increases in overall survival and can be used sequentially to extend the patient's life.

Key Points

- The optimal sequence of agents is yet to be determined.
- Docetaxel chemotherapy or abiraterone/prednisone should be offered to patients with hormone-sensitive disease.
- Immunotherapy should be given early in asymptomatic non-visceral patients.
- AR-V7 is a promising biomarker for sensitivity to enzalutamide and abiraterone.
- PARP inhibition is a promising therapeutic target in patients with BRCA mutations
- All CRPC patients should be tested for MSI to identify those patients eligible for pembrolizumab.

ALTHOUGH SURGERY AND RADIATION are potentially curative in clinically localized prostate cancer, as many as one-third of patients will have disease progression after the initial treatment. At the time of disease progression to metastatic disease, patients are offered androgen deprivation therapy (ADT) to achieve a castration level of testosterone. ADT results in dramatic tumor reduction, but after 18 to 24 months the prostate specific antigen (PSA) levels begin to rise and disease increases on bone scans. This is now an androgen independent state (castration-resistant prostate cancer, CRPC). Treatment options, once the disease is at this stage, are limited, transiently effective, and include abiraterone, enzalutamide, sipuleucel-T, chemotherapy (docetaxel, cabazitaxel), and radium 223.

Approximately 27,000 men will die from CRPC in the United States (U.S.) annually. It is the second leading cause of cancer-related disease for men. CRPC is defined as increasing PSA levels or progressive disease on imaging, despite a castrate level of serum testosterone (< 50 ng/dL). There are many different mechanisms how CRPC is thought to develop. Examples are androgen receptor (AR) mutations and splice variants and cancer cells learning how to make their own testosterone.[1] All of these alterations can lead to restored AR activity, as evidenced by rising PSA. The common genetic mutations found in CRPC are noted in Exhibit 1.[2]

Numerous molecular biomarkers are under investigation for improving clinical decision making for patients with advanced prostate cancer. These include markers from metastatic tumor biopsy (mutation analyses, DNA methylation), plasma (circulating tumor cells and tumor DNA), and imaging (functional evaluation—NaF, DHT, PSMA)

Exhibit 1: Common Genomic Alterations in CRPC[2]

- *ERG* gene fusion (40% to 50%)
- *AR* gene point mutation or amplifications (50% to 60%)
- *TP53* mutation or deletion (40% to 50%)
- *PTEN* deletion (40% to 50%)
- *RB1* deletion (20%)
- DNA repair genes (10% to 20%) — *BRCA1/2, ATM*

to understand which patients should be treated with which therapy. An issue with identifying genetic mutations in prostate cancer is the difficulty in determining if the mutations are present in all cancer cells. Prostate cancer typically metastasizes to bone, which is much harder to biopsy than soft tissue metastases; each site of metastases can be genetically different. Circulating tumor cell assays may have an advantage over biopsy-based markers.

The therapies for CRPC can be divided into immunotherapeutic (sipuleucel-T, checkpoint inhibitors; hormonal (enzalutamide, abiraterone); cytotoxic (docetaxel, cabazitaxel) and DNA damage (Radium 223) classes. Cabazitaxel is the only agent with an FDA approved indication that is dependent on prior treatment; it is indicated when docetaxel has failed. The choice of therapy is based on clinical characteristics (symptomatic versus asymptomatic, visceral versus non-visceral disease, pre- versus post-docetaxel, other prior treatments) and biological markers (androgen receptor and DNA repair). Adverse events of the various agents also are considered.

Sipuleucel-T is an immunotherapy that works by programming the patient's immune system to seek out prostate cancer cells and attack them. The patient's antigen presenting white blood cells are extracted in a leukapheresis procedure and sent to a production facility where they are incubated with a fusion protein (PA2024) consisting of two parts: antigen prostatic acid phosphatase (PAP), which is present in 95 percent of prostate cancer cells and granulocyte-macrophage colony stimulating factor (GM-CSF) that helps the white blood cells to mature. The activated blood product (APC8015) is returned from the production facility to the infusion center and reinfused into the patient. A complete sipuleucel-T treatment includes three courses at two-week intervals. This is a well-tolerated treatment. Patients in the lowest PSA quartile have the greatest overall survival (OS) benefit with sipuleucel-T (13.8 months versus 2.8 to 7.1 months).[3] Sipuleucel-T is indicated for asymptomatic metastatic CRPC.

Immunotherapy with checkpoint inhibitors has also been investigated for treating prostate cancer. About 50 percent of hormone-sensitive prostate cancer specimens express high levels of programmed death ligand one (PD-L1), which may indicate possible effectiveness of checkpoint inhibitors.[4] The rate of PD-L1 positivity tends to be lower in CRPC (~15%).[5] Expression may be hormonally related; patients progressing on enzalutamide have significantly increased PD-L1 positive dendritic cells in blood compared to those not progressing on treatment.[6] Nivolumab was not effective in 17 patients with CRPC.[7]

Microsatellite instability, a state of genetic hypermutability that results from impaired DNA mismatch repair (MMR), may be a better indicator of checkpoint inhibitor efficacy in prostate cancer than PD-L1 expression. MMR corrects errors that spontaneously occur during DNA replication, such as single-base mismatches or short insertions and deletions. The proteins involved in MMR correct polymerase errors by forming a complex that binds to the mismatched section of DNA, excises the error, and inserts the correct sequence in its place. The aberrant process leads to DNA fragments with microsatellite instability (MSI) structure that consists of repeated nucleotides, most often seen as GT/CA repeats.

In a study of 1,033 patients with prostate cancer, 32 (3.1%) had MSI-high/deficient MMR.[8] Twenty-three of the 1,033 patients (2.2%) had tumors with high MSI sensor scores, and an additional nine had indeterminate scores with evidence of dMMR. Seven of the 32 MSI-H/dMMR patients (21.9%) had a pathogenic germline mutation in a Lynch syndrome-associated gene. Six patients had more than one tumor analyzed, two of whom displayed an acquired MSI-H phenotype later in their disease course.

Pembrolizumab (Keytruda®), a checkpoint inhibitor, is FDA approved for treatment of MSI-H cancers, so it is an option for mCRPC with MSI-H. The Keynote-199 trials demonstrated a response in CRPC with pembrolizumab. Approximately 11 percent of subjects experienced a ≥ 50 percent PSA reduction from baseline and about 50 percent of subjects had some tumor reduction.[9] The patients who had BRCA 1/2 or mutations in the ataxia-telangiectasia gene (ATM) appeared to have the best response; DNA repair deficiency may be a biomarker of response to checkpoint inhibitor therapy in this disease. Whether this therapy impacts OS in CRPC is not yet known. Because there is an approved therapy, all patients with CRPC should have a MSI analysis to see if they qualify.

Exhibit 2: AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer[11]

Outcome	AR-V7[–] → AR-V7[–] (n = 36)	AR-V7[–] → AR-V7[+] (n = 6)	AR-V7[+] → AR-V7[+] (n=16)
PSA Response	68% (95%CI, 52 – 81%)	17% (95%CI, 4 – 58%)	0% (95%CI, 0 – 19%)
PSA Progression-Free Survival	6.1 months (95%CI, 5.9 mo – NR)	**3.0 months** (95%CI, 2.3 mo – NR)	1.4 months (95%CI, 0.9 – 2.6 mo)
Progression-Free Survival	6.5 months (95%CI, 6.1 mo – NR)	**3.2 months** (95%CI, 3.1 mo – NR)	2.1 months (95%CI, 1.9 – 3.1 mo)

Hormonal therapy with abiraterone (Zytiga®) or enzalutamide (Xtandi®) is another treatment option in metastatic CRPC. Abiraterone is an androgen biosynthesis inhibitor that will inhibit cancer cell auto-synthesis of testosterone. In the pre-chemotherapy metastatic CRPC setting, abiraterone improved median OS by approximately three months. Enzalutamide binds to the androgen receptor so testosterone cannot bind. In the post-chemotherapy setting, it improves median OS by 4.7 months and reduces the risk of death by 37 percent.[10] Both abiraterone and enzalutamide are FDA approved for the pre-chemotherapy and post-chemotherapy setting.

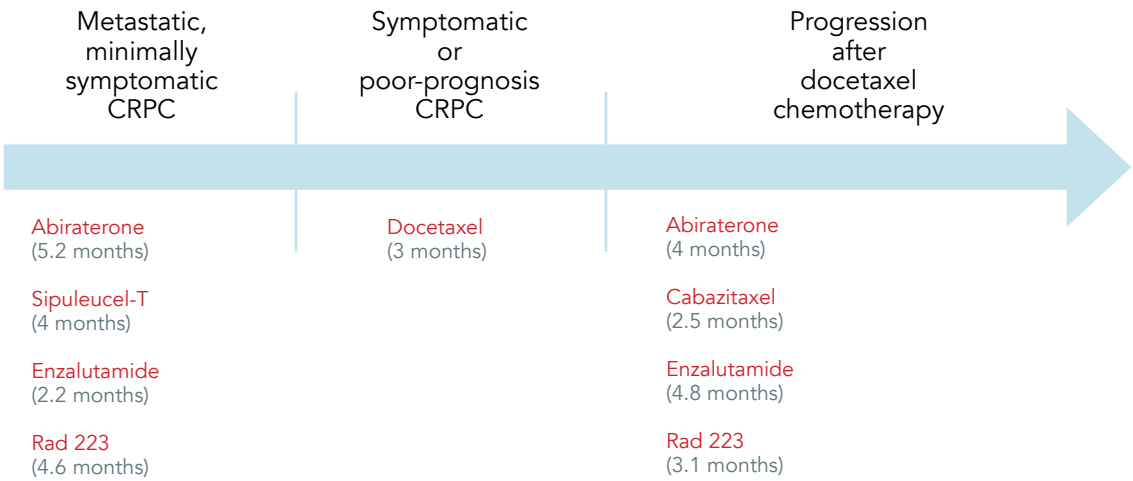
Androgen receptor variant-7 (AR-V7) is a biomarker that can be used to select hormonal therapy in CRPC. AR-V7 is a truncated form of the receptor that lacks the ligand binding region, the target of abiraterone and enzalutamide, but remains constitutively active. Abiraterone and enzalutamide are much less effective in those with AR-V7, so these patients should be treated with chemotherapy. Exhibit 2 illustrates the difference in efficacy with and without the variant.[11] It is fairly easy to clinically predict which patients are AR-V7 positive; they are typically very sick with rapidly progressive disease. For most patients who are not very sick but whose disease is progressing on one of the hormonal therapies but who do not yet want to undertake chemotherapy, most clinicians will try the other hormonal therapy for a month to see if it works, instead of doing the AR-V7 test.

There are patients who have rising PSA, which indicates castrate resistance, but who do not have metastatic disease. Until recently, there were no approved therapies for non-metastatic CRPC, and it was controversial whether these patients needed treatment. Studies have shown that a short doubling time (less than 6 months) of PSA is predictive of the patients who will go on to develop metastatic disease and thus should be treated. Apalutamide (Erleada®), which has the same mechanism of action as enzalutamide, improved the metastatic-free survival by 24 months in the non-metastatic CRPC setting.[12] Enzalutamide in combination with ADT provides similar benefits. Darolutamide (Nubeqa®), structurally different from the other two agents, may have some adverse event benefit over the other agents, but appears to have similar efficacy. All three are now FDA approved for non-metastatic CRPC. Survival data with these three treatments in this setting is not yet available.

Exhibit 3 shows the options of sequencing therapy. Where there are several options, treatment can be selected based on potential adverse events. For example, a patient with diabetes may not be the best candidate for abiraterone because it has to be given with prednisone. Heart failure and liver function abnormalities may be worsened by abiraterone.

A future therapy for CRPC may be poly ADP ribose polymerase (PARP) inhibitors. PARP repairs double-strand breaks in DNA; cells with BRCA mutations only have PARP as an option to repair double-strand breaks and thus PARP inhibition leads to cell death. Approximately 12 percent of men with prostate cancer have BRCA 1/2 mutations, which would make their cancers susceptible to PARP inhibition.[13] Olaparib (Lynparza®) and rucaparib (Rubraca®), which are already FDA approved for BRCA-mutated breast and ovarian cancers, are both under investigation and are showing promising results. At many treatment centers, patients with mCRPC are being tested for BRCA mutations in order that they can be steered toward clinical trials of the PARP inhibitors.

Exhibit 3 Sequencing mCRPC Therapy



Conclusion

Although it is considered incurable, there are a few treatment options for CRPC; however, the optimal sequence of agents is yet to be determined. Docetaxel chemotherapy or abiraterone/prednisone should be offered to patients with hormone-sensitive disease. Immunotherapy should be given early in asymptomatic non-visceral patients. AR-V7 is a promising biomarker for sensitivity to enzalutamide and abiraterone. PARP inhibition is a promising therapeutic target in patients with BRCA mutations. All CRPC patients should be tested for MSI to identify those patients eligible for pembrolizumab.

Daniel P. Petrylak, MD is a Professor of Medicine and Urology, Director of the GU Translational Working Group, and Co-Director of the Signal Transduction Program at the Smilow Cancer Center at Yale University in New Haven, CT.

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Latest Updates in the Treatment and Management of Psoriatic Arthritis

Joseph A. Markenson, MD, FACP, MACR

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

Summary

Psoriatic arthritis is a chronic, inflammatory disease of the joints and the connection of tendons and ligaments to bone. Left untreated, psoriatic arthritis can cause permanent joint damage. Though there is no cure, there are a growing number of biologic treatments which stop the disease progression, lessen pain, and protect joints by targeting the underlying inflammatory pathology.

Key Points

- It is important to start treatment early in psoriatic arthritis to prevent joint damage.
- Because of systemic inflammation, there are significant comorbidities which also need to be managed.
- Several therapies that target the underlying pathology of psoriatic disease are now available.

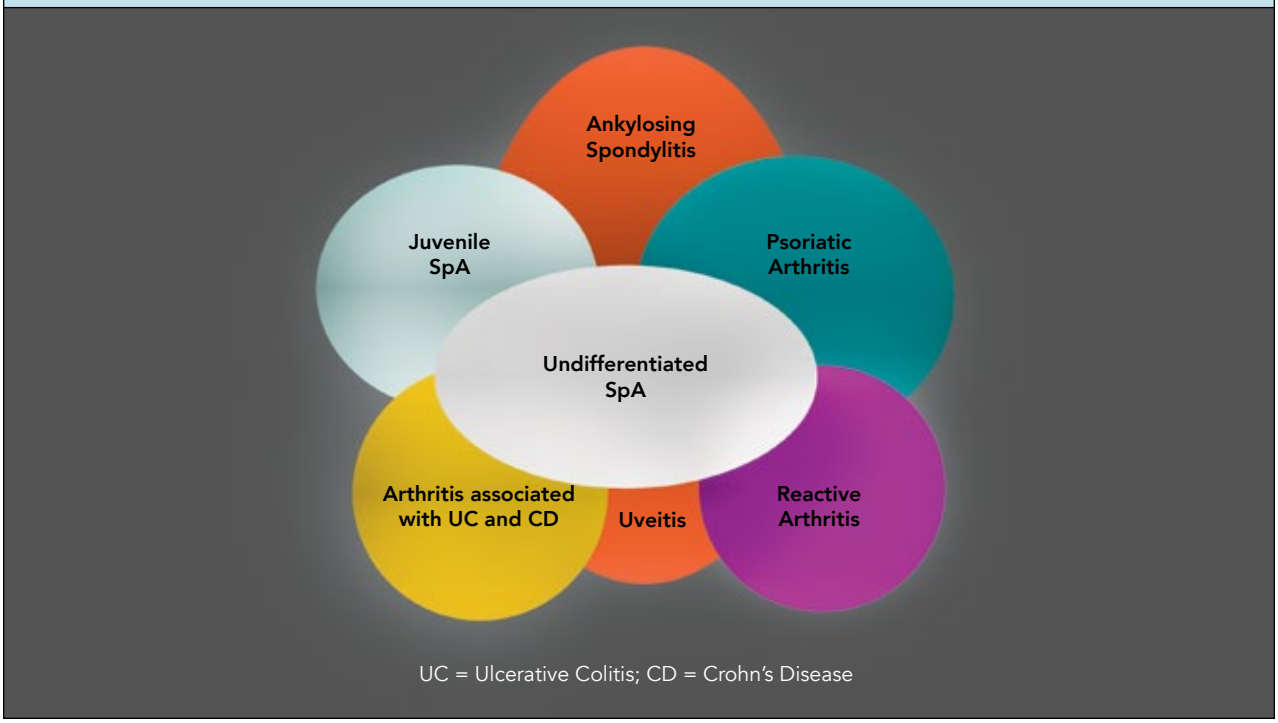
SPONDYLOARTHRITIS (SPA) DESCRIBES A group of interrelated rheumatic conditions comprising ankylosing spondylitis, psoriatic arthritis (PsA), arthritis/spondylitis with inflammatory bowel disease, and reactive arthritis (Exhibit 1). These diseases share genetic, molecular, immunological, clinical, and imaging features. The Assessment of Spondyloarthritis International Society (ASAS) classification criteria define SpA as either axial (characterized by predominant involvement of the spine or sacroiliac joints) or peripheral (characterized predominantly by peripheral arthritis, enthesitis, and/or dactylitis).[1] Patients with SpA can be distinguished according to their clinical presentation as patients with predominantly axial SpA, or with predominantly peripheral SpA. PsA, although predominantly peripheral, is classified as a spondyloarthropathy because spondylitis occurs in up to 40 percent of patients with this disease.[2]

SpA conditions share a propensity for certain clinical manifestations (Exhibit 2).[3-5] Common elements of SpA include autoimmune inflammatory arthropathies distinct from rheumatoid arthritis (RA), including genetic markers (e.g., HLA B27, Cw6), spine involvement (especially sacroiliitis), asymmetric joint involvement, enthesopathy (tendon insertion site inflammation), iritis and uveitis, and male involvement more common than in RA. SpA tends to have a slower progression than RA.

Up to 40 percent of people with psoriasis will develop PsA.[6] Psoriasis is a T-cell mediated disease with elevated levels of pro-inflammatory cytokines in blood and lesioned skin. It is commonly characterized by chronic flares and remissions and progressive joint damage when PsA is present. Psoriatic skin lesions generally appear about 10 years before arthritis symptoms. The amount of skin affected by psoriasis has no bearing on whether a patient will develop PsA or how bad the PsA will be. This particular arthritis can affect any joint in the body, and symptoms vary from person to person.

Prognostic indicators for disease progression in PsA are the following at presentation: actively inflamed joints (> 5), swollen joints (> 5), and high erythrocyte sedimentation rate.[7] Earlier age at onset of joint disease may be associated with development of deforming arthritis and arthritis mutilans. In one

Exhibit 1: Spondyloarthropathies



UC = Ulcerative Colitis; CD = Crohn's Disease

study, radiographs revealed erosive disease in 67 percent of PsA patients, and 40 percent developed deforming, erosive arthropathy.[8]

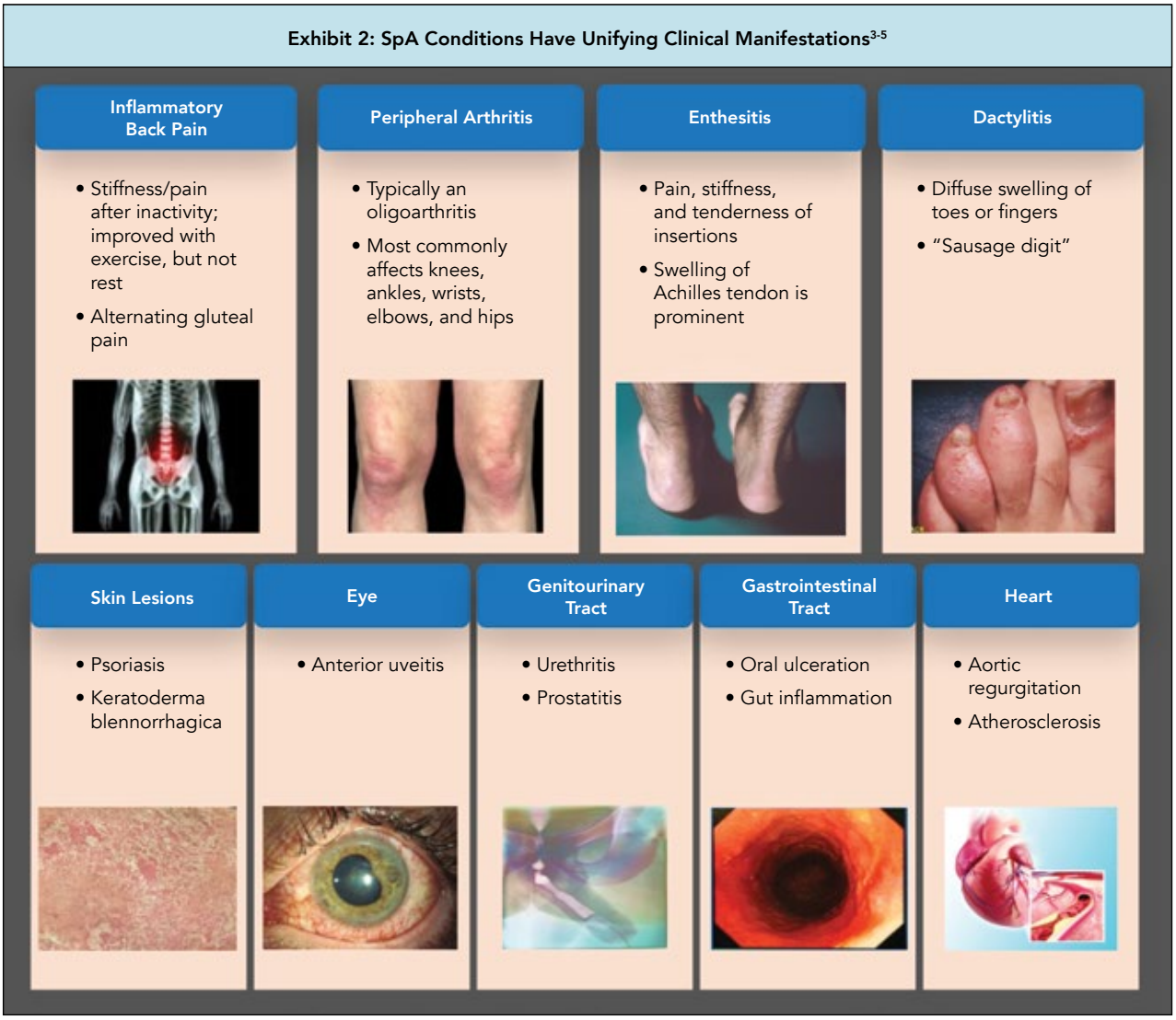
PsA is a systemic inflammatory disease with multiple cardiovascular disease (CVD) and metabolic comorbidities (Exhibit 3).[9-11] Psoriatic disease—psoriasis and PsA—is an independent risk factor for myocardial infarction, stroke, and heart failure. There is an increased prevalence of traditional CVD risk factors (e.g. hypertension, cigarette smoking, dyslipidemia, diabetes mellitus, and obesity) in patients with psoriatic disease. Alcohol misuse and depression are increased in this patient population and may contribute to excess CVD mortality. Patients with moderate to severe psoriasis have a reduced life expectancy of four to five years from CVD.[11] The rheumatologist, dermatologist, primary care provider, and cardiologist should be working together to assess and manage CVD risk in these patients.

The new paradigm in treating psoriatic disease is to treat the entire patient and not just the arthritis or the skin lesions. This means monitoring body weight, vitals, alcohol intake, sleep issues, skin involvement, development of inflammatory arthritis in those who do not already have, dentition, fasting lipids, C-reactive protein, fasting glucose, and hemoglobin A1C. Prescribing a diet/exercise and weight loss program if appropriate, smoking cessation, and CVD risk reduction therapies are all important non-pharmacologic interventions.

Numerous pharmacologic therapies are available for psoriasis, but not all are FDA approved for specifically treating PsA (Exhibit 4). It is now known that interleukin 17 and 23 are involved in the pathogenesis of psoriatic disease; the newer therapies target these two interleukins rather than nonspecific inhibition of the immune system like the older disease-modifying antirheumatic drugs (DMARDs), such as MTX.

The American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) published PsA treatment guidelines in 2018.[12] The guidelines are somewhat controversial because they rely on low to moderate grade evidence and recommend TNF inhibitors, or traditional oral small molecules as first-line therapy. For treatment-naïve patients with active PsA, the use of a tumor necrosis factor (TNF) inhibitor biologic or traditional oral small molecules (methotrexate, leflunomide, sulfasalazine, cyclosporine) is recommended over an interleukin (IL)-17 inhibitor or IL-12/23 inhibitor biologic.[12] An IL-17 or IL-12/23 inhibitor may be used instead of TNF inhibitors in patients with severe PsA or contraindications to TNF inhibitors, and may be used instead of oral small molecules in patients with severe PsA. MTX is recommended over nonsteroidal anti-inflammatory drugs (NSAIDs) in

Exhibit 2: SpA Conditions Have Unifying Clinical Manifestations[3-5]



treatment of naive patients with active PsA. NSAIDs may be used instead of MTX after consideration of possible contraindications and the adverse event profile in patients without evidence of severe PsA or severe psoriasis and in those at risk for liver toxicity. An IL-17 inhibitor is recommended over an IL12/23i biologic.[12] The IL-12/23 inhibitors may be used in patients who have concomitant inflammatory bowel disease (IBD) or who desire less frequent drug administration. The guidelines do point out that because they rely on very low to moderate evidence, and there needs to be active discussion between the physician and patient on the treatment choice.

The traditional oral small molecules, while they have been shown to be disease modifying in RA, have not been shown to be disease modifying in PsA. The advantages of these agents are long years of experience with them, they are helpful in some cases, they are inexpensive, they prevent antibody generation, and MTX is synergistic in RA with TNF inhibitors. In addition to lack of disease-modifying benefit, there is a lack of high-quality data and typically suboptimal dosing in real-world practice. There are only a few small trials that have been done in PsA with MTX, despite it being a cornerstone medication. Prior to the introduction of biologics, it was one of the only effective options. Most clinicians who treat PsA are moving away MTX. There are many issues with adverse events and required monitoring which make the traditional oral small molecules a less appealing option compared to biologics.

In PsA trials, several measures are required by the FDA to decide if a medication is effective. The ACR20 is a composite measure defined as both improvement of 20 percent in the number of tender and number of swollen joints, and a 20 percent improvement in three of the following five criteria: patient global assessment, physician global assessment, functional

Exhibit 3: Comorbidities Associated with PsA[9-11]

- Hypertension
- Dyslipidemia
- Diabetes/Insulin resistance
- Metabolic syndrome
- Obesity
- Osteoporosis
- Nonalcoholic fatty liver disease
- Cardiovascular disease including myocardial infarction and cerebrovascular disease
- Depression and anxiety
- Inflammatory bowel disease
    - Crohn's disease
    - Ulcerative colitis
- Keratoconjunctivitis sicca
- Hypothyroidism
- Gout
- Fibromyalgia

Exhibit 4: Disease Modifying Treatment Options

Traditional DMARDs	Newer Therapies
• Methotrexate	• Ustekinumab (Stelara®, IL12/23
• Leflunomide	• Secukinumab (Cosentyx®, IL17A)
• Sulfasalazine	• Abatacept (Orencia®, CTLA4-Ig)
• Cyclosporine	• Apremilast (Otezla®, PDE4)
	• Ixekizumab (Taltz®, IL17)
Anti-TNFa	• **Tofacitinib (Xeljanz®, JAK3)**
• Etanercept	**Approved for Psoriasis***
• Adalimumab	• Brodalumab (Siliq®, IL17R)
• Infliximab	• Guselkumab (Tremfya®, IL23)
• Golimumab	• Risankizumab (Skyrizi™, IL23)
• Certolizumab	• Tildrakizumab (Ilumya™, IL23)

*FDA approved for psoriasis but not psoriatic arthritis

TNFα = tumor-necrosis factor alpha
DMARD = disease-modifying antirheumatic drug
IL = interleukin; CTLA4 = cytotoxic T lymphocyte associated (molecule)-4
Ig = immunoglobulin; PDE = phosphodiesterase; JAK = Janus kinase.

ability measure [most often Health Assessment Questionnaire (HAQ)], visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (CRP). Although a 20 percent improvement is not a dramatic benefit, it is the minimum cut-point at which a difference can be shown between agents. The Psoriasis Area and Severity Index (PASI) is the most widely used tool for the measurement of severity of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease). The PASI 75 is typically what is used in PsA studies and is a 75 percent decrease in area affected and severity.

The TNF inhibitors all appear to have similar efficacy in treating PsA. They produce a 58 percent ACR20 compared to an 8 to14 percent placebo response rate.[13] It is important to note that the placebo group in most of the trials is not truly a placebo. Patients are usually allowed to stay on prednisone or MTX. For skin clearing (PASI 75), adalimumab appears to be more effective (85%) than the other TNF inhibitors.

Enthesopathy plays a major role in PsA and IL-23 has been shown to be involved in its development. Ustekinumab, an IL-23 and IL-12 inhibitor, improves PsA, with 43 percent of subjects achieving ACR20 and 55 percent PASI 75.[14,15] Three IL-23 specific agents, guselkumab, risankizumab, and tildrakizumab, are currently FDA approved for treating psoriasis and are under study for PsA.

IL-17 has also been shown to be another important mediator in PsA. Secukinumab, an IL-17 inhibitor, results in a 50 percent ACR20 rate compared with 15 percent with placebo and 54 percent versus 12 percent for PASI 75.[16,17] Ixekizumab, another IL-17 inhibitor, has been compared to placebo and adalimumab in one trial in biologic naïve patients with PsA. Higher PASI 75, PAS I90, and PASI 100 rates and higher ACR20 rates were shown with ixekizumab compared to adalimumab, but the study was not powered to test equivalence or non-inferiority of ixekizumab versus adalimumab, so no statistics were done comparing the rates.[18] Brodalumab, a third IL-17 inhibitor, is approved for treating psoriasis, but it is not yet approved for PsA.

Many times, patients prefer oral therapy over injectable biologics. Apremilast and tofacitinib are both oral agents that are FDA approved for treating PsA and psoriasis. Apremilast decreases inflammatory cytokines, including TNF, IL-12, IL-17, IL-22, and IL-23. In the PsA trials, 37 percent of patients achieved ACR20 and 21 percent a PASI 75 compared to 18 percent and 7 percent of placebo-treated patients.[19-21] Apremilast is not preferred in erosive disease; its ability to prevent joint injury is unproven. Tofacitinib,

a Janus kinase inhibitor (JAK), also reduces various inflammatory cytokines. In the PsA trials with this agent, 54 percent of TNF inhibitor naïve patients and 48 percent of TNF inhibitor inadequate responders achieved ACR20 compared to 30 percent of placebo-treated patients.[22,23] Forty-two percent of tofacitinib-treated patients, who were TNF inhibitor naïve, and 32 percent of TNF inhibitor non-responders achieved PASI 75 compared to 14 percent of the placebo group. Although no comparative statistics were done, tofacitinib treatment produced higher PASI 75 and ACR20 responses than adalimumab.

Conclusion

It is important to start treatment early in PsA to prevent damage. Multidisciplinary care is required to manage both the disease itself and the comorbidities, especially related to cardiovascular disease. Communication among the various specialties and the patient is key to achieving good clinical outcomes. Several therapies that target the underlying pathology of psoriatic disease are now available. Multiple new targets (IL-12/23, IL-17, JAK, and PDE4) allow for various treatment choices if a patient does not respond to one particular class of therapy.

Joseph A. Markenson, MD, FACP, MACR is a Professor of Clinical Medicine at the Joan and Sanford Weill Medical College of Cornell University Hospital for Special Surgery, and Attending Physician at New York Presbyterian Hospital Memorial Sloan Kettering Cancer Center in New York, NY.

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Exploring New Perspectives in the Treatment and Management of Spinal Muscular Atrophy

Julie A. Parsons, MD

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

Summary

Spinal muscular atrophy (SMA) is a devastating neuromuscular disorder characterized by loss of motor neurons and muscle atrophy, generally presenting in childhood. It is currently a very exciting time for clinicians, patients, and parents for treating this disorder because a new gene therapy and other treatments are altering the natural course of affected patients.

Key Points

- Nusinersen is effective for all types of SMA.
- Onasemnogene abeparvovec-xioi, gene replacement therapy, is effective for SMA Type I.
- Efficacy is improved when treatment is initiated before symptom onset.

SPINAL MUSCULAR ATROPHY (SMA) IS A clinically and genetically heterogeneous group of diseases in which there is a loss of anterior horn cells and progressive muscle atrophy without involvement of the corticospinal tract. SMA is characterized by loss of lower motor neurons in the spinal cord and brainstem nuclei, leading to progressive symmetrical muscle weakness and atrophy. It affects approximately 1 in 6,000 to 1 in 10,000 individuals and is the most common genetic cause of death in children under two years of age; however, this may soon change given recent treatment developments. With supportive care only, poor weight gain with growth failure, restrictive lung disease, scoliosis, and joint contractures are common complications of SMA. Death results primarily from respiratory failure.

SMA was first described in 1891, but the cause of the most common form, inactivating mutations of the survival of motor neuron 1 (SMN1) gene, was not identified until 1995. The most common form of SMA, caused by mutations of SMN1, is termed SMA5q, because of its location on the 5Q chromosome, or SMN1-related SMA.[1] SMN1-related SMA is an autosomal recessive neuromuscular disease caused by homozygous deletion or pathogenic variant in the survival of the SMN1 gene and for the remainder of this article will be referred to as SMA. It has an incidence of 1:10,000 live births. Carrier frequency is 1:40 to 1:60, which is similar to cystic fibrosis. It is a pan-ethnic disorder.

In SMA, the affected person has a non-functional SMN1 gene, which normally produces 90 percent of the SMN protein. They still have a functional SMN2 gene, which is a back-up gene and produces some low amounts of SMN protein. In humans, SMA disease severity correlates with the number of copies of the SMN2 gene and the level of functional protein produced.[2] Those with one or two copies of the gene have SMA Type 1, the most severe form. Those with two to three copies have SMA Type 2 and four copies have SMA Type 3. Anyone with five or more copies of SMN2 is clinically unaffected, even though they have non-functioning SMN1. Unlike years when muscle biopsies were required, SMA is now diagnosed based on genetic testing to identify non-functional SMN1 and the number of SMA2 gene copies.

Those with SMA are classified based on function as non-sitters, sitters, and walkers (Exhibit 1).[3] Type 1

Exhibit 1: Classification of SMN1-related SMA

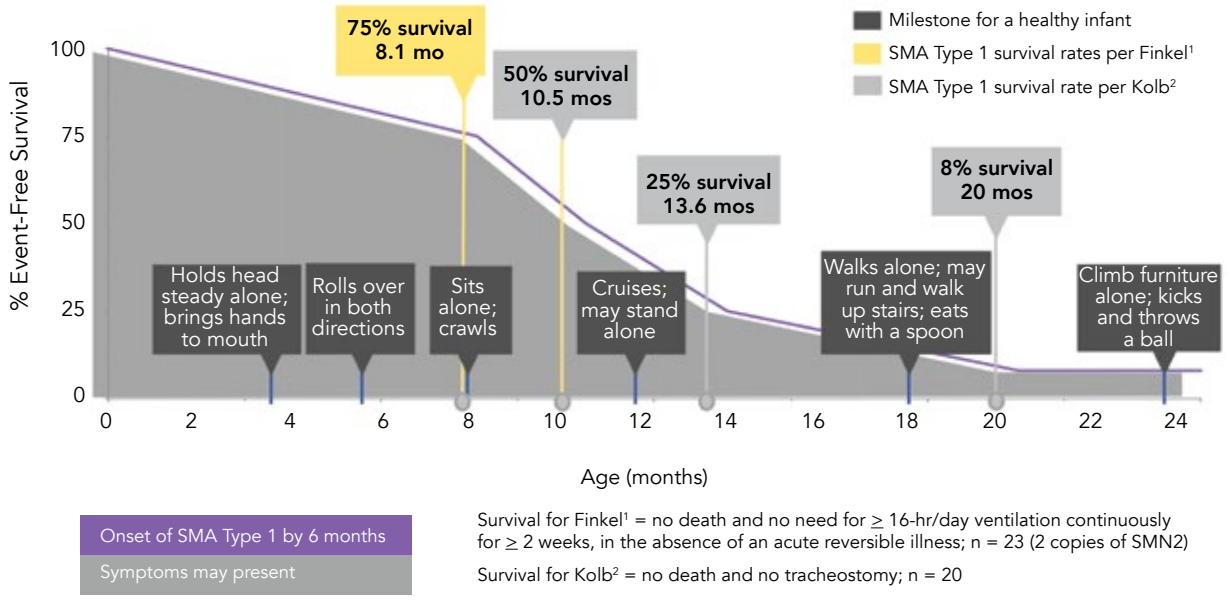
SMA Type 1—Non sitters	Most severe form Symptom onset < 6 months of age The patients never sit Very limited life expectancy (< 2 years) without treatment Respiratory failure is cause of death Inability to feed orally
SMA Type 2—Sitters	Intermediate Form Symptom onset 6 to 12 months Patients sit or stand but never walk Life expectancy may be shortened Skeletal deformities and chronic pain
SMA Type 3—Walkers	Mild form Life expectancy normal Prominent proximal weakness which can increase over time Orthopedic issues

comprises approximately 60 percent of cases, Type 2 30 percent, and Type 3 10 percent. The natural history of Type 1 is shown in Exhibit 2; without treatment, only 8 percent of patients survive to 20 months of age.[4,5] The patients with more severe disease require a significant amount of supportive care and equipment; this can include power chairs, walkers, constant noninvasive ventilation, and cough assist devices. There are consensus guidelines on managing these patients.[6,7] Improved standards of care, especially for nutrition and aggressive pulmonary care, have dramatically improved the survival of those with SMA Type I, even without specific treatments that alter the underlying pathology.[8,9] The prolongation of survival from improved care does not impact achievement of motor milestones; thus non-sitters will never become sitters with improved standards of care.

The mechanistic strategies to treat SMA are aimed at SMN or at muscle activation, which is SMN independent. The SMN strategies include improving production of functional SMN protein by modification of SMN2 mRNA splicing and gene replacement. Nusinersen (Spinraza®) was the first FDA approved therapy for SMA, and it targets splicing modification. Risdiplam and branaplam are two investigational agents. Gene replacement is replacement of the faulty SMN1 gene using viral-vector-based gene therapy. Onasemnogene abeparvovec-xioi (Zolgensma®) is the FDA approved gene replacement product. Muscle activation therapies try to improve muscle force-frequency response in skeletal muscle via activation of fast skeletal muscle troponin; reldesemtiv is an investigational muscle activation therapy.

Nusinersen, an antisense oligonucleotide, increases the amount of SMN protein that is produced. It has been studied in infantile onset SMA, later onset SMA, and pre-symptomatic SMA. The trials of SMA therapies all use survival, need for ventilation assistance, and measures of motor function to assess efficacy. In a randomized, double-blind, sham-controlled study of nusinersen in 121 infants (≤ 7 months) with SMA Type I, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] versus 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; $P = 0.005$).[10] In a multicenter, double-blind, sham-controlled study in 126 patients with later-onset SMA (2 to 12 years), 57 percent of the children in the nusinersen group, as compared with 26 percent in the control group, had an increase from baseline to month 15 in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score of at least 3 points ($P < 0.001$), and the overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively).[11] Long-term results from the later onset cohorts found benefit out to three years with continued therapy.[12] The pre-symptomatic study was an open-label, single-arm trial of nusinersen in infants with genetically diagnosed SMA (mostly ≤ 1

Exhibit 2: Natural History of SMA Type1[4,5]



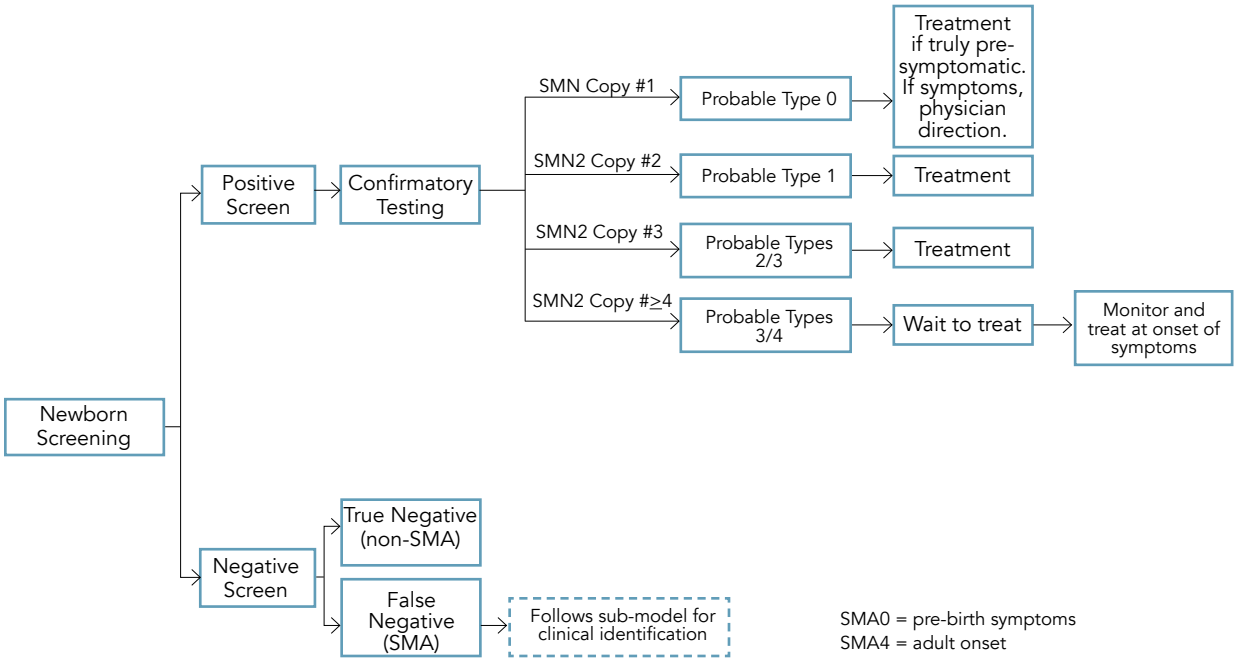
month at enrollment). At the end of this trial, the 25 children were a median 34.8 months of age and past the expected age of symptom onset for SMA Types I or II; all were alive and none required tracheostomy or permanent ventilation.[13] Four (16%) participants with two SMN2 copies utilized respiratory support for > 6 hours/day for ≥7 consecutive days that was initiated during acute, reversible illnesses. All 25 participants achieved the ability to sit without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) achieved walking independently. Overall, 88 percent of the participants were able to maintain full oral feeds.

Nusinersen is given by intrathecal bolus injection, which requires a spinal tap for each dose. This agent has a long half-life (several months) in the central nervous system tissue, but dosing is required relatively frequently to keep the drug levels up. Initially, loading doses to saturate motor neurons are given four times over three months. Maintenance doses to maintain effective drug levels are then given every four months. It does take time to see positive motor function benefits (~15 months of treatment). The motor benefits may include the ability to sit or walk, ability to feed orally, and the ability to operate a power chair, write, and feed themselves. These are striking benefits compared to the natural history for Type 1. Declines in function in the placebo groups of the nusinersen trials illustrate the importance of starting therapy early in the disease process. Nusinersen appears to be well tolerated by the patients with no major adverse events, which is different from placebo. On December 23, 2016 nusinersen was approved by the FDA for treatment of SMA in pediatric and adult patients with SMN1-related SMA. Nusinersen costs $125,000 per dose, which makes the first-year cost of the drug alone $750,000, and that does not include the administration costs. Subsequent years cost $375,000 for the drug alone.

Risdiplam is an oral SMN2 splicing modifier which was granted priority review by the FDA in November 2019. Risdiplam is designed to increase and sustain SMN protein levels, both throughout the central nervous system and the peripheral tissues of the body. It has been studied in infants with Type 1 SMA and children and young adults (2 to 25 years old) with Type 2 or 3 SMA and increases SMN levels about twofold. In addition to the studies included in the FDA submission, risdiplam is being studied in a broad clinical trial program in SMA, with patients ranging from newborns to 60 years old, and includes patients previously treated with other SMA therapies. If approved, risdiplam, an orally administered liquid, would be the first at-home administered medicine for SMA.

Branaplam is another oral SMN2 splicing modifier

Exhibit 3: Proposed Treatment Protocol + SMA Newborn Screen[16]



which is in Phase I/II trials for Type 1 infantile-onset SMA. Because animal toxicity studies showed axonal neuropathy changes, trials with this agent were suspended for a few years, but they have resumed with a modified molecule. Gene transfer therapy was the next iteration in SMA therapy. This therapy is designed to deliver a fully functional human SMN gene into target motor neuron cells, leading to production of sufficient levels of SMN protein required to improve motor neuron function. This therapy leads to a rapid onset of effect in addition to sustained SMN protein expression. Within a day of infusion, the SMN levels begin to increase.

Onasemnogene abeparvovec-xioi, the FDA approved agent, crosses the blood-brain barrier and targets neurons. It is non-integrating, has a rapid onset of effect, remains stable within the nucleus, and produces sustained SMN expression. Its FDA approved indication is treatment of pediatric patients less than two years of age with SMA with bi-allelic mutations in the SMN1 gene. In the clinical trial that led to approval, all 15 patients treated with a single infusion were alive and event free at 20 months of age, as compared with a rate of survival of 8 percent in a historical cohort. Additionally, all of these patients are still alive several years after treatment. In the high-dose cohort (12 subjects, 2.0×10^{14} vg per kilogram), a rapid increase from baseline in the score on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale followed gene delivery, with an increase of 9.8 points at one month and 15.4 points at three months, as compared with a decline in this score in a historical cohort. Of the 12 patients who received the high dose, 11 sat unassisted, 9 rolled over, 11 fed orally and could speak, and 2 walked independently. Elevated serum aminotransferase levels occurred in four patients and were attenuated by prednisolone.[14]

This gene therapy is given as a single intravenous weight-based infusion. Systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) must be given for one day before infusion and continued for a total of 30 days after administration to dampen or circumvent the expected immune response to the adeno-associated virus effects of viral capsid in the host liver cells. At the end of 30 days of corticosteroid dosing, liver function tests are checked. For patients with unremarkable findings, the corticosteroid dose is tapered over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids until findings become unremarkable, and then taper the corticosteroid dose over the next 28 days. This therapy costs $2.1 million along with additional related medical and pharmacy costs of hospitalization for receiving the therapy and follow-up medications and laboratory monitoring and clinical care.

The other target being investigated in SMA is

improving muscle activation. Reldesemtiv is an investigational small molecule activator of Type 2 fast muscle troponin complex which aims to improve muscle fatigue. It is being studied in SMA Types II, III, and IV in children 12 and older and is given orally twice a day. Preliminary results show improved muscle endurance and pulmonary function. This will likely be used as an adjunctive therapy with agents that increase SMN levels.

SRK-015 is a selective and local myostatin inhibitor antibody that prevents myostatin activation, leading to increased muscle cell growth. Given as a monthly intravenous infusion, it showed improved muscle function in mice. Human clinical trials are in the start-up phase. Because there are now effective treatments, SMA was added to the recommended uniform screening panel, a list of conditions that all states are encouraged to include in their newborn screening panels. Several states have already added SMN1 to their screening.

Identification of homozygous deletion of SMN1, combined with three or fewer SMN2 gene copies, is a powerful predictor of disease and identifies the groups (Type 1 and Type 2) who would benefit substantially from the new and emerging therapies.[15,16] There is strong evidence that the irreversible loss of motor neurons in humans with SMA Type 1 begins early in the perinatal period, with severe denervation in the first three months and loss of more than 90 percent of motor units within six months of age. Patients dosed early in age (less than three months) and early in disease progression can achieve the ability to stand or walk. Nusinersen and onasemnogene abeparvovec-xioi results suggest that dosing early in disease progression will yield the best outcomes in infants with SMA1; therefore, early diagnosis and dosing should be encouraged.

A proposed treatment protocol is shown in Exhibit 3.[16] All clinicians agree on treating those with three or fewer SMN1 gene copies, but treatment of those with four copies of the SMN1 gene while asymptomatic is controversial. For those patients in whom treatment is not initiated immediately, routine follow-up care should ideally be provided by a neuromuscular specialist.

Conclusion

The new therapies for SMA are changing the natural history of this disorder. Patients who previously could not sit or stand can now do so, they can also breathe without assisted ventilation, and they can take in food orally or even feed themselves. More medications are on the horizon which will be easy to take for those patients who have some functioning SMN but need boosted levels.

Julie A. Parsons, MD is Professor of Clinical Pediatrics and Neurology and the Haberfeld Family Endowed Chair in Pediatric Neuromuscular Disorders at the University of Colorado Medical School in Aurora, CO.

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Best Practices in the Management of Metastatic Colorectal Cancer (mCRC): Expert Perspectives on Evolving Treatment Paradigms

Richard Kim, MD

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

Summary

Although not curable, metastatic colorectal cancer (mCRC) has many different treatment options which can be given sequentially and all of which improve survival. The selection of treatment requires genetic testing to identify targetable mutations and other alterations.

Key Points

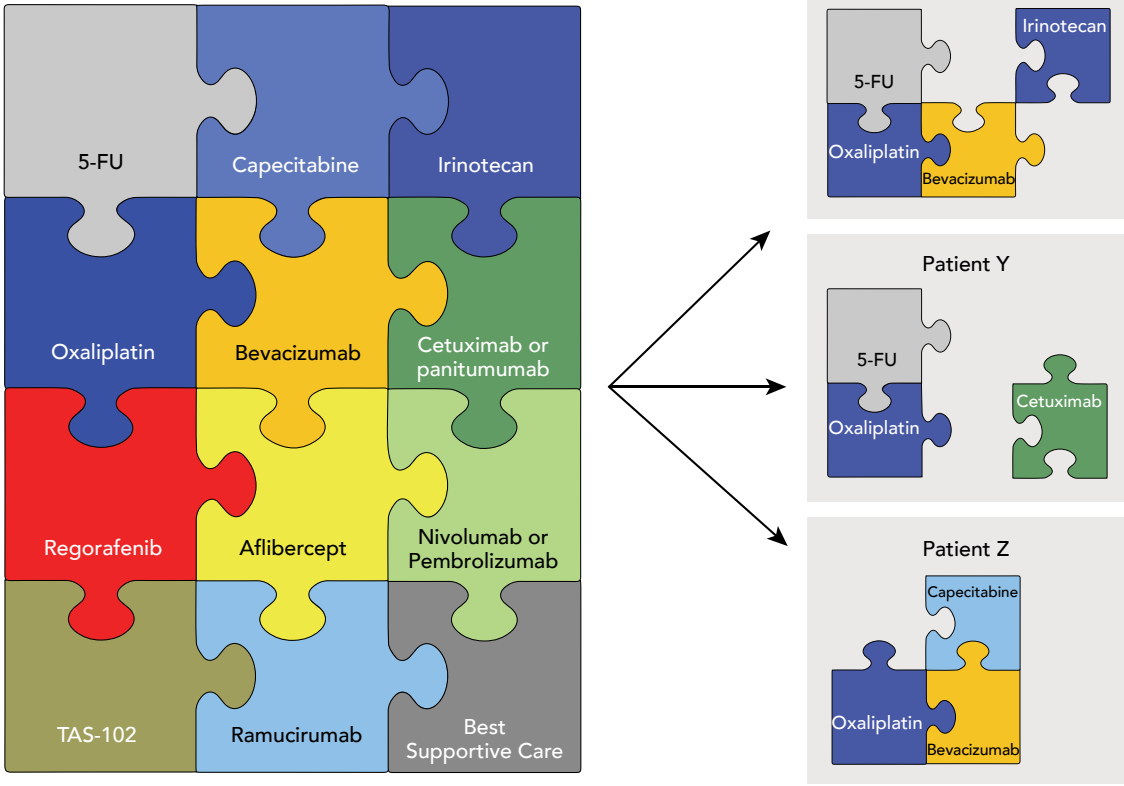
- Therapy for metastatic colorectal cancer is selected based on tumor genetics, patient factors, and the side of the colon in which the cancer originated.
- Anti-VEGF and anti-EGFR agents are competing for first-line therapy in patients in RAS wild-type mCRC.
- Right-sided colorectal cancers do not benefit from anti-EGFR therapy but do benefit from bevacizumab.
- Left-sided tumors benefit from both bevacizumab and anti-EGFR therapy.
- BRAF-mutated and HER-2 amplified disease can also be targeted with specific therapies.
- TRK inhibitors are available for those with NTRK fusions.
- Checkpoint inhibitors are highly active in select molecular subsets.

SOME PATIENTS WITH LIMITED METASTATIC colorectal cancer (mCRC) disease can be cured with chemotherapy and radiation. Collaboration within a multi-disciplinary team is essential for achieving a cure. For the majority of patients with mCRC, the treatment goal is to extend life and maintain quality of life as long as possible. The five-year survival rate for mCRC is 14 percent.[1]

Because targeted therapies are available for mCRC, next-generation genetic sequencing tests are essential to optimize clinical outcomes for patients with mCRC cancer, and all patients should be tested. There are biomarkers which identify cancers which do not respond to certain therapies and biomarkers that select patients for a specific therapy. The primary location of the tumor is also a factor in selecting therapy and a predictor of prognosis. Patients with right-sided disease have an overall worse prognosis. The molecular profiles are also different based on the location of origin. Tumors originating on the right side of the colon have a higher rate of BRAF and KRAS mutations and higher rate of micro-satellite instability high (MSI-H), which is a biomarker for immunotherapy efficacy.

There are at least 12 different therapies that are FDA approved for mCRC. Patients benefit from access to all active agents and therapies are given sequentially. Overall, treatment of mCRC is a marathon and not a sprint. With the luxury of so many treatment options, the question for oncologists is which agent to use in which patient in order to best personalize therapy (Exhibit 1). All patients who are appropriate for

Exhibit 1: How do We Personalize Therapy with so many Options?



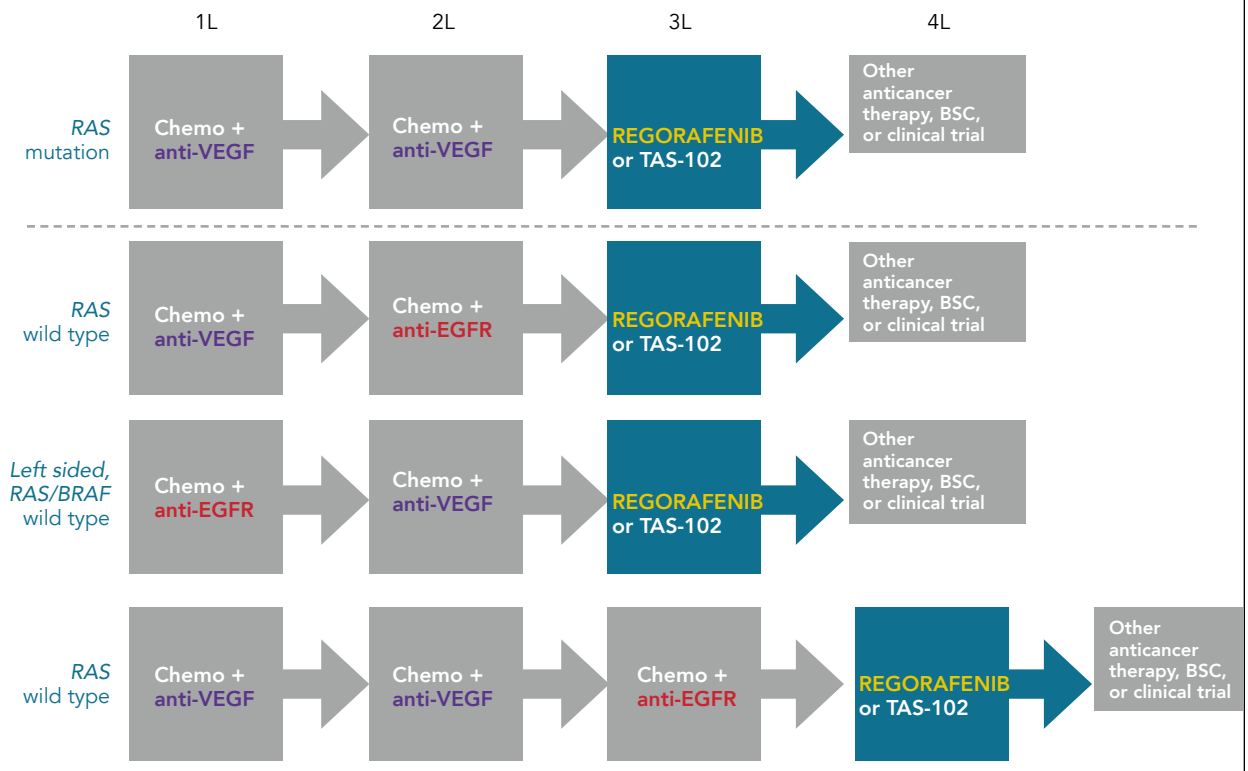
intensive therapy will receive chemotherapy as first-line treatment for mCRC, along with a biologic agent shown to improve survival as shown in Exhibit 2.[2,3] The initial personalization choice is whether to use bevacizumab (Avastin®, biosimilars), an anti-vascular endothelial growth factor (VEGF) agent, or an anti-epidermal growth factor receptor (EGFR) agent [cetuximab (Erbitux®), panitumumab (Vectibix®)] as the first-line choice of biologic. This choice is based on whether the tumor has RAS mutations and from what part of the colon the cancer originated.

There are three anti-VEGF agents approved for treating mCRC: bevacizumab, ziv-aflibercept (Zaltrap®), and ramucirumab (Cyramza®). Only bevacizumab is FDA approved for first-line therapy. The others are approved for second-line and beyond. The anti-VEGF agents are more cytostatic than cytotoxic, and there is evidence for using them for maintenance therapy after completion of chemotherapy and beyond progression.[4-6]

Anti-EGFR agents are not effective in mCRC that originates in the right-side of the colon, or in RAS-mutated disease. These agents have activity in mCRC as a single agent, so for patients who cannot take chemotherapy and are RAS wild-type with left-sided disease, they may be an option. There is also evidence of first- and second-line efficacy in combination with chemotherapy. The main reason to be cautious using anti-EGFR agents in the first-line setting is severe rash, which develops in almost all patients. The perfect candidates for anti-EGFR therapy are those who do not have RAS or BRAF mutations or HER2 amplification. If a patient fits these criteria, the response rate is approximately70 percent, but only about 20 percent of patients fit the criteria. Exhibit 3 compares the strengths and weaknesses of anti-VEGF and anti-EGFR therapies.

Immunotherapy with checkpoint inhibitors is now a treatment option for some patients with mCRC. In non-selected mCRC patients, checkpoint inhibitors are not effective, but they are effective in those with high levels of MSI-H or deficient mismatch repair (dMMR).[7,8] Nivolumab (Opdivo®) with or without ipilimumab (Yervoy®) and pembrolizumab (Keytruda®) are first-line treatment options for patients with MSI-H or dMMR if they are unable

Exhibit 2: *NCCN and ESMO mCRC Guidelines[2,3]



* For patients appropriate for intensive therapy
BSC = best supportive care
EGFR = epidermal growth factor receptor
ESMO = European Society for Medical Oncology
NCCN = National Comprehensive Cancer Network
VEGF = vascular endothelial growth factor.

to undergo intensive treatment with chemotherapy.[2] These agents are also options for second or later lines of treatment after chemotherapy in those with MSI-H/dMMR.

BRAF mutations occur in 4 to 14 percent of patients with colorectal cancer. BRAF is the primary effector of KRAS signaling. BRAF mutations occur most frequently in exon 15 (V600E) and are mutually exclusive with KRAS mutations. According to the National Comprehensive Cancer Network (NCCN) guidelines, dabrafenib (Tafinlar®) in combination with trametinib (Mekinist®) or encorafenib (Braftovi®) are BRAF mutation targeted therapy options in the second-line for mCRC.[2] Dabrafenib and trametinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Use of dabrafenib and trametinib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation-positive tumor xenografts compared with either drug alone. Encorafenib is a small molecule BRAF inhibitor that targets key enzymes in the MAPK signaling pathway. Dabrafenib/trametinib and encorafenib are currently only FDA approved for treating BRAF-mutated melanoma and non-small cell lung cancer and BRAF-mutated melanoma, respectively.

Trastuzumab (Herceptin®, biosimilars) in combination with pertuzumab (Perjeta®) or lapatinib (Tykerb®) is a treatment option for those with HER2 amplification, based on clinical trial data.[2] None of these agents are FDA approved for treating mCRC but are approved for other indications. Anti-HER2 therapy is only indicated for tumors that are also RAS and BRAF wild type.[2]

Neurotrophic receptor tyrosine kinase (NTRK) fusions are rare events, occurring in 0.1 to 2 percent of all cancers, but there is a much higher prevalence in certain rare cancers.[9] Fusions involving NTRK1, NTRK2, and NTRK3 have all been detected. The

Exhibit 3: Anti-VEGF versus Anti-EGFR Antibodies in Advanced CRC

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

Exhibit 4: Patient Adherence and Persistence with Oral Anticancer Treatment

Signs and Predictors of Poor Adherence	Interventions for Improving Adherence
Missed appointments, inadequate follow-up	**Increased accessibility to healthcare** • More convenient follow-up appointments • Access to pharmacists, behavioral specialists, social workers
Poor patient–provider relationship	**Improved dosing plan** • Simplify schedule • Supply pill boxes to organize doses • Reminders to take medications (e.g., wristwatch alarm, support from family/friends)
Unfilled prescriptions	**Educational intervention to increase patient's understanding of** • Disease characteristics • Risk/benefits of treatment • Proper use of medication
Adverse events from medication, medication cost	**Physician initiatives** • Simplify the oral regimen • Increase patient understanding, shared decision making • Listen to the patient • Learn about drug costs, insurance coverage • Reinforce adherent behaviors
Lack of belief in treatment	
Psychologic problems, particularly depression	

estimated annual incidence of TRK fusion–positive cancers in the United States (U.S.) is 1,500 to 5,000 cases. Larotrectinib (Vitrakvi®) was the first selective pan-TRK tyrosine kinase to be approved by the FDA for TRK fusion-positive cancers; entrectinib (Rozlytrek®) was the second one approved. They are highly selective and potent against TRKA, TRKB, and TRKC, and they are oral agents. In the trials, the overall response rate in TRK fusion-positive cancers has been 75 percent, with 13 percent of patients having a complete response. The FDA approval for both is for adult and pediatric patients with solid tumors that

have a NTRK gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments, or whose cancer has progressed following treatment. This is the second tissue-agnostic FDA approval for the treatment of cancer where the particular organ (i.e., colon, liver, etc.,) of origin is not specified. The NCCN guidelines list both as a treatment option for those with NTRK gene fusion.[2]

Regorafenib (Stivarga®) and TAS 102 (Lonsurf®) are used as a third- or fourth-line treatments of mCRC, after chemotherapy and targeted therapeutics have failed. Regorafenib is an oral, multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor tyrosine kinase. TAS 102 is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor. Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis, and inhibits cell proliferation. Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Many of the newer anti-cancer agents are oral therapies. This includes the TRK inhibitors, BRAF inhibitors, and lapatinib, which are all used in mCRC. Maintaining long-term adherence and persistence with oral anti-cancer agents can be an issue for patients. To optimize adherence and persistence, clinicians should assess the patient for possible physical and cognitive barriers, discuss access considerations, maintain open communication with the patient, review the treatment plan on an ongoing basis, and educate the patient and their caregiver(s) on the importance of adherence in managing cancer. Preemptive education on toxicity management is especially important. Patients need to know what adverse events to expect before starting therapy and how to manage them should they occur. Exhibit 4 lists some predictors of nonadherence and interventions for improving adherence.

Conclusion

Genetic tumor testing is essential to optimize clinical outcomes for patients with mCRC, and all patients should be tested. Anti-VEGF and Anti-EGFR agents are competing for first-line therapy in patients in RAS wild-type mCRC. Right-sided colorectal cancers do not benefit from anti-EGFR therapy but do benefit from bevacizumab. Left-sided tumors benefit from both bevacizumab and anti-EGFR therapy. BRAF-mutated and HER2-amplified disease can also be targeted with specific therapies. TRK inhibitors are now available for those with NTRK fusions. Checkpoint inhibitors are highly active in select molecular subsets.

Richard Kim, MD is an Associate Professor and Service Chief of Medical Oncology in the Department of Gastrointestinal Oncology at the Moffitt Cancer Center in Tampa, FL.

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