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Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Vol. 25, No. 2, 2022

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Navigating an Increasingly Complex Treatment Paradigm in the Management of HIV: Individualized Therapy for Improved Clinical and Economic Outcomes

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Summary

The management of HIV infection continues to evolve, and it is now possible for it to be managed as a chronic disease. Initial recommended regimens focus on single-tablet therapy to improve long-term adherence. Managed care can play a significant role in the management of their patients with HIV infection.

Key Points

- If diagnosed early and appropriate viral suppression is gained, HIV has become a manageable chronic disease.

- There are still unmet needs in the treatment of this disease state.

- Advances in therapy in the last two to three years have been significant.

- The goal of ending the epidemic by 2030 can be assisted by payer management activities.

HUMAN IMMUNODEFICIENCY VIRUS (HIV), a retrovirus that attacks immune cells that help the body fight infection, is spread by contact with certain bodily fluids of a person with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV), or through sharing injection drug equipment.[1] If left untreated, HIV infection can lead to acquired immunodeficiency syndrome (AIDS).

The HIV genome consists of two identical single-stranded RNA molecules that are enclosed within the core of the virus particle. The genome of the HIV provirus, also known as proviral DNA, is generated by the reverse transcription of the viral RNA genome into DNA. There is then degradation of the RNA and integration of the double-stranded HIV DNA into the human genome.

The virus is composed of a capsid (protein) coat which contains the two RNA strands. The protein envelope has many spikes of glycoprotein. The outer part of glycoprotein is gp120, which is attached to the inner part of the glycoprotein, gp41. The enzyme reverse transcriptase is responsible for the conversion of the viral RNA to form the DNA. Integrase helps the viral genome to become incorporated into the host cell. Binding of the virus to the chemokine coreceptor 5 (CCR5) allows HIV to enter human cells. Reverse transcriptase, integrase, gp120, and CCR5 are all targets of antiretroviral therapy (ART).

Researchers found the earliest case of HIV in a blood sample of a man from the Democratic Republic of Congo.[2] It is likely that the most common form of the virus spread from chimpanzees to humans sometime before 1931. Before the 1980s, researchers estimate that about 100,000 to 300,000 people were infected with HIV. The earliest case in North America was confirmed as occurring in 1968, in a 16-year-old who never left the Midwest and never received a blood transfusion. Exhibit 1 shows the significant milestones in the fight against HIV/AIDS in the United States (U.S.) since 1981.[3]

The prevalence of HIV infection in the U.S. has remained stable in recent years. In 2018, the Centers for Disease Control and Prevention (CDC) estimated that 1,173,900 persons 13 years of age and older were living with HIV in the U.S.[1] This

Exhibit 1: Significant Milestones[3]

Progress Against HIV/AIDS

■ HIV/AIDS   ■ HHS   ■ HHS and HIV/AIDS

1981 — CDC publishes first MMWR Report relating to the disease later named AIDS.

NIH provides first HIV/AIDS funding. — **1982**

1983 — Congress passes first bill with funding for AIDS research and treatment.

Virus causing AIDS officially dubbed HIV. — **1986**

1987 — Zidovudine (AZT) is the first HIV drug pre-approved by the FDA for treatment for people with HIV.

Congress establishes OAR to coordinate HIV/AIDS research across the NIH. — **1988**

1993 — CDC expands definition of AIDS to include conditions prevalent in women.

Congress passes the NIH Revitalization Act. — **1993**

1994 — CDC recommends AZT therapy for preventing mother-to-child HIV transmission.

Highly active antiretroviral therapy (HAART) becomes new standard of HIV care. — **1997**

1998 — CDC issues first national guidelines for the use of antiretroviral therapy in adults and adolescents with HIV.

Creation of PEPFAR (President's Emergency Plan for AIDS relief). — **2003**

2011 — Treatment as prevention becomes a game changer.

FDA approves first drug for pre-exposure prophylaxis (Truvada® for PrEP). — **2012**

2019 — Ending the HIV Epidemic announced.

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includes an estimated 161,800 who are undiagnosed. Young people are most likely to be unaware of their infection. According to a CDC analysis, an estimated 44.9 percent of young people aged 13 to 24 years were living with HIV and were unaware of their infection. New infections occur most often in homosexual men especially African Americans and Latinos. Half of the diagnosed cases in the U.S. are in those 50 and older.

Importantly, even when diagnosed, not everyone

Exhibit 2: Projections Show Cost Savings with a Comprehensive Approach[7]

All cities

Legend:
- ART (green)
- Medical care (red)
- Implementation (gray)
- PrEP (blue)
- MOUD (yellow)

Y-axis: Total Incremental Costs (2018 U.S.$, millions)
X-axis: Time (years)
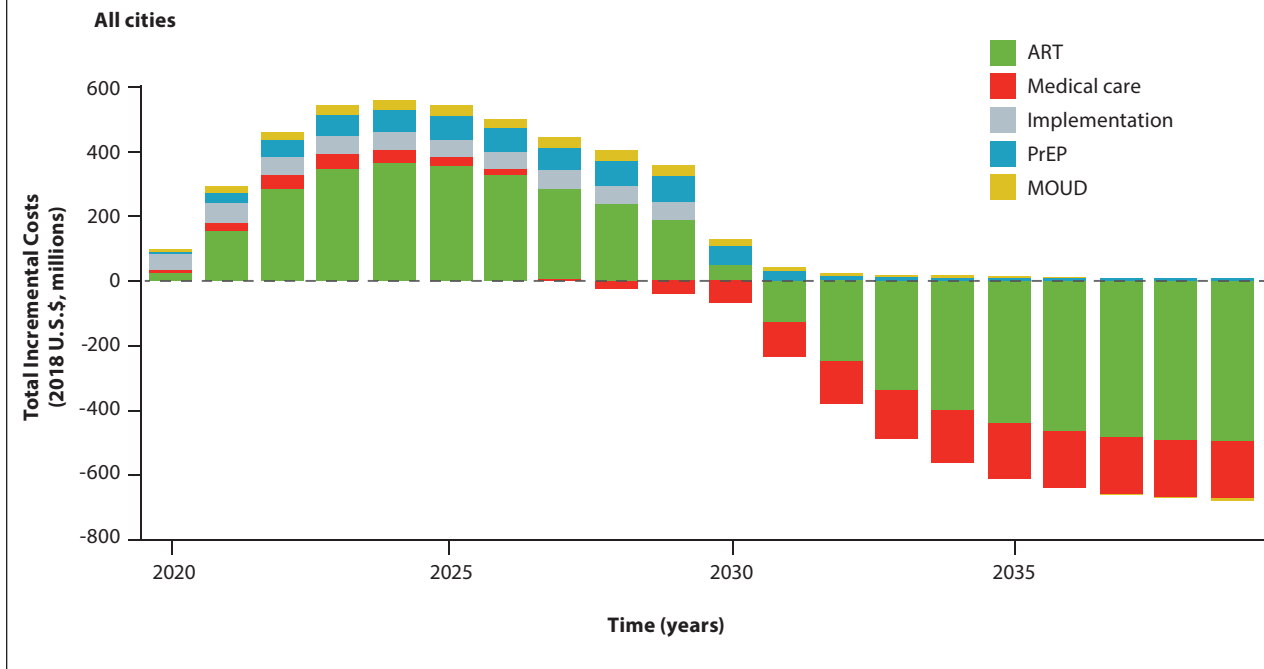
receives adequate care. According to a CDC report, 76 percent of those diagnosed have received some HIV care, 58 percent are retained in care, and 65 percent are virally suppressed or have undetectable virus levels. Having a suppressed or undetectable viral load protects the health of a person living with HIV by preventing disease progression. A person living with HIV who takes HIV medicine daily as prescribed and achieves and maintains viral suppression can stay healthy and has effectively no risk of sexually transmitting the infection to HIV-negative partners. Getting people diagnosed, into and retained in care, and virally under control is an enormous public health goal, which could help eventually end the HIV/AIDS epidemic.

The U.S. economic burden for managing HIV is significant. The average annual cost of HIV care has been estimated at $32,000 to $38,000 per person.[4] Mean all-cause annual healthcare costs from ages 25 to 69 were almost seven times higher in HIV patients compared with individuals without HIV.[4] The most recent published estimate of lifetime HIV treatment costs was $326,500 (2015 dollars).[5] Of the total cost, 60 percent is for ART, 15 percent for chronic disease medications and opportunistic infection prophylaxis and treatment medications, and 25 percent for non-medication costs. Costs increase as patients age with the disease.

Current guidelines advocate early ART to decrease morbidity and prevent transmission, but suboptimal engagement in care compromises impact. A cost-effectiveness analysis of improvements along the HIV care continuum found that despite early ART initiation, a projected 1.39 million new HIV infections will occur at a cost of $256 billion over two decades at existing levels of HIV care engagement.[6] The analysis found that enhanced testing with increased linkage to care had modest epidemiologic benefits and could reduce incident HIV infections by 21 percent at a cost of $65,700 per quality-adjusted life year (QALY) gained. By contrast, comprehensive improvements that couple enhanced testing and linkage with improved retention would reduce HIV incidence by 54 percent and mortality rate by 64 percent at a cost-effectiveness ratio of $45,300 per QALY. The U.S. Department of Health and Human Services (HHS) has set a goal of a 75 percent reduction in HIV infections by 2025 and 90 percent by 2030.

Projections show cost savings with a comprehensive approach (Exhibit 2).[7] Expenditures would peak between 2023 and 2025, with a peak annual overall annual expenditure of $559 million in 2024. Overall costs over a 10-year implementation period would total $3.51 billion, with 63 percent of these costs attributable to expanding access to ART medications. When ART is used to prevent HIV transmission, this strategy is called treatment as prevention, commonly known as Undetectable = Untransmittable or U = U. In order for persons

Exhibit 3: Undetectable = Untransmittable (U = U)[8]

1 to 6 Months TO BECOME UNDETECTABLE	Once HIV-1 RNA < 200 c/mL REPEAT VL Q3-4 MO	If VS and immunologic status stable x 2 years REPEAT VL Q6 MO
ART adherence is essential	Continued adherence is required	• Continued ART adherence • ART D/C negates U = U

PROVIDE SERVICES THAT PROMOTE ADHERENCE AND RETENTION IN CARE

RISK

UNDETECTABLE
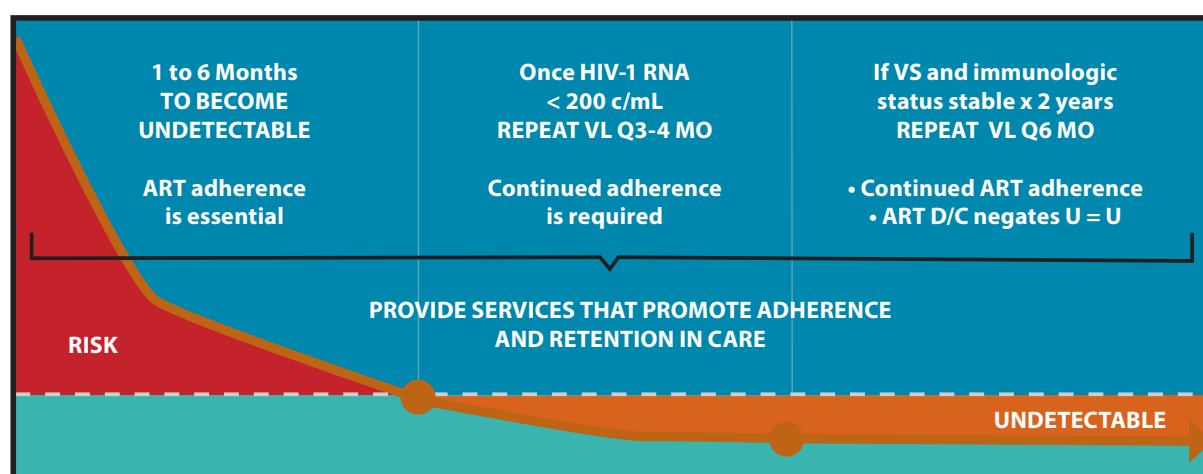
c/mL = copies per milliliter; D/C = discontinuation; mo = month; Q = every;
RNA = ribonucleic acid; VL = viral load.

Exhibit 4: Recommended Initial Regimens for Most People with HIV[9]

- Bictegravir/emtricitabine/ tenofovir alafenamide (Biktarvy®)[a]
- Abacavir/dolutegravir/lamivudine(Triumeq®)[b]
- Dolutegravir(Tivicay®) + tenofovir alafenamide or tenofovir disoproxil fumarate + lamivudine or emtricitabine[a]
- Dolutegravir/lamivudine(Dovato®)[c]

[a] also recommended for rapid ART
[b] if HLA-B*5701 negative
[c] HIV RNA < 500,000K copies, no hepatitis B (HBV) coinfection, must have genotype and HBV test results completed prior to prescribing

with HIV to benefit from early diagnosis, ART should be started immediately or as soon as possible after diagnosis to increase the uptake of ART. Also, rapid start ART decreases the time required to achieve linkage to care and virologic suppression for individual patients, reduces the risk of HIV transmission, and improves the rate of virologic suppression among persons with HIV. U = U is a campaign that we should all be talking to our patients about (Exhibit 3).[8] The crux of U = U is that an individual will achieve and maintain viral suppression and yet transmission risk is still present while the patient is getting to an undetectable viral level. Once undetectable, maintenance of adherence and viral load suppression are critical. U = U is central to rapid ART initiation and benefits public health. Decreased community viral load is associated with reduced risk of transmission. It also incentivizes systems and programs to provide

support for the individual to remain engaged in care and on ART.

The published HIV management guidelines for the U.S. are constantly being updated, and the guideline website should be consulted for the most up-to-date recommendations (clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv). Current recommendations for initial therapy in treatment naïve patients are shown in Exhibit 4.[9] A single tablet a day formulation is recommended, if possible, to maximize adherence, but patient characteristics, such as liver or kidney function or concomitant diseases, will impact treatment selection.

Available antiretroviral (ARV) drugs for the treatment of HIV have expanded significantly since 2018, and a long-acting combination of injectable agents has been approved. Novel types of ARVs with new mechanisms of action have been approved for patients who are heavily treatment experienced

Exhibit 5: CDC Goals[10]

DIAGNOSE all people with HIV as early as possible.

TREAT people with HIV rapidly and effectively to reach sustained viral suppression.

PREVENT new HIV transmissions by using proven interventions, including pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs).

RESPOND quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.

(ibalizumab, fostemsavir). There have also been approvals of combination tablets of previously available drugs (bictegravir/emtricitabine/tenofovir alafenamide and dolutegravir/lamivudine). Finally, there has been an expansion in approved indications for previously available ARVs themselves, including emtricitabine/tenofovir alafenamide for use in pre-exposure prophylaxis (PrEP).

The two medication regimen of long-acting injectable cabotegravir and long-acting injectable rilpivirine (Cabenuva®) is indicated as a complete regimen for the treatment of HIV infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV RNA less than 50 copies per mL) on a stable ART regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. Prior to initiating the injectables, oral lead-in dosing with the separate components should be used for approximately one month to assess the tolerability to each component. Injectable therapy is initiated on the last day of oral dosing with monthly intramuscular injections (each medication requires a separate intramuscular injection). This combination may be an option for those who prefer not to take daily medications or have adherence issues. Trials have examined use of this combination as switch therapy and for treatment-naïve patients. Injection site reactions are the most common adverse event.

Ibalizumab (Trogarzo®) is an injectable recombinant monoclonal antibody that binds to the surface proteins of CD4 cells leading to conformational changes that prevent the steps required for HIV fusion and entry into the cell. Because of its unique binding specificity, ibalizumab blocks viral entry without causing immunosuppression. It is indicated in combination with other ARVs for treatment in heavily treatment-experienced (HTE) adults with multidrug resistant (MDR) HIV who are failing their current ARV therapy regimen.

Fostemsavir (Rukobia®) is a novel ARV indicated for combination therapy in HTE adults with known multi-drug resistant (MDR) HIV, and specifically for patients who are failing current ART due to potential resistance, intolerance, or safety considerations. It is the first FDA-approved attachment inhibitor. After enzymatic activation to the active molecule temsavir, it binds to gp120 which prevents viral entry into CD4 cells, effectively stopping viral replication. The most commonly reported adverse event from fostemsavir was nausea. More severe reactions including elevations in liver enzymes were reported in patients with hepatitis B or C coinfection.

Dolutegravir/lamivudine (Dovato®) is the first two-drug combination tablet approved by the FDA as a complete regimen for the treatment of HIV infection in treatment-naïve adult patients. This contrasts with the traditionally required three-drug standard-of-care regimen options required to prevent resistance and offers a new opportunity in patients who cannot tolerate any of the more common three-drug regimens due to adverse events or unavoidable drug interactions.

Payer engagement can help achieve the HHS goals toward ending the HIV epidemic (Exhibit 5).[10] Payers can have a role in promptly linking individuals newly diagnosed with HIV to care and treatment, including through rapid start treatment programs. They can also find innovative and effective ways to re-engage the estimated 250,000 individuals who are aware of their infection but are not receiving HIV care and treatment. Plans can also support those already in care who have not yet achieved viral suppression to achieve control of the virus and once viral suppression is achieved to maintain therapy adherence. Payers (especially in high unmet areas) can promote PrEP use. PrEP use varies widely across the country. In 2018, there were only three PrEP users for every new HIV diagnosis in the South U.S. compared to 5.8 in the Northeastern U.S.[11] Overall, payers need to take a comprehensive approach to increase PrEP use, increase testing, improve treatment access and availability, and improve adherence to therapy and minimize dropouts.

Conclusion

Infection with the HIV virus if untreated leads to devastating consequences. Because of our growing understanding of this virus since the 1980s outbreak, multiple therapeutic targets have been identified. If diagnosed early and appropriate viral suppression is gained, HIV has become a manageable chronic disease. However, there are still unmet needs in the treatment of this disease state. Advances in therapy in the last two to three years have been significant. The goal of ending the epidemic by 2030 can be assisted by payer management activities to support the HHS goals.

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Recent Advances in the Treatment, Management and Prevention of Obesity

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Summary

With a better understanding of the underlying pathophysiology of weight loss and regain in obese people, it is now known that weight management requires long-term treatment. Several medications are approved by the FDA for long-term use and can provide up to a 15 percent weight loss when combined with lifestyle management.

Key Points

• The body adapts to weight loss making it more difficult to keep weight off.

• Weight loss medications need to be continued long-term.

• The most effective weight loss medication targets satiety hormones.

• Future treatment will be a combination of satiety hormones.

ALMOST 50 PERCENT OF THE UNITED States (U.S.) population is obese, and obesity is a costly disease both in terms of finances and morbidity. Patients with obesity incur costs that are 42 percent higher than healthy-weight peers.[1-4] Costs for patients with obesity are going up due to increasing prevalence of obesity and not cost of medical care. Medical costs of obesity care are driven by comorbid diseases, including diabetes, hypertension, heart failure, and depression. These costs are increasing the most for diabetes management. It is important to remember that a comorbid disease starts when someone has prediabetes. For example, the economic burden of obesity due to diabetes increases with increasing weight.[5] Costs actually start increasing with just being overweight in the diabetic patient and increase geometrically with obesity and morbid obesity. Also, cardiovascular disease starts in prediabetes.[6] Costs related to comorbid disease can also start going up in the morbidly obese prediabetes.

Weight loss is the best treatment for diabetes and its complications. For example, treatments to get a hemoglobin A1C less than eight include more diabetes mediations or weight loss through dietary changes, exercise, weight loss medications, and weight loss surgeries.[7] Some diabetes medications can make weight issues worse (e.g., sulfonylureas) or help with weight loss (e.g., metformin, GLP-1 agonists). Weight loss can improve glycemic control and improvement begins with a loss of greater than 2 percent of starting body weight (Exhibit 1).[8] Five percent or more weight loss provides an A1C benefit equivalent to most anti-diabetes medications. In one trial, compared with weight-stable participants, those who lost 5 to < 10 percent of their body weight had increased odds of achieving a 0.5 percent point reduction in HbA1c, a 5-mmHg decrease in diastolic blood pressure, a 5-mmHg decrease in systolic blood pressure, a 5 mg/dL increase in HDL cholesterol, and a 40 mg/dL decrease in triglycerides.[8] The odds of clinically significant improvements in most risk factors were even greater in those who lost 10 to 15 percent of their body weight.[8] Although weight loss improves HDL cholesterol and triglycerides, it does not substantially reduce LDL cholesterol, but the LDL cholesterol is less atherogenic because of lower triglyceride levels.

Overall, diet and exercise can induce a typical weight loss of 5 percent to 10 percent of starting body weight. Only about 20 percent of patients do well with diet. Current weight loss medications typically induce weight loss of 5 percent to 15 percent. In the past, only 50 percent to 60 percent of those on medications lost a clinically significant amount of weight; however, newer weight loss medications allow 85 percent of patients to do well. Bariatric

Exhibit 1: How Much Weight Loss is Needed to Improve Glycemic Control?[8]

Change in A1C (%) by Weight-Loss Category
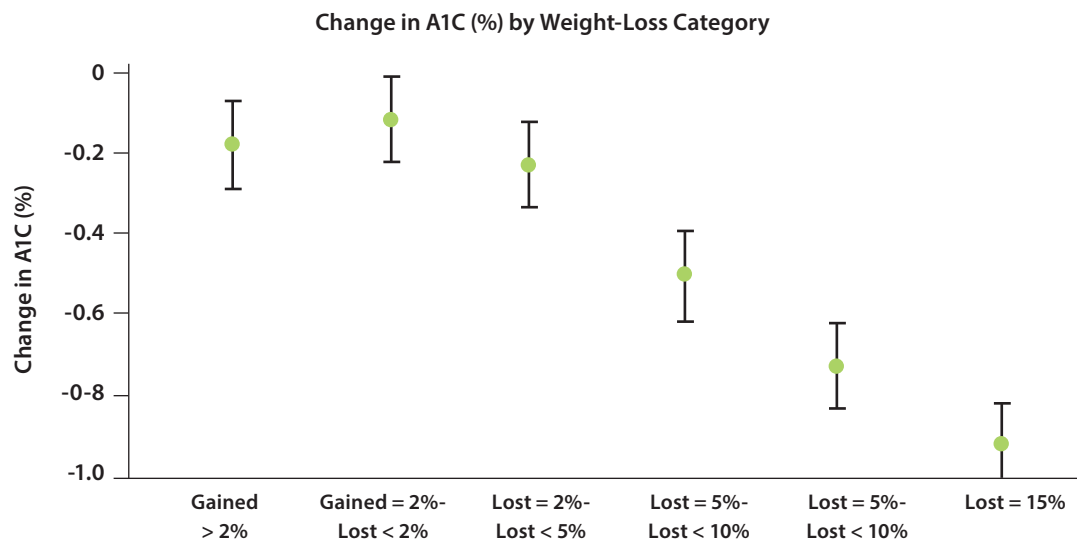
A1C = glycated hemoglobin.

Exhibit 2: Physiology of Weight Regulation and food Intake[10]
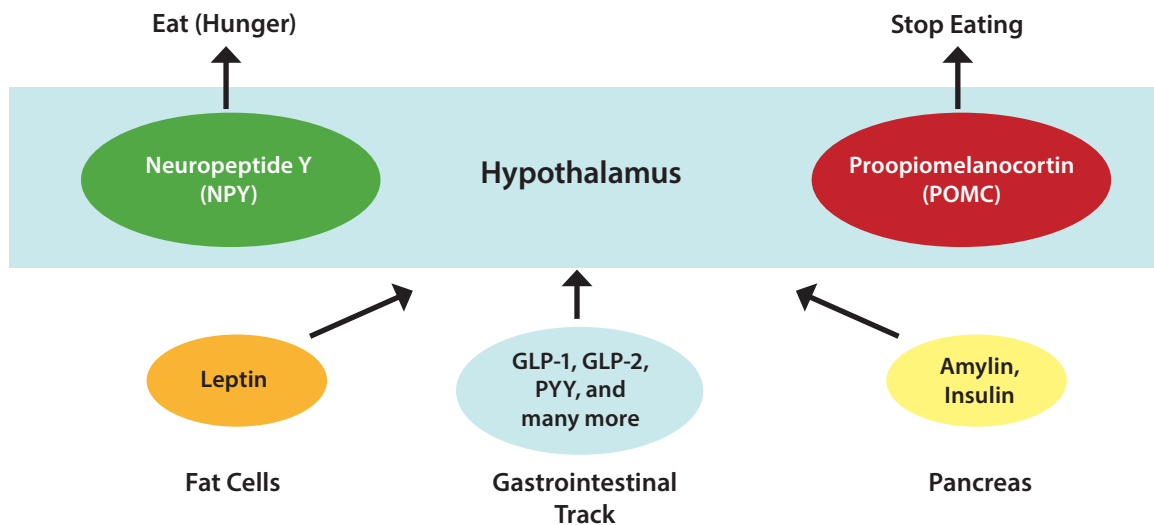
surgery benefits vary by the procedure. Weight loss of 20 percent is seen with the gastric sleeve and 25 percent with gastric bypass.[9] Overall, 85 percent of bariatric surgery patients reach their goals.

Weight loss is hard to accomplish because of signals in the body which promote eating are typically much stronger than the signals to stop eating (Exhibit 2).[10] The hypothalamus is turned on continuously to feed, leading to increased hunger and decreased satiety.

The gastrointestinal tract releases satiety hormones [glucagon-like peptide one (GLP-1), GLP-2, peptide YY, and many more] that tell the brain to stop eating when food is in the intestines. Fat cells release leptin to tell the brain the status of the fat cells and the body wants to maintain a sufficient level of fat for survival. Exogenous insulin also tells the body to hold onto fat. Reward eating also has an impact on weight and weight loss difficulty.

Once people lose weight, it is very difficult to keep if off. There is a permanent metabolic adaptation after weight loss that leads to lower levels of satiety hormones. The weight set point in the hypothalamus lowers metabolic rate and drives up appetite. The hypothalamus will reset to the highest weight a patient has reached in their lifetime. This change is permanent or until the patients gets back to the highest weight. The set point will never readjust down to a lower weight. The take home message is that treatment for obesity has to be lifelong.

There are many valid reasons why healthcare providers are reluctant to use pharmacotherapy for weight management, including the negative record of accomplishment of weight-loss medications that has led to numerous safety concerns. Additionally, there is lack of formal training in obesity medicine and general discomfort with using these medications. Newer weight-loss medications better target the mechanisms which stimulate eating and have increased safety. Exhibit 3 shows some of the agents which have been taken off the market because of safety concerns.

After 1997, the FDA set a very high bar for safety evaluation for weight loss medications to be approved. A cardiovascular outcomes trial looking at major adverse cardiovascular events is also required for every new agent. Any potential major adverse event will have a Risk Evaluation Mitigation Strategy (REMS). For example, the phentermine/topiramate combination has a REMS regarding potential risk of harm to an unborn fetus because topiramate is a teratogen. The purpose of REMS is to inform prescribers, pharmacists, and women of reproductive potential about the increased risk of congenital malformation with exposure to topiramate during pregnancy.

Weight management medications increase the likelihood that patients will achieve clinically meaningful improvements in cardiovascular, metabolic, and other weight-related measures of health. However, the weight loss achieved with any weight management intervention can vary widely among individuals, and patients who do not respond to pharmacotherapy by achieving clinically meaningful weight loss should discontinue therapy. If the patient has not lost 5 percent of weight within the first four months on a given agent, the agent is unlikely to help the patient lose clinically significant weight and should be stopped.[11,12]

The currently available weight loss medications are liraglutide (Saxenda°), semaglutide (Wegovy°), phentermine/topiramate (Qsymia°), and naltrexone/bupropion (Contrave°). Each is effective in helping patients lose more weight than diet and exercise alone. Naltrexone/bupropion is especially good for patients with extreme food cravings. Patients lose 7 to 9 percent of body weight with phentermine/topiramate and 8 percent with naltrexone/bupropion. It should be noted that liraglutide and semaglutide are both marketed under different brand names (Victoza°, Ozempic°, respectively) at lower doses for type 2 diabetes treatment.

The GLP-1 agonists, liraglutide and semaglutide, affect both hunger and satiety and are effective in helping people lose at least 10 percent of their body weight. GLP-1 agonists slow down gastric emptying and reduce insulin secretion in response to eating. Based on one placebo controlled comparison trial, semaglutide is more effective than liraglutide for reducing weight (Exhibit 4).[13] In the trial that led to an FDA-approved weight-loss indication for

Exhibit 4: Weight Loss with GLP-1s in Non-Diabetics[13]

GLP-1 agonists, to promote satiety. Amylin decreases gastric emptying, glucagon (directly effects the alpha cells), and post prandial glucose. Pramlintide, an injectable amylin analogue, is currently FDA approved for glucose control in patients with diabetes on insulin and is given with meals three times a day because of its short half-life. The three times a day injection regimen does not make this agent easy to adhere to long-term for weight loss. Cagrilintide is an investigational long-acting amylin analogue given subcutaneously once a week. It is being investigated alone and in combination with semaglutide. A Phase Ib trial found a 17 percent weight loss over just 20 weeks with the combination.[15,16]

Tirzepatide is an investigation agent that targets both gastric inhibitory polypeptide (GIP) and GLP-1. The key role of GIP is to stimulate insulin secretion.[17] When there are elevated levels of glucose, GIP leads to increase in insulin which will then lower glucagon levels. With low levels of glucose, GIP increases glucagon. In theory GIP potentiates GLP-1's ability to lower food intake possibly by lowering ghrelin or a direct effect on fat cells (lipolytic).[18] One trial found glucose improvement greater with tirzepatide compared to the glucose lowering dose of semaglutide (weight loss dose is 2.4 mg/week).[19] This agent will likely be FDA approved first as a treatment for type 2 diabetes, but patients also lose 8.5 to 13 percent of body weight.

Since 2013 when obesity was officially declared to be a disease, insurance coverage of weight loss medications has improved, but there are significant variations from state to state. Coverage is often employer driven. Many anti-obesity agents have cash discount cards to reduce patients cost (cash prices are $15 to $135 per month). Because obesity is now coded as a disease, the patient outcomes can be tracked. The increase in the use of healthcare metrics and accountable care will push toward payment of weight loss medications that treat the multiple comorbid problems of obesity (glucose, blood pressure, dyslipidemia, etc.).[10,20,21]

semaglutide, the mean change in body weight from baseline to week 68 was -14.9 percent in the semaglutide 2.4 mg subcutaneously once a week as compared with -2.4 percent with placebo, for an estimated treatment difference of -12.4 percentage points ($p < 0.001$).[14] More participants in the semaglutide group than in the placebo group achieved weight reductions of 5 percent or more (86.4% versus 31.5%), 10 percent or more (69.1% versus 12.0%), and 15 percent or more (50.5% versus 4.9%) at week 68 ($p < 0.001$ for all three comparisons of odds). The change in body weight from baseline to week 68 was -15.3 kg in the semaglutide group as compared with -2.6 kg in the placebo group (estimated treatment difference, -12.7 kg). Thus, semaglutide is the most effective weight loss medication available. Participants who received semaglutide had a greater improvement with respect to cardiometabolic risk factors and a greater increase in participant-reported physical functioning from baseline than those who received placebo. The GLP-1 agonist agents do need to be titrated slowly to reduce the incidence of nausea.

The future of weight management pharmacotherapy will be giving combination therapy with satiety hormones. One combination under study is GLP-1 agonists with amylin analogues. Amylin comes from the beta cell in a one-to-one ratio with insulin and goes to several parts of the brain, different from

Conclusion

Clinicians now have a good understanding of the pathophysiology of obesity, including the hormonal changes of metabolic adaptation with a decrease in satiety hormones, an increase in hunger hormones, and a profound drop in metabolism with weight loss. Because of pathophysiology, management of obesity requires long-term treatment. Targeted replacement of the satiety hormones is becoming the mainstay of weight loss therapy. The current weight loss medications can achieve a clinically meaningful 5 to 10 percent weight loss. The newest weight loss

medications result in 15 percent weight loss or better. Managed care should expect to see patients on a combination of hormones in the future to control weight.

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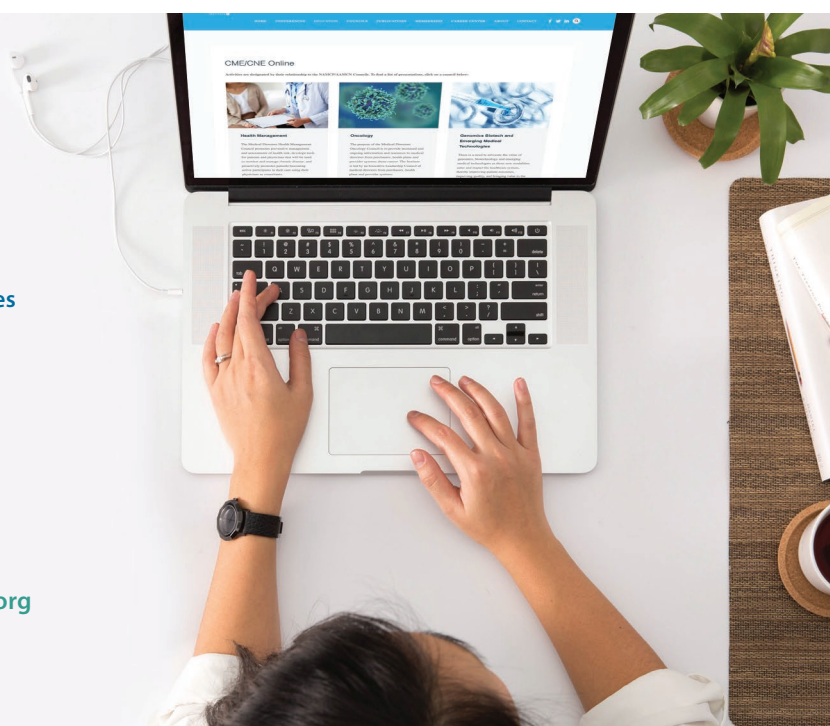
New Frontiers in the Treatment and Management of Alzheimer's Disease: Expert Perspectives on the Role of Emerging Therapies

Marc E. Agronin, 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

As the United States (U.S.) population continues to age, Alzheimer's disease is a growing concern. Although improvements in diagnoses have been made, finding a disease-modifying treatment has been a challenging task. Symptomatic treatments which modestly improve cognition and one potentially disease-modifying agent are available. Treating this disease in the very earliest stage is the likely place in therapy for the newest agent.

Key Points

• Biomarkers for Alzheimer's disease (AD) are available to help improve diagnosis.

• The combination of memantine and a cholinesterase inhibitor is optimal for symptomatic control.

• Aducanumab is the first FDA-approved agent targeting the pathophysiology of AD.

OVER OUR LIFETIME, THE BRAIN IS constantly adapting and resculpting itself (neuroplasticity). Experience and learning increase our brain and cognitive reserves which help when declines begin to occur. The brain does age like the rest of the body.[1] Neurons have a buildup of cellular debris, decreased production of neurotransmitters, slower transmission, and less energy production. Additionally, neurons die. Atrophy is the rule with an aging brain, not the exception, but connections among the remaining neurons are more important than the number of neurons.

Different skills within the brain change at different rates over time (Exhibit 1). Fluid intelligence (problem solving, reasoning, logic, pattern recognition) begins a slow decline after the age of 20.[2,3] This results in slower processing speed, increased frequency of tip-of-the-tongue lapses, decreased cognitive inhibition or suppression of distractions, and slower and less efficient multi-tasking. Crystallized intelligence (skills, knowledge, experience) remains stable and/or increases over time. Vocabulary increases and overall knowledge increases as we age. Older brains are better at recruiting additional brain circuits and at using both sides of the brain than younger brains.

The beginning stage of cognitive decline is mild cognitive impairment (MCI). MCI is defined by self-reported memory complaints and memory scores lower than average peers.

Daily function is essentially normal. One-third of people with MCI revert to normal over two to three years and one-third develop dementia over two to three years. The remaining third remain stable.

Dementia is now called major neurocognitive disorder, and it is a brain disease with impairment in one or more of cognitive domains (Exhibit 2). It is a growing epidemic as the U.S. population continues to age. More than six million Americans are living with Alzheimer's disease which is just one of the many dementias.[4] By 2050, the number of people aged 65 and older with AD is projected to reach 12.7 million. One in nine people aged 65 and older has AD and two in three Americans with AD are women. The estimated lifetime risk for AD at age 45 is 20 percent for women and 10 percent for men. AD is the fifth leading cause of death in those over

Exhibit 1: The Aging Brain

Skills peak from 30s to 60s

Moderate declines in 60s to 70s

More severe declines in 80s

MEAN PERFORMANCE VALUES

30   40   50   60   70   80
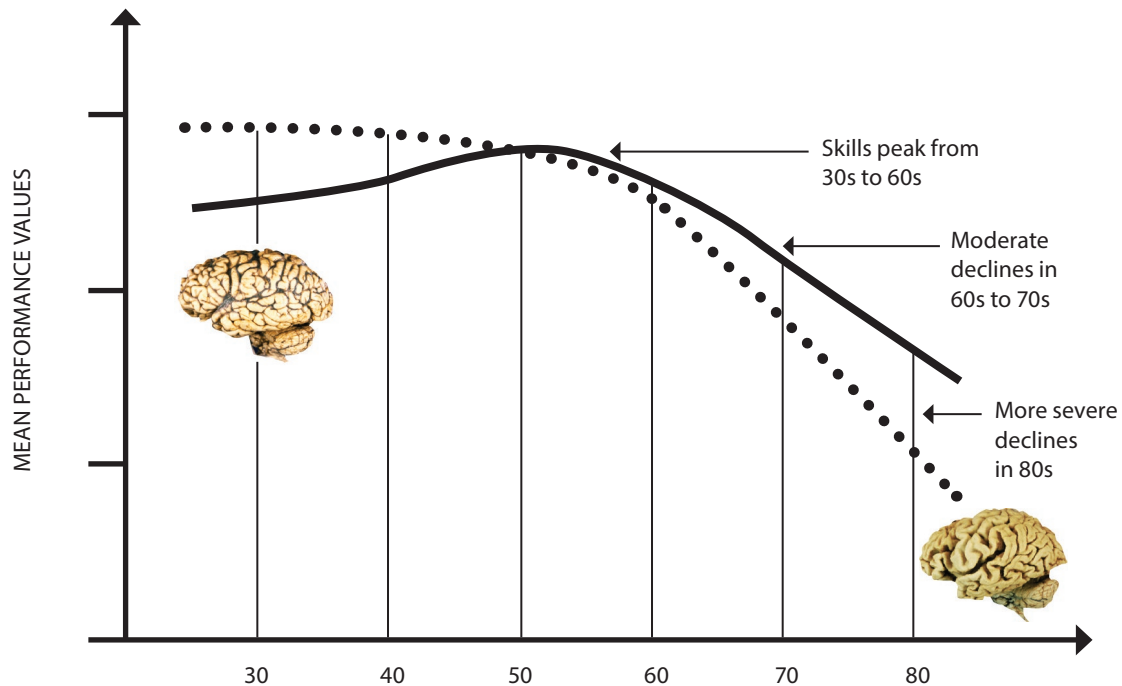
——— Inductive reasoning, verbal ability, spatial orientation

•••• Numeric ability, word fluency

Exhibit 2: Cognitive Domains

Domain	Description
Complex Attention	Multi-tasking
Executive Function	Planning, organizing, prioritizing
Learning and Memory	Learning and remembering
Perceptual Motor	Using and recognizing faces, maps, items
Language	Speaking and understanding what we hear
Social Cognition	Acting appropriately with others

65 years of age in the U.S. Even after adjusting for differences in age distributions over time, the annual AD death rate in the U.S. increased substantially between 1999 and 2014.

AD accounts for 60 to 70 percent of dementia cases. Other causes include vascular (15 to 20%), Lewy bodies (10 to 15%), Parkinson's disease (<5%), frontotemporal (<5%), and medically-induced

(< 5 %, due to trauma, toxins, illness, etc.).

The most important risk factors for developing AD over one's lifetime are genetics and education in early life; hearing loss, hypertension, and obesity in mid-life; and smoking, depression, physical inactivity, social isolation, and diabetes in late life.[5] Of all AD risk factors, only about 35 percent are potentially modifiable.

Exhibit 3: Early versus Late Onset AD Genetic Risk Factors[6-13]		
Type of Alzheimer's Disease	**Chromosome**	**Genes**
Early onset (EOAD)	1	Presenilin 2
	14	Presenilin 1
	21	APP (Amyloid precursor protein)
Late onset AD (LOAD)	1	CR1
	2	BIN1
	5	MEF2C
	6	CD2AP, TREM2
	7	EPHA1, NME8, ZCWPW1
	8	CLU, PTK2B
	11	CELF, MS4A6A, PICALM, SORL1
	14	FERMT2, SLC24A4/RIN3
	18	DSG2
	19	ABCA7, CD33, APOE-ε4
	20	CASS4
	X	INPP5D

Genetics are a risk factor for both early and late onset AD (Exhibit 3).[6-13] Most early onset AD (EOAD) is not familial. Rarely in familial cases do deterministic genes cause autosomal dominant inheritance. Late onset AD (LOAD) can be sporadic or familial and accounts for 90 to 95 percent of cases. The risk genes probabilistically increase the likelihood of developing the disease.

A main genetic risk factor for late-onset AD is the apolipoprotein E (APOE) gene located on chromosome 19. APOE 4 increases risk and lowers age of onset twofold, and having two copies of this gene increases risk almost fivefold. APOE 2 decreases risk and APOE 3 is neutral. At this time, the other genetic risk factors are not routinely tested in part because they are not well understood.[5]

Delays in diagnosis are a major issue with AD. On average, individuals with cognitive impairment do not see a physician for up to two years after symptoms become noticeable and do not receive a diagnosis for up to one year thereafter. Up to 20 percent of individuals in the U.S. with AD are misdiagnosed as having another dementia.[14,15] This is a major problem because reversible causes of cognitive impairment become less reversible with time (i.e., the damage is done). Delays in diagnosis result in delays in treatment, research, assistance, and safeguards. An uncertain or incorrect diagnosis leads to misdirected, inappropriate, or unsafe treatments. Knowing that memory difficulties are not dementia can bring great relief to the patient and an appropriate search for other issues and comorbidities.

A comprehensive evaluation for suspected AD includes a thorough mental status examination, a brief cognitive screen, physical and neurological examination, basic laboratory screening (thyroid function, complete blood count, electrolytes, liver function, vitamin B12, folate), brain scan, and neuropsychological testing.[16] More extensive lab testing should only be done when other causes of memory difficulty such as infection are suspected. A brain scan will rule-out major anatomical causes such as tumor or stroke, rather than rule-in most dementias. An MRI is better for identifying small infarcts and white matter changes. A CT is acceptable if results are needed quickly after trauma or MRI is not possible. A fluorodeoxyglucose positron

Exhibit 4: Biomarker Changes during Alzheimer's Disease Progression[18]
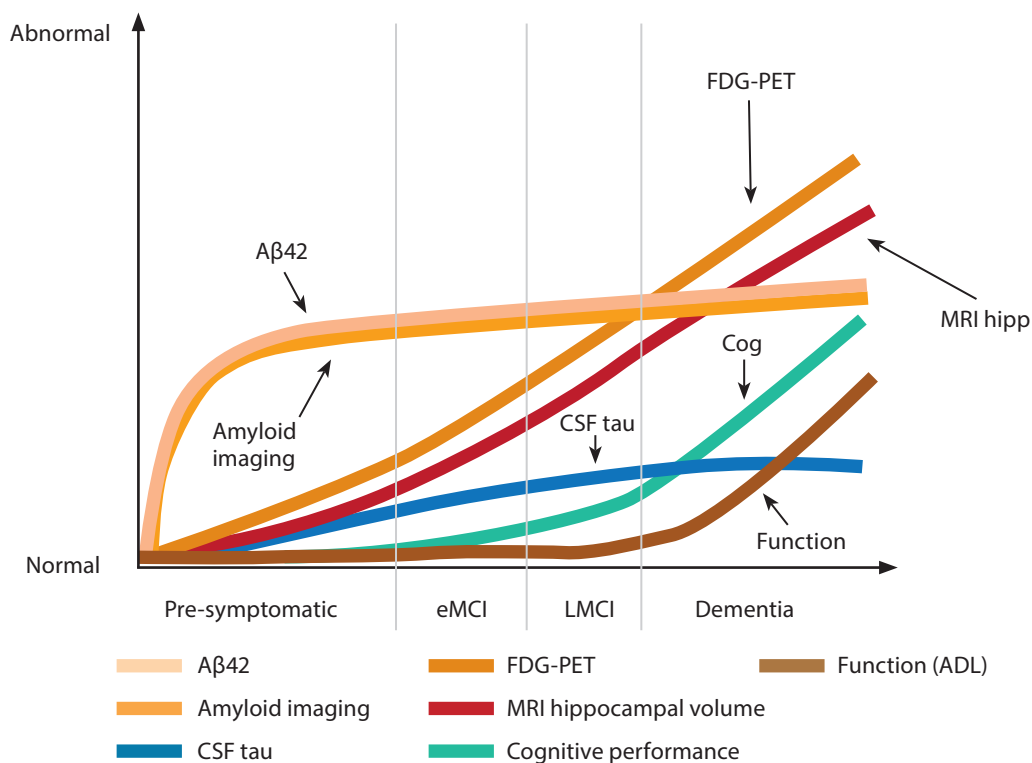
MCI = mild cognitive impairment; LMCI = late MCI

emission tomography (FDG-PET) scan can assess brain function as well as the presence of amyloid plaques and tau protein, biomarkers of AD. It is the best test for diagnosing AD but is only covered by Medicare in limited circumstances.

Pathologically, AD is a progressive, cortical dementia. It typically begins with short-term memory complaints but progresses over eight to 12 years on average to involve every cognitive domain and impact function, mood, and behavior with time. The pathology of AD, as currently understood, involves accumulations of amyloid plaques [comprised of the toxic beta-amyloid protein (Aβ)] and neurofibrillary tangles (aggregates of the tau protein, NFT) in the brain.[4] The abnormal accumulation of plaques and tangles cause neuron cells to die, leading to dramatic cell loss and brain atrophy affecting areas of the brain that are responsible for memories, thoughts, sensations, emotions, movements, and skills. Aggregated Aβ plaques are deposited within the brain as a result of reduced Aβ clearance. This typically begins early in the disease process before the onset of cognitive impairment. NFTs are formed

in the brain by the abnormal accumulation of hyperphosphorylated-tau protein. Unlike Aβ, the formation of NFTs typically occurs in parallel to the progression of cognitive decline.[17] Exhibit 4 shows how the biomarkers of AD change over time.[18]

Without treatment, those with AD will typically have a steady decline in cognition and function over time. The goals of treatment are to provide symptomatic improvement and disease modification. At this time, a cure is not possible. Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and an N-methyl-D-aspartate receptor antagonist (memantine) are the symptomatic treatment options. There is no noteworthy evidence that any other agents provide any symptomatic benefit for AD or other forms of dementia. Combination with memantine and a cholinesterase inhibitor provides the most symptomatic benefit and slows long-term cognitive decline. Patients receiving combination therapy showed significantly slower cognitive decline compared with patients receiving a cholinesterase inhibitor alone ($p < 0.001$) and compared with untreated patients ($p < 0.001$).[19] This

Exhibit 5: Cognitive Enhancers in AD

- Do keep expectations modest – the goal is symptomatic improvement, NOT a cure

- Don't promise disease slowing or modification, but educate patients and caregivers about adverse events and realistic expectations.

- Do start with the lowest dose and titrate as indicated.

- Don't rush titration.

- Don't combine cholinesterase inhibitors with one another.

- Do combine cholinesterase inhibitors with memantine.

- Do monitor closely for important side events.
  - Memantine – confusion, sedation, constipation.
  - Cholinesterase inhibitors – nausea, vomiting, diarrhea, loss of appetite, dizziness, syncope.

- Do start early:

  The later the cognitive enhancer is started in the disease course, the less benefit seen – BUT there may still be benefit even in moderate to severe disease.

effect was sustained over four years and became more pronounced each year. Exhibit 5 shows some important clinical tips about using cognitive enhancers.

Many different disease-modifying therapies are under investigation and most are aimed at slowing down the buildup of Aβ plaques and/or NFT in the brain. One potentially disease-modifying agent (aducanumab) was approved by the FDA in June 2021. Current clinical trials are studying antibody immunotherapy, cerebral metabolic enhancement, anti-aggregation, neuroprotection, and stem cells.

Aducanumab (Aduhelm™) is a fully-human IgG1 monoclonal antibody that binds selectively to aggregated Aβ fibrils and soluble oligomers. This agent is given as a monthly intravenous infusion. In March 2019, after an interim futility analysis predicted the Phase III placebo-controlled EMERGE and ENGAGE trials would not meet their primary endpoints, the termination of all aducanumab clinical trials was announced. However, in a subsequent analysis of a larger data set from the EMERGE trial, aducanumab met the primary endpoint, the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score after 18 months of treatment.[20,21] The highest dose (10 mg/kg) demonstrated a 23 percent reduction in the CDR-SB (p = .01); this translates to an absolute change of –0.4 on an 18-point scale. The high-dose

group also declined less on secondary endpoints, including the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog ,–27%; p = .01) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL-MCI; –40%; p = .001). Although the ENGAGE trial did not meet the primary endpoint, an exploratory analysis suggested a slower decline in patients who received at least 10 doses of the highest dose. In sub-studies of EMERGE and ENGAGE, aducanumab caused a dose-dependent reduction in Aβ and some reduction in cerebrospinal fluid phosphorylated-tau. Neither of these trials has been published.

Aducanumab was submitted for priority review to the FDA in July 2020. On November 6, 2020, an FDA-advisory panel voted against approval of aducanumab, saying evidence from a single positive study (EMERGE) was not enough to demonstrate the drug's efficacy in AD in light of conflicting results. The panel voted eight to one that the positive EMERGE trial could not be viewed on its own as providing compelling evidence supporting the effectiveness of aducanumab, without taking into account the conflicting ENGAGE data. In February 2021, the FDA delayed a decision on licensing by three months, pushing the deadline from March to June 2021 and had requested more information from the manufacturer.[22] This agent was finally approved under an accelerated approval in June 2021 based on the surrogate marker of amyloid plaque reduction. The controversy over this approval led to two resignations from the FDA-expert advisory panel.[23] Biogen has to do a post-approval trial to confirm any clinical benefit; this post-marketing trial has not yet been initiated.

On the day of the FDA's decision, the Institute for Clinical and Economic Review (ICER) posted a news release about the approval of aducanumab.[24] The organization conducted its own analysis of the available data and said that the FDA failed in its responsibility to protect patients and families from unproven treatments with known harms. Another analysis of the trial data found that biomarker data were consistent with target engagement, but no evidence was presented to correlate biomarker changes to cognitive benefits.[25]

The most common adverse event with aducanumab is amyloid-related imaging abnormalities (ARIA). ARIA are white-matter lesions with or without evidence of brain edema obtained by neuroimaging. ARIA-E are vasogenic edema and sulcal effusions on MRI and ARIA-H are MRI abnormalities due to microhemorrhages and hemosiderosis. ARIA-E are more common than ARIA-H occurring in 35 percent of patients in the trials; 74 percent of cases

were asymptomatic and episodes resolved within four to 16 weeks. In the EMERGE trial, the rate of permanent treatment discontinuation for an adverse event was 2.9 percent with placebo versus 7.7 percent with low-dose and 8.8 percent with high-dose aducanumab. Respective discontinuation rates because of any type of ARIA were 0.2 percent, 4.6 percent, and 6.6 percent.

ARIA typically resolve without stopping therapy and their presence is not always associated with symptoms. They can cause headache, dizziness, and confusion. APOE E4 carrier status and higher doses of anti-amyloid antibodies are risk factors for ARIA.[26,27] Recommendations for the detection, monitoring, and managing ARIA need to be developed.

The initial price of this agent was $56,000 annually, which has since been reduced to $28,200 for a patient of average weight. The manufacturer reported only $3 million in U.S. sales in the six months it was approved in 2021.[28] In a recent ruling, the Centers for Medicare and Medicaid Services (CMS) said it has restricted Medicare coverage for anti-beta-amyloid drugs like aducanumab to patients who participate in a clinical trial.[29]

Until more data are available, aducanumab should only be considered for use in people who have a firmly established diagnosis of AD, with evidence of amyloid plaques, in its very mildest symptomatic stages. This may include people with MCI or mild dementia. Aducanumab is administered intravenously via a 45- to 60-minute infusion every four weeks. Infusion can be done at hospitals or infusion therapy centers. In addition to pre-therapy amyloid testing, MRI monitoring for ARIA needs to be performed. Patients and caregivers should be educated on the potential benefits and risks of this agent, including potential out-of-pocket costs before they make the decision to start this therapy.

Targeting tau is another therapeutic approach in AD. Tangles correlate well with clinical progression in symptomatic AD. There are multiple targets against tau. Immunotherapies currently under investigation include active and passive approaches aiming at preventing pathological tau aggregation, stabilizing microtubules, and blocking of tauons.

Conclusion

The development of biomarkers for AD has been one of the major developments in AD diagnosis. Symptomatic treatment of AD should be considered with combination therapy. Aducanumab, which targets the underlying pathophysiology of the disease, has been FDA approved. Uptake of this agent, efficacy over time, and Medicare and third-party payer coverage are still to be determined.

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Meeting the Challenges of Integrating Biosimilars in the Healthcare Treatment Paradigm

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

Summary

More biosimilars are being approved every year by the FDA, and several are finally on the market. The uptake of biosimilars has been slow in the United States (U.S.), but this may accelerate as more experience is gained. Biosimilars are leading to significant cost reductions and improved patient access in the European Union and whether this same success transfers to the U.S. is not yet known.

Key Points

• A biosimilar is a biologic demonstrated to be highly similar to a reference product through appropriate comparative, head-to-head quality, non-clinical and clinical studies.

• The comparability exercise used to demonstrate that a biosimilar is highly similar to a reference biologic is scientific, robust, and regulated.

• Several biosimilars are now approved in the U.S., with more under FDA review and many more under development.

BIOLOGICS HAVE REVOLUTIONIZED THE treatment for serious conditions including cancer. The 1970s brought the first biologics which consisted of vaccines and blood products. They accounted for less than 10 percent of the pharmaceutical market.[1] The 1980s saw the rise of cloning and gene expression technology, biosynthesis of genetically modified organisms, and increasingly complex molecules. Genentech's recombinant human insulin was introduced in 1982. In 1986, the FDA approved the first monoclonal antibody (muromonab). The first recombinant monoclonal antibodies for cancer treatment were introduced in 1997. Available biologics have exploded since the year 2000.

The cost of biologic pharmaceuticals has reached an all-time high. Cancer drug costs have been increasing at twice the general healthcare costs, primarily because of new biologics like immunotherapy. Biologics net spending in the U.S. reached $125.5 billion in 2018 and continues to grow.[2] In 2020, Medicare Part B spent $27.6 billion on the top 50 biologics.[3] Some definitions are important when discussing biologics and biosimilars. According to the U.S. Code of Federal Regulations, a biologic is any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man. Biologics are derived from living sources, including bacteria, viruses, humans, or animals. Biologics in this discussion can be thought of as therapeutic proteins. Biologics have very different characteristics compared to typical chemical or small molecule drugs (Exhibit 1), which make them difficult to duplicate.[4] Unlike producing small molecule drugs, the manufacturing process for biologics is complex (Exhibit 2).[5] Some example biologics include adalimumab, epoetin alfa, and pembrolizumab.

The FDA defines a biosimilar as a biological product that is highly similar to a U.S.-licensed reference biological product and for which there are no clinically meaningful differences in safety, purity, or potency.[6] The FDA allows biosimilar to be different from the reference product in terms of formulation and delivery device.[7] Biologics can have fewer than all routes of administration for which reference product is licensed. They can also have fewer than all conditions of use for which reference product is licensed. The strength of the biosimilar and reference product must be the same.

Exhibit 1: Differences Between Small Molecule Drugs and Biologics[4]

	Small Molecule Drugs	Biologics
Size	Small, low molecular weight	Large, high molecular weight
Structure	Simple, well-defined	Complex, heterogeneous
Manufacturing	• Reproducible chemical reactions • Identical copies can be made	• Living cells or organisms • Impossible to ensure identical copies
Characterization	Completely characterized	Impossible to fully characterize molecular composition
Stability	Stable	Unstable, sensitive to external conditions
Immunogenicity	Mostly non-immunogenic	Immunogenic

Exhibit 2: The Manufacturing Process for Biologics is Complex[5]
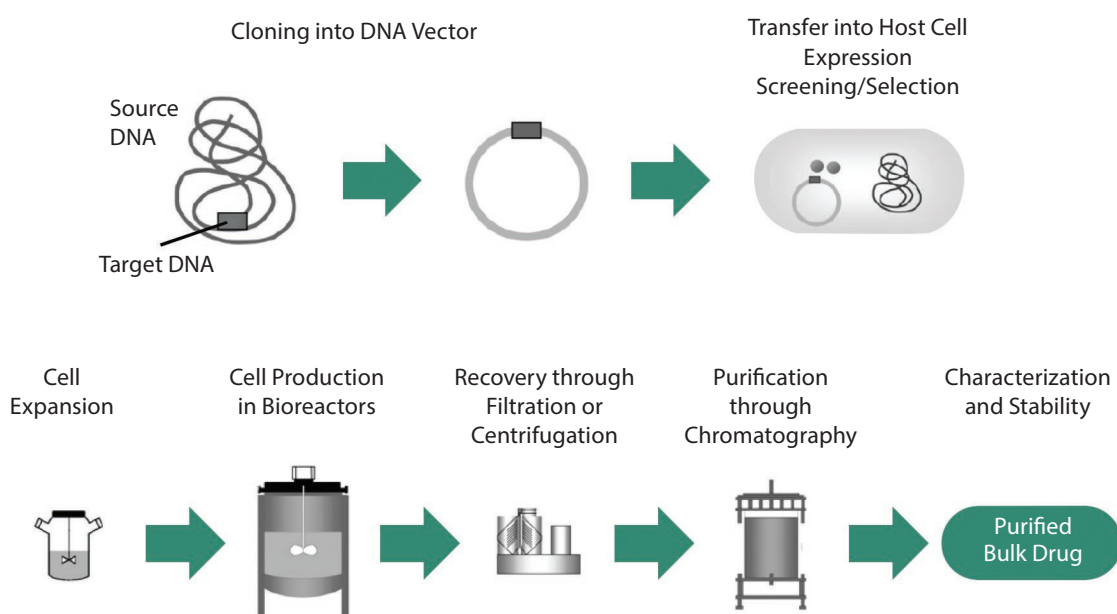
Importantly, biosimilars are not generics of existing biologics.[8] Traditional generic drugs are exact copies of existing drugs. Biologics are made up of amino acids, which form unique folds and glycosylation patterns may also vary. Combined with the complicated manufacturing process, an exact copy of a biologic cannot be made. Two basic principles that have allowed development of biosimilars include that biologics undergo natural variability with time and an identical copy of a biologic cannot be made. The biosimilar does not need to be exactly like the reference biologic because the reference biologic is not identical to itself over time. For example, infliximab and etanercept have undergone 37 and 20 manufacturing changes, respectively, since their initial FDA approval.[9] Small modifications in manufacturing may result in gradual changes. Despite differences, when the products are within a pre-specified acceptable range, a biologic product is marketed with no change in label. If large alterations occur, analytical studies (and additional clinical studies) are required to

Exhibit 3: Comparing Approval Processes[11]

Generics: Exact Copies		Biosimilars: Highly Similar	
Small Molecules – Approved via FDCA		**Biologics – Approved via PHSA**	
Small Molecules	**Generics**	**Biologics**	**Biosimilars**
New Drug Applications **505(b)(1) and 505(b)(2)**	**Abbreviated New Drug Applications** **505(j)**	**Biologics License Applications** **351(a)**	**Biosimilar Biologics Applications** **351(k)**
Full report of safety and efficacy investigations	Identical to an already approved product	Full report of safety and efficacy investigations	Highly similar to a 351(a) product
Two pathways [505(b)(1) and 505(b)(2)] Based on right reference	No safety/efficacy data required (only bioequivalence)	Applicant has right of reference to essential investigations	Data showing absence of clinically meaningful difference
		Interchangeable biologics are approved under the biosimilars pathway, but must meet higher standards	

FDCA = Food, Drug, and Cosmetics Act ; PHSA = Public Health Service Act

compare post-change product with existing pre-change product.[10]

To demonstrate biosimilarity, the biosimilar sponsor submits evidence that the candidate biosimilar is not significantly different from the reference product. The clinical efficacy and safety of the biologic molecule has already been demonstrated by the reference product. The goal is not to replicate unnecessary clinical trials but to use smaller-scale direct comparisons and extrapolation. When a biosimilar is approved, there should not be an expectation that there will be differences in safety and efficacy. The process of biologic and biosimilar approval is through the Public Health Service Act instead of the Food, Drug, and Cosmetics Act which outlines the approval process for small molecule medications. Each undergoes a different approval process (Exhibit 3).[11] The biosimilar development

program objective is to establish biosimilarity based upon totality of evidence, not re-establish clinical benefit. The highly similar designation is determined based on analytics and clinical pharmacology data. If extensive structural and functional comparability assessment does not reveal significant differences between a biosimilar and reference biologic, it is highly unlikely that trials in patients would uncover any difference in safety and efficacy.[12] The determination of no clinically meaningful differences is based on targeted clinical trials in a sensitive population (i.e., the indication for which difference is likely to be detected). Clinical trials are designed to establish statistical evidence that the proposed product is neither inferior nor superior to the reference product, by more than a specified margin. When a biosimilar is approved, there should not be an expectation that there will be

Exhibit 4: FDA-Approved Biosimilars[17]

Biosimilar	Approval Date	Biosimilar	Approval Date	Biosimilar	Approval Date
Filgrastim-sndz	March 2015	Adalimumab-adaz	October 2018	Adalimumab-afzb	November 2019
Infliximab-dyyb	April 2016	Pegfilgrastim-cbqv	November 2018	Infliximab-axxq	December 2019
Etanercept-szzs	August 2016	Rituximab-abbs	November 2018	Pegfilgrastim-apgf	June 2020
Adalimumab -atto	September 2016	Trastuzumab-pkrb	December 2018	Adalimumab-fkjp	July 2020
Infliximab-abda	May 2017	Trastuzumab-dttb	January 2019	Rituximab-arrx	December 2020
Adalimumab-adbm	August 2017	Trastuzumab-qyyp	March 2019	Insulin glargine-yfgn (INT)	July 2021
Bevacizumab-awwb	September 2017	Etanercept-ykro	April 2019	Ranibizumab-nuna	September 2021
Trastuzumab-dkst	December 2017	Trastuzumab-anns	June 2019	Insulin glargine-aglr	December 2021
Infliximab-qbtx	December 2017	Bevacizumab-bvzr	June 2019	Adalimumab-aqvh	December 2021
Epoetin alfa-epbx	May 2018	Rituximab-pvvr	July 2019	Filgrastim-ayow	February 2022
Pegfilgrastim-jmdb	June 2018	Adalimumab-bwwd	July 2019		
Filgrastim-aafi	July 2018	Pegfilgrastim-bmez	November 2019		

differences in safety and efficacy.

Some issues which are relevant to biosimilars include extrapolation, interchangeability, immunogenicity, and naming. Extrapolation is where the indications for a biosimilar are the same as those for the reference product even though studies are not required to be done with the biosimilar for each indication. The approved indications for the biosimilar are justified based on the total data package. Interchangeable or interchangeability means that two products can be directly interchanged (i.e., if a prescription is written for reference drug A and there is an interchangeable biosimilar B no intervention with the original prescriber is required for a substitution of A with B to be made subject to individual state regulations).

Interchangeable is an FDA designation that requires different data standards than biosimilarity alone. It requires dedicated switching study and post-marketing monitoring. Any biological product under consideration for substitution must first be approved by the FDA as interchangeable. Biosimilar studies may be designed to address considerations for switching treatments. An example trial, which has been published, compared reference infliximab to a biosimilar and found no differences in efficacy, immunogenicity, or safety.[13,14] There is currently one approved biosimilar in the U.S. with an interchangeable designation (Lantus®/ Semglee®). Immunogenicity is a concern with all biologics, not just biosimilars. The consequences of immunogenicity are loss of efficacy through neutralization of the administered biologic agent by antibodies against a biologic and general immune responses (allergy, anaphylaxis). A comparative parallel head-to-head study is required to assess immunogenicity of a biosimilar.

There has been controversy about the naming of biosimilars. Some experts believe that biosimilars should have the same exact non-proprietary name as their respective reference to communicate that these products are highly similar and to facilitate adoption and substitution of interchangeable biologics.[15,16] This approach makes it hard to trace adverse events to a specific product. The other side believes that biosimilars should each have a distinct non-proprietary name to distinguish them from the originator and other biosimilars to improve pharmacovigilance for adverse events and to recognize that these are distinct products. This approach can lead to confusion about whether they are highly similar, may impede adoption of biosimilars, and can lead to issues with substitution. The FDA Guidance on Naming established that there will be a core nonproprietary name and distinguishing suffix (devoid of meaning and composed of 4 lower case letters) for each biosimilar. Newly approved originator or biosimilar products will have the distinguishing suffix; older biologics do not have the suffix. For example, infliximab (Remicade®) is a reference product and infliximab-abda (Renflexis®)

is a biosimilar. The core name will group similar biologics in electronic systems and having the suffix for all products reduces perception that biosimilars are inferior to the reference product. The goal of this naming scheme is to facilitate pharmacovigilance and prevent inadvertent substitution. Inadvertent substitution may lead to unintended alternating or switching of biological products that have not been determined by FDA to be interchangeable. Exhibit 4 includes the biosimilars approved in the U.S. as of March 24, 2022.[17]

Biosimilars create the potential to save the U.S. healthcare system $54 billion over 10 years and increase access for an additional estimated 1.2 million U.S. patients by 2025. Starting in March 2020, insulins are now regulated as biologics versus drugs or small molecules. This will allow manufacturers to develop their insulin medicines via the biosimilar, or 351(k), pathway and is why one interchangeable biosimilar insulin has been approved.

There are numerous barriers to biosimilar uptake, including interchangeability (provider must write for specific biosimilar), perception (providers and patients), and economics.[18] Medicare, Medicaid and commercial payers have all approached biosimilar reimbursement differently. For example, Medicaid may reimburse each biosimilar at a different rate. Also, many payers have still favored reference products because of manufacturer rebates. Large health plans may see multimillion-dollar budget reductions if biosimilars are placed in a preferred position, jeopardizing the rebate stream from reference products.[19] This has been called "*the rebate trap*", in which considerable rebates on highly utilized reference agents, like etanercept or adalimumab, may be lost if only a portion of the plan population is switched to the biosimilar. The plan may pay a greater amount as a result, even with significant (but not complete) biosimilar adoption. With Medicare Part B in 2020, 85 percent of infliximab spending was for the reference product.[3] Three biosimilars, the first of which was approved in 2016, had 15 percent of the market.

One area of particular interest and anticipation for marketed biosimilars is oncology. Biologics represent approximately 50 percent of the pharmaceutical market in oncology and play a critical role in clinical care for supportive care (myeloid growth factors, erythropoietin stimulating agents) and active therapy (monoclonal antibodies, antibody drug conjugates, interferons, immunotherapy). Many of the most expensive drugs are used in oncology.

There is potential for enormous impact of biosimilars on costs and availability of biologics in oncology, especially as oncology care and reimbursement moves further into value-based care. Value-based care aims to improve the quality of care, while containing costs. The Centers for Medicare and Medicaid Services (CMS) have developed value-based care programs as alternatives to fee-for-service reimbursement, including oncology, that reward healthcare providers with incentive payments for improving the quality of care they provide.[20] Utilizing biosimilars in a value-based model has the potential to allow more patients to receive biologics.

The biosimilar segment of the pharmaceutical industry is exploding. Some 700 biosimilars are at some stage of development, and more than 660 companies are involved. Many patents of blockbuster and budget busting biologics are expiring, but biosimilar developers will not have it easy. The companies behind the brand-name products are going to continue to protect their turf with rebates and marketing. Two examples whose patents expire in 2023 are ipilimumab and ustekinumab. Eventually, there may be five or more biosimilar products for each reference biologic competing against each other.

Conclusion

Healthcare is experiencing a therapeutic biologic revolution with the tremendous increase in the number of FDA-approved biosimilars. Although biologics are complex drugs that cannot be made generic, a biosimilar is a biologic demonstrated to be highly similar to a reference product through a rigorous and well-defined approval pathway. Incorporation of biosimilars into U.S. clinical practice offers opportunity for healthcare cost savings and increased patient access to biologic therapies. While challenges and barriers still exist, there is tremendous future potential.

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Patient-Focused Treatment Decisions in Metastatic Head and Neck Squamous Cell Carcinoma: A Closer Look at the Evolving Role of Immunotherapy

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

Summary

Metastatic head and neck cancer is a devastating disease with poor prognosis. The introduction of immunotherapy to treatment for this disease is improving survival. Managed care payers are having to confront the high cost of immunotherapy for this disease and other cancers.

Key Points

- Checkpoint inhibitor immunotherapy has become a standard of care for first-line or subsequent-line therapy for metastatic disease.

- Payers are struggling to manage the costs of immunotherapy.

- Old methods of management of cancer costs are being replaced with newer reimbursement models and value-based contracting.

HEAD AND NECK CANCER IN THE UNITED States (U.S.) accounts for approximately 4 percent of all cancers.[1] In 2021, the total new cases were estimated at 66,630 and 14,620 deaths. Males are affected more than females, ranging anywhere from a two to one to four to one ratio.

Multiple risk factors exist for head and neck cancers (Exhibit 1).[2-4] Tobacco use increases risk five-fold to 25-fold. Risk from tobacco is dependent on duration and amount of exposure. Smokeless tobacco products are especially a risk for oral cavity and pharynx cancers. Alcohol use increase risk five- to six-fold, but risk from alcohol is often difficult to distinguish from the risk of using tobacco because these risk factors typically occur together. Human papillomavirus (HPV) primarily results in base of tongue and tonsil cancers. Head and neck cancers may present in a variety of sites, including the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. There are multiple histologic types – squamous, adenocarcinoma, mucoepidermoid, and adenoid cystic. Ninety-five percent of cases are of squamous origin, and the focus of this article is on this type.

Often head and necks cancer cases present with metastatic disease due to the somewhat "silent" nature of early disease.[5] At diagnosis, there is regional nodal involvement in 43 percent of cases. Distant metastases are present in about 10 percent of cases with an additional 20 to 30 percent developing metastases during the course of their disease. Metastatic disease has a poor prognosis with survival, often less than six to 12 months.

While many patients with locally advanced disease are cured with some combination of surgery, radiation, and chemotherapy, those with metastatic disease are considered incurable. Systemic therapy is indicated with best supportive care for most patients with metastatic head and neck squamous cell carcinoma (HNSCC). Treatment options include chemoimmunotherapy, immunotherapy, or various chemotherapy regimens. Cytotoxic chemotherapy alone has limited efficacy and substantial toxicity in metastatic HNSCC, with a median overall survival (OS) of less than a year.

Positive prognostic factors to consider when treating metastatic HNSCC include ambulatory performance status [Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 versus 2], poorly differentiated histology, prior response chemotherapy, and HPV-associated oropharyngeal cancers.[6] Negative prognostic factors such as weight

Exhibit 1: Risk Factors[2-4]

- Tobacco use
- Alcohol use
- Viral infections
  - Epstein Barr
  - Human Papilloma Virus (primarily type 16)
  - Herpes Simplex
  - Hepatitis C
- Immuno-deficiency
- Occupational exposure
- Radiation

loss, poor performance status, prior radiation therapy, active smoking, and significant comorbidity burden may lead to less aggressive therapy selection.

Immunotherapy is revolutionizing the treatment of many cancers, including HNSCC. Programmed cell death protein 1 (PD-1) is a cell surface receptor that plays a key role in down-regulating the immune system by promoting self-tolerance through suppressing T cell inflammatory activity.[7] PD-1 is an immune checkpoint and guards against autoimmunity through a dual mechanism of promoting apoptosis (programmed cell death) in antigen specific T cells in lymph nodes and simultaneously reducing apoptosis in regulatory T cells. The effect of PD-1 can also prevent the immune system from killing cancer cells. Both nivolumab and pembrolizumab are checkpoint inhibitors that target PD-1 and unleash the immune system against cancer cells.

Pembrolizumab initially received FDA-accelerated approval in August 2016 for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. This approval was based on data from the KEYNOTE-012 study, which included patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy.[8] Subjects had an ECOG performance status of zero or one. In this trial, objective responses were observed in 18 percent, and the response rate was similar in HPV positive and negative patients. Median progression-free survival (PFS) was two months and median overall survival (OS) was eight months. OS at 12 months

was 38 percent.[9] The results of KEYNOTE-012 were confirmed in KEYNOTE-055, a Phase II trial that focused exclusively on patients with recurrent or metastatic HNSCC after progression on both platinum and cetuximab.[10]

Based upon these promising results, two randomized Phase III studies were initiated to definitively evaluate immunotherapy in platinum-refractory recurrent or metastatic HNSCC. In CHECKMATE-141, 361 patients were randomized to the PD-1 inhibitor nivolumab or investigator's choice of docetaxel, cetuximab or methotrexate.[11] Nivolumab was associated with a significantly longer overall survival (7.5 versus 5.1 months, $p = 0.01$) with less toxicity. One-year survival rate was 34.0 versus 19.7 percent. In KEYNOTE-040, 247 patients were randomized to pembrolizumab or investigator's choice of docetaxel, cetuximab, or methotrexate.[12] At the time of the preplanned survival analysis, the median OS was 8.4 months for pembrolizumab and 6.9 months for chemotherapy. While this result did not meet the pre-specified cutoff for survival improvement, longer follow-up has demonstrated a statistically significant improvement in OS. Based upon these data, both pembrolizumab and nivolumab have been approved by the FDA for the treatment of platinum refractory metastatic HNSCC.

Chemoimmunotherapy is one way to improve response rates to immunotherapy. In KEYNOTE-048, patients with untreated recurrent or metastatic HNSCC were randomized to pembrolizumab monotherapy, platinum/5-fluorouracil/cetuximab (the EXTREME regimen), or platinum/5-fluorouracil/pembrolizumab.[13] At the second interim analysis, pembrolizumab alone improved OS versus cetuximab with chemotherapy in the programmed death ligand one (PD-L1) combined positive score (CPS) of 20 or more population (median 14.9 months versus 10.7 months, $p = 0.0007$) and CPS of 1 or more population (12.3 versus 10.3, $p = 0.0086$) and was non-inferior in the total population (11.6 versus 10.7). Pembrolizumab with chemotherapy improved OS versus cetuximab with chemotherapy in the total population (13.0 months versus 10.7 months, $p = 0.0034$) at the second interim analysis and in the CPS of 20 or more population (14.7 versus 11.0, $p = 0.0004$) and CPS of 1 or more population (13.6 versus 10.4, $p < 0.0001$) at final analysis. Exhibit 2 provides an overview of responses from this trial based on PD-1 expression levels.[13] Grade 3 or worse all-cause adverse events occurred in 55 percent in the pembrolizumab alone group, 85 percent in the pembrolizumab with chemotherapy group, and 83 percent in the cetuximab with chemotherapy group. Adverse events led to death in 8 percent in

Exhibit 2: First-Line Pembrolizumab[13]

Overall Response Rate			
	Pembro Alone	**Pembro + Chemo**	**EXTREME**
CPS > 20	26%	43%	36%
CPS > 1	19%	36%	35%
Total Population	17%	36%	35%

Median Duration of Response			
	Pembro Alone	**Pembro + Chemo**	**EXTREME**
CPS > 20	22.6 mo.	7.1 mo.	4.2 mo.
CPS > 1	23.4 mo.	6.7 mo.	4.5 mo.
Total Population	22.6 mo.	6.7 mo.	4.5 mo.

Pembro = pembrolizumab; Pembro + Chemo = platinum/5-fluorouracil/pembrolizumab; EXTREME = platinum/5-fluorouracil/cetuximab.

the pembrolizumab alone group, 12 percent in the pembrolizumab with chemotherapy group, and 10 percent in the cetuximab with chemotherapy group. The authors concluded that based on the observed efficacy and safety, pembrolizumab plus platinum and 5-fluorouracil is an appropriate first-line treatment for recurrent or metastatic HNSCC, and pembrolizumab monotherapy is an appropriate first-line treatment for PD-L1-positive recurrent or metastatic HNSCC.

For metastatic or advanced HNSCC without prior exposure to systemic therapy, the combination of pembrolizumab plus chemotherapy improves OS beyond that seen with cetuximab plus chemotherapy. For those with high PD-L1 expression, single-agent pembrolizumab also improves OS, compared with cetuximab plus chemotherapy, with less toxicity. Responses to pembrolizumab, either alone or in combination with chemotherapy, are more durable than those seen with cetuximab plus chemotherapy. On June 11, 2019 the FDA approved the use of pembrolizumab for this indication along with cisplatin and fluorouracil and as a single agent for those whose tumors express PD-L1 CPS ≥ 1. The National Comprehensive Cancer Network (NCCN) guidelines recommend pembrolizumab/cisplatin or carboplatin/5-flurouracil or pembrolizumab monotherapy (with CPS ≥ 20) as Category 1 preferred first-line regimens for recurrent, unresectable, or metastatic non-nasopharyngeal head and neck cancers.[14] Pembrolizumab monotherapy is also a

first-line option when CPS is ≥ 1 but not a Category 1 recommendation. First-line therapy in the NCCN guidelines for recurrent, unresectable, oligometastatic or metastatic nasopharyngeal cancer is cisplatin/gemcitabine. Nivolumab and pembrolizumab are 2B recommendations for subsequent-line therapy for this type of cancer. When given as a single agent or in combination, pembrolizumab is administered for a maximum of two years.

While virtually all areas of cancer costs grew between 2010 and 2020, the costs related to immunotherapy skyrocketed. In the past, managed care used various techniques in an attempt to limit cancer care spending. This included limited prior authorizations, case management of catastrophic cases, site of care shifts to outpatient treatment, and management of infusion therapy cost with average sales price-based reimbursement. Newer techniques are now in use or development (Exhibit 3). There has been much discussion in the payer community about the role of value-based or outcomes-based contracting for drugs. There are examples of this type of approach in diabetes, cardiovascular diseases, respiratory diseases, and a few other areas. Many groups are working toward value/outcomes-based contracting for cancer treatments and immunotherapies across multiple cancer types.

Conclusion

HNSCC accounts for only about 3 percent of all cancers in the U.S. It is a highly aggressive tumor type

Exhibit 3: Cancer Management Approaches in 2022

Aggressive prior authorization programs

- To labeled indication at a minimum.
- Restriction to populations studied in the clinical trials.
- Restriction to selected genetic subtypes using genetic markers.
- Limited use by only "approved" centers or groups.

Risk shifting or sharing

- Increased contracting with accountable care organizations and other risk-bearing entities.
- Increased use of pathways by many organizations, but success has been variable with new agents.
- Risk-based or value-based contracting with oncology groups.
- Contracting with Centers of Excellence

Contracting strategies

- Aggressive contracting for preferred agent positioning.
- Closed formularies even on the medical side.
- Value/Outcomes-based contracting.

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that is often only found after it has become metastatic. Checkpoint inhibitor immunotherapy has become a standard of care for first-line or later-line therapy, but there is a cost to these agents that payers are now struggling to manage. Old methods of management of cancer costs are being replaced with newer reimbursement models and value-based contracting. Because of the growing interest in new agents and the success of the treatment of metastatic HNSCC with immune checkpoint inhibitors, payers will need to understand this disease and the emerging treatments to better manage cost and access to appropriate care.

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Treatment Advances in Idiopathic Pulmonary Fibrosis: Recent Guidelines and Evidence to Support Optimal Patient Outcomes

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

Summary

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease. Two antifibrosis therapies which slow the progression of the disease are available and appear to improve survival. Tolerability of these therapies is important for long-term use.

Key Points

• Early diagnosis of IPF requires suspicion of interstitial lung disease.

• Antifibrotic therapy is a viable approach to preserve lung function and improve outcomes.

• Close attention to tolerability is key to use of antifibrotics.

• Evaluation and management of comorbid conditions and patient engagement are important for improving outcomes.

INTERSTITIAL LUNG DISEASE (ILD) IS AN umbrella term used for a large group of diseases that cause fibrosis of the lungs. There are over 130 different ILDs with similar symptoms, physiology, and radiographic findings (Exhibit 1).[1] An accurate diagnosis for a given ILD can be difficult to make. Idiopathic pulmonary fibrosis (IPF), one of the ILDs, is a chronic fibrosing interstitial pneumonia of unknown cause that is limited to the lungs and comprises about 12 to 20 percent of all ILD cases.[2-4] IPF occurs primarily in older adults and is more common in men. There is a history of smoking in two-thirds of patients. This is a uniformly fatal disease which also causes significant morbidity. Median survival after diagnosis is two and a half to five years. The only cure for the disease is lung transplantation.

IPF is diagnosed by ruling out other causes of ILD and the presence of typical findings on high-resolution computed tomography (HRCT) and histopathologic pattern of usual interstitial pneumonia (UIP).[1] Sometimes a lung biopsy is required when the pattern in the lung is probable UIP or indeterminate. Exhibit 2 presents the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society diagnostic algorithm.[1] Exhibit 3 shows the many potential causes of ILD which have to be ruled out. Multidisciplinary communication between the evaluating clinician, radiologist, and pathologist is essential to an accurate diagnosis.

The most common presenting symptoms of IPF are breathlessness, cough, and fatigue. Patients with IPF can have symptoms for years before they receive an accurate diagnosis and are often misdiagnosed with heart failure or chronic obstructive pulmonary disease. One study found symptoms present up to five years before diagnosis.[5]

The comprehensive care of the patient with IPF involves balancing the three pillars of disease-centered management, symptom-centered management, and patient education and self-management upon a solid foundation of provider-patient partnership.[6] Disease-centered management involves both pharmacological (antifibrotic agents) and nonpharmacological approaches (including supplemental oxygen and pulmonary rehabilitation). Because this is a fatal disease, palliative care should be an integral and routine component of the care of those with IPF. Education and self-management

Exhibit 1: The Family of Interstitial Lung Disease[1]

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                                    ┌─────────┐
                                    │   ILD   │
                                    └─────────┘
        ┌───────────────┬───────────────┴──────────────────┬──────────────────┐
   ┌──────────┐   ┌──────────┐   ┌────────────────────────────┐   ┌──────────────┐
   │  Known   │   │ Granulo- │   │ Idiopathic interstitial    │   │Miscellaneous │
   │ etiology │   │ matous   │   │ pneumonias (IIP)           │   │              │
   └──────────┘   └──────────┘   └────────────────────────────┘   └──────────────┘
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Known etiology
- Connective tissue disease
- Drugs
- Occupational exposures

Granulomatous
- Sarcoidosis
- Hypersensitivity pneumonitis

IPF

Non-IPF IIP
- non-specific interstitial pneumonia
- cryptogenic organizing pneumonia
- respiratory bronchiolitis ILD
- desquamative interstitial pneumonia
- acute interstitial pneumonia
- lymphocytic interstitial pneumonia
- idiopathic pleuroparenchymal fibroelastosis

Miscellaneous
- LAM
- Histiocytosis

IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis

strengthen the provider-patient partnership by enabling patients to set realistic goals, remain in control of his or her care, and prepare for the future.

Two disease-modifying antifibrotics, pirfenidone (Esbriet®) and nintedanib (Ofev®), have been shown to significantly reduce lung function decline, reduce mortality, increase progression-free survival, and improve six-minute walk test results.[1,7] In Phase III trials, decline in forced vital capacity (FVC) was reduced by approximately 50 percent over one year, compared with placebo.[7] Pirfenidone has also been shown to decrease risk of respiratory-related hospitalization by 48 percent.[8] Mortality benefits have been shown with therapy that has been continued even when lung function continues to decline.[9] Two registry trials have also shown survival benefits with antifibrotic therapy.[10,11] In a registry study, pirfenidone significantly increased five-year overall survival (OS) over no antifibrotic treatment (55.9% versus 31.5% alive, $p = 0.002$).[11] Using data from a large United States (U.S.) insurer, one study found that the use of antifibrotic medications was associated with a decreased risk of all-cause mortality compared to no treatment [hazard ratio (HR), 0.77; $p = 0.034$].[12] However, this association was present only through the first two years of treatment. There was also a decrease in acute hospitalizations

in the treated cohort (HR, 0.70; $p < 0.001$). There was no significant difference in all-cause mortality between patients receiving pirfenidone and those on nintedanib ($p = 0.471$). Antifibrotic therapy is started as soon as the diagnosis is confirmed and continued indefinitely as long as the selected agent is tolerated.

Twenty-five to 30 percent of those receiving antifibrotic therapy will discontinue treatment because of adverse events, but dose reductions can help patients stay on therapy. The primary treatment-related adverse events associated with pirfenidone therapy are gastrointestinal upset, rash, and photosensitivity and diarrhea and nausea with nintedanib.[13] Gastrointestinal events may be mitigated by ensuring either medication is taken with food, while skin symptoms may be reduced with pirfenidone by avoiding sun exposure and frequent use of sunblock. Educating patients about the potential adverse events and providing instructions prior to treatment to avoid reactions are an important means of ensuring patients may derive the important benefits provided by long-term treatment. Pirfenidone, after dose titration, is given as three tablets or capsules three times a day. Nintedanib is given as one capsule twice a day, and this regimen may be easier for patients to adhere with. Because IPF is more common in the

Exhibit 2: IPF Diagnostic Algorithm[1]

2018

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                          ┌─────────────────────────────┐
                          │ Patient suspected to have IPF│
                          └──────────────┬──────────────┘
                                         │
                          ┌──────────────▼──────────────┐
                          │ Potential cause/associated   │
                          │         condition            │
                          └──────────────┬──────────────┘
           No                            │                        Yes
                                         │
                                         │          ┌─────────────────────────────┐
                                         │          │ Further evaluation (including│
                                         │          │            HRCT)             │
                                         │          └─────────────────────────────┘
  ┌──────┐    ┌──────────────────┐   No    ┌─────────────────┐
  │ UIP  │────│ Chest HRCT pattern│────────│ Specific diagnosis│
  └──────┘    └──────────────────┘         └─────────────────┘
                                                          Yes
              ┌──────────────────────────────────────┐
              │ Probable UIP, indeterminate,          │
              │        alternative diagnosis          │
              └──────────────────────────────────────┘

  ┌─────────────────────────────────────────────────┐
  │                      MDD                          │
  └─────────────────────────────────────────────────┘

         ┌──────┐      ┌─────────────────────────┐
         │ BAL  │─────▶│   Surgical lung biopsy*  │
         └──────┘      └─────────────────────────┘

  ┌─────────────────────────────────────────────────┐
  │                      MDD                          │
  └─────────────────────────────────────────────────┘

  ┌──────┐                              ┌──────────┐
  │ IPF  │                              │ Not IPF  │
  └──────┘                              └──────────┘
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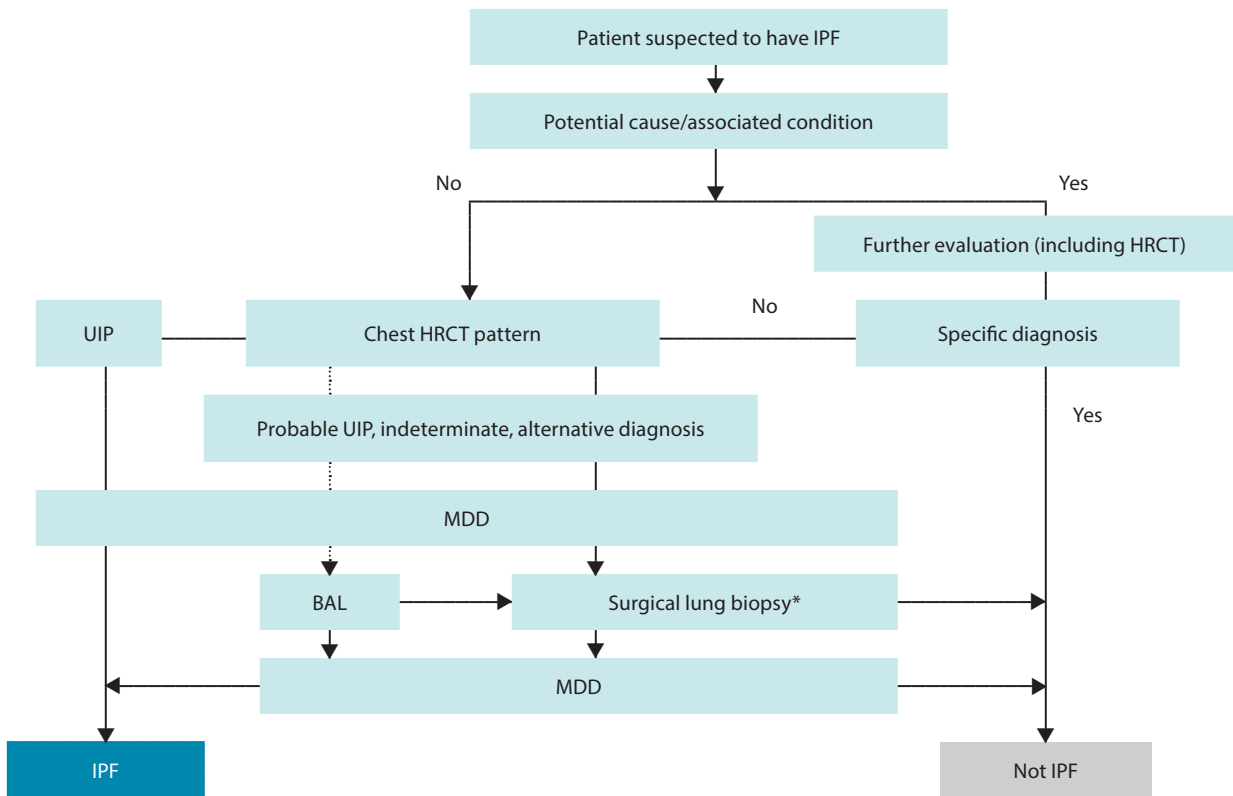
IPF = idiopathic pulmonary fibrosis; HRCT = high resolution computed tomography; UIP = usual interstitial pneumonia; MDD = multidisciplinary discussion ; BAL = bronchoalveolar lavage

elderly population, general health, life expectancy regardless of IPF, and comorbid conditions all factor into treatment decisions. Exhibit 4 shows some of the considerations which need to be taken into account when deciding whether to initiate antifibrotic therapy.[14,15]

Close monitoring is required while on antifibrotic therapy. Liver enzymes are monitored for the first three to six months depending on the therapy chosen and then every three months afterward. Clinicians should consider monitoring complete blood counts with platelets with pirfenidone. Gastrointestinal symptoms, weight, and appetite should be tracked. For patients with fatigue, other causes in addition to IPF should be considered, such as sleep apnea, anemia, and thyroid disease. Concomitant medications should be monitored to avoid drug interactions at each three-monthly visit. Practices can ask patients to call with any new medications or changes between visits.

In addition to antifibrotic therapies, supplemental oxygen is a strong recommendation in the treatment guidelines for patients with resting hypoxemia.[1] Oxygen saturation should be measured at rest and exertion to determine if supplemental oxygen is necessary. Desaturation below 88 percent during a six-minute walk test often dictates prescription of supplemental oxygen. It is recommended that oxygen saturation is monitored at baseline and every three to six months to assess the need for supplemental oxygen.

Pulmonary rehabilitation is another important nonpharmacologic intervention. Patients with IPF often experience fatigue and lack of energy. Pulmonary rehabilitation may improve walk distance, IPF-related symptoms, and quality of life. Patients should be encouraged to continue pulmonary rehabilitation programs despite worsening symptoms, as the immediate benefits are not sustained for a lengthy period of time.

Exhibit 3: Potential Causes of ILD

■ **Inhaled Agents**

– **Inorganic**: silica, asbestos, beryllium

– **Organic:** animal/bird antigens, farm antigens

■ **Drug induced**

– antiarrhythmics

– chemotherapy

– antidepressants

– radiation

– oxygen

– antibiotics

– cocaine

■ **Connective tissue disease**

– scleroderma

– polymyositis/ dermatomyositis

– systemic lupus erythematosus

– rheumatoid arthritis

– mixed connective tissue disease

– ankylosing spondylitis

– primary Sjogren's syndrome

– Bechet's syndrome

■ **Idiopathic**

Exhibit 4: Issues in the Elderly when Considering IPF Therapies[14,15]

- Underweight or active weight loss.

- Bedbound, poor quality of life, or in hospice.

- Severely hypoxic with severe reductions in pulmonary function testing or high flow oxygen need.

- Expected survival less than one year.

- Severe medical disease with limited life expectancy or poor quality of life due to diseases other than IPF.

- Complicated medication regimens/polypharmacy.

- Drug interactions or compounded adverse effects from other medications.

- Comorbidities

    - Coronary artery disease/peripheral vascular disease/clotting diseases.

    - Risk of thrombosis or bleeding.

    - Hypothyroidism.

    - Acute or chronic kidney disease.

    - Liver disease.

Managing various comorbidities is another important aspect of IPF management. Patients with IPF frequently experience various comorbidities, such as gastroesophageal reflux, obstructive sleep apnea, pulmonary infection, emphysema, pulmonary hypertension, lung cancer, cardiovascular disease, and diabetes mellitus. These comorbidities are associated with disease progression and mortality in IPF. For example, about 90 percent of IPF patients have gastroesophageal reflux, but only half are symptomatic. Reflux worsens cough and breathlessness. Standard doses of proton pump inhibitors may not suppress acid reflux fully in IPF patients.[16] Acid-suppression therapy is associated with longer survival in IPF.[17]

Sleep in patients with IPF is significantly impaired, with alterations in sleep architecture, changes in sleep breathing patterns, and decreases in oxygen saturation during vulnerable rapid eye movement sleep.[18] There also is evidence that obstructive sleep apnea (OSA) has an increased prevalence in these patients, playing a significant role in the already

worse sleep quality related to the disease itself. OSA therapy has a role in IFP treatment by improving sleep, quality of life and disease outcome.

Lung transplant is the only known cure for IPF. Patients should be referred for lung transplant evaluation if there is histologic or radiographic evidence of UIP or fibrosing non-specific interstitial pneumonia (NSIP) irrespective of lung function, forced vital capacity (FVC) < 80 percent or diffusing lung capacity for carbon dioxide (DLCO) < 40 percent predicted, any dyspnea or functional limitation attributable to lung disease, any oxygen requirement even if during exertion, and failure to improve with medical therapy.[19] Factors which would prompt listing for a transplant include decline in FVC > 10 percent or DLCO > 15 percent during six months of follow-up, desaturation < 88 percent or distance < 250 meters or 50 meter decline over six months, pulmonary hypertension, or hospitalization due to respiratory disease, pneumothorax, or acute exacerbation.

Conclusion

Early diagnosis of IPF requires suspicion of ILD. Once diagnosed, antifibrotic therapy is a viable approach to preserve lung function and improve outcomes. Close attention to tolerability is key to use of antifibrotics. Evaluation and management of comorbid conditions and patient engagement throughout the entire treatment process are important for improving outcomes.

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Evolving Considerations in the Treatment and Management of Metastatic Melanoma: Expert Strategies on Immune Checkpoint Inhibitors

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

Summary

Checkpoint immunotherapy treatment is making a difference in metastatic melanoma survival. This treatment is an option for all patients, including those for which targeted therapy is also an option. The choice between immunotherapy and targeted therapy may become easier once ongoing comparative trials are completed.

Key Points

• Checkpoint immunotherapy is an option for all patients with metastatic melanoma as a single agent or combined immunotherapy.

• Targeted therapy is an option for patients with BRAF-mutated tumors.

• Triple therapy is also a possibility for BRAF-mutated tumors.

• Comparative clinical trials between immunotherapy and targeted therapy are ongoing.

IN 2022, THE AMERICAN CANCER SOCIETY estimates that about 99,780 new melanomas will be diagnosed (57,180 in men and 42,600 in women) and 7,650 people are expected to die of melanoma (5,080 men and 2,570 women).[1] Prior to about a decade ago, there was no therapy that improved survival in advanced melanoma. Chemotherapy was ineffective and interleukin two (IL-2) and interferon (IFN) provided marginal improvements.

Local and regionally spread melanomas are typically treated with surgery. Once metastatic and unresectable, the treatment options are checkpoint immunotherapy and targeted therapy. Checkpoint immunotherapy used in metastatic melanoma include the programmed death one (PD-1) inhibitors (nivolumab, pembrolizumab) and nivolumab in combination with the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab. Both classes of checkpoint immunotherapy take the breaks off of T-cell activation within the immune system. This allows the immune system to find and destroy tumor cells but can also lead to autoimmune attacks on the body. Targeted therapy includes v-Raf murine sarcoma viral oncogene homolog B (BRAF)/ mitogen-activated protein kinase (MEK) inhibitor

combinations. An up-and-coming treatment is a triple combination of BRAF/MEK/PD-1 inhibitors.

Ipilimumab was the first studied in melanoma and completely changed the treatment landscape. The long-term durability of response with ipilimumab was shown in long-term follow-up data from the Phase II and III trials of ipilimumab monotherapy.[2] Among 1,861 patients, median overall survival (OS) was 11.4 months, which included 254 patients with at least three years of survival follow-up. The survival curve began to plateau around year three, with follow-up of up to 10 years. Three-year survival rates were 22 percent, 26 percent, and 20 percent for all patients, treatment-naïve patients, and previously treated patients, respectively. Ipilimumab monotherapy became the standard of care for advanced melanoma in 2011.

Pembrolizumab (PD-1) was compared to ipilimumab (CTLA-4) in the KEYNOTE-006 trial.[3] In the final survival analysis, median OS was not reached in either pembrolizumab group (every 2 weeks or every 3 weeks) and was 16.0 months with ipilimumab [hazard ratio (HR) 0·68, $p = 0.0009$ and $p = 0.0008$]. The 24-month overall-survival rate was 55 percent in the two-week group, 55 percent in the

Exhibit 1: Metastatic Melanoma Therapy Decision Point

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                    ┌─────────────────────────┐
                    │    BRAF mutation test   │
                    └─────────────────────────┘
                         │                 │
              ┌──────────┘                 └──────────┐
              ▼                                       ▼
     ┌─────────────────┐                    ┌─────────────────┐
     │    BRAFᵛ⁶⁰⁰      │                    │    BRAFᵛ⁶⁰⁰      │
     │    mutation      │                    │    mutation      │
     │    negative      │                    │    positive      │
     └─────────────────┘                    └─────────────────┘

     ┌─────────────────┐                    ┌─────────────────┐
     │                 │                    │  Immunotherapy  │
     │  Immunotherapy  │                    │       or        │
     │                 │                    │   BRAF/MED      │
     │                 │                    │ Targeted Therapy│
     └─────────────────┘                    └─────────────────┘
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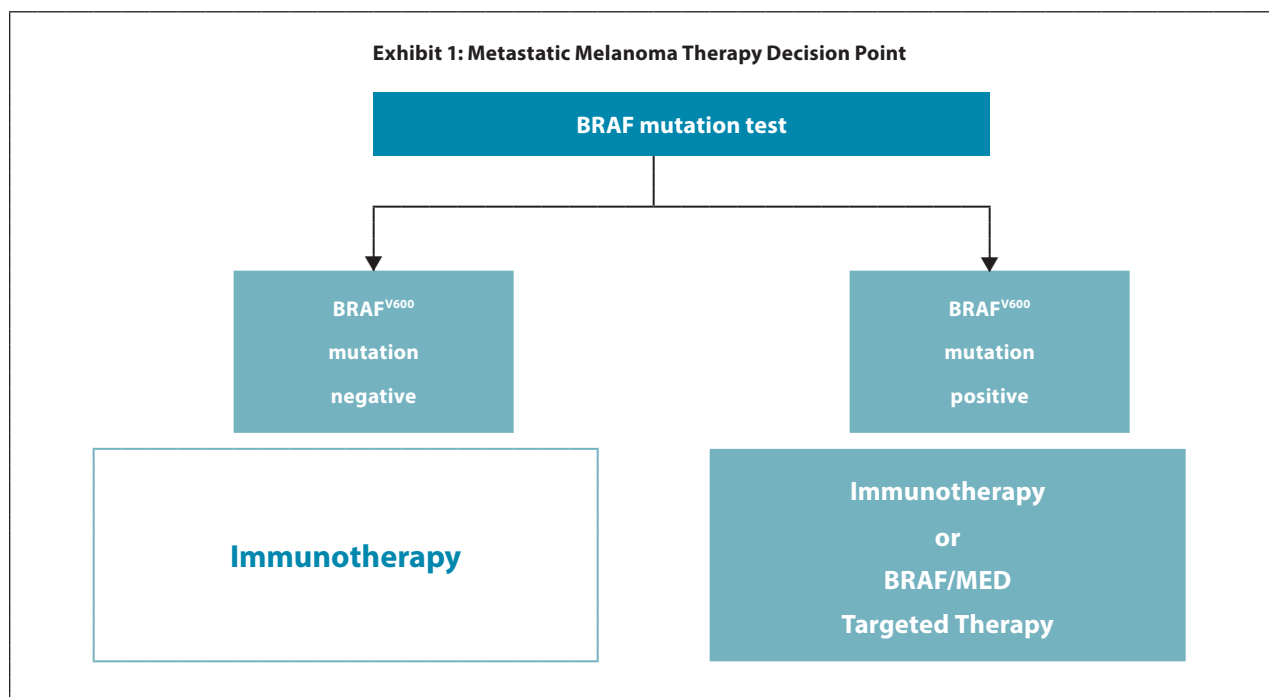
three-week group, and 43 percent in the ipilimumab group. Based on this trial, PD-1 inhibitors appear to improve OS more than ipilimumab front-line, and responses are durable even after stopping treatment.

Ipilimumab is now more typically given with nivolumab. The combination improved five-year survival better than ipilimumab or nivolumab alone.[4] Thus, clinicians have to make a choice between PD-1 immunotherapy alone or the PD-1/CTLA-4 combination. The choice is based on efficacy and toxicity. The combination was more effective in improving OS over nivolumab but has not been directly compared to pembrolizumab. Clinical features that suggest aggressive disease including elevated lactate dehydrogenase (LDH), acral primary, brain metastases, liver metastases, and/or other symptomatic systemic metastases indicate that more aggressive combination immunotherapy should be considered.[5] The significant difference between monotherapy and combination immunotherapy is in toxicity. By taking the brakes off of two checkpoint inhibitors, the PD-1/CTLA-4 combination causes a higher rate of immune-related adverse events (irAEs). These irAEs occur earlier than with PD-1 inhibition alone and last longer. In a real-world data analysis of 172 patients, Grade 3 to 4 adverse events were reported in 60 percent of the patients who received nivolumab/ipilimumab, almost all of whom were exposed to steroid treatments (59%), events were fatal in four patients, and led to permanent treatment discontinuation in 31 percent.[6] The real-world rate of Grade 3 to 4 adverse events and

discontinuation rate are consistent with the trial data (58%, 31%, respectively).[4]

BRAF mutation, primarily V600, is present in approximately 50 percent of melanomas. Previously, those with BRAF mutation were only treated with a BRAF inhibitor, but the effectiveness of this approach was short lived because of resistance development. Dual BRAF and MEK inhibition is associated with high response rates and improved OS compared to single-agent therapy and has replaced BRAF inhibition monotherapy.[7-9] Three combinations are approved in the U.S. — dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib.

As shown in Exhibit 1, if the patient with metastatic melanoma does not have a BRAF mutation, treatment selection is easy. If BRAF mutation is present, then a choice must be made between targeted therapy and immunotherapy. Immunotherapy is effective in BRAF-mutated disease, but because there are no direct comparison data, it is not known yet which is the better option or the optimal sequencing of targeted therapy and immunotherapy. There are several ongoing trials evaluating targeted therapy compared to nivolumab/ipilimumab (Exhibit 2).[10]

The Phase II SECOMBIT clinical trial (NCT02631447) is evaluating the best sequencing strategy in patients with metastatic melanoma and BRAF V600 mutation. In this study, the combination of ipilimumab and nivolumab followed by the combination of encorafenib and binimetinib, combination targeted therapy followed

	SECOMBIT	EORTC-1612-MG	DREAMseq
Population	Stage III (unresectable) or IV	Stage III or IV (cutaneous or mucosal)	Stage III (unresectable) or IV
	BRAF V600-mutant	*BRAF V600E or V600K-mutant*	*BRAF V600-mutant*
Numbers	251	270	300
Primary Endpoint	OS	PFS	OS
Primary Completion	Apr-21	Apr-22	Oct-22
IO Regimen	NIVO 1 mg/kg IV + IPI 3 mg/kg IV Q3W x 4 → NIVO 3 mg/kg IV Q2W	NIVO 3 mg/kg Q3W + IPI 1 mg/kg Q3W x4 → NIVO 480 mg Q4W	NIVO 1 mg/kg + IPI 3 mg/kg or NIVO 3 mg/kg + IPI 1 mg/kg → NIVO 3 mg/kg maintenance
Targeted Regimen	Encorafenib 450 mg PO QD + Binimetinib 45 mg PO BID	Encorafenib 450 mg QD + Binimetinib 45 mg BID	Dabrafenib 150 mg PO BID + Trametinib 2 mg PO QD
Sequencing	Targeted → IO IO → Targeted Targeted → IO → Targeted	Targeted → IO IO only	Targeted → IO IO → Targeted

Exhibit 2: Key Ongoing Trials Evaluating Targeted Therapy versus Combination Immunotherapy[10]

BID = twice daily; IO = immunotherapy; IPI = ipilimumab; IV = intravenous; NIVO = nivolumab; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PO = orally; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; QD = once daily.
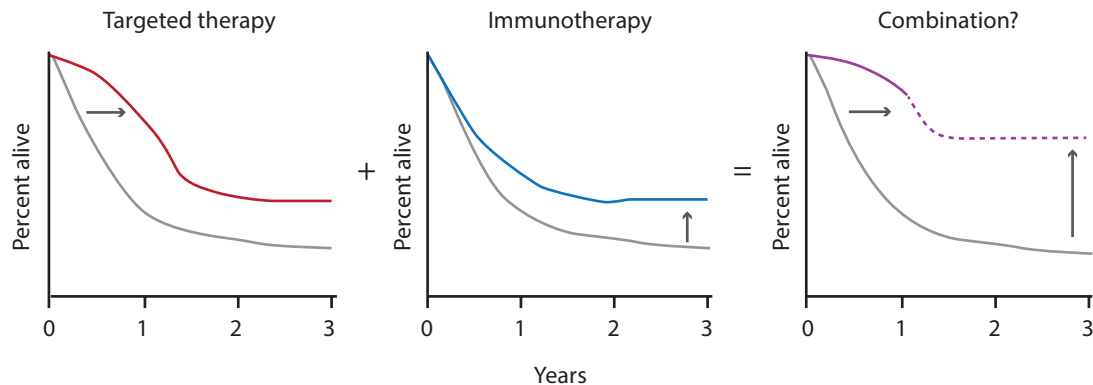
by combination immunotherapy, or combination targeted therapy followed by combination immunotherapy followed by combination targeted therapy again are being evaluated. Early data presented at professional meetings show a trend in favor of combination immunotherapy as the first treatment, with a two- to three-year OS of 73 percent and 62 percent respectively, in comparison to 65 percent and 54 percent for patients treated with combination targeted therapy first, and 69 percent and 60 percent for patients in the sandwich arm. Similarly, the response rate for patients first treated with combination immunotherapy was 45 percent, in comparison to 25 percent for patients first treated with combination targeted therapy. No results for this trial have yet been published.

Whether sequencing immunotherapy and targeted therapy is a better approach in those with BRAF V600 mutation or starting with an initial triple combination is still up for debate. Exhibit 3 shows where a triple approach with PD-1/BRAF/MEK inhibition up-front may be the ideal therapy.[11,12] Targeted therapy produces an early benefit and immunotherapy produces a long-term benefit. IMspire150 is a trial studying an initial cycle of vemurafenib/cobimetinib followed by

atezolizumab, a programmed death ligand one (PD-L1) inhibitor, or placebo in combination with vemurafenib/cobimetinib. At a median follow-up of 18.9 months, progression-free survival (PFS) was significantly prolonged with atezolizumab/vemurafenib/cobimetinib versus placebo/vemurafenib/cobimetinib (15.1 versus 10.6 months; $p = 0{\cdot}025$).[13] Final survival data from this trial have not yet been published, but immature survival data presented at an American Association for Cancer Research meeting in 2020 showed benefit on median OS (28.8 months versus 25.1 months) and 24-month survival (60.4% versus 53.1%).[14]

Metastatic melanoma treatments have also moved into earlier-stage treatment. Single-agent anti-PD-1 (pembrolizumab or nivolumab) is an option for adjuvant treatment after surgery in all high-risk patients. The National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma recommend immunotherapy as adjunctive therapy after initial surgical removal for stages of melanoma with positive sentinel nodes and after localized treatment of recurrence.[15] Choosing to treat a patient with adjuvant immunotherapy after surgical removal of Stage II or III disease requires an evaluation of recurrence risk and

Exhibit 3: Is Upfront Triple Therapy the Best Way to Improve Survival in Metastatic Melanoma?[11,12]

irAE with immunotherapy. Targeted therapy with BRAF/MEK combination is also an adjuvant option for BRAF-mutated tumors. Prior adjuvant use of immunotherapy will complicate treatment decisions in the metastatic setting. Ipilimumab monotherapy may be the only option if nivolumab or pembrolizumab was used earlier.

Conclusion

Immunotherapy is an option for all patients with metastatic melanoma as a single agent or combination. Targeted therapy is an option for BRAF-mutated tumors. Triple therapy for BRAF- mutated tumors and sequencing immunotherapy and targeted therapy continue to be evaluated and are likely to become standard therapies in the future. For now, the choice between immunotherapy and targeted therapy is still a clinical decision, but randomized comparative clinical trial data are awaited.

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Navigating Advances in the Treatment of Pulmonary Arterial Hypertension: Understanding Multidisciplinary Approaches to Optimize Outcomes

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

Summary

Pulmonary arterial hypertension is a fatal disease and should be treated with combination therapy in most patients. With effective therapies, the aim of treatment is to reduce risk of death. Many patients will require triple therapy to achieve low-risk status. Management for most patients requires a multi-disciplinary team at an expert center.

Key Points

• Pulmonary arterial hypertension is a fatal disease that requires aggressive management.

• The goal of treatment is to achieve a low-risk status.

• Guidelines recommend combination therapy, regular assessment, and escalating care in patients not at goal.

PULMONARY ARTERIAL HYPERTENSION (PAH) is characterized by worsening right-sided heart failure, decreasing functional status, and poor survival.[1] It is a subtype of pulmonary hypertension (PH) and is a progressive disease of the small pulmonary arteries. As disease worsens, a steady rise is seen in peripheral vascular resistance (PVR) and pulmonary arterial pressure (PAP) to sustain cardiac output (CO). If the right ventricle can compensate for the resistance, PAP 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.

PAH should be suspected in a patient with unexplained dyspnea with or without other signs and symptoms. Initial screening is an echocardiogram and then other tests for other diseases which might account for the symptoms. If these tests suggest PAH, the patient should be referred to a PH expert for diagnosis which requires right heart catheterization and may require other tests to rule out other forms of PH.[2] Many patients referred to PH expert centers may not even have PAH.

The basic principles of treating PAH are to ensure a proper diagnosis, perform a risk of death within one-year assessment to guide therapy, and closely follow the patient adjusting therapy to achieve low-risk status. Patients should be treated to the goal of low-risk status based on how they feel and function. Because this is a fatal disease, aggressive treatment is warranted. Management for most patients requires a multi-disciplinary team at a PH expert center.

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) PH guidelines included a model for tailoring treatment according to a patient's risk profile as defined by certain, prespecified determinants of prognosis (Exhibit 1).[3] Assessment of prognosis for each individual patient is based on the clinical variables outlined in Exhibit 1, Patients are classified into three risk categories (low, intermediate, and high) for death within one year. Patients may not be neatly categorized as low-risk or high-risk but have test findings that fall in both columns. The goal of this schematic is to encourage a physician to compile a composite assessment of an individual patient's status. There are numerous

Exhibit 1: Risk Assessment in PAH[3]			
Determinants of Prognosis (estimated one-year mortality)	**Low Risk < 5%**	**Intermediate Risk 5% to 10%**	**High Risk > 10%**
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO functional class	I, II	III	IV
6MWD	> 440 m	165 to 440 m	< 165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 ml/min/kg (> 65% pred.) VE/VCO_2 slope < 36	Peak VO_2 11 to 15 ml/min/kg (35 to 65% pred.) VE/VCO_2 slope 36 to 44.9	Peak VO_2 < 11 ml/min/kg (< 35% pred.) VE/VCO_2 ≥ 45
NT-proBNP plasma levels	BNP < 50 ng/l NT-proBNP < 300 ng/ml	BNP 50 to 300 ng/l NT-proBNP 300 to 1,400 ng/l	BNP > 300 ng/l NT-proBNP > 1,400 ng/l
Imaging (echocardiography, CMR imaging)	RA area < 18 cm² No pericardial effusion	RA area 18 to 26 cm² No or minimal, pericardial effusion	RA area > 26 cm² Pericardial effusion
Hemodynamics	RAP < 8 mmHg CI ≥ 2.5 l/min/m² SvO_2 > 65%	RAP 8 to 14 mmHg CI 2.0 to 2.4 l/min/m² SvO_2 6 to 65%	RAP > 14 mmHg CI < 2.0 l/min/m² SvO_2 < 60%

6MWD = 6 minute walking distance; BNP = brain natriuretic peptide;
CI = cardiac index; CMR = cardiac magnetic resonance;
NT-proBNP = N-terminal pro-brain natriuretic peptide; pred = predicted;
RA = right atrium; RAP = right atrial pressure; SvO_2=mixed venous oxygen
saturation; VE/VCO_2 =ventilatory equivalents for carbon dioxide;
VO2 = oxygen consumption; WHO = World Health Organization

other risk-scoring systems; the REVEAL risk score calculator 2.0 is based on the United State (U.S.) PAH registry and uses some of the same factors but adds others such as all-cause hospitalizations within the past six months.[4]

There are several classes of FDA-approved PAH therapies (Exhibit 2). The PAH-specific medications target three of the known signaling pathways in PAH – endothelin, nitric oxide, and prostacyclin. All the approved therapies have been demonstrated to improve exercise capacity and functional class. These improvements are probably associated with improvement in pulmonary hemodynamics (increased cardiac output, decreased PVR). Epoprostenol, a prostanoid delivered via continuous IV infusion, was the first therapy specifically approved by the FDA for the treatment of PH and is still generally considered to be to the gold standard for the severe Class IV patients. Overall, there is an unpredictable magnitude of response to a given therapy which necessitates close follow-up and

Exhibit 2: FDA-Approved Treatment Options for PAH

- ■ **Prostanoids**
  - • Epoprostenol IV
  - • Treprostinil (IV, SQ, inhaled, oral)
  - • Inhaled Iloprost
  - • Oral Selexipag
- ■ **Endothelin receptor antagonists (ERA)**
  - • Bosentan
  - • Ambrisentan
  - • Macitentan
- ■ **Phosphodiesterase-5 (PDE-5) Inhibitors**
  - • Sildenafil
  - • Tadalafil
- ■ **Soluble guanylate cyclase (sGC) Stimulators**
  - • Riociguat

Exhibit 3: Current Treatment Algorithm[5]
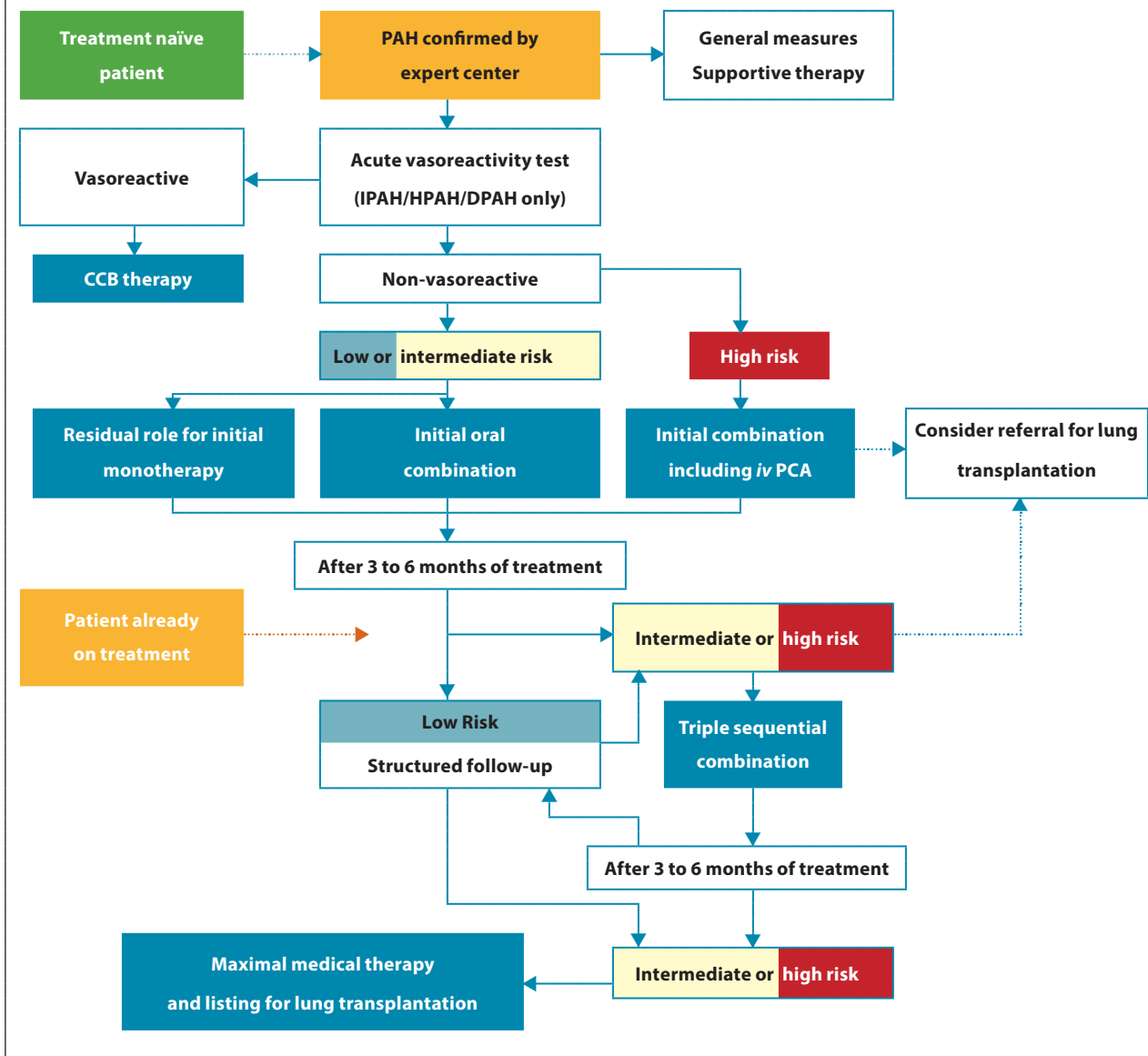
CCB = calcium channel blocker; iv PCA = intravenous prostacyclin analogue

possibility frequent medication changes.

Exhibit 3 shows the current treatment algorithm from the 6th World Symposium on Pulmonary Hypertension.[5] Sequential therapy starting with one agent was the standard of care, but this has evolved into combination therapy with at least two agents for most patients. Combination therapy targeting two or more pathways is now proven to provide better outcomes and is the best strategy for most patients.[6,7] For some low-risk patients, there is still a minor role for initial monotherapy. For those at high-risk, clinicians should consider starting with triple combination therapy. In one study of the survival benefits of a triple combination regimen consisting of epoprostenol, bosentan, and sildenafil in PAH patients with severe disease (New York Heart Association functional Class III/IV and severe hemodynamic impairment), all patients who started PAH treatment with upfront triple combination therapy were still alive after a mean follow-up of 41.2 + 13.4 months.[8] Survival at one, two, and three years was 100 percent. It is important in terms of overall survival to achieve low-risk status with therapy. The more categories of determinants of prognosis the patient can be in the low-risk category the better their survival.[9-11]

Several outcome endpoints are emerging to be added to the PAH patients ongoing evaluation. These include right ventricle function and data are suggesting that improved function, either by MRI or advanced echo, better predicts outcome than hemodynamic improvements. Quality of life (QOL) is another endpoint that will be measured more often. Currently, there are little data on the impact of treatment on QOL, and it is still not accepted by regulatory agencies as a factor in drug approval. PAH-specific instruments are being developed and studied.

Several additional therapies are currently under development, so the landscape is rapidly evolving and the options for treating this disease will be increasing. Sotatercept is a novel, first-in-class fusion protein composed of the extracellular domain of the human activin receptor type IIA fused to the Fc domain of human immunoglobulin G1. Sotatercept acts as a ligand trap for members of the transforming growth factor beta (TGF-β) superfamily, thus restoring balance between the growth-promoting activin growth differentiation factor pathway and the growth-inhibiting bone morphogenetic protein (BMP) pathway. It successfully decreased PVR in a 24-week multicenter trial in 106 adults who were receiving background therapy and subcutaneous sotatercept every three weeks compared to placebo.[12] Other possible therapeutic targets are platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) signaling which contribute to intimal and medial vascular remodeling in PAH. Various tyrosine kinase inhibitors whose targets include PDGF and FGF receptors, are being studied in PAH.

Conclusion

PAH is a fatal disease that requires aggressive management. Overall, the goal of treatment is to achieve a low-risk status. The guidelines recommend combination therapy from the beginning for most, regular assessment, and escalating care in patients not at goal.

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Best Practices in the Treatment and Management of Metastatic Breast Cancer: Essential Strategies for Improved Clinical and Economic Outcomes

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

Summary

The use of poly (ADP-ribose) polymerase (PARP) inhibitors which target how cells repair DNA damage is leading to improvements in progression-free survival in those with metastatic breast cancer (MBC). Use of this class of agents is likely to expand in the future with additional indications and in combination with immunotherapy.

Key Points

- Significant progress has been made with the approval of PARP inhibitors for germline BRCA1/2 mutated metastatic breast cancer, but limitations remain.
- There is growing evidence of efficacy of PARP inhibitors beyond germline BRCA1/2 mutations.
- Ongoing trials are evaluating synergism with immunotherapy.

ONE IN EVERY EIGHT WOMEN WILL develop breast cancer during their lifetime, and 85 percent of those women will have no family history of breast cancer. Excluding basal cell and squamous cell skin cancers, breast cancer is the most commonly diagnosed cancer among women in the United States (U.S.) Many women will be diagnosed initially with MBC, and others will progress to this stage. Median survival for MBC is four years with hormone receptor (HR) positive human epidermal growth factor receptor two (HER2) negative disease, five years for HER2-positive disease, and two years for triple-negative breast cancer (TNBC).

TNBC accounts for 15 to 20 percent of breast cancers. It disproportionally affects young women, breast cancer gene protein one (BRCA1) mutation carriers, African Americans, and Hispanics. Early recurrences are common after initial treatment and it has the lowest survival rates of all types of breast cancer.[1]

The concept of synthetic lethality has been applied to breast cancer treatment in general and TNBC specifically. Loss of a DNA damage repair (DDR) pathway can create vulnerability in cells because they are dependent on remaining DDR pathways for survival.[2] PARP and BRCA1 and 2 are important in DDR pathways. BRCA is involved in repairing breaks in double-stranded DNA though homologous recombination (HR) and PARP is involved in base-excision repair. Cells with BRCA mutations have homologous recombination repair deficiency (HRD) but can repair DNA through base-excision repair (non-homologous repair) using PARP, but use of this pathway alone results in genomic instability and increases the risk of developing breast, ovarian, prostate, and pancreatic cancer.

Germline BRCA mutations occur in about 0.25 percent of the general population, excluding those of Ashkenazi Jewish descent.[3] In the Ashkenazi Jewish population, BRCA mutations occur in 2.5 percent in the overall population and in 10 percent of those with breast cancer. Two percent of women with breast cancer at any age and 10 percent of women with breast cancer who are younger than 40 years of age have BRCA mutations. These mutations also occur in about 5 percent of men with breast cancer.

Exhibit 1: Current Treatment of gBRCA1/2-Associated MBC

ER/PR+ HER2-		**TNBC**	

	If PDL1+	If PDL1-

ET + CDK4/6i				IO+ Chemotherapy	PARPi[a]	Chemotherapy[b]

PARPi[a]	Alpelisib + fulvestrant	ET + CDK4/6i	Chemotherapy[b]	PARPi[a]	Chemotherapy[b]	Sacituzumab Govitecan
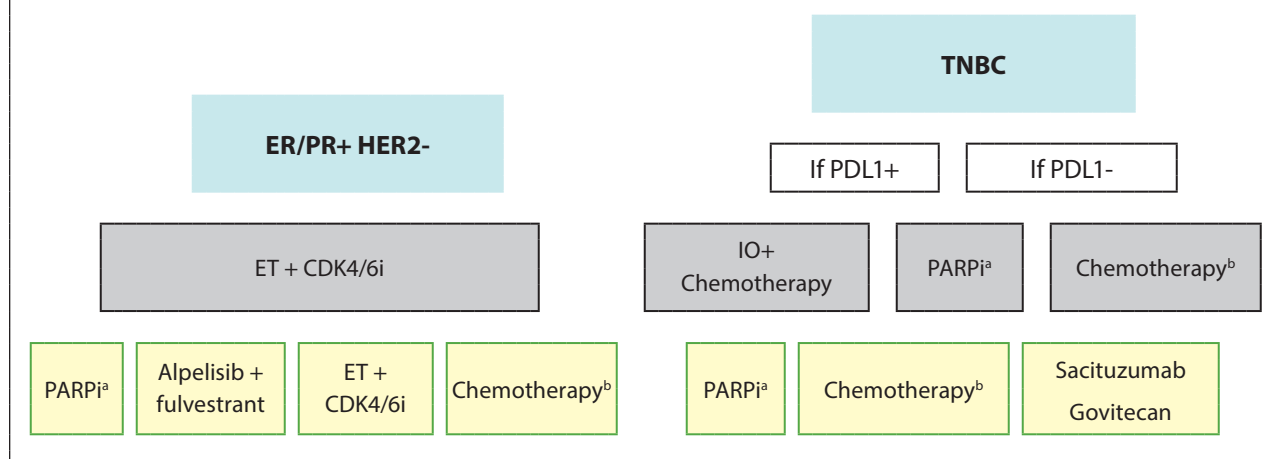
ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor two; ET = estrogen therapy;
CDK = cyclin dependent kinase 4/6 inhibitor; PARPi = Poly(ADP-ribose)polymerase inhibitor; IO = immunotherapy;
PD-L1 = programmed death ligand one; TNBC = triple negative breast cancer
[a] olaparib or talazoparib; [b] concern with cross-resistance between PARPi and platinum

PARP inhibitors prevent repair of breaks in single-stranded DNA and induce synthetic lethality in cells with HRD. In cells with functional homologous recombination, the cell can still repair DNA when PARP inhibition is present. These agents work by both PARP inhibition and PARP1 trapping. Olaparib, talazoparib, niraparib, and rucaparib are all FDA-approved PARP inhibitors for several types of cancers with HRD, but only olaparib and talazoparib are indicated for MBC. Talazoparib is a more potent PARP1 trapper than olaparib, however, the clinical significance of this difference is unknown.[4,5]

Olaparib (Lynparza®) was FDA approved for treating germline BRCA-mutated (gBRCAm) MBC based on results from a Phase III trial (OlympiAD) that included subjects who had HER2- negative, gBRCAm MBC treated with no more than two prior lines of chemotherapy. Olaparib 300 mg twice a day was compared to standard of care chemotherapy (capecitabine, eribulin, or vinorelbine). Median progression-free survival (PFS) was significantly longer in the olaparib group than in the chemotherapy group (7.0 months versus 4.2 months; $p < 0.001$).[6] Final median overall survival (OS) was 19.3 months with olaparib versus 17.1 months with chemotherapy, which was not statistically significant.[7] Olaparib was better tolerated than chemotherapy. Overall, olaparib monotherapy provided a significant benefit over standard therapy with a better median PFS but not a survival benefit.

Talazoparib (Talzenna®) was evaluated in the Phase III Embraca trial. Subjects had no more than three prior lines of chemotherapy but had to have been treated with a taxane and anthracycline. This trial compared talazoparib 1 mg once a day to standard of care chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months versus 5.6 months; $p < 0.001$).[8] Median OS was 19.3 months with talazoparib versus 19.5 months which, similar to olaparib, was not statistically significant.[9] The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% versus 27.2%; $p < 0.001$). Similar to olaparib, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to PFS and was well tolerated.

Why the PARP inhibitor studies did not show an OS benefit is not known, as these agents have been shown to improve OS in ovarian and prostate cancer. Reasons may be the high prevalence of post-progression crossover to PARP inhibitors from the chemotherapy group, especially platinum compounds which have some efficacy among BRCA1/2 carriers with advanced TNBC related to HRD and synthetic lethality.[10] Other reasons may be the development of resistance, cross resistance because of prior platinum-based chemotherapy, or that PARP inhibitors are being used too late in the disease process.

Both olaparib and talazoparib are FDA approved for gBRCAm HER2-negative MBC but are also used in gBRCAm TNBC. Exhibit 1 shows the current treatment paradigm for gBRCAm HER2

Exhibit 2: PARP Inhibition May…

Enhance Immune Response

• Upregulate PD-L1 expression

• Increase the release of neoantigens

Inhibit Immune Response

• Induces apoptosis ➜ depletion of immune cells

• Proinflammatory role of PARP1

negative and TNBC MBC. BRCA testing should be done for all patients with recurrent or MBC to identify candidates for PARP inhibitor therapy. There are FDA-approved companion assays for both agents which should be used for the testing. PARP inhibitors are currently being studied in MBC with other homologous recombination deficiency (HRD) gene mutations. Olaparib Expanded, a Phase II study, assessed olaparib response in patients with MBC with somatic BRCA1/2 mutations or germline or somatic mutations in homologous recombination-related genes other than BRCA1/2.[11] Seventy-six percent of 54 patients had estrogen receptor-positive HER2-negative disease. Eighty-seven percent had mutations in PALB2 (partner and localizer of BRCA) somatic BRCA1/2, ATM, or CHEK2. In those with MBC with measurable disease and germline mutations in non-BRCA1/2 HR-related genes, overall response rate (ORR) was 33 percent and in those with somatic mutations in non-BRCA1/2 HR-related genes or BRCA1/2, 31 percent. Confirmed responses were seen only with germline PALB2 and somatic BRCA1/2 mutations. Median PFS was 13.3 months for germline PALB2 and 6.3 months for somatic BRCA1/2 mutation carriers. No responses were observed with ATM or CHEK2 mutations alone. The authors concluded that PARP inhibition is an effective treatment for patients with MBC and germline PALB2 or somatic BRCA1/2 mutations, significantly expanding the population of patients with breast cancer likely to benefit from PARP inhibitors.

The combination of PARP inhibition with checkpoint immunotherapy is also being investigated. PARP inhibition has been shown to upregulate programmed death ligand one (PD-L1) expression in vitro and in vivo, which enhances cancer-related immunosuppression and PD-L1 expression is a biomarker for checkpoint immunotherapy efficacy.[12] Talazoparib increases the number, and enhances function of CD8+ T cells and natural killer cells which also supports combination of PARP inhibition with checkpoint immunotherapy.[13] Additionally, PARP-1 plays a relevant role in Th2 cell differentiation and the inflammatory process.[14] Exhibit 2 illustrates how PARP inhibition has both beneficial and potentially negative effects in cancer treatment. Combination with checkpoint immunotherapy may have synergetic benefits while countering the potentially negative effects.

The combination of olaparib and durvalumab, a PD-L1 antagonist, showed promising antitumor activity and safety similar to that previously observed in olaparib and durvalumab monotherapy studies in the MEDIOLA trial, a multicenter, open-label, Phase I/II, basket trial of durvalumab and olaparib in solid tumors.[15]

Patients were enrolled into four initial cohorts:
• gBRCAm MBC
• gBRCAm metastatic ovarian cancer
• metastatic gastric cancer
• relapsed small-cell lung cancer.

In the MBC cohort, patients could not have received more than two previous lines of chemotherapy. Patients received 300 mg olaparib

in tablet form orally twice daily for four weeks and thereafter a combination of olaparib 300 mg twice daily and durvalumab 1.5 grams via intravenous infusion every four weeks until disease progression. Thirty-four patients were enrolled and received both study drugs and were included in the safety analysis. Thirty-two percent experienced Grade 3 or worse adverse events, of which the most common were anemia, neutropenia, and pancreatitis. Three (9%) patients discontinued due to adverse events and four (12%) patients experienced a total of six serious adverse events. There were no treatment-related deaths. Twenty-four of 30 patients (80%) eligible for activity analysis had disease control at 12 weeks. The ORR was 63.3 percent and PFS was 8.2 months.

When either is given as monotherapy, PARP inhibitors and checkpoint immunotherapy have shown limited clinical activity in patients with advanced TNBC. A small trial evaluated the clinical activity (primary) and safety (secondary) of combination treatment with niraparib and pembrolizumab in patients with advanced or metastatic TNBC.[16] Within the full study population of 55 women, five patients had confirmed complete responses, five had confirmed partial responses, 13 had stable disease, and 24 had progressive disease. Median duration of response was not reached at the time of the data cutoff, with seven patients still receiving treatment at the time of analysis. In 15 evaluable patients with tumor BRCA mutations, ORR was 47 months and median PFS was 8.3 months. ORR and PFS was much lower in those without BRCA mutations. The most common treatment-related adverse events of Grade 3 or higher were anemia, thrombocytopenia, and fatigue. Immune-related adverse events were reported in 15 percent of patients and no new safety signals were detected. The authors concluded that combination niraparib plus pembrolizumab provides promising antitumor activity in patients with advanced or metastatic TNBC, with numerically higher response rates in those with tumor BRCA mutations. The combination therapy was safe with a tolerable safety profile, warranting further investigation.

Two other combination trials are ongoing. TALAVE is a pilot trial of induction talazoparib followed by the combination of talazoparib and avelumab in advanced breast cancer (NCT03964532). It includes those with BRCA 1/2 mutations and TNBC with no BRCA mutations. Olaparib with or without atezolizumab in locally advanced unresectable or metastatic non-HER2-positive breast cancer is another ongoing trial (NCT02849496).

Conclusion

Significant progress has been made with the approval of PARP inhibitors for gBRCA1/2m MBC, but limitations remain. Evidence of efficacy of PARP inhibitors in other HRD gene mutations has been found. Ongoing trials are evaluating synergism with checkpoint immunotherapy. More studies in mechanisms of resistance are needed.

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Advanced Treatment Strategies in Prostate Cancer: A Closer Look at the Current and Emerging Therapeutic Options

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

Summary

The treatment of prostate cancer continues to evolve. There is now a new imaging tool for identifying prostate-specific metastases and a radiopharmaceutical for treating one subtype of metastatic disease.

Key Points

• Next-generation imaging is going to impact diagnosis and treatment.

• Movement of therapies into the earlier stages of disease complicates advanced disease management.

• Optimal management of patients is not specialty dependent; it is expertise dependent.

PROSTATE CANCER UNLIKE MANY OTHER cancers is managed by a very diverse group of clinicians. This includes community urologists, academic urologists, urologists in large urinary group practices, medical oncologists, urologic medical oncologists, and radiation oncologists. Management diverges based on who is managing a given patient and how much interdisciplinary care is integrated into that overall care.

Prostate cancer needs to be thought of in subsets, and there is heterogeneity in those subsets. The subsets include organ confined, locally advanced, de novo metastatic, oligometastatic, castrate sensitive, and castrate-resistant metastatic disease (Exhibit 1).[1] These various subsets are managed differently. The focus of the remainder of this article is metastatic castration-resistant prostate cancer and nonmetastatic castration-resistant prostate cancer, where there have been recent advances in treatment. Metastatic castration-resistant prostate cancer (mCRPC) is metastatic disease on imaging, testosterone ≤ 50 ng/dL, and a rising PSA or new metastases on imaging. Nonmetastatic castration-resistant prostate cancer (nmCRPC) is where there is no evidence of metastatic disease on imaging and a castrate testosterone level (≤ 50 ng/dL) but a rising PSA.

Exhibit 2 shows the wide range of therapies approved for treating mCRPC. With mCRPC, management is increasingly impacted on therapy administered earlier in the disease process. The androgen receptor does remain the Holy Grail throughout the disease continuum, but there is no standard sequence of therapeutic agents.

The newest agent for mCRPC is lutetium Lu 177 vipivotide tetraxetan (Pluvicto®). This is a radioligand therapeutic agent indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive mCRPC who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. PSMA-positive disease is demonstrated with a PSMA-PET scan, a next-generation imaging technique. The active moiety, the radionuclide lutetium-177, is linked to a moiety that binds to PSMA, a transmembrane protein that is expressed in prostate cancer, including mCRPC. Upon binding to PSMA expressing cells, the beta-minus emission from lutetium-177 delivers radiation to PSMA-expressing cells, as well as to surrounding cells, and induces DNA damage which can lead to cell death.

The trial that led to FDA approval in early 2022 was an international, open-label, Phase III trial

Exhibit 1: The Clinical States of Prostate Cancer[1]
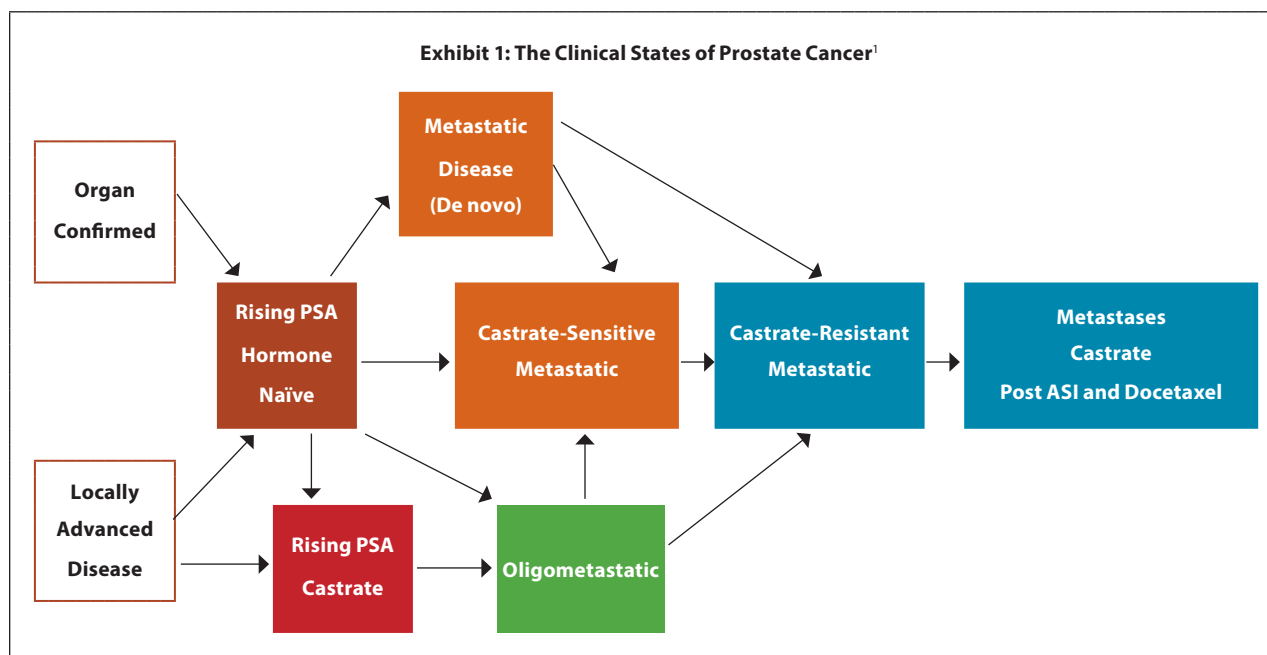
ASI = androgen signaling inhibitor

evaluating this agent in patients who had mCRPC previously treated with at least one androgen-receptor-pathway inhibitor and one or two taxane regimens and who had a PSMA-positive PET scan.[2] Lutetium Lu 177 vipivotide tetraxetan plus standard care significantly prolonged, as compared with standard care, both imaging-based progression-free survival (median, 8.7 versus 3.4 months; $p <$ 0.001) and overall survival (median, 15.3 versus 11.3 months; $p <$ 0.001). The incidence of adverse events of Grade 3 or above was higher with this agent than without (52.7% versus 38.0%), but quality of life was not adversely affected. There are numerous ongoing trials with this and other radioligands targeting prostate cancer.

It is given intravenously once every six weeks for up to six treatments, or until disease progression, or unacceptable toxicity. Dose interruption, reduction, or permanent discontinuation may be required due to adverse reactions. The most common adverse reactions ($\geq$ 20%) are fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation, and the most common laboratory abnormalities ($\geq$ 30%) are decreased lymphocytes, hemoglobin, leukocytes, platelets, calcium, and sodium.
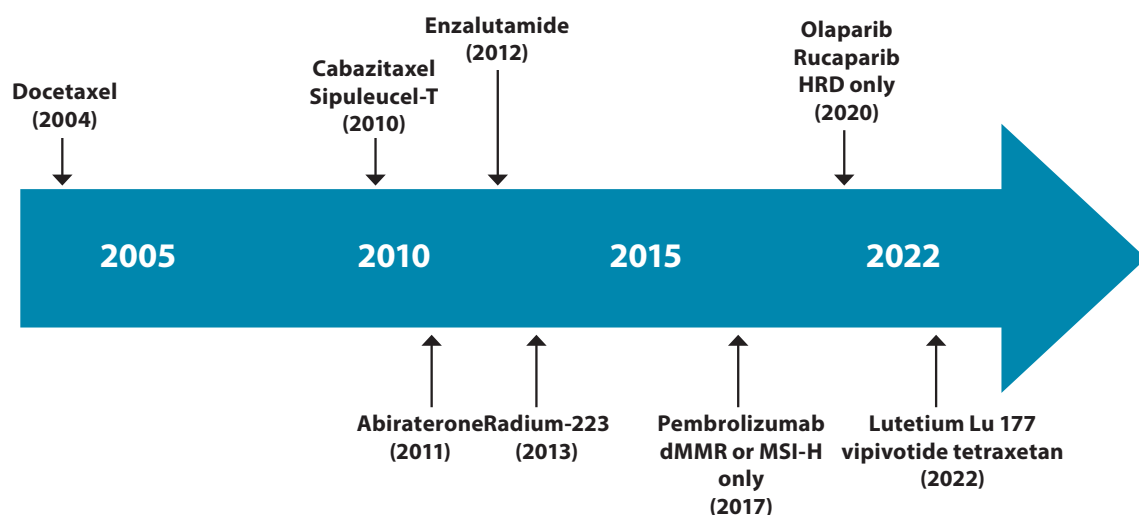
Three agents have been demonstrated to improve metastases-free survival and overall survival (OS) in nmCRPC – apalutamide, enzalutamide, and darolutamide.[3-5] These three agents are androgen-receptor antagonists and are all FDA approved for nmCRPC. The patient population in the approval

trials for these three agents must have previously been treated with androgen deprivation therapy and conventional imaging was used to demonstrate benefit. An increasing number of patients with nmCRPC will be treated based on advanced imaging with PSMA-PET.

There is compelling evidence that PSMA-PET has superior sensitivity and specificity to conventional imaging. PSMA-PET scans were FDA approved in December 2020 and are Medicare reimbursable. In a retrospective study that included 200 patients with nmCRPC, PSA > 2 ng/mL, and high-risk for metastatic disease [PSA doubling time (PSADT) of $\leq$10 months and/or Gleason score of $\geq$ 8] from six high-volume PET centers found PSMA-PET was positive in 196 of 200 patients.[6] Overall, 44 percent had pelvic diseases, including 24 percent with local prostate bed recurrence, and 55 percent had metastatic (M1) disease despite negative conventional imaging. Fifty-five percent had mCRPC instead of nmCRPC. PSMA-PET should be the imaging test of choice in prostate cancer because of its specificity.

There are going to be challenges in incorporating much more sensitive imaging tests into the management of advanced prostate cancer. One challenge will be the need to make clinical decisions without supporting evidence. An example is locally advanced disease which is typically managed with surgery followed by radiation therapy with or without two to three years of androgen deprivation therapy. With next-generation imaging, a lot more

Exhibit 2: FDA-Approved Agents for mCRPC

Docetaxel (2004)

Cabazitaxel Sipuleucel-T (2010)

Enzalutamide (2012)

Olaparib Rucaparib HRD only (2020)

2005 · 2010 · 2015 · 2022

Abiraterone (2011)

Radium-223 (2013)

Pembrolizumab dMMR or MSI-H only (2017)

Lutetium Lu 177 vipivotide tetraxetan (2022)

dMMR = deficient mismatch repair;
MSI-H = microsatellite instability;
HRD = homologous repair deficiency

occult metastatic disease will be found, and this may alter the approach to therapy, but there are no studies to back up these changes.

Overall, all the FDA-approved agents and level one evidence from therapeutic prostate cancer trials utilized conventional CT/bone scans except the new radiopharmaceutical. Earlier detection with next-generation imaging may not mean earlier therapeutic intervention is beneficial but may result in this in any case. History has shown that earlier therapeutic intervention may not change the ultimate outcome of the disease for the patient. Earlier detection may result in aborting planned curative intent therapies without data. Adoption of next-generation imaging will occur over time and be admixed with conventional imaging.

There is an evolving impact of genomics in prostate cancer treatment. Genetic testing should be a standard of care and offered to all patients with metastatic prostate cancer. Mutations may be either germline or somatic (tumor). Somatic DNA testing results may change over time due to the genetic instability of tumor DNA.[7] Twelve to 23 percent of mCRPC cases have DNA repair alterations including breast cancer one and two (BRCA1, BRCA2) mutations.[8,9] BRCA 1 or 2 mutations are targetable with poly(ADP-ribose) polymerase (PARP) inhibitors. Olaparib has been shown to improve overall survival compared to physician selected androgen receptor therapy in those with mCRPC.[10] The FDA approved olaparib in 2020 for mCRPC with deleterious or suspected deleterious germline or somatic homologous DNA repair gene mutations after progression following prior treatment with enzalutamide or abiraterone. Rucaparib, another PARP inhibitor, is also approved for the same indication. The combination therapy of olaparib and abiraterone is being studied for first-line treatment of mCRPC.

As previously noted, multiple specialties engage in the care of patients during their disease course. Historically, urology and radiation oncology have had a close working relationship in localized/locally advanced disease. Advanced disease is managed by a variety of clinicians with varying levels of experience. Uptake of new data, imaging, genomics, and therapeutics is more optimal with interdisciplinary care.

Conclusion
Prostate cancer is an extremely heterogenous disease in its biology and clinical manifestations. The impact of next-generation imaging will be significant and challenging given the limited prospective evidence to guide management. The movement of therapies into earlier stages of disease complicates advanced disease management. Optimal management of patients is not specialty dependent, it is expertise dependent.

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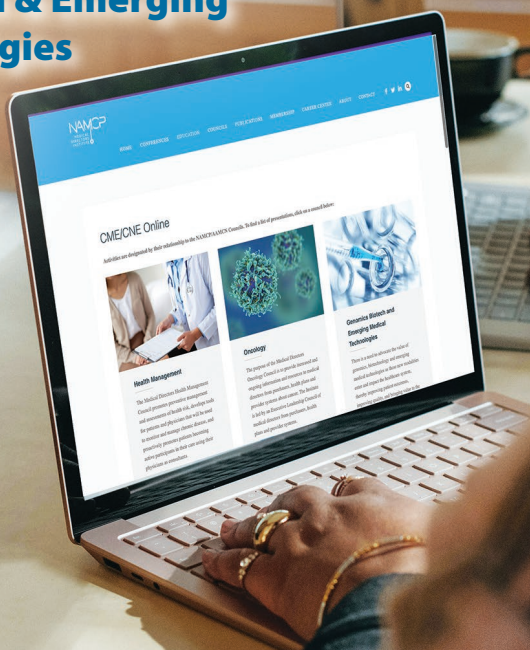
New Horizons in the Treatment of Psoriasis:
Key Strategies to Target Optimal Patient Outcomes

Junko Takeshita, MD, PhD, MSCE

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

Summary

Psoriasis, especially when moderate to severe, has a significant impact on patients. Targeted therapies which are highly effective in clearing skin and reducing underlying inflammation have transformed the treatment of this disease.

Key Points

- Numerous therapies are available that target the underlying pathophysiology of this disease.

- These agents are primarily for those with moderate to severe disease or with limited disease in disabling locations (such as the hands and feet).

- Treatment selection is highly dependent on individual patient characteristics and preferences.

- It is important to routinely assess treatment response and discuss treatment goals with patients.

PSORIASIS IS A CHRONIC RELAPSING immune-mediated inflammatory disease characterized by psoriatic plaques which are red, thick, and scaly. It is not just a skin disease, and there are multiple associated comorbidities related to systemic inflammation. Psoriasis affects 2 percent to 4 percent of the adult population (~7.5 million in the U.S.). Rates are higher in Caucasians, but African Americans are more likely to have moderate to severe disease. About 15 percent of those affected have moderate disease [3 to 10% body surface area (BSA) affected] and 5 percent have severe disease (> 10% BSA). A sizable portion of those with psoriasis are thought to be undiagnosed. Psoriasis causes significant clinical, social, emotional, and economic burden.

Mild psoriasis (< 3% of BSA) is treated with topical therapies. Moderate to severe disease requires more aggressive treatment with phototherapy and systemic treatments. There are four oral and 11 biologics FDA approved for treating moderate to severe psoriasis. The International Psoriasis Council has recommended replacing severity designation with two designations—candidate for topical or candidate for systemic therapy.[1] Candidates for systemic therapy may have one or more of the following features—more than 10 percent BSA involved, disease involving specific areas (e.g., face, palms, soles, genitalia, scalp), or failure of topical therapy.

Exhibit 1 shows the therapeutic targets in the treatment of psoriasis.[2] Agents targeting many aspects of the underlying pathophysiology of psoriasis are available. This includes the tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, adalimumab, certolizumab), interleukin (IL) 12 and 23 inhibitor (ustekinumab), IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab), IL-17A inhibitors (ixekizumab, secukinumab), and IL-17A receptor blocker (brodalumab). Based on clearing of skin [Psoriasis Area and Severity Index (PASI) scores], the IL-17 and IL-23 inhibitors are the most effective biologics, but there are few head-to-head studies to identify the most effective agents. Secukinumab, ixekizumab, risankizumab, brodalumab, guselkumab have been shown to be superior to ustekinumab.[3-7] Bimekizumab, an investigational IL-17A and IL-17F inhibitor, has also been shown superior to ustekinumab in 52-week trial.[8] As shown in Exhibit 2, the PASI 90 rates with various orals and biologics, and demonstrates that the IL-17 and IL-23 targeting agents, with the exception

Exhibit 1: Therapeutic Targets in the Treatment of Psoriasis[1]
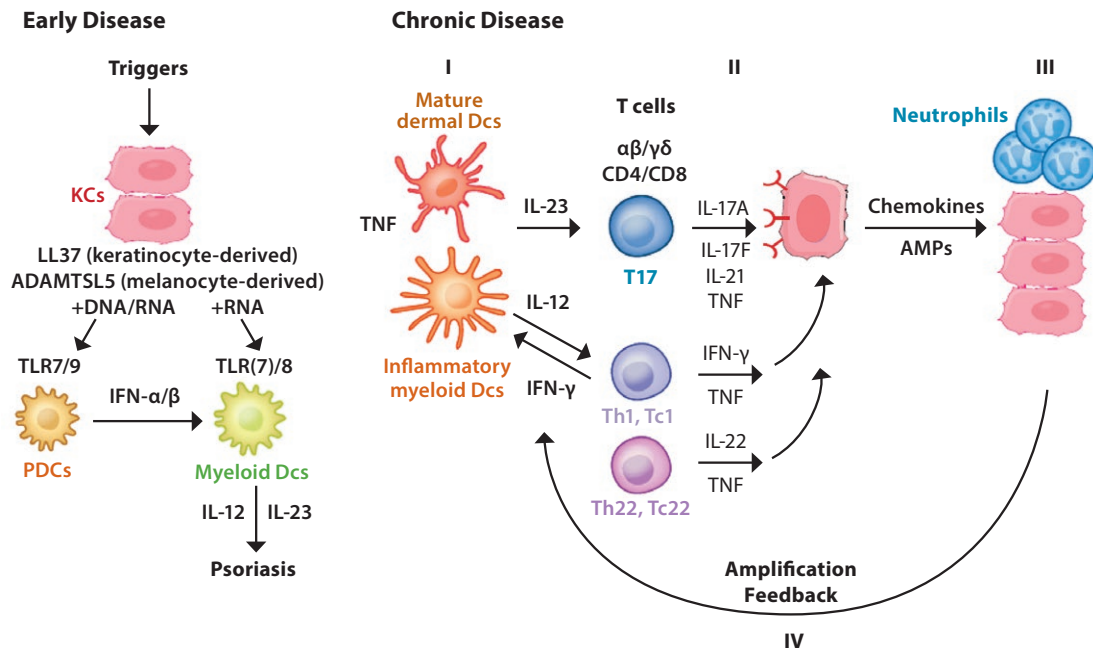
KC = keratinocyte; DC = dendritic cell; IL = interleukin; IFN = interferon;
TNF = tumor necrosis factor; AMP = antimicrobial peptide

Exhibit 2: PASI 90 Response with Biologics and Commonly Used Oral Treatments[8-14]
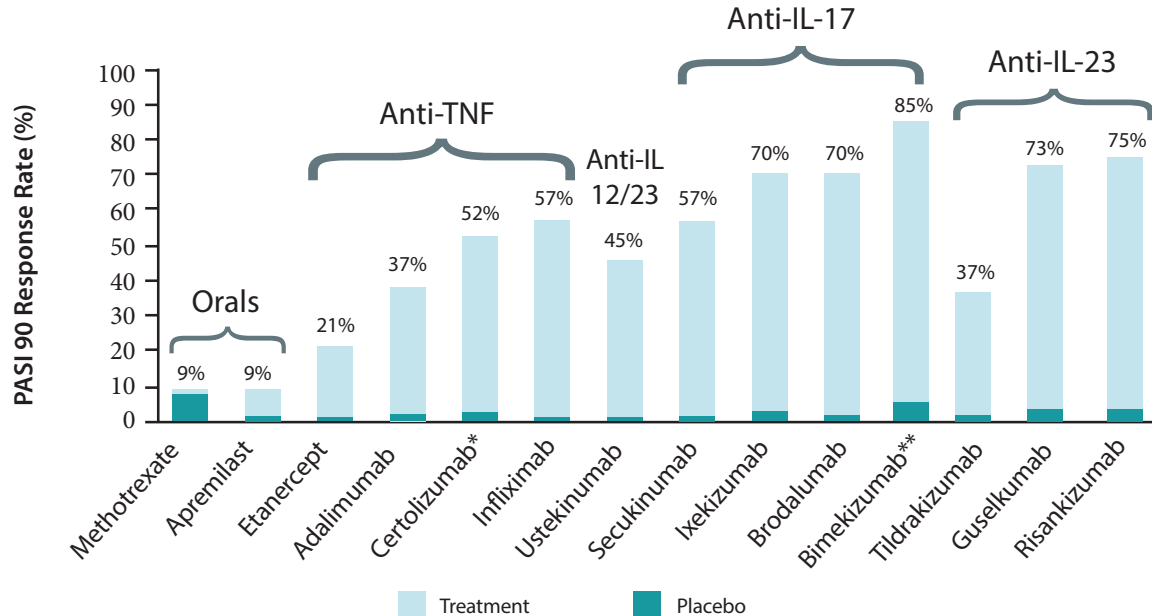
*400 mg Q2W dose for certolizumab pegol
**Not FDA approved for psoriasis

of tildrakizumab, are the most efficacious.[8-14]

Real-world data shows that the effectiveness of methotrexate, adalimumab, etanercept, infliximab, ustekinumab, and phototherapy for moderate to severe psoriasis is lower than what is seen in clinical trials.[15-16] Data on real-world response to the newer agents are not available. In terms of therapy persistence, one Danish registry found

Exhibit 3: Biologic Selection for Psoriasis Treatment Depends on Many Factors

Scenario	TNF	IL-12/23	IL-23	IL-17
Psoriatic arthritis	☆ FDA approved	FDA approved	FDA approved*	FDA approved**
Crohn's disease	FDA approved adalimumab, certolizumab, infliximab	FDA approved	TBD	Warning!
Associated with decreased MI and stroke	Yes	TBD	TBD	TBD
Heart Failure	Warning!	No warning	No warning	No warning
Multiple sclerosis		No benefit or harm Phase II	No warning	Promising Phase II
Ease of administration		☆	☆	
Patient is obese	Infliximab preferred	Weight-based dosing		Flexible dosing***
Rapid onset				☆
Long-term persistence		☆	TBD	TBD
Pediatric psoriasis	Etanercept only (≥ 4yo)	Adolescents only (≥ 12yo)		Ixekizumab only (≥ 6yo)

TBD = to be determined; MI = myocardial infarction
* Guselkumab only
** Ixekizumab and secukinumab only
*** Flexible dosing relevant for secukinumab

that patients stayed on ustekinumab the longest and secukinumab the shortest, although most patients on secukinumab were non-naïve.[17] Another analysis found comparable results. For etanercept, use dropped from 66 percent at year one to 41 percent at year four, from 69 percent to 47 percent for adalimumab, from 61 percent to 42 percent for infliximab, and from 82 percent to 56 percent for ustekinumab, respectively.[18] Tolerance and efficacy both influence persistence. Etanercept was most commonly discontinued for loss of efficacy. Infliximab was most frequently associated with discontinuation due to adverse events.

Biologic selection depends on many factors including concomitant conditions which can be improved or worsened by a particular class of agents (Exhibit 3). Each of the agents can cause some significant adverse events which have to be considered. Additionally, dosing regimens range from weekly to every 12 weeks, and the dosing regimen may impact adherence and patient acceptance since all the biologics are injectable. All but infliximab are self-administered. The joint American Academy of Dermatology and National Psoriasis Foundation guidelines support dose and dosing regimen escalation for etanercept (twice weekly), adalimumab (once weekly), infliximab (up to 10mg/kg, every 4 weeks), and ustekinumab (every 8 weeks) to improve disease control with these agents.[19]

Patient-centered treatment goals are important for psoriasis management because of its significant impact on health-related quality of life (HRQOL). Psoriasis continues to be a stigmatizing disease. In one study, layperson participants endorsed social avoidance items such as not wanting to shake hands (39.4%) or have those with psoriasis in their home (32.3%).[20] Participants stereotyped persons with psoriasis as contagious (27.3%) and endorsed the myth that psoriasis is not a serious disease (26.8%). Psoriasis causes as much disability as other major

medical diseases, including diabetes, heart failure, and arthritis.[21] Treatment can benefit HRQOL. Higher improvements in PASI achieve better quality-of-life outcomes (i.e., PASI 75 versus PASI 100).[22] Unfortunately, most patients with moderate to severe psoriasis are undertreated.[23] Those who are African American or with higher out-of-pocket drug costs are less likely to receive biologic therapies for psoriasis.[24]

Treatment goals recommended by the medical board of the National Psoriasis Foundation include achieving affected BSA ≤ 1 percent within three months after treatment initiation and maintaining this level with follow-ups every six months.[25] An acceptable treatment target at three months after initiation is BSA ≤ 3 percent or BSA reduction ≥ 75 percent. This group recommends that payers should not use treatment targets to deny access to therapies if targets are not met.

Psoriasis is the first dermatologic outcome measure in the Medicare merit-based incentive payment system (MIPS). The outcome targets are physician global assessment score of ≤ 2, affected BSA < 3 percent, PASI score < 3, and Dermatology Life Quality Index (DLQI) score ≤ 5. In 2017, the performance rate was only 60.3 percent.[26] Thus, there is significant room for improvement of the care of those with psoriasis, especially through increased access to the most efficacious biologics.

Conclusion

Many efficacious treatment options are available for patients with moderate to severe psoriasis with improved safety over older oral immune suppressants. Treatment selection is highly dependent on individual patient characteristics and preferences. It is important to routinely assess treatment response and discuss treatment goals with patients.

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Recent Therapeutic Strategies for Psoriatic Arthritis: Optimal Management for Personalized Care

Leonard H. Calabrese, DO

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, a chronic, inflammatory disease of the joints and where tendons and ligaments connect to bone, has a significant impact on patients. There are a growing number of treatments targeted at the underlying pathophysiology which help stop the disease progression, lessen pain, protect joints, and preserve quality of life.

Key Points
• Psoriatic arthritis affects up to 30 percent of those with psoriasis.

• Minimal disease activity is the target of treatment.

• Multidisciplinary care, especially with rheumatology and dermatology, is a way to improve outcomes.

PSORIATIC ARTHRITIS (PSA) IS A CHRONIC, seronegative inflammatory arthropathy associated with psoriasis which causes joint damage. There is no serologic marker that is reproducibly associated with PsA, and rheumatoid factor is negative in most patients. PsA affects about 30 percent of all patients with psoriasis.[1] The age of onset for PsA is typically 30 to 50 years with a median of 35 years.

PsA is a peripheral spondyloarthritis that involves both the joints and the entheses (the sites where the ligaments and tendons attach to the bones).[2] With entheses, inflammation of the tendon insertion site leads to calcification and fibrosis. The most common sites are plantar fascia (9%), finger flexor tendons (7%), and the Achilles tendon (7%). These occur in 30 percent to 50 percent of PsA patients. The five subtypes of PsA are oligoarticular asymmetrical, polyarticular, distal predominant pattern, spondylitis, and arthritis mutilans, the most severe presentation. The patient's pattern of disease can change or progress. A significant portion of patients will have axial disease [axial spondylitis (AS) or non-radiographic axial spondyloarthritis (nrAXspa)] at the time of initial diagnosis or develop it within 10 years of diagnosis.[3] The diagnostic criteria for PsA are shown in Exhibit 1.[4] Importantly, psoriasis and PsA have a significant impact on quality of life and psychosocial burden.[5,6] Coping with the psychosocial aspects of the disease may require care from several clinicians (Exhibit 2).[5]

The available treatments for PsA have become much more targeted to the underlying pathophysiology of this disease in recent years. Key cytokines in PsA include Janus kinases and signal transducers and activators of transcription (JAK-STATs), tumor necrosis factor (TNF), interleukin (IL)-17, and IL-23. There are FDA-approved agents which target all these cytokines (Exhibit 3). Some agents are only approved for PsA, and others are approved for both PsA and psoriasis. Some have also been specifically studied in axial disease (ankylosing spondylitis and non-radiographic axial spondyloarthritis) and are the better choices when axial disease is present.

The TNF inhibitors have been mainstays in moderate to severe PsA treatment. These agents reduce joint symptoms and improve psoriasis. This class of agents also improves enthesitis, dactylitis, functional ability, quality of life, and fatigue.[7,8] Psoriasis Area and Severity Index 75 percent clearing (PASI75) rates are higher with infliximab, golimumab, certolizumab, and adalimumab and lower for etanercept. A similar pattern for 20 percent, 50 percent, and 70 percent reduction in joint inflammation and symptoms [American College of Rheumatology (ACR) 20, 50, 70] was also seen.

Treatment with secukinumab, an IL-17A inhibitor,

Exhibit 1: CASPAR Criteria for the Diagnosis of PsA[4]		
PsA is diagnosed when ≥ 3 points below are assigned in the presence of inflammatory articular disease (joint, spine, or entheseal)		
Category	**Description**	**Points**
Current psoriasis or personal or family history of psoriasis.	Psoriatic skin or scalp disease confirmed by dermatologist or rheumatologist; history of psoriasis from patient, family physician, dermatologist, rheumatologist, or other qualified practitioner; patient-reported history of psoriasis in first- or second-degree relative.	2
Psoriatic nail dystrophy on current physical exam.	Includes onycholysis, pitting, and hyperkeratosis.	1
Negative for RF	Enzyme-linked immunosorbent assay or nephelometry preferred (no latex) using local laboratory reference range.	1
Current dactylitis or history of dactylitis documented by a rheumatologist.	Swelling of entire digit	1
Radiographic evidence of juxta articular new bone formation.	Ill-defined ossification near joint margins excluding osteophyte formation, on plain x-rays of hand or foot.	1

CASPAR = Classification Criteria for Psoriatic Arthritis

Exhibit 2: Psychosocial Aspects of PsA[5]
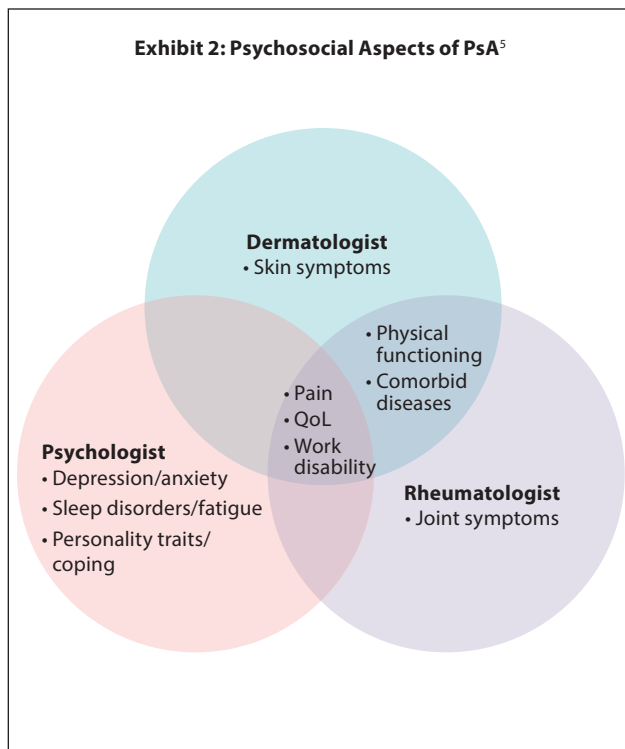
achieves an ACR50 in 28 percent and a PASI75 in 32 percent of patients better than placebo.[9] Enthesitis resolution was 18 percent better than placebo. Ixekizumab, another IL-17A inhibitor, produces an ACR50 in 30 percent and PASI75 in 41 percent.[10] Enthesitis resolution was 13 percent better than placebo. Guselkumab, an lL-23 inhibitor, produces an ACR20 response in about 40 percent of patients, ACR50 in 24 percent, and PASI75 in 70 percent.[11] A recent trial found that guselkumab is as effective in those who were previously treated with TNF inhibitor as those who are treatment naïve.[12]

Tofacitinib and baricitinib are oral JAK inhibitors FDA approved for PsA treatment. With tofacitinib, the ACR50 response occurs in about 17 percent, PASI75 in 18 percent, and enthesis resolution in 15 percent of patients.[13] Other JAK inhibitors are under study for PsA. Only ixekizumab (IXE) has been studied in a head-to-head trial against another biologic.[14] Ixekizumab was non-inferior to adalimumab for ACR50 response (IXE: 51%, ADA: 47%; treatment difference: 3.9%) and superior for PASI100 response (IXE: 60%, ADA: 47%; p = 0.001). Ixekizumab had greater response versus

Exhibit 3: Targeted Therapy in PsA			
Mechanism of Action	**Therapy**	**Also has PsO Indication**	**Indication for Axial Disease**
Approved Therapies			
CD80/86	Abatacept	No	None
PDE4	Apremilast	Yes	None
JAK 1/3	Tofacitinib	No	AS
	Upadacitinib	No	None
TNF-α	Etanercept	Yes	AS
	Infliximab	Yes	AS
	Adalimumab	Yes	AS
	Golimumab	No	AS
	Certolizumab	Yes	AS and nr-AxSpA
IL-12/23	Ustekinumab	Yes	None
IL-23	Guselkumab	Yes	None
IL-17A	Secukinumab	Yes	AS and nr-AxSpA
	Ixekizumab	Yes	AS and nr-AxSpA

Pso = psoriasis; CD = cluster of differentiation; PDE4 = phosphodiesterase; JAK = janus kinase; TNF = tumor necrosis factor;
IL = interleukin; AS = ankylosing spondylitis; nr-AxSPA = Non-Radiographic Axial Spondyloarthritis

adalimumab in additional PsA, skin, nail, treat-to-target, and quality-of-life outcomes. Serious adverse events were reported in 8.5 percent (ADA) and 3.5 percent (IXE) of patients.

There are three treatment guidelines used for PsA.[15-17] The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations (2015) are based on the disease presentation (i.e., affected domains).[15] Importantly, the JAK inhibitors were approved after this update and are not included. These guidelines recommended that the choice of therapy should address as many affected domains as possible. For patients with moderate to severe disease, an expedited therapeutic route is advocated by this group where the initial step of nonsteroidal anti-inflammatories is skipped, and therapy is started with an oral disease-modifying agent or a biologic.

The American College of Rheumatology/National Psoriasis Foundation (ACR/NPF) guidelines recommend using a treat-to-target strategy to make decisions based on individual patient factors including severity or activity of PsA, severity or activity of psoriasis, comorbidities, contraindications to medications, preferences of route or frequency of administration, concerns over therapies, and others.[16] For treatment-naïve patients with active PsA, the use of a TNF inhibitor biologic or oral small molecule (methotrexate, sulfasalazine, leflunomide, cyclosporine, and apremilast) is recommended over an IL-17 inhibitor, IL-12/23 inhibitor, or JAK inhibitor. The preference for oral small molecules is controversial given the higher efficacy of the biologic agents and JAK inhibitors. These guidelines recommend an IL-17 or IL-12/23 inhibitor as options instead of TNF inhibitors in patients with severe psoriasis or contraindications to TNF inhibitors, and they may be used instead of oral small molecules in patients with severe psoriasis or severe PsA.

The European League Against Rheumatism (EULAR) guidelines are the most recently updated. These guidelines also give preference to oral small molecules as an initial first step before moving to biologics or JAK inhibitors.[17] Many factors influence treatment selection in PsA including disease, patient, and treatment factors. Disease factors include number of tender and swollen joints, joints involved, disability, structural damage, psoriasis severity, and presence of axial disease. Patient factors include age, gender, impact on life, treatment history, likelihood of adherence, patient expectations, fear of adverse

Exhibit 4: Minimal Disease Activity (MDA) Definition[18]

The MDA criteria assess seven domains:

- Total joint count ≤ 1
- Swollen joint count ≤ 1
- Enthesitis count ≤ 1
- Skin (Psoriasis Area and Severity Index ≤ 1 or body surface area ≤ 3%)
- Function (Health Assessment Questionnaire) ≤ 0.5
- Patient's global visual analogue on a 100-mm scale ≤ 20
- Patient pain visual analogue on a 100-mm scale ≤ 15

If five of seven of the cutoffs for these domains are met, then the patient is deemed to have minimal disease activity

events, and comorbidities. Efficacy, tolerability, safety, onset of action, ease of use, administration route, and cost/insurance coverage are treatment factors which must be considered.

A treat-to-target approach should be used for managing PsA to optimize outcomes. Minimal disease activity (MDA) is the target of therapy while also balancing therapy-related risks (Exhibit 4).[18] Patients should be seen every three to six months for efficacy and safety assessment and for changing of therapy if MDA is not reached. Multidisciplinary management approaches can benefit patients with immune-mediated inflammatory diseases such as PsA. Rheumatologists and dermatologists partner to manage patients in the Psoriatic Arthritis/Psoriasis multicenter advancement network.[19] Other clinicians including ophthalmology, gastroenterology, psychology, nursing, pharmacy, and social work may also be needed. Utilizing multidisciplinary care can lead to improved outcomes.

Conclusion

Psoriatic arthritis affects up to 30 percent of those with psoriasis and it is important that it be diagnosed and treated early to prevent joint damage. Minimal disease activity is the target of treatment. Multidisciplinary care, especially with rheumatology and dermatology, is a way to improve outcomes.

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Recent Therapeutic Approaches for Migraine Management: The Latest Developments in Diagnosis and Prevention

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

Summary

The treatment of migraine has taken a significant leap forward since 2018 with seven new agents. The place in therapy of all these agents is still to be determined; however, for especially hard to treat patients, they can be life changing.

Key Points

• Migraine is common and is a significant cause of disability.

• Two new classes of migraine-specific medications are available for acute treatment, and two others are available for preventive treatment.

MIGRAINE IS IMPORTANT BECAUSE IT IS the second-leading cause of time spent disabled of all disorders.[1] Over one billion people worldwide are affected by migraine.[2] It affects one in five women, one in 16 men, and one in 11 children.[3,4] The majority of people initially seek help for migraine from primary care providers and migraine accounts for 10 percent of primary care visits annually in the United States (U.S.).[5-7]

Migraine has a wide spectrum of disease. There are individuals who have one or two attacks a year which are effectively treated with acute therapy, and there are those who have almost daily headaches. Even those who only have a migraine one or two days per month can be significantly impacted. They are losing one to two days of productivity and quality of life per month. Episodic migraine is fewer than 15 headaches per month, and chronic migraine is 15 or more.
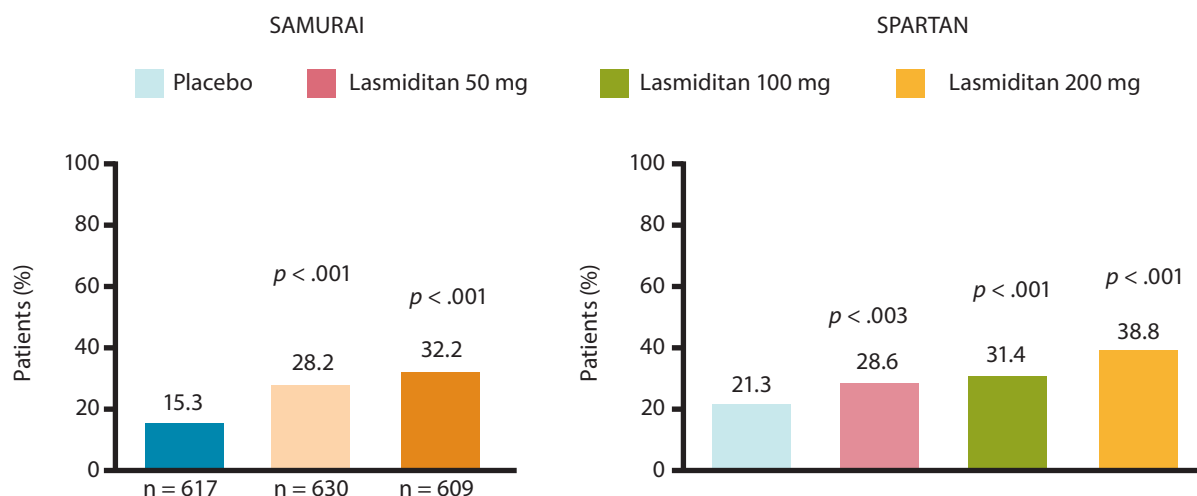
Migraine is not just a headache; it is a complex neurologic event with a constellation of symptoms which occur over four to 72 hours. Prodromal symptoms such as neck pain, fatigue, mood change, light sensitivity, sound sensitivity, and nausea can start hours before the headache begins. Functional brain imaging shows that different regions of the brain are activated in each phase of a migraine attack. Several concepts about migraine have changed recently because of better brain imaging. Migraine is primarily a disorder of brain excitability instead of vasodilation. Vasodilation may occur as part of the disorder, but it is not the cause of migraine pain. It is now known that migraine therapies do not work by constricting blood vessels.

The approach to managing a patient with migraine starts with giving the patient a diagnosis and reassuring them that they do not have a secondary headache from a brain tumor or an aneurysm. It is important to educate them regarding the features of migraine and the principles of treatment and how to identify and change exacerbating environmental factors and medications. There should be an established regimen for acute therapy of headache. Some patients may need preventive therapy because of the frequency of headaches or the disability related to them. Some simple environmental changes can help patients with migraine manage. Consistency is important. Patients should regularly eat meals, sleep, and exercise aerobically. If having caffeine, they should have small amounts on a regular basis. They especially need to be consistent during stressful periods.

Primary endpoint: proportion of patients free from pain
at two hours post-dose

SAMURAI   SPARTAN

☐ Placebo   ■ Lasmiditan 50 mg   ■ Lasmiditan 100 mg   ■ Lasmiditan 200 mg

SAMURAI data:
- Placebo: 15.3 (n = 617)
- Lasmiditan 100 mg: 28.2, $p < .001$ (n = 630)
- Lasmiditan 200 mg: 32.2, $p < .001$ (n = 609)

SPARTAN data:
- Placebo: 21.3
- Lasmiditan 50 mg: 28.6, $p < .003$
- Lasmiditan 100 mg: 31.4, $p < .001$
- Lasmiditan 200 mg: 38.8, $p < .001$

Patients (%) axis: 0–100

Patients need a regimen for acute therapy of headache. Whatever acute therapy is used, it is important that the patient treat the episode as early as possible. This requires patients to identify their own pattern of headache and prodromal symptoms. Combination therapy is acceptable, but caffeine-containing analgesics are problematic for causing medication overuse headaches. Triptans are safe and effective for acute treatment and have been the standard first-line agents. These agents are actually non-prescription in Europe. Triptans may work better in combination with a nonsteroidal anti-inflammatory in many patients. Some limitations with triptans are incomplete and inconsistent pain relief, high rates of headache recurrence, and cardiovascular disease contraindication. Antiemetics may also be necessary if nausea and vomiting are an issue. Once an acute treatment is instituted, it is important to assess efficacy to see if it is working and to see if preventive therapy is required.

Several new migraine-specific therapies for both acute and preventive use have recently been FDA approved. These include a selective serotonin 1F (5-HT$_{1F}$) receptor agonist (lasmiditan), small molecule oral calcitonin gene-related peptide (CGRP) antagonists, and monoclonal antibodies against CGRP. Lasmiditan (Reyvow®) is the first FDA-approved ditan (a high-affinity 5-HT$_{1F}$ receptor agonist). It is similar to a triptan but without vascular effects, as this class does not interact with 5-HT 1B or 1D receptors. The 5-HT$_{1F}$ receptors, involved in modulating pain signaling, are present on both the peripheral and central pain pathways.[8,9] Based on the location of 5-HT1F receptors, lasmiditan is thought to act both centrally and peripherally. In two Phase III trials, it increased the percentage of patients free of pain at two hours after dosing compared to a placebo (Exhibit 1).[10,11] The most common adverse events with this agent are dizziness, fatigue, paresthesia, and sedation.

CGRP became a target for drug development because it is released during a migraine attack. CGRP levels are elevated in those with chronic migraine, and administration can trigger a migraine.[12-15] It is a peptide produced in neural cells throughout the body that is involved in pain transmission, gut motility, vasodilation, inflammation, and regeneration of motor neurons. The impact on gut motility leads to some of the adverse events seen with these agents. The small molecule oral CGRP antagonists (gepants) that have been FDA approved are ubrogepant (Ubrelvy®) and rimegepant (Nurtec®). Both are currently indicated for acute migraine treatment and rimegepant has a preventive indication. In the approval trials, about 20 percent of patients were pain free at two hours after dosing.[16] The recommended dosage of ubrogepant is 50 or 100 mg as needed, and a second dose can be used at least two hours after the first. Rimegepant for acute

Exhibit 2: Monoclonal Antibodies Targeting CGRP

	Eren**umab** Aimovig®	Galcane**zumab** Emgality®	Fremane**zumab** Ajovy®	Eptine**zumab** Vyepti®
Studied for	EM, CM	EM, CM, eCH, cCH	EM, CM, eCH, cCH	EM, CM
Dosing	Monthly SC Autoinjector	Monthly SC Autoinjector	Monthly or Q3 month SC Syringe; IV load for CH	Q3 month IV
Half-life	21 days	~ 25 to 30 days	32 days	~ 32 days
	Fully human	Humanized	Fully Humanized	Humanized
Target	**CGRP receptor**	**CGRP peptide**	**CGRP peptide**	**CGRP peptide**

umab = fully human; zumab = humanized; Humanized = 90% human; Fully Humanized = 95% human.
EM = episodic migraine; CM = chronic migraine; eCH = episodic cluster headache; cCH = chronic cluster headache.

Exhibit 3: Considerations for Starting a Preventative Medication for Migraine[27]

- Attacks significantly interfere with patient's daily routines despite acute treatment.
- Four (4) or more monthly headache days.
- Contraindication to, failure, or overuse of acute treatments, with overuse defined as 10 or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused.
- Fifteen (15) or more days per month for nonopioid analgesics, acetaminophen, and nonsteroidal anti-inflammatory drugs.
- Adverse events with acute treatments.
- Patient preference

treatment of migraine is given as 75 mg once daily as needed. The package labeling suggests a 30-day maximum limit for prescriptions of 18 doses. As a preventive, it is given as 75 mg every other day with a recommended 30-day max quantity of 18 doses. Rimegepant can be used for acute treatment on off days and a non-CGRP acute treatment can be used on days when it is taken. Unlike triptans, there are no vascular contraindications and these agents may be better tolerated than triptans. Nausea is a more common adverse event than with triptans. These agents have a longer half-life than most triptans (except frovatriptan) which may confer a longer duration of event with reduced recurrence. They also appear effective in some for whom triptans fail.

Injectable CGRP antagonists which bind to the CGRP receptor or CGRP peptide have also come to market as migraine preventives (Exhibit 2). These are given by self-injection or by intravenous infusion (depends on agent). In three-month-long studies, these agents reduced monthly headache days in episodic and chronic migraine by a median of approximately two days per month compared to placebo.[17-22] For a subset of patients, the response is dramatic. The reduction in headache days with the CGRP antagonists is similar to other preventive therapies on the surface. These agents are effective within one month, unlike with traditional preventive therapies which can take up to six months to see benefit. Additionally, the patient's migraine attacks continue to reduce over six months of treatment. In general, real-world experience is showing that efficacy exceeds that observed in clinical trials with reduced headache days, reduced acute medication use, and improved quality of life. They are effective in patients with medication overuse headaches and in those who have failed multiple preventives.

In Phase II/III trials of the CGRP antagonists,

Exhibit 4: Indications for Initiating CGRP-Targeted Preventive Therapies[27]

❑ Patient is at least 18 years of age

❑ Inability to tolerate or inadequate response to a six-week trial of at least two of the following:

- Topiramate
- Divalproex sodium/valproate sodium
- Beta-blocker (metoprolol, propranolol, timolol, atenolol, nadolol)
- Tricyclic antidepressant (amitriptyline, nortriptyline)
- Serotonin-norepinephrine reuptake inhibitor (venlafaxine, duloxetine)
- Other Level A or B treatments (established efficacy or probably effective) according to the American Academy of Neurology-American Headache Society guidelines

❑ In Chronic Migraine Patients

- Inability to tolerate or inadequate response to a minimum of two quarterly injections (6 months) of onabotulinumtoxinA

❑ International Classification of Headache Disorder-3 diagnosis of one of the following

- Migraine with or without aura with 4 to 7 monthly headache days and at least moderate disability (MIDAS > 11, HIT-6 > 50)
- Migraine with or without aura with 8 to 14 monthly headache days

MIDAS = Migraine Disability Assessment; HIT = Headache Impact Test

the discontinuation rate due to adverse events was 0 percent to 3.7 percent compared with 8 percent to 27 percent for placebo. This discontinuation for CGRP antagonists is much lower than occurs with the traditional oral preventive drugs which are not migraine specific. The tolerability of the CGRP antagonists is good. Injection-site reactions, constipation, and sensitivity reactions like urticaria are the most common adverse events. Potentially serious adverse events include severe constipation and hypertension with erenumab. Overall, safety has been excellent, with no safety signals and no plan for requiring blood monitoring or other monitoring. Long-term open-label studies indicate sustained efficacy and excellent tolerability.[23-26] The dropout rates from the long-term studies are very low as was shown in the Phase II/III trials.

The cost of these agents has been an issue. The approximate cost for monoclonal antibodies is $600 to $1,200 per month. Insurance coverage varies, but failure of at least two classes of traditional preventive therapies is typically required for coverage to be considered. Potential benefits of this very effective class are reduced disability, improved quality of life, reduced acute medication use, reduced healthcare utilization including urgent care, and reduced comorbidity (e.g., depression).

Exhibit 3 provides considerations for starting a preventative medication.[27] In addition to the injectable CGRP antagonists, other preventives include beta blockers, anti-epileptics (topiramate, divalproex), antidepressants (amitriptyline, nortriptyline, venlafaxine), rimegepant, and botulinum toxin. Exhibit 4 shows the American Headache Society Consensus indications specifically for initiating a CGRP-targeted preventive therapy.[27] The criteria for using the CGRP antagonists is likely to evolve to use earlier rather than requiring failure of two traditional non-migraine-specific agents because of their efficacy compared to traditional agents which do not have FDA approval for migraine prevention.

Some open questions are how to prioritize acute and preventive migraine treatments based upon efficacy, tolerability, safety, and cost. There are no direct comparison trials for any of the new agents against any older agents. In comparing the gepants and the monoclonal antibodies for prevention, the monoclonal antibodies have a higher target specificity and may be more effective (2 days reduction in headache days compared to 1, but there are no comparative trials), and they have a much longer half-life. Development of predictors of therapeutic response to the various agents for both acute and preventive use could help guide the decision process.

Conclusion

A better understanding of the specific biology of migraine has led to the development of multiple new migraine-specific acute and preventive therapies. Important questions remain regarding the place of new migraine therapies relative to previously available therapies in the management of this extraordinarily common and disabling disease.

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Best Practices in the Treatment and Management of Ovarian Cancer: An In-Depth Look at the Evolving Role of PARP Inhibitors

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

Summary

The management of ovarian cancer is an evolving landscape. Maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors is being used in many patients after initial platinum-based chemotherapy to significantly extend progression-free and overall survival. Various combination therapies are likely to be the next evolution in therapy.

Key Points

• PARP inhibitors are now being used much earlier in this disease as maintenance than previously.

• Combination therapy of PARP inhibitors with chemotherapy, immunotherapy, or other targeted therapies may be the next evolution.

• PARP inhibitors have not yet been shown to be cost effective at current pricing.

THE PROCESS OF DNA REPLICATION during cell division is prone to error and can result in mutations and single- and double-strand breaks in the DNA.[1] DNA is also subject to assault from the environment, and any resulting damage, if not repaired, will lead to mutation and possibly disease. Repair of these errors is a multistep process to maintain genomic stability. Many mechanisms are involved in DNA repair, including base excision repair, mismatch repair, nucleotide excision repair, single-strand annealing, homologous recombination (HR), and nonhomologous end joining.[2]

Poly (ADP-ribose) polymerase (PARP) and breast cancer gene protein (BRCA) are both involved in DNA repair.[3] BRCA is involved in repairing breaks in double-strand DNA though HR and PARP is involved in base-excision repair. Cells with BRCA mutations have homologous recombination deficiency (HRD) but can repair DNA through base-excision repair (non-homologous repair), but use of this pathway alone results in genomic instability and increases the risk of developing breast, ovarian, prostate, and pancreatic cancer. Blocking PARP

with PARP inhibitors causes synthetic lethality in cells with deficient HRD due to BRCA mutations or other DNA repair pathway mutations. All women diagnosed with ovarian cancer should have testing for germline BRCA1/2 and other ovarian cancer susceptibility genes.[4] DNA repair deficiency, which includes HRD, is present in approximately 50 percent of epithelial ovarian cancer, which is the most common histologic type, due to genetic and epigenetic alterations of the HR pathway gene (Exhibit 1).[5]

PARP inhibitors were first reported to specifically kill BRCA1/2-deficient cancer cells in 2005.[6] A Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced ovarian cancer was one of the first to show benefit in this cancer.[7] This trial showed a 33 percent response rate in heavily pretreated patients, which was a previously unheard-of response. Olaparib was first approved by the FDA in 2014 for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines

Exhibit 1: DNA-Repair Deficiency (DRD) Present in ~ 50% of Epithelial Ovarian Cancer[5]
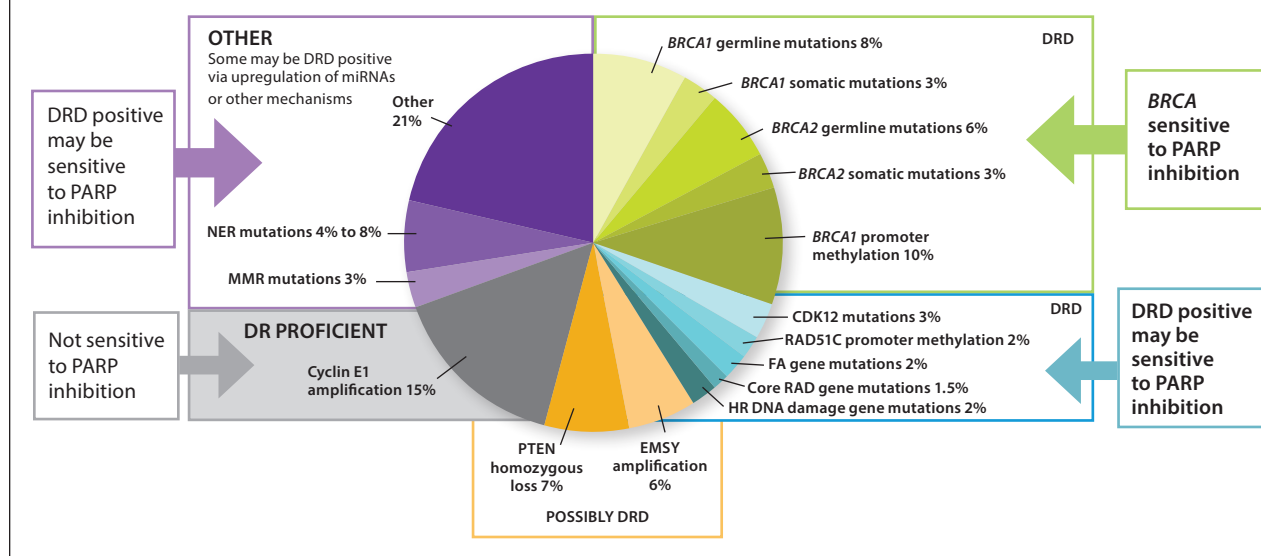
CDK12 = cyclin dependent kinase 12
EMSY = BRCA2-interacting transcriptional repressor
FA = Fanconi anemia
MMR = mismatch repair
miRNA = micro messenger ribonucleic acid
NER = nucleotide excision repair
PTEN = phosphatase and tensin homolog

of chemotherapy. Niraparib and rucaparib were subsequently FDA approved for this same indication (two lines of prior therapy in the case of rucaparib).

The five-year survival for newly diagnosed advanced ovarian cancer is 30 to 50 percent, and patients are at high-risk of relapse after primary therapy with platinum-based chemotherapy.[8,9] Treatment goals in this setting include delay of recurrence and, for some patients, increased chance of cure which is why maintenance therapy has been studied. Trials with PARP inhibitors began showing that maintenance therapy was important after response to platinum-based chemotherapy to delay recurrence and ultimately to improve survival.[10-13] For example, in the SOLO-1 trial which gave olaparib and placebo as maintenance for two years after a complete or partial to platinum-based chemotherapy in those with BRCA mutation, the median progression-free survival (PFS) at five years was 56 months compared to 13.8 months with placebo.[14] In the SOLO2 trial, median overall survival (OS) improved by 12.9 months with maintenance olaparib over placebo, despite 38 percent of placebo patients receiving subsequent PARP inhibitor therapy.[15] Importantly, median OS improved by 16.3 months with maintenance olaparib over placebo, after adjusting for subsequent PARP inhibitor therapy in

placebo patients. Trials with niraparib and rucaparib in post-platinum maintenance showed benefit if the patient had BRCA mutation, other HRD mutations, or even no BRCA mutation.[12,13] Maintenance after both primary and recurrent disease treatment has become the standard of care for those with BRCA and other HRD mutations.

In general, PARP inhibitors are well tolerated by patients. Exhibit 2 compares the three that are FDA approved for ovarian cancer treatment.[11-13] Niraparib causes more hematologic toxicity while olaparib and rucaparib cause more diarrhea. Rucaparib also caused elevated liver function tests which has not been reported with the other agents and caused a higher discontinuation rate in the Phase III clinical trials. Niraparib has the fewest drug interactions and is given once daily as compared to twice daily for the other two. PARP inhibitors do increase the risk of developing secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).[16]

An outline of the current treatment paradigm for Stage II/IV advanced ovarian cancer and BRCA-mutated ovarian cancer are shown in Exhibit 3. Platinum-sensitive disease is defined by tumor histology and genetic signature, treatment-free interval (how long until patient progresses after the end of platinum-based chemotherapy), and the

Exhibit 2: PARP Inhibitor Toxicity Data[11-13]			
	Olaparib	**Niraparib**	**Rucaparib**
Study	SOLO2	NOVA	ARIEL3
Dose	400 mg BID	300 mg QD	600 mg BID
Anemia Grade 3 - 4	20%	25%	19%
Neutropenia Grade 3 - 4	5%	20%	7%
Thrombocytopenia Grade 3 - 4	0%	34%	5%
Fatigue Grade 3 - 4	4%	8%	7%
Nausea Grade 3 - 4	3%	11%	4%
Diarrhea all grades	33%	19%	36%
Insomnia all grades	7%	24%	14%
Hypertension Grade 3 - 4	2%	8%	2%
Transaminitis Grade 3 - 4	–	–	11%
Discontinuation	11% versus 2%	15% versus 2%	21% versus 3%
MDS/AML	2% versus 4%	1.3% versus 1.2%	1% versus 0%
Drug Interactions	-CYP3A4 + 2B6	CYP1A2 (week)	-CYP,2C19,2C9,3A4 + 1A2

MDS = myelodysplastic syndrome; AML = acute myeloid leukemia

number of prior lines of therapy. For BRCA-mutated ovarian cancer, there are many more lines of therapy.

The National Comprehensive Cancer Network (NCCN) guidelines recommend olaparib, olaparib plus bevacizumab, niraparib, or bevacizumab for most patients with epithelial ovarian cancer as maintenance therapy after primary chemotherapy for Stage II to Stage IV disease when there was a complete or partial response.[17] Which agent as an option depends on response to primary treatment, whether bevacizumab was used during primary treatment, and presence of BRCA1/2 or other HRD mutations. The PARP inhibitors are also options for maintenance after second-line chemotherapy and as single-agent treatment for recurrence with platinum-resistant disease.

Resistance to PARP inhibitors can also develop, and there is some concern about cross resistance with platinum-based chemotherapy. PARP inhibitor resistance develops through multiple mechanisms. Broadly speaking, BRCA1/2-deficient tumor cells can become resistant to PARP inhibitors by restoring HR repair and/or by stabilizing their replication forks.[18] There is some evidence that the underlying mechanism of PARP inhibitor resistance that emerges could influence the success of subsequent therapies.[19] Research on strategies to overcome these various forms of acquired resistance is ongoing.

Several cost-effectiveness analyses have been done using PARP inhibitor trial data, but most have found them not to be cost effective at current prices. A cost-effectiveness analysis published in 2020 found that the PARP inhibitors are not cost effective for treatment of platinum-resistant, recurrent ovarian carcinoma.[20] This analysis found that non platinum-based intravenous chemotherapy was most cost effective ($6,412 per PFS-month) compared with bevacizumab-containing regimens ($12,187 per PFS-month), niraparib ($18,970 per PFS-month), olaparib ($16,327 per PFS-month), and rucaparib ($16,637 per PFS-month). Incremental cost-effectiveness ratios (ICERs) for PARP inhibitors were 3 to 3½ times greater than intravenous non-platinum-based regimens when considering costs of infusion and managing toxicities of intravenous regimens typically associated with lower response and shorter median PFS.

Another recent analysis examined PARP

Exhibit 3: Advanced Ovarian Cancer
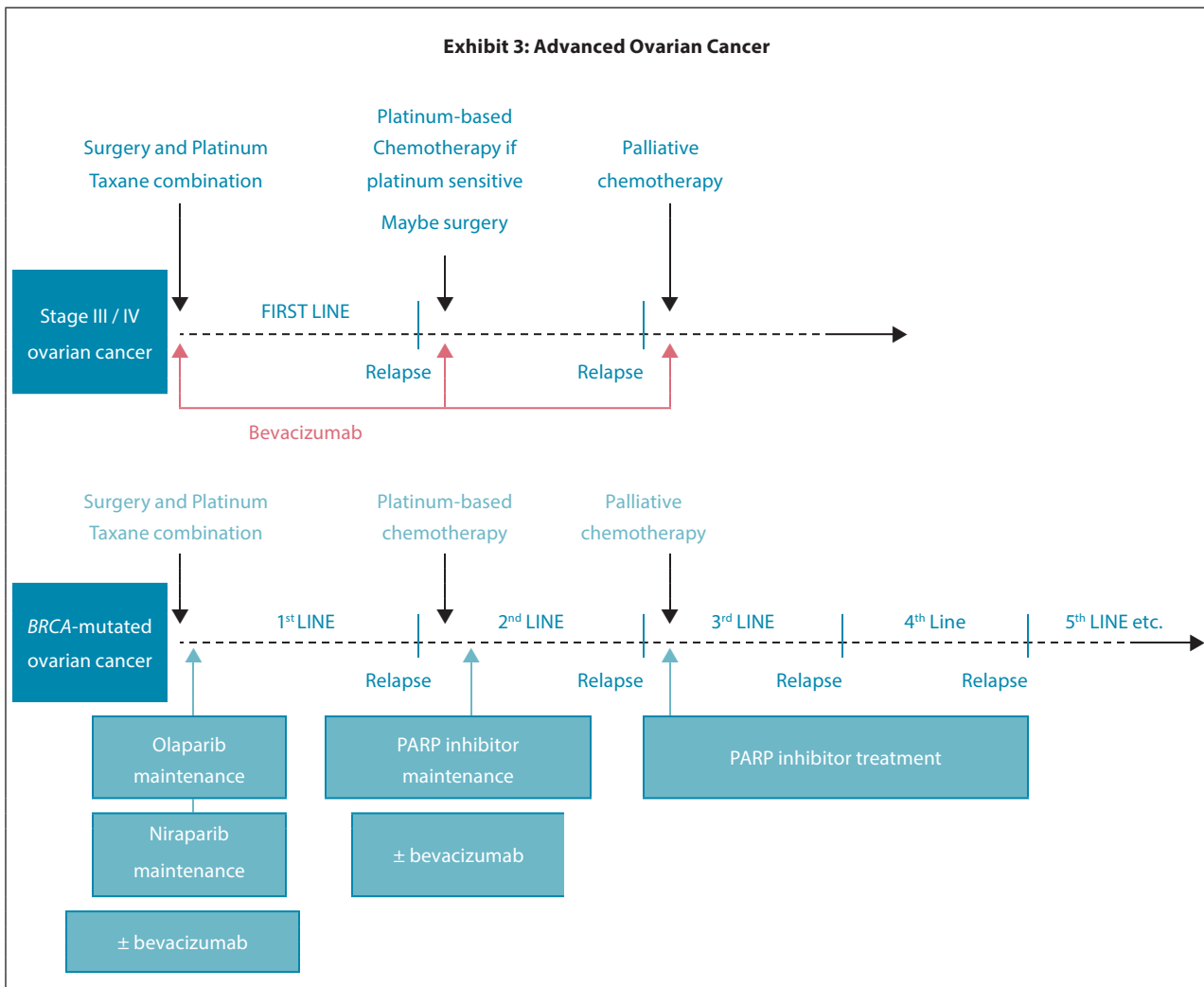
inhibitor maintenance therapy in the first-line setting for all patients (PARPi-for-all).[21] The mean cost per patient for the PARPi-for-all strategy was $166,269, $286,715, and $366,506 using data from the PRIMA (niraparib), VELIA (veliparib), and PAOLA-1 (olaparib/bevacizumab) trial, respectively. For a biomarker-directed strategy (only used for those HRD positive), the mean cost per patient was $98,188, $167,334, and $260,671, respectively. ICERs of PARPi-for-all compared to biomarker-directed maintenance were, $593,250 per quality-adjusted progression-free life year (QA-PFY), $1,512,495 per QA-PFY, and $3,347,915 per QA-PFY, respectively. At current drug pricing, there is no PFS improvement in a biomarker negative cohort that would make PARPi-for-all cost-effective compared to biomarker-directed maintenance. The authors concluded that maintenance therapy in the front-line setting should be reserved for those with germline or somatic HRD mutations until the cost of therapy is significantly reduced. Balancing modest clinical benefit with costs of novel therapies remains problematic and could widen disparities among those with limited access to care.

A patient preference study on maintenance PARP inhibitor therapy found that women with ovarian cancer are most motivated to take maintenance by gains in OS.[22] Participants valued OS and monthly costs, followed by risk of death from MDS/AML, nausea, PFS, and fatigue. Participants would accept a 5 percent risk of MDS/AML if treatment provided 2.2 months additional OS or 4.8 months PFS. Participants would require gains of 2.6 months PFS to accept mild treatment-related fatigue and 4.4 months to accept mild nausea.

The use of PARP inhibitors in ovarian cancer treatment will continue to expand. PARP inhibitors are currently being studied as first-line treatment in combination with platinum-based chemotherapy, checkpoint immunotherapy, and anti-angiogenic agents (bevacizumab). Trials are also ongoing with different maintenance regimens and in platinum-

resistant and sensitive populations. There are numerous other tumor and immune system targets which are also being studied for which targeted therapy is being developed.

Conclusion

The management of ovarian cancer is an evolving landscape. PARP inhibitors are now being used much earlier in disease as maintenance. Combination therapy with PARP inhibitors for first-line treatment may be the next evolution in treatment. PARP inhibitors are far from cost effective, but biomarker informed use may be the most cost-effective option.

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