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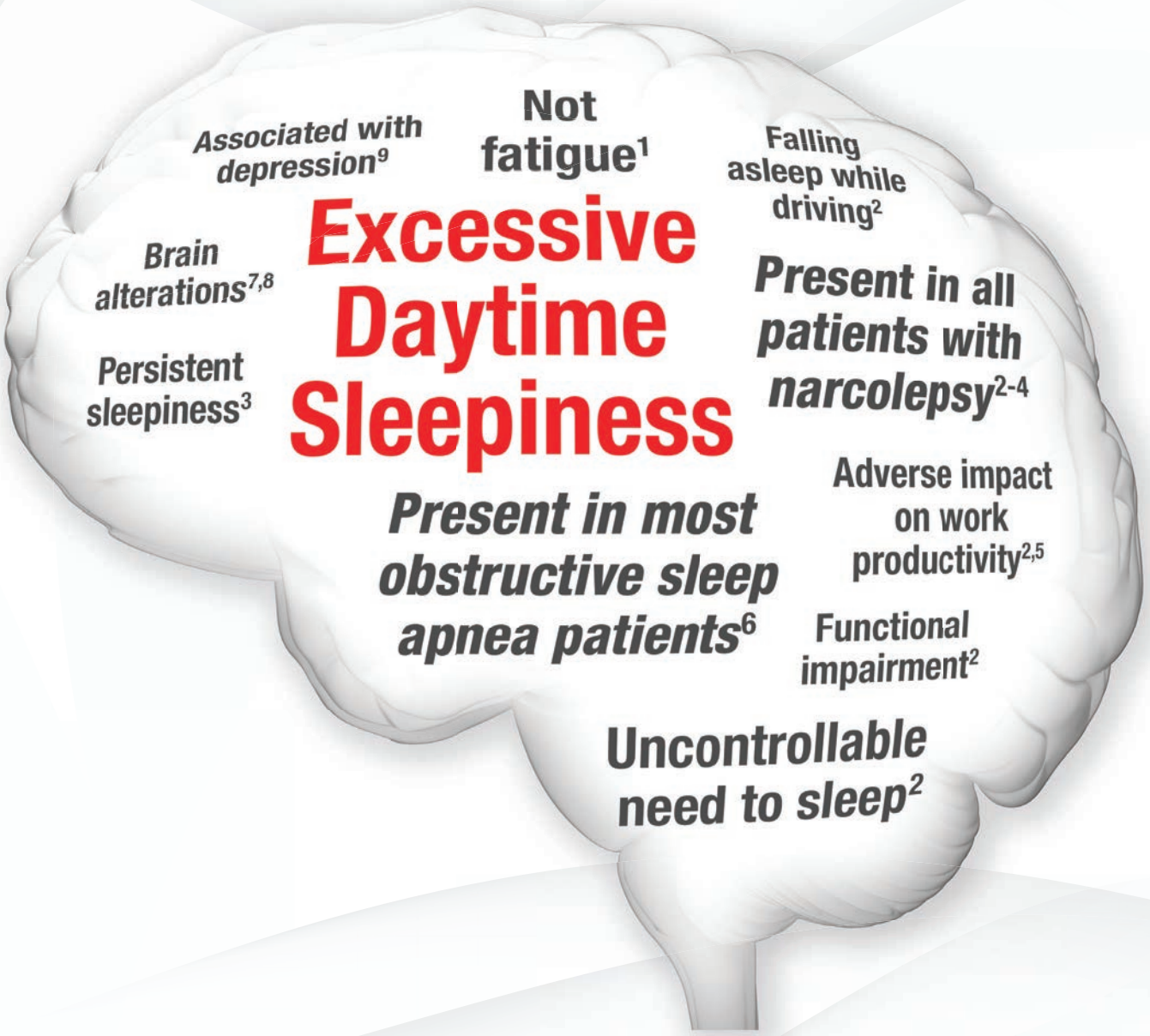

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Editorial Review Board

Personalized Treatment Strategies for IBD: Improving Patient Care and Outcomes

Joseph D. Feuerstein, 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

Personalizing treatment in inflammatory bowel disease (IBD) requires selecting a medication which is effective in the particular form of disease the patient has. If the initial therapy fails, it is important for clinicians to recognize why the therapy was ineffective and to determine what steps to take next. Therapeutic drug monitoring and patient engagement can both be utilized to optimize outcomes.

Key Points

- Ulcerative colitis and Crohn's disease are different diseases.
- Disease management for each has some similarities; however, not all medications are effective in both diseases.
- Therapeutic drug monitoring may be helpful in certain situations to optimize drug therapy.
- Patient engagement is critical to providing optimal patient care.
- Many agents with new mechanisms of action and oral administration are coming in the future.

INFLAMMATORY BOWEL DISEASE (IBD) IS A chronic inflammatory condition divided into three categories - ulcerative colitis, Crohn's disease, and indeterminate colitis. To develop IBD, it is thought that individuals have to have certain genetics and an initiating event, such as a change in the gut microbiome from infection, food exposure, or travel. IBD is a global disease with increasing incidence in newly industrialized countries that are becoming more westernized. It is estimated that 3.1 million adults in the United States (U.S.) adults have IBD (1.3% of the population).[1]

Ulcerative colitis (UC) was first described by Samuel Wilks in the 1800s. It is continuous colonic mucosal inflammation extending proximally from the rectum. The natural history includes periods of remission and flares. In theory, there is a bimodal onset age of 15 to 40 years and 50 to 80 years, but it can really occur at any age.[2] Traditionally, UC was thought of as a disease of selected ethnic groups, but it can occur in any race. The prevalence of UC is rising, especially among Hispanics and non-Hispanic whites. Symptoms of UC include bloody diarrhea, urgency, tenesmus, and abdominal pain. It is rare to have weight loss or fevers with UC. Because UC is primarily limited to the colon, only 25 percent of individuals with UC will have extraintestinal manifestations (peripheral arthropathy, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis, uveitis, scleritis, and optic neuritis). About 10 percent of patients initially present with severe UC, and 15 percent will require hospitalization for the disease.

Diagnosis of UC is based on typical symptoms and evidence on colonoscopy. On colonoscopy, continuous inflammation starting in the rectum and

progressing continuously is seen. Erythema, granularity, friability, erosions, and/or ulcers can be seen visually. Chronic changes can be seen in pathology specimens obtained during the colonoscopy; however, pathology is confirmatory rather than diagnostic. Serologic testing can be done, but the currently available tests lack adequate positive or negative predictive value.

Management of UC includes pharmacologic and surgical options. Medications include corticosteroids, five acetylsalicylic acid derivatives (e.g., mesalamine), thiopurines (e.g., azathioprine/mercaptopurine), anti–tumor necrosis factor (TNF) biologics (e.g., infliximab/adalimumab/golimumab), anti-integrin biologic (e.g., vedolizumab), and Janus kinase inhibitor (e.g., tofacitinib). Surgical options include colon removal with an ileal pouch-anal anastomosis or a total abdominal proctocolectomy with permanent ileostomy.

Crohn's disease (CD) was first described by Dr. Burrill B. Crohn in 1932. It is characterized by inflammation that can involve any aspect of the gut from the mouth to the anus. Classically, the disease has skip lesions (diseased areas separated by intervening normal mucosa). Like UC, CD has periods of remission and flares. The peak age of onset of CD is bimodal (20 to 30 and 50 years). The most common areas of involvement are the colon and small bowel in 50 percent of cases, only small bowel involvement in 30 percent of cases, and only colonic involvement in 20 percent of cases.[3] Overall, about 25 percent of patients also have perianal involvement. Perianal disease can include abscesses, fistulas, fissures, and skin tags. There are multiple different disease phenotypes – inflammatory, stricturing, penetrating, and combined stricturing and penetrating. Stricturing is the development of fibrous scar tissue and narrowing of the bowel lumen. Stricturing is not reversible with medication treatment and may require surgical treatment; medications are used to prevent further inflammation and additional strictures. Penetrating disease is when the disease penetrates through the bowel wall and develops inappropriate connections with another part of the body (fistulas). Penetrating disease is difficult to treat and can require extensive surgery. The subtype of CD is used by many prior authorization protocols for approving some medications.

The symptoms of CD are variable based on the subtype and the location of the disease. Because of the variability in symptoms, it can take longer to seek care for and receive a diagnosis of CD than it does for UC. Inflammation causes abdominal pain, diarrhea, weight loss, and fatigue. Significant unintended weight loss is the most typical presentation of inflammatory CD. Strictures can cause lack of bowel movements, lack of flatus, abdominal pain, nausea, and vomiting. Penetrating disease leads to abscesses, fever, and fistulas to other organs. Like with UC, the extraintestinal manifestations of IBD occur in up to 25 percent of patients.

CD diagnosis is based on typical symptoms with evidence on colonoscopy or radiology. A CT scan or a MRI can show small bowel CD. Capsule endoscopy and small bowel follow through are also sometimes needed to make the diagnosis. On pathology exam, the presence of granulomas is seen in only 25 percent of cases, and this is not required to diagnose CD. Like UC, the currently available serologic tests for CD lack adequate positive or negative predictive value.

Treatment of CD is more complicated than that of UC. Without adequate treatment, 80 percent of patients will eventually require surgery after 20 years of disease activity. Thus early aggressive therapy is important to prevent complications of strictures, penetration, and abscess. Pharmacologic management includes many of the same agents as UC. Agents only used in CD include methotrexate and interleukin (IL) 12/23 inhibitors (e.g., ustekinumab). Surgical interventions for CD include localized resection, total proctocolectomy with permanent ileostomy, diverting ileostomy, seton placements, stricturoplasty, and fistulotomy. Exhibit 1 compares UC and CD.

The classic approach to IBD had been to use step therapy, starting with the oldest, cheapest or safest medications and working toward the more expensive or less well tolerated agents. The current treatment paradigm is to treat the disease based on severity rather than wasting time using an agent that only works for mild disease in a severe case (Exhibit 2).[2-4] Treatment usually begins with induction to aggressively reduce inflammation and symptoms (remission) and then progresses to maintenance therapy, which is required long term.

Mesalamine is most appropriate for mild to moderate UC. It is frequently used in mild CD but evidence to support this is very poor, it is not recommended by the guidelines, and it is not FDA approved for CD. It is the most commonly used agent for IBD and works for induction and remission maintenance of UC. Advantages of mesalamine are that various dosage forms (oral, rectal) are available, it can be dosed once daily, it is extremely safe, and there is no risk of antibodies against the medication. The major disadvantage is that mesalamine is only efficacious for mild to moderate UC.

Corticosteroids are used for induction of remission for both UC and CD and have no role in mainte-

Exhibit 1: Ulcerative Colitis vs Crohn's Disease[2,3]

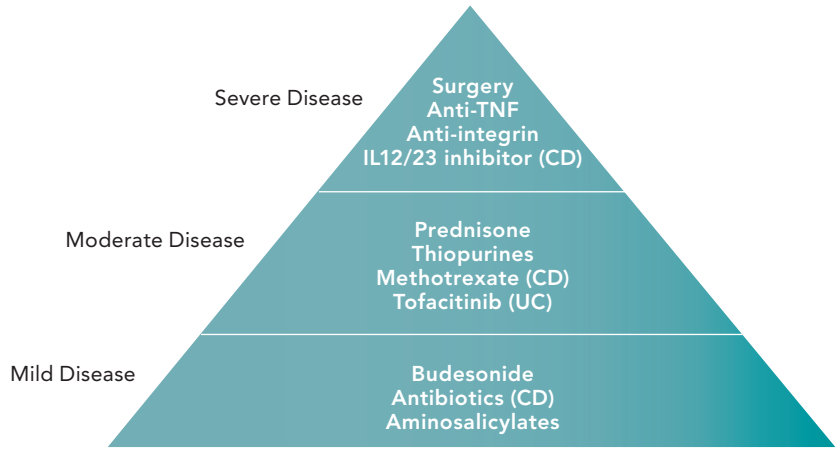
Ulcerative Colitis

- Continuous inflammation starting in the rectum and can involve any portion of the colon
- Inflammation is limited to the luminal surface
- Medical management with immunosuppressants or biologics is common
- Surgical removal of the colon and rectum cures the disease

Crohn's Disease

- Can involve any part of the GI tract from mouth to anus
- Most commonly involves the ileum, ileo-colonic, or colonic
- ~25% of individuals develop perianal disease (e.g., fistula, abscess, fissures)
- Inflammation is transmural
- Multiple different types of disease inflammation (inflammatory, stricturing, penetrating)
- Medical management with immunosuppressants or biologics is common
- Surgery temporarily treats the disease but the disease recurs in most cases

Exhibit 2: New Paradigm – Treat Disease Based on Severity of Disease[2-4]



nance. Corticosteroids are the most efficacious class for induction of remission, have fast onset of action, and come in many dosage forms. Oral budesonide and rectal preparations of any corticosteroid are not associated with typical systemic adverse effects, but they are less efficacious than oral prednisone or intravenous agents. The disadvantage of corticosteroids is the many adverse effects (weight gain, hypertension, cataracts, glaucoma, diabetes, osteoporosis, skin changes, irritability, insomnia etc.).

Thiopurines (azathioprine and mercaptopurine) used to be a staple for maintenance of remission in UC and CD, but more and more studies are questioning their efficacy. Patients must be tested for thiopurine S-methyltransferase (TPMT) deficiency before starting a thiopurine. TPMT metabolizes this class of agents and hematopoietic toxicity is more likely to occur in those with deficient TPMT. Ongoing lab monitoring of blood counts and liver function is also required. Advantages of the thiopurine class are oral administration, no antibody development, and they can be combined with anti-TNF. Disadvantages are delayed onset of effect (up to three months) and numerous adverse effects (nausea,

vomiting, abdominal pain, pancreatitis, bone marrow suppression, infection, hepatitis, lymphoma, non-melanoma skin cancer, and cervical dysplasia).

Methotrexate is commonly used to induce and maintain remission in CD. It has no role in UC. Methotrexate was previously used more often, but it is now primarily being used in combination with anti-TNF therapy or when nothing else is working. Ongoing lab monitoring of blood counts and liver function tests is required. Advantages of methotrexate in treating CD are that it is available orally, no antibody development, and it can be combined with anti-TNF. Disadvantages are the long onset of efficacy, teratogenicity (Category X), and multiple adverse effects (nausea, vomiting, abdominal pain, bone marrow suppression, infection, hepatitis, and lymphoma). Overall, efficacy of methotrexate appears inferior to anti-TNF drugs.

Anti-TNF (Infliximab, Adalimumab, Golimumab, and Certolizumab-Pegol) biologics are used in UC and CD for induction and maintenance of remission. Infliximab is given by infusion, whereas the others are self-injected. For a patient with severe disease, infliximab would be the preferred agent because of the ability to easily escalate doses; this may be in conflict with managed care policies of using another anti-TNF agent first line. Infliximab is the only one with an FDA approved indication for penetrating CD. TB and hepatitis B testing are both required prior to starting an anti-TNF agent and ongoing monitoring of blood counts and liver function tests is required. This is the most efficacious class for IBD, and they have a rapid onset of action. Additionally, infliximab can be used for rescue therapy in those failing steroids. Disadvantages include multiple adverse effects (infusion/injection site reactions, infection, skin cancer, possible lymphoma risk, reactivation of TB or hepatitis B, drug-induced lupus) and risk of developing antibodies and loss of efficacy. The listing of adverse effects on the Internet related to anti-TNF therapy can prompt some anxiety in patients. These agents are not more dangerous than the thiopurines, but they are more effective.

Vedolizumab (Entyvio®), an anti-integrin, is used for induction and maintenance of remission in both UC and CD. This agent has changed the approach for many IBD clinicians because it is specific to the gut mucosa. It prevents further neutrophil aggregation into the already inflamed gut. Given by infusion, this agent requires ongoing lab monitoring, including complete blood counts (CBC). This agent is efficacious, especially in the setting of moderate disease activity, and has the fewest systemic side effects of any of the biologics (infection, infusion reactions, and joint pains) because of gut selectivity. There is a risk of developing antibodies and subsequent loss of efficacy, and this is not the fastest acting drug. Because this is a newer agent, most managed care plans require step therapy before using this agent; however, using this agent as a second-line therapy may be too late in the disease process to show efficacy.

Anti-IL 12/23 (ustekinumab, [Stelara®]) is approved for CD induction and maintenance. This agent is initially given as an infusion followed by self-injection every eight weeks. TB testing is required prior to starting and blood count and liver function tests should be monitored ongoing. This is a very efficacious agent on par with anti-TNF biologics and has a rapid onset of action. It does cause some adverse effects, including infusion/injection site reactions, infection, and possible reactivation of TB; there is a risk of developing antibodies and loss of efficacy.

Patients really prefer oral agents over injectable or infusion agents. Tofacitinib (Xeljanz®), an oral Janus kinase inhibitor, is FDA approved for UC. Initial data on CD found it was not effective, but there may be some efficacy in more severely active CD. Adverse effects include increased lipids, infection, and reactivation of herpes zoster. Previously, patients on biologics could not be vaccinated against zoster because the vaccine was a live virus; now they can be given the new Shingrix® vaccine which can prevent zoster.

Therapeutic drug monitoring (TDM) is becoming more of a hot topic in the treatment of IBD. TDM is checking serum drug concentrations to ensure sufficient drug is in the body. Biologic drugs require a set trough level concentration (measured before a dose) to be therapeutic. Exhibit 3 shows the goal trough values.[5] These trough values are for patients who have controlled disease; it is not known what values are appropriate for active disease. The values in active disease are at least at these trough values and likely much higher. For example, levels of 10 to 15 μg/mL are probably the goal in active disease with infliximab.

Keeping a therapeutic level with biologics dramatically reduces the risk of antibody formation. All current IBD biologic drugs are associated with a risk of antibody formation (Exhibit 3). The risk is present even with the advent of fully humanized monoclonal antibodies. Antibodies are associated with an increased risk of infusion reactions with infliximab and loss of response to therapy with all the agents.

With TDM, clinicians have to assess both the serum drug concentration and the level of antibodies. Low trough values can be caused by inadequate dosing, antibodies against the medication, or nonadherence. Only infliximab is dosed based on weight; the

Exhibit 3: Current Biologic Drugs[5]

Drug	Disease	Mechanism of Action	Type of Antibody	Goal Trough	Risk of Antibody Formation
Infliximab	UC/CD	Anti-TNF	75% Human 25% Murine	≥ 5 µg/mL	0.0 - 65.3%
Adalimumab	UC/CD	Anti-TNF	Human	≥ 7.5 µg/mL	0.3 - 38%
Golimumab	UC	Anti-TNF	Human	Unclear (? 1.4 - 2.6 µg/mL	0.4 - 2.9%
Certolizumab-Pegol	CD	Anti-TNF	Humanized antibody fragment	≥ 20 µg/mL	3.3 - 25.3%
Vedolizumab (Natalizumab)	UC/CD	Anti-integrin α4β7	Human	Unclear (? 40 - 42.5 µg/mL at wk 6)	1.0 - 4.1%
Ustekinumab	CD (? UC in future)	Anti-IL-12/23	Human	Unclear (? 0.8 - 4.5 µg/mL)	0.7%
Tofacitinib	UC (? CD in future)	Janus Kinase Inhibitor (1/3)	Synthetic small molecule	N/A	N/A

other biologics are given based on set doses, which may be inadequate in a given patient, to achieve the target trough levels. Most of the other biologics should probably be dosed based on body weight.

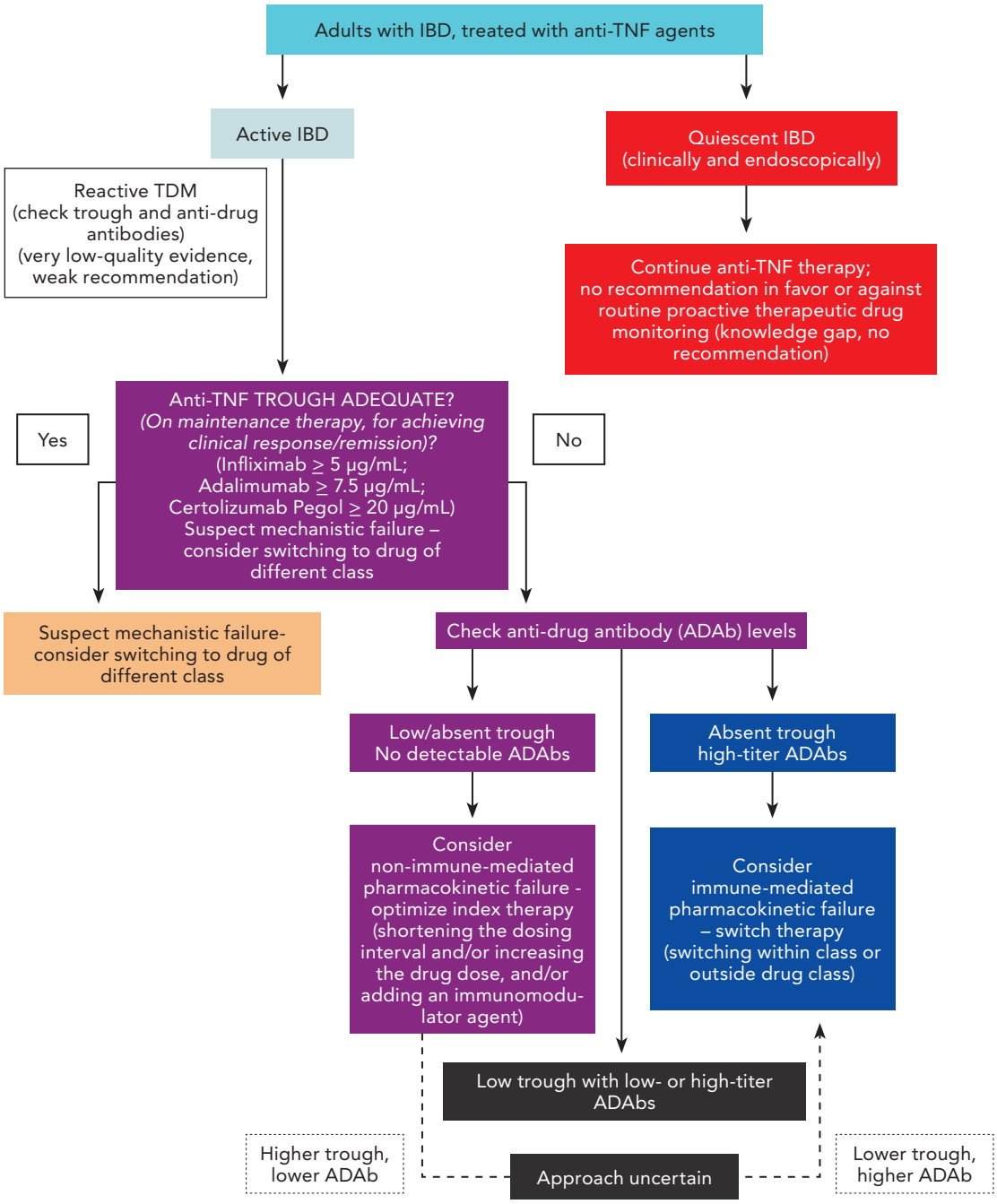
Many patients will have an inadequate response to a given biologic. There are three categories of biologic failures – mechanistic failure, non-immune-mediated pharmacokinetic failure, and immune-mediated pharmacokinetic failure.[6] Mechanistic failure is a primary non-response where the medication is adequately dosed (i.e. therapeutic trough level) and antibodies are not present/of no clinical significance (i.e. non-neutralizing antibodies). The disease inflammation is not being suppressed with the current medication's mechanism of action. In this case, therapy should be changed to a different drug class. There is likely no benefit of trying a second drug in the same class and likely no benefit of adding an immunomodulator in this case. Managed care stepped care rules can make changing therapy difficult when there is a requirement to fail two agents in a given class; this rule makes no sense for cases of mechanistic failure.

With non-immune-mediated pharmacokinetic failure, the medication trough level is subtherapeutic; thus, the lack of response may be secondary to suboptimal dosing. This failure is commonly seen in cases when the drug is initiated in the setting of severe inflammation/high disease burden and typical dose and dosing intervals are utilized. Antibodies may develop, but typically they are at low levels initially. The solution is to shorten the dosing interval and probably increase the dose. In some cases, clinicians can consider a full re-induction dose of the drug or addition of an immunomodulator. If the medication is already dose optimized and the disease is still active, consideration should be given to changing to a second drug within the same class before switching classes.

Immune-mediated pharmacokinetic failure is when the immune system recognizes the biologic drug as "non-self," triggering a humoral or cell-mediated immune response against the drug. Immune response results in development of anti-drug antibodies which neutralize the efficacy of the drug. The antibodies block antigen-binding sites, form complexes with the drug molecules, or increase drug clearance. If there is a low level of antibodies, consideration should be given to overcoming the antibodies by increasing the dose of the drug, shortening the dosing interval, and possibly adding an immunomodulator. Consideration should be given to switching to a different drug in the same class, with or without an immunomodulator.

Proactive therapeutic drug monitoring is testing drug trough levels and anti-drug antibodies when no symptoms of active disease are present and no endoscopic/radiologic/laboratory tests indicate ac-

Exhibit 4: AGA Clinical Decision Support Tool[9]



tive inflammation. The goal is to optimize the drug prior to loss of response. Typically, testing is done prior to the first maintenance dose (e.g., week 14 for infliximab). The interval for ongoing proactive monitoring is unknown, but some experts suggest every four to six months. Studies show reduced rates of hospitalization, surgery, colectomy, and loss of drug response with proactive monitoring. In the most commonly cited study showing benefit of proactive testing, all patients on maintenance dosing of infliximab were first dose optimized to achieve a goal trough of 3-7µg/mL (goal is now known to be ≥5 µg/mL).[7] Once at goal, patients were randomized to trough-based dosing or clinic-based dosing (based on symptoms and C- reactive protein levels). At one year of follow-up, clinic-based dosing result-

Exhibit 5: Selected Agents Under Investigation for IBD

	Target	Disease	Route	Phase
Ustekinumab	IL 12/23 inhibitor	UC	Intravenous and subcutaneous	III
Ertolizumab	Anti-integrin β7 subunit of the heterodimeric integrins α4β7 and αEβ7	UC	Subcutaneous	III
Alicaforsen	Inhibitor of ICAM-1	Chronic pouchitis	Enema	III
AJM-300	α4 integrin antagonist	UC	Oral	III
PF-00547659	IgG2 antibody directed against MAdCAM-1	CD/UC	Subcutaneous	II
Risakizumab	Monoclonal antibody against the p19 subunit of IL-23	CD	Intravenous	III
Brazikumab	Monoclonal antibody that targets the p19 subunit of IL-23	CD	Intravenous	II
Filgotinib	Jak 1 inhibitor	UC/CD	Oral	II/III
Upadacitinib	Jak 1 inhibitor	UC/CD	Oral	II/III
Ozanimod	S1P receptor 1 - 5 inhibitor	UC/CD	Oral	II/III
Laquinimod	Anti-inflammatory properties	CD	Oral	II

ed in remission in 66 percent of patients compared with 69 percent of the trough-based dosing group.[7] In patients starting with low trough levels prior to randomization, more patients were in remission with dose optimization (65% vs 88%). Based on this study, checking a trough level before starting maintenance seems reasonable to make sure patients are therapeutic. In long-term follow-up in this study, there was no difference in IBD-related hospitalization (clinic-based dosing group 13% vs trough-based dosing group 15%), abdominal surgery (6% vs 7%), corticosteroid use (13% vs 8%), and continued use of infliximab (75% vs 80%).[8]

Current available data on proactive monitoring is retrospective. Confounders in the studies that may alter drug levels and results are numerous, and the potential bias in retrospective study design is not avoidable. Long-term follow-up in at least one study did not find a difference between proactive monitoring and clinical-based decision guided therapy changes.[8] Proactive monitoring is more expensive than reactive monitoring, and there is a lack of standardization of how often it should be performed. The current American Gastroenterology Association (AGA) guideline on TDM makes no recommendation regarding proactive monitoring given the lack of data.[9] The ability to test and conceptual justification does not necessarily equate with improved outcomes.

Reactive testing is testing drug trough levels and anti-drug antibodies when symptoms of active disease are present and/or endoscopic/radiologic/laboratory tests indicate active inflammation. The goal is to optimize the drug prior to changing to a different drug in the same or new class. Typically, testing should be done as a true trough level (i.e., day of the next infusion or injection). The AGA guideline on TDM recommends reactive TDM (conditional recommendation, very low-quality evidence).[9] Overall, reactive testing provides information to determine if a drug should be optimized or changed and reduces time lost on empiric drug changes that may not improve response.[10] Exhibit 4 shows the AGA recommendations for managing anti-TNF therapy with TDM.[9]

There is a deep pipeline of drugs for IBD under development (Exhibit 5), but there are challenges in drug development for IBD. UC and Crohn's are not the same disease, so one drug might not work for both. Patients prefer oral formulations, but many biologics are large molecules which must be given by

infusion or injection. Oral biologic therapies are the future of IBD treatment. Manufacturers are searching for ways to give biologics without infusion or injection. Insurance coverage of new agents is variable as many managed care plans require step therapy failures. The second drug to market in a class usually has less market share, making it less desirable for the manufacturer.

No matter what drug therapy is chosen, patient engagement is most important for enhancing outcomes in IBD. It is required for adherence with drug therapy, getting the care the patients need (health care visits, laboratory testing), and preventing complications (cancer screenings, vaccines). In addition to clinicians working directly with patients, numerous applications (apps) are available to help patients manage their IBD.[11] Some examples include My IBD Manager (AGA), IBD Diary, and eIBD (UCLA). UCLA's application is integrated into their electronic medical record. For the non-application user, a checklist can help patients keep up with recommended vaccines, laboratory monitoring, and cancer prevention screening. There are many challenges with patient engagement. Many applications and websites are not evidence based and lack updating with changes in evidence. Underserved and non-English speaking patients are not helped by many of the applications or websites.

Conclusion

Ulcerative Colitis and Crohn's disease are different diseases. Disease management for each has some similarities; however, not all medications are effective in both diseases. Therapeutic drug monitoring may be helpful in certain situations to optimize drug therapy. Patient engagement is critical to providing optimal patient care. Many agents with new mechanisms of action and oral administration are coming in the future.

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New Frontiers in the Treatment and Prevention of Migraine: A Closer Look at the Role of Emerging GCRP Targeted Therapies

Deborah I. Friedman, MD, MPH, FAAN, FAHS

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

Summary

Migraine is a common neurologic disorder that significantly impacts a patient's quality of life and ability to work and is costly to treat. Although numerous agents have been available for preventing migraine, none was specifically designed to target the underlying pathologic process. The new class of agents is targeting one of these underlying pathologic processes.

Key Points

- Migraine is common, disabling and invisible.
- A new class of preventive agents designed specifically for migraine treatment is now available.
- Anti-CGRP monoclonal antibodies are well tolerated with no safety signals and are effective in reducing migraine headache days and improving quality of life.

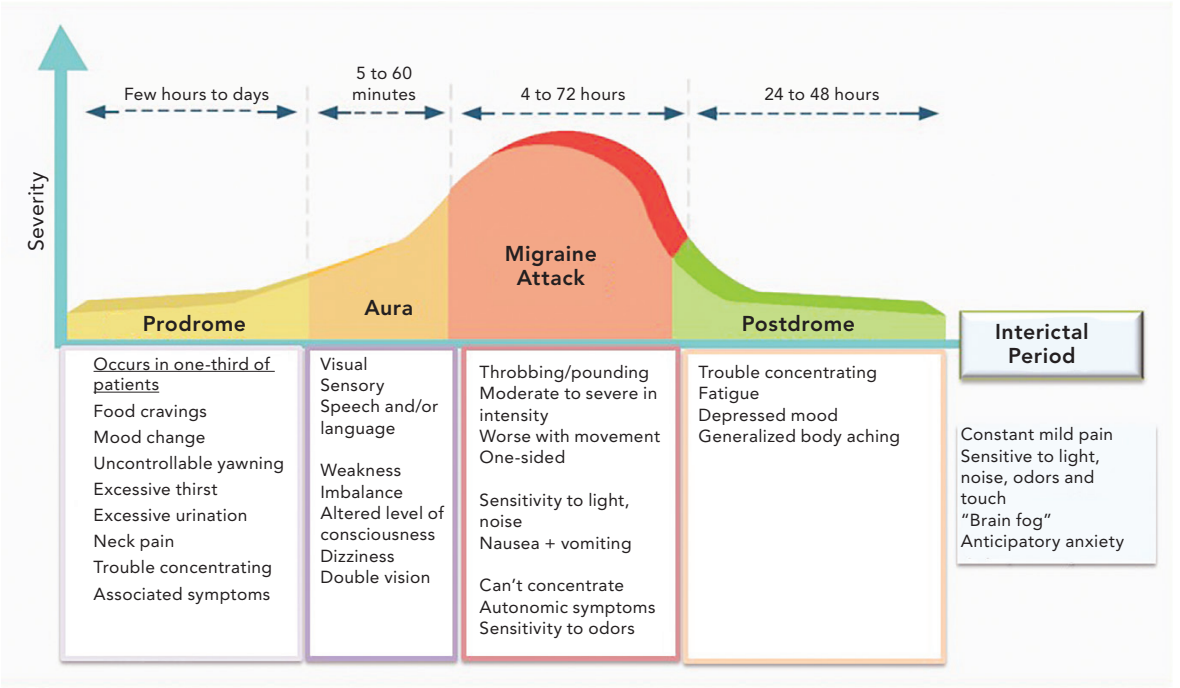
MIGRAINE IS THE MOST COMMON RECURRING headache disorder seen by health care practitioners and the number three cause of disability-adjusted life years (DALYs) in those under the age of 50 worldwide.[1-3] Migraine affects over 39 million Americans (12%) and touches one in four families. It affects 6.5 to 9.7 percent of males, 18 to 20.7 percent of females, and 7 percent of children.[4] It is the most common neurological disorder by a factor of 10 and is more common than diabetes, epilepsy and asthma combined. More than 11 million people with migraine headaches have moderate to severe pain. Migraine prevalence peaks during peak productive years (30 to 50 years).

Migraine is under-recognized by patients and underdiagnosed by clinicians. In two studies, only half of those with headaches that meet criteria for migraine correctly identified their headaches as migraine.[5] In another study, 97 percent of people with self-reported sinus headache met criteria for migraine.[6] Many patients attribute their symptoms to sinus headache because of stuffiness, runny nose, and weather association, but these are all hallmarks of migraine.

Migraine is also invisible and stigmatized. Individuals with migraine experience stereotyping, devaluation, and discrimination. In a study of episodic and chronic migraine in epilepsy patients using the stigma scale for chronic illness, those with chronic migraine had the highest scores, followed by episodic migraine and epilepsy.[7] Subjects with migraine reported greater inability to work, which was the strongest predictor of stigma. Individuals with migraine hide their suffering and often do not talk about it – even to their doctor.

Migraine is also financially costly. Migraine accounts for 0.5 percent of all ambulatory visits. Almost 53 percent of visits occurred in primary care settings, 23.2 percent in specialty outpatient settings, and 16.7 percent in emergency departments,

Exhibit 1: A Migraine is More than Just a Headache



where opioids are the most common initial treatment. Headache is the third leading cause of emergency department visits. In the United States (U.S.), the annual direct health care costs of migraine are estimated at $11,010 per patient, and the overall indirect costs are estimated at $11 billion per year.[8]

As shown in Exhibit 1, a migraine is more than a headache; it is a neurological event. Between episodes, people can have constant mild pain and other symptoms, especially after having migraine for many years. Migraine can occur with an aura, without an aura, and as an aura without a headache. About 75 percent of cases are without an aura. A typical aura includes visual disturbances and sensory effects and may include speech and language issues. Visual disturbances include blurred vision, photopsia (bright flashes of light), photophobia, teichopsia (bright, shimmering, jagged lines), tunnel vision and blindness. The aura with a hemiplegic migraine can include one-sided weakness. Migraine with brainstem aura can cause speech and language issues, double vision, dizziness, vertigo, hearing issues, imbalance, and loss of consciousness.

Migraine can be episodic or chronic (Exhibit 2).[9] In the International Burden of Migraine Study, disability progressively increased with an increasing frequency of headache days.[10] In this study, four headache days monthly were the inflection point for significant disability. Approximately 70 percent of those with episodic migraine had moderate-to-severe disability. Ninety percent of those with chronic migraine had moderate to severe disability.

There is a genetic predisposition for migraine. Eighty percent of patients have a family history of a primary relative with migraine. Those with a predisposition to migraine appear to have lower thresholds for brain activation in response to certain stimuli. Motion sickness, infantile colic, sensitivity to light, noise, odors, or episodes of vertigo, vomiting, and abdominal pain in childhood are thought to be precursors to migraine. Episodes of migraine may be triggered, but the specific triggers are often not identified. Commonly reported triggers are shown in Exhibit 3.

When making the diagnosis of migraine, other conditions causing headaches need to be ruled out. Red flags for other causes include onset after age 50 or new daily persistent headache (giant cell arteritis, cancer, mass lesion, cerebrospinal fluid leak), sudden onset severe headache with altered mental status (subarachnoid hemorrhage, arteriovenous malformation, reversible cerebral vasoconstriction syndrome, pituitary apoplexy, hemorrhage, tumor), acceleration or change in pattern of headache (mass, subdural hematoma, medication overuse), and new headache in patient with cancer or HIV (meningitis, abscess, metastasis). There are also red flags on physical examination, which can suggest another

Exhibit 2: Episodic versus Chronic Migraine[9]

Episodic: 0-14 days monthly		Chronic: 15 or more headache days monthly (8 are migraines):	
< 1 to 9 days	9 to 14 days	Not daily	Daily
Low frequency	High frequency		

Exhibit 3: Commonly Reported Migraine Triggers

Stress (during or after, "let down") or anger

Skipping meals, dehydration

Dietary (controversial)
Aged foods, MSG, artificial flavorings and coloring, alcohol, caffeine, nuts, chocolate, others

Odors (perfume, cleaning products, gasoline)

Menses and other hormonal changes

Sleep (too much, too little, wrong time)

Poor air quality

Smoke

Weather

cause for headaches, including headache with systemic illness (meningitis, encephalitis, systemic infection, collagen vascular disease), focal neurologic symptoms or signs other than typical aura (brain mass, arteriovenous malformation, stroke, abscess, collagen vascular disease), papilledema (mass, pseudotumor cerebri, meningitis), and postural or "end of day" headache (cerebrospinal fluid leak). Neuroimaging is not needed for diagnosis in patients with a typical history, a normal neurologic examination, and no red flags.

Treatment options for aborting a migraine once it has started are numerous. Only the triptans and ergots were designed as migraine treatments. Other options include nonsteroidal anti-inflammatories, OTC combination analgesics (caffeine, acetaminophen, and aspirin), prescription analgesic combinations, antiemetics, sedatives, and nutraceuticals. Nonpharmacologic interventions such as rest, ice, and neurostimulation devices are also options. Opioids should not be used for acute management.

Prevention of migraine is also an option and an important aspect of treatment for many patients. Up until the recent approval of a new class of agents, agents from various drug classes that were originally approved for other indications were used. Antidepressants, mood stabilizers, antihypertensives, antiepileptics, and nutraceuticals have all been used. Exhibit 4 shows the level of evidence recommendations from the American Academy of Neurology for the various options.[11,12]

In-office treatments include onabotulinumtoxinA injections, trigger point injections, nerve blocks, and infusion therapy. Onabotulinum injections are FDA approved for chronic migraine. Nerve blocks and infusion therapy are often not covered by insurance, but they can keep patients out of the emergency department.

Limitations of these acute and prophylactic treatments include adverse effects, lack of efficacy, incomplete relief, recurrence of headache within 24 hours, wearing off of effect, cost, lack of insurance coverage for some, quantity limits, contraindications, lack of options in pregnancy, lack of pediatric data, inconvenience, induction of medication overuse headaches, or abuse of medications. Discon-

Exhibit 4: Evidence-Based Guidelines for Preventive Treatment[11,12]

Prescription Preventives				
Level A Established (≥ 2 Class I Trials)	Level B Probable (1 class I or 2 class II)	Level C Possible (1 Class II)	Level U Inadequate or conflicting data	Other Probably or possibly ineffective
Valproic acid Topiramate Metoprolol Propranolol Timolol Frovatriptan* Onabotulinumtoxin A**	Amitriptyline Venlafaxine Atenolol Nadolol Naratriptan* Zolmitriptan*	Lisinopril Candesartan Clonidine Guanfacine Carbamazepine Nebivolol Pindolol Cyptoheptadine	Acetazolamide Antithrombotics Fluvoxamine Fluoxetine Gabapentin Protriptyline Verapamil and other CCBs Cyclandelate	Lamotrigine Clomipramine Clonazepam Oxcarbazepine Acebutolol Telmisartan Nabumetone
*Menstrual migraine short-term prophylaxis ** Chronic migraine prophylaxis **(FDA approved)**				
NSAIDs and Nutraceutical Preventive Treatments				
Petasites (Butterbur)	Fenoprofen Ibuprofen Ketoprofen Naproxen Magnesium Feverfew Riboflavin (B2) Histamine subcutaneous	Flurbiprofen Mefenamic acid Co-Q10 Estrogen Cyptoheptadine	Aspirin Indomethacin Omega-3 Hyperbaric oxygen	Montelukast

tinuation rates of acute and oral preventive treatments are well over 50 percent.[13] Adherence with long-term therapy is also poor. With these agents, it may take months to years to optimize prevention. The efficacy rate for the Level A agents is about 50 percent improvement in 50 percent of patients, thus there is much room for improvement in prevention.

Various mechanisms by which migraine starts and perpetuates have been identified. It appears to start with a cortical spreading depression, which starts in the back of the brain and moves forward to activate the trigeminovascular system. The trigeminal nerve delivers sensation to the brain and is divided into three branches. The first division supplies the dura and blood vessels, which are the only two structures in the brain that sense pain. Messages flow along the trigeminal nerve to the brainstem. Projections from the trigeminal nucleus caudalis in the brainstem go to the thalamus, cortex and other brain regions (pain perception). Sensitivity to light and sound with migraine probably comes from the thalamus. Neurotransmitter release (calcitonin gene-related peptide [CGRP], pituitary adenylate cyclase-activating polypeptide-38 [PACAP-38], glutamate, nitric oxide) causes blood vessels to dilate and inflammation at the level of the dura.[14] Overall, trigeminovascular system activation leads to peripheral sensitization (dura) which leads to central sensitization (brain). It takes less and less of a trigger to produce a painful response. Patients become sensitive to things that should not be painful, such as noise, smell, and touch (allodynia).

CGRP, a 37-amino acid peptide found throughout the brain and body, is a potent vasodilator and key mediator of neurogenic inflammation. It transmits pain information from intracranial blood vessels to the nervous system and produces migraine-like headache within hours when injected into individuals with migraine. Levels in blood and saliva are increased during migraine attacks and between attacks.[15]

Anti-CGRP monoclonal antibodies have been developed specifically to target migraine. These biologic agents, like triptans, have very low central nervous system penetration and work outside the brain. The mechanism of action is to reduce the activity of CGRP by binding to the CGRP ligand or its receptor. These antibodies have very long half-life (~30 days) and are used for prevention. Elimination is through the reticuloendothelial system, similar to endogenous antibodies, thus neither kidney nor liver dysfunction impact dosing. Because they are large molecules they must be administered by injection. Exhibit 5 presents information about the three currently approved anti-CGRP agents and an additional one likely to be FDA approved. The FDA approved indication for these agents is for migraine prevention in adults.

Exhibit 5: Anti-CGRP Monoclonal Antibodies for Migraine

	Erenumab (Aimovig)	Fremanezumab (Ajovy)	Galcanezumab (Emgality)	Eptinezumab
Antibody vs:	IgG2	IgG2a	IgG4	IgG1
Derivation	Human	Fully humanized	Fully humanized	Genetically engineered
Binding site	Receptor	Ligand	Ligand	Ligand
Administration	SC	SC	SC	IV
Bioavailability	50 - 74%	Not reported	~ 40%	100%
Dosing interval	Q month	Q month/Q 3 months	Q month	Q 3 months
FDA approval	June 2018	September 2018	September 2018	??
Episodic migraine/ high frequency episodic (4/5-14d)	Yes	Yes	Yes	Yes
Chronic migraine (≥15 d)	Yes	Yes	Yes	Yes

There are a great deal of similarities in the efficacy trials for the anti-CGRP agents. The subjects are primarily Caucasian women around 40 years old with migraine for many years who have failed many other therapies. In a randomized trial of erenumab compared to placebo in episodic migraine, the change in monthly migraine days (assessed from baseline to month three) was one day less of migraine.[16] Thirty-nine percent of patients had a 50 percent reduction in monthly headache days compared with 29 percent in the placebo group. There was statistically significant improvement in patient-reported outcomes, including physical impact, overall impact on daily activities, disability score, presenteeism, role function restriction, and emotional function. There was also a reduction in the number of acute migraine medications used. It has also been studied in chronic migraine with similar results.

In a study of galcanezumab for chronic migraine, the subjects had a mean of 19 migraine per month, approximately 30 percent had failed less than two preventives, 14 percent were on a current preventive, and 60 percent had medication overuse.[17] The change in monthly migraine days was two days less of migraine. Twenty-seven percent of subjects had a 50 percent reduction in monthly headache days compared with 15 percent in the placebo group. The FDA labeled dose for this agent is a 240 mg loading dose, followed by monthly 120 mg injections. In the chronic migraine trial with this agent, only the 240 mg dose was superior to placebo on key secondary endpoints: proportion of patients with 75 percent or greater reduction in monthly headache days, reduction in monthly headache days with acute medication use, improvement in role function restriction, and reduction in the Patient Global Impression of Severity.

Fremanezumab has been evaluated in high-frequency episodic migraine and chronic migraine prevention.[18,19] Monthly headache days and monthly migraine days were significantly reduced. Compared to placebo in episodic migraine, both doses of fremanezumb decreased the number of acute medication consumption days, number of moderate to severe headache days, number of days with nausea and vomiting, number of headache hours, and the number of days with photophobia and phonophobia. A 50 percent reduction in migraine days occurred in 28 percent for placebo, 53 percent for 225 mg dose, and 59 percent for 675 mg dose. The FDA labeled dosing is 225 mg monthly, or 675 mg every three months. Antibodies against the drug were detected in 1 percent of subjects, but did not appear to affect efficacy. In the fremanezumab chronic migraine study, it reduced monthly migraine and headache days by 1.7 to 2.0 days compared to placebo. It also significantly reduced acute medication days and the Headache Impact Test score.

Eptinezumab is an investigational intravenous infusion anti-CGRP agent given every three months. Data from episodic and chronic migraine studies have been presented at professional society meetings, but they have not yet been published.[20,21] This agent appears to be as effective as, and possibly better than, the subcutaneous agents. Positive benefits on migraine have been seen within one day of infusion (52% reduction compared to 27% for placebo). The 50 percent, 75 percent, and 100 percent respond-

Exhibit 6: Pros and Cons of Current Preventive Therapy

Monoclonal Ab

- Injection (SC, monthly or every three months)
- Rapid onset in many
- "Super-responders" (75 to100%)
- Low incidence of side effects
- Good option for patients with potential drug interactions
- Reticuloendothelial clearance
- Potential for increased adherence
- FDA approved for migraine
- Pre-authorization
- High cost ($575 per month)

Oral Preventives

- Daily oral
- Require titration
- Two months of adequate dose to assess effectiveness
- Treatment limited by side effects and comorbid conditions
- Hepatic and renal clearance
- Poor adherence
- None FDA-approved for chronic migraine
- Most generic and covered by insurance
- No pre-authorization for most

OnabotulinumtoxinA

- Monthly injection
- Adherence > orals
- FDA Indication for Chronic migraine
- Good option for patients with multiple medical problems or potential drug interactions
- Low incidence of side effects
- Two to three treatments required to assess effectiveness (36 to 48 weeks)
- Requires pre-authorization and failed oral treatment by most insurers
- Office procedure

er rates were better in the chronic migraine study compared to the rates in the subcutaneous studies.

Adverse effects with the anti-CGRP agents are generally mild and the agents are well tolerated. The most common adverse effects are injection site reactions. Within a month of initiation, the anti-CGRP agents have efficacy. There have not been any comparative trials with the three approved agents, but they appear to have similar efficacy in episodic and chronic migraine prevention. There are pros and cons to each of the classes of preventive medications (Exhibit 6).

One preventive will not work for all patients, and clinicians will still have to use multiple therapies in some patients. Improved prevention of migraine should decrease health care utilization, but it may take one to two years to see population effect. Headache medicine specialists can work with patients and payers to achieve effective and cost-effective care.

There are small molecule oral anti-CGRP agents under study for migraine treatment. Ubrogepant, rimegepant, and atogepant are all under investigation. Ubrogepant and rimegepant, have completed positive pivotal trials and likely will reach the market in the next few years.

Conclusion

Migraine is very common and is still underdiagnosed, causing significant disability and economic impact. Current oral preventive treatments are inadequate with high nonadherence rates. A new preventive designed for migraine treatment, anti-CGRP monoclonal antibodies, are well tolerated with no safety signals. Effects and side-effects are fairly similar across the available agents. The place in therapy of these new agents, compared to older preventives, has not yet been determined.

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Patient-Focused Treatment Decisions in Metastatic Bladder Cancer: A Closer Look at the Integration of Immunotherapy

Peter H. O'Donnell, 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

Immunotherapy has revolutionized the treatment of bladder cancer. It is now being used in both the first- and second-line setting for metastatic disease. It will likely be moving into even earlier use as a neoadjuvant treatment after surgery.

Key Points

- Cystectomy can cure early stage bladder cancer.
- Cisplatin-based chemotherapy is used as first-line therapy for metastatic disease.
- Immunotherapy is the best option for first-line therapy in those who cannot take cisplatin.
- Immunotherapy is also the second-line therapy after chemotherapy.

THE TREATMENT OF BLADDER CANCER has changed radically over the last few years. Prior to the approval of immunotherapy, the traditional treatment of this disease was cystectomy and chemotherapy. Surgery alone for bladder cancer only cures some patients, primarily those with early stage disease which has not yet progressed beyond the bladder structure. Exhibit 1 shows bladder cancer from invasion of the urothelium to extension beyond the bladder wall. Survival after radical cystectomy is entirely dependent on the stage of the cancer at the time of diagnosis. The median time to recurrence in those who have radical cystectomy is approximately one year.[1]

Once disease is metastatic, the primary treatment has been chemotherapy. The first chemotherapy regimen, a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), was initially used in 1985. In 1997, gemcitabine was reported to have activity in this disease and was found to be comparable to MVAC in 2000 when used in combination with cisplatin. Response rates to gemcitabine/cisplatin are tumor regression in 50 to 55 percent of cases and stable disease in an additional 33 percent. The median progression-free survival (PFS) after gemcitabine/cisplatin treatment in those with metastatic disease is 7.5 months and median overall survival (OS) is 14 months.[2,3] Approximately 14 percent of patients who receive this regimen will have their disease eliminated. The combination of gemcitabine and cisplatin has been first-line therapy for advanced bladder cancer since 2000.

Renal function is a hurdle in the treatment of bladder cancer, especially in older patients. For example, about 33 percent of those over the age of 70 and 68 percent of those over 80 are ineligible for cisplatin-based chemotherapy based on estimated renal function.[4] For those who cannot take cisplatin, carboplatin is an alternative; however, it is less effective and does not extend OS.[5] Second-line therapy after failure of gemcitabine/platinum has been a taxane combined with pemetrexed. Response rates to this second-line combination are 5 percent to 28 percent, PFS is two to three months, and OS is six to nine months.[6-8]

Immunotherapy is the newest treatment for bladder cancer. It was studied because it has been shown that an immune response is important in survival

Exhibit 1: Bladder Cancer

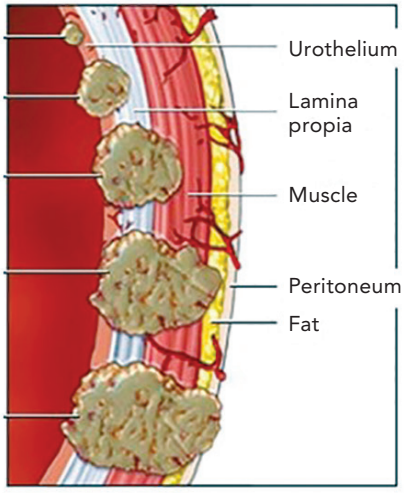


Exhibit 2: Immune Checkpoint Inhibitors in Platinum-Refractory Setting[13-18]

	Pembrolizumab	Durvalumab	Nivolumab	Avelumab	Atezolizumab
Dosing	200mg q 3 wk	10mg/kg q 2 wk	240 mg q 2 wk or 480 mg q 4wk	10mg/kg q 2 wk	1200mg q 3 wk
ORR	21%	18%	20%	17%	13%
OS (months)	10.3	18.2	8.7	6.5	8.6
PFS (months)	2.1	1.5	2.0	1.5	2.1
12 month survival	44%	55%	43%	47%	38%
Grade 3/4 adverse effects	15%	7%	18%	8%	16%

with bladder cancer. In a study of tumor biopsies in those who underwent radical cystectomy, the quantity of tumor-infiltrating T cells found in the biopsy correlated with survival.[9,10] The mutational load with bladder cancer is fairly high; it is the fourth highest of all cancers.[11] The higher the mutational load in a given tumor, the higher the likelihood of response to immunotherapy.[12]

There are now five checkpoint immunotherapies approved for treating bladder cancer that is resistant to platinum-based chemotherapy (i.e., second-line therapy) - atezolizumab (anti-programmed death-ligand one [PD-L1]), nivolumab (anti-programmed death one [PD-1]), durvalumab (anti-PD-L1), avelumab (anti-PD-L1), and pembrolizumab (anti-PD-1). The FDA indication for these agents is for the treatment of patients with locally advanced or metastatic bladder carcinoma who have disease progression during or following platinum-containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Exhibit 2 shows the response data from the studies with these agents in bladder cancer.[13-18] About 40

Exhibit 3: Front-Line Immunotherapy in Those Who Are Cisplatin Ineligible[20,21]

	Pembrolizumab	Atezolizumab
Dosing	200mg q 3 wk	1,200mg q 3 wk
0RR	29%	23%
CR	7%	9%
OS (mo)	not reported	15.9
PFS (mo)	2.0	2.7
Landmark survival	67% (6 mo)	57% (12 mo)

Exhibit 4: Current Treatment Paradigms for Metastatic Bladder Cancer

- Cisplatin eligible
  - gemcitibine/cisplatin
- Cisplatin ineligible
  - immunotherapy (pembrolizumab or atezolizumab)
  - gemitibine/carboplatin
- Platinum refractory
  - five immunotherapies (pembrolizumab level 1 evidence)

percent of patients with advanced disease are going to get some benefit from immunotherapy. None of the immunotherapies have been shown to extend PFS. None of these have been compared head-to-head, but they have been compared to second-line chemotherapy. For example, pembrolizumab was compared with paclitaxel or docetaxel or vinflunine. Like with the other immunotherapies, OS (10.3 months versus 7.4 months) and response rates (21% versus 11%) were higher with pembrolizumab compared with second-line chemotherapy.[13]

The immunotherapy agents are dosed on every two to four-week schedules. The longer dosing intervals are helpful for patient convenience, especially given that these agents will be continued for a long time if the patient has a response. Durvalumab is being investigated for an every four-week interval and will likely be approved as such.

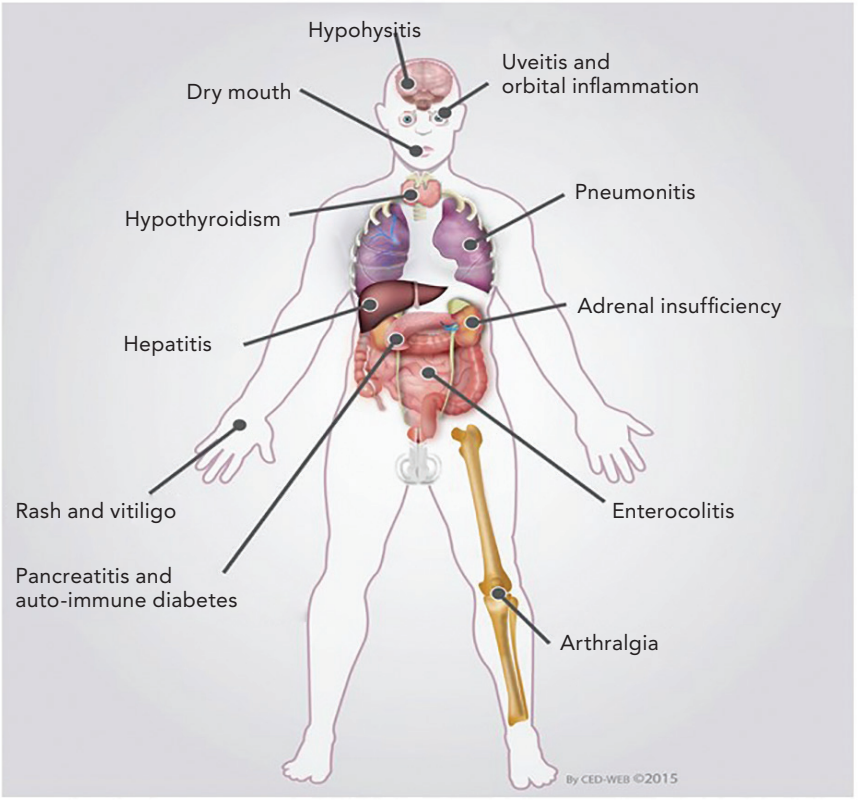
In a study of atezolizumab in the second-line setting in patients with high levels of PD-L1 expression, atezolizumab and taxane-based chemotherapy were not statistically different in terms of OS.[14] Other studies are ongoing with atezolizumab to determine if it does have a benefit. In the National Comprehensive Cancer Network (NCCN) guidelines, pembrolizumab has a Level 1 designation and is preferred over the other immunotherapies for second-line treatment.[19]

Two agents (atezolizumab and pembrolizumab) are also FDA approved for first-line treatment in those who are cisplatin ineligible. Exhibit 3 shows the efficacy data from the first line trials.[20,21] Immunotherapy in the first-line setting produces a similar response to gemcitabine/cisplatin. In patients with a combined positive score (CPS) greater than 10 percent for PD-L1 staining, the objective response rate to pembrolizumab was 51 percent compared with 23 percent in those with CPS less than 10 percent.[20] Exhibit 4 shows the current treatment paradigm for metastatic bladder cancer.

The role of PD-L1 testing for choosing immunotherapy is controversial. The FDA approved a complementary diagnostic assay for atezolizumab, but there is no requirement for testing in the product labeling for any of the immunotherapies for the bladder cancer indication. The clinical utility of PD-L1 testing appears limited in this particular disease.

The main toxicities of immunotherapy are shown in Exhibit 5.[22] Most treatment-related adverse effects in the published studies are low grade and no treatment-related deaths were seen. Grade 3 to 4 immune-related adverse effects occurred in about 5 percent of study subjects. In general, immuno-

Exhibit 5: Immune Adverse Effects of Immunotherapy[22]



therapy is much better tolerated than chemotherapy and preferred by patients. The future of bladder cancer treatment is likely combination therapy with either chemotherapy and immunotherapy or dual immunotherapy. The combination of pembrolizumab, gemcitabine, and cisplatin has been studied in the first-line setting for advanced disease where no prior chemotherapy has been given.[23] Dual immunotherapy with a PD-1 inhibitor and an anti-cytotoxic T-lymphocyte-associated antigen four (CTLA-4) monoclonal antibody, tremelimumab has also been studied with excellent response rates.[24] The issue with the immunotherapy combinations is the combined immune adverse effects of dual checkpoint inhibition. Adjuvant immunotherapy is also being studied in those who are high risk for recurrence after cystectomy.

Personalized medicine with genomic biomarkers is being used to select therapy for bladder cancer, especially for the post chemotherapy and immunotherapy patient. DNA repair gene mutations present in tumors may inform recurrence risk after cystectomy. Median PFS for patients with DNA repair mutations is longer than those without the mutations (32.4 months versus 14.8 months).[25] Patients with tumors with ERCC2 (a DNA repair gene) mutations are more likely to be cisplatin-responders with neoadjuvant therapy and have better OS compared to those without the mutation.[26,27] Numerous other genetic mutations are being studied as targets of therapy or as biomarkers of response. An example is human epidermal growth factor receptor two and three (HER-2, HER-3), which is more commonly linked with breast cancer. HER-2 and HER-3 mutations are present in 6 percent and 4 percent of bladder cancers, respectively. In one small trial, patients with bladder cancer received afatinib, an irreversible HER family inhibitor. Those with HER alterations had a longer response versus those without alterations.[28] Median time to progression/discontinuation was 6.6 months in patients with alterations versus 1.4 months in patients without alterations. Another example is fibroblast growth factor receptor (FGFR) which is mutated in about 15 percent of bladder cancer patients. An oral FGFR inhibitor, erdafitinib, was recently given breakthrough designation by the FDA as a treatment for metastatic bladder cancer. This agent was submitted to the FDA for approval in September of 2018.

Conclusion

Dramatic treatment changes in the treatment of bladder cancer have occurred. Immunotherapy has completely changed the treatment paradigm. The treatment has the potential to change further with the use of chemotherapy and immunotherapy combinations. The application of molecular studies/genomics as predictors of response to identify sub-populations most likely to respond to immunotherapy is becoming standard of care.

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Effective Management of Chemotherapy-Induced Nausea and Vomiting (CINV): Appropriate Treatment for Improved Outcomes

Susan G. Urba, 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

Chemotherapy-induced nausea and vomiting (CINV) causes significant problems for patients. Prevention is very important and requires several medications which provide coverage for both acute and delayed CINV. Following the guidelines and communicating with patients will significantly reduce the rates of uncontrolled CINV.

Key Points

- The financial and human costs of uncontrolled CINV are substantial.
- Prevention is most important with CINV.
- Guidelines should guide antiemetic selection.
- Both acute and delayed CINV need to be prevented.
- Communication between patients and providers is important.

CHEMOTHERAPY CAN CAUSE NAUSEA AND vomiting by two major ways – peripheral or central mechanisms. In response to chemotherapy, enterochromaffin cells in the gastrointestinal tract release serotonin which starts the syndrome of chemotherapy-induced nausea and vomiting (CINV). Serotonin stimulates vagal afferent nerves which communicate with the brain. Through the dorsal vagal complex, the brain communicates back to stomach causing reverse peristalsis, which results in nausea and vomiting. Centrally, stimulation of the neurokinin 1 (NK_1) receptors by substance P in the brainstem can also lead to CINV. Although many other neurotransmitters are involved, serotonin and substance P are the primary neurotransmitters targeted with medications.

There are four types of CINV. Acute CINV is nausea and vomiting that occurs within the first 24 hours after administration of chemotherapy. Acute CINV occurs in 70 to 80 percent of patients given emetogenic chemotherapy without preventive medications. Patients may think that they only have to get through the day of chemotherapy, but delayed CINV causes just as many problems. Delayed CINV starts more than 24 hours after administration of chemotherapy and typically lasts three to four days. Delayed CINV can occur in up to 80 percent of patients who do not receive prophylaxis. Anticipatory CINV is a conditioned response that happens after a negative past experience with chemotherapy and has been reported in 33 percent of patients. Breakthrough CINV is that which occurs despite prophylaxis and requires rescue medications. Acute CINV is predominately mediated by serotonin-dependent mechanisms, whereas delayed CINV is predominately substance P-mediated, but there is some overlap.[1] The overlap of differential involvement of neurotransmitters supports combination therapy to enhance prevention of emesis. Both acute and delayed mechanisms need to be covered from the first day that chemotherapy is given.

There are chemotherapy and patient-related

Exhibit 1: Chemotherapeutic Agents with High Potential for Acute Emesis

Level	Agent
High (>90% Frequency of Emesis)	AC combination Carboplatin AUC >/= 4 Carmustine > 250 mg/m^2 Cisplatin Cyclophosphamide > 1,500 mg/m^2 Dacarbazine Doxorubicin > 60 mg/m^2 Epirubicin > 90 mg/m^2 Ifosfamide > 2 g/m^2 Mechlorethamine Streptozocin

risk factors for CINV. The most important factor for determining whether CINV will occur is the emetogenic potential of the chemotherapy being given. Chemotherapy agents can be classified as having high, moderate, low, or minimal potential for inducing emesis. Examples of highly emetogenic agents are cisplatin and doxorubicin. Exhibit 1 lists those agents considered highly emetogenic. Because combinations of chemotherapy agents are commonly given, the emetogenic potential of all the agents used have to be considered in choosing prophylactic therapy. The dose of some agents is also important in determining the emetogenic category. Additionally, there are now many oral chemotherapy agents which can also cause CINV. The National Comprehensive Cancer Network (NCCN) guidelines provide guidance on the emetogenic category for each chemotherapy agent.[2] Since immunotherapy is being used frequently in cancer treatment, it is important to note that most immunotherapy agents have low or minimal emetic risk. Patient factors which predispose to the development of CINV include low alcohol consumption (< 10 drinks/week), younger age (< 50), female gender, history of motion sickness, and poor control with prior chemotherapy.

There can be significantly different perceptions about CINV between patients and providers. In one study, the greatest discrepancy between predicted and actual nausea and emesis occurred for the delayed period, with physicians and nurses underestimating the presence of nausea and/or vomiting by approximately 30 percent. Of interest, even with treatment with a 5-HT3 receptor antagonist, 47 percent of patients experienced acute nausea and 57 percent experienced delayed nausea.[3] Thus, communication between providers and patients is important in identifying adequate control of CINV.

Some tools are available to help patients manage CINV and to communicate issues to their providers. The NCCN publishes Guidelines for Patients: Nausea and Vomiting (available at www.nccn.org). Some of the coping strategies from these guidelines are to eat small meals, avoid greasy or strong-smelling foods, eat room temperature food, drink plenty of fluids, and talk to a dietician. It is also suggested that patients keep a diary of side effects of chemotherapy to provide to their caregivers. The Multinational Association of Supportive Care in Cancer Antiemesis Tool's purpose is to make sure that the patient communicates their complete experience with CINV to the health care practitioner. It includes questions on both acute and delayed CINV.

Uncontrolled CINV is costly for both the patient and the health care system. The major financial costs of uncontrolled CINV include nursing time, physician time, antiemetic rescue medication, additional office visits, trips to the emergency room, intravenous hydration, and hospital admission. Uncontrolled CINV has a significant effect on quality of life.[4] Dread of future chemotherapy can lead to anticipatory nausea which requires significant health care provider time to manage. Chemotherapy may have to be stopped or delayed because of uncontrolled CINV. This can have an impact on the ultimate treatment outcome. It can also lead to loss of work days or missing out on social and family events. In one survey, 48 percent of patients said CINV caused them to miss work, and 61 percent said CINV caused them to miss family events.

Three sets of treatment guidelines for preventing CINV are available to assist clinicians.[2,5,6] The guidelines are similar with some subtle differences. The major agents used for CINV prevention when highly emetogenic chemotherapy (HEC) is given

Exhibit 2: NCCN Guidelines for Preventing CINV with Highly Emetogenic Chemotherapy (HEC)

Option A

Acute	Delayed
NK_1 Antagonist • Aprepitant 125 mg PO • Aprepitant injectable emulsion 130 mg IV • Fosaprepitant 150 mg IV once • Netupitant/palonosetron • Rolapitant 180 mg PO once • Rolapitant 166.5 mg IV once	• If aprepitant PO given on day 1, aprepitant 80 mg PO on days 2 and 3 • Dexamethasone 8 mg PO/IV on days 2,3,4
Serotonin Antagonist • Dolasetron 100 mg PO once • Granisetron 10 mg sub-Q once, or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24 h transdermal patch • Ondansetron 16-24 mg PO once or 8-16 mg IV • Palonosetron 0.25 mg IV once	
Dexamethasone 12mg PO/IV once	

Option B

Acute	Delayed
• Olanzapine 10 mg PO once • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once	• Olanzapine 10 mg PO on days 2, 3, and 4

Option C

Acute	Delayed
• Olanzapine 10 mg PO • NK_1 antagonist • Serotonin Antagonist • Dexamethasone	• Olanzapine 10 mg PO on days 2,3,4 • If aprepitant PO given on day 1, aprepitant 80 mg PO on days 2 and 3 • Dexamethasone 8 mg PO/IV on days 2,3,4

are serotonin antagonists, corticosteroids, and neurokinin 1 (NK1) antagonists. The recommended regimens include all three; omission of the steroid is the most common mistake that clinicians make when prescribing these regimens.

The serotonin antagonists include dolasetron (Anzemet®), granisetron (Kytril®), ondansetron (Zofran®, generic), and palonosetron (Aloxi®). These are given on the same day as HEC to prevent acute CINV and are available in a variety of dosing forms – intravenous, oral, and transdermal patch – that vary by agent. For example, transdermal ondansetron can be especially useful in patients who are having difficulty keeping oral agents down.

Aprepitant (Emend®) and rolapitant (Varubi®) are selective high affinity antagonists of NK_1 receptors used for delayed CINV. Both are available as an oral and intravenous dosage form (fosaprepitant or aprepitant emulsion and rolapitant emulsion). The aprepitant emulsion appears to be better tolerated than the fosaprepitant, with a lower rate of infusion site pain and dyspnea. They are given once on the day of HEC administration. The intravenous formulations of aprepitant and both formulations of rolapitant have long enough duration of action that a single dose covers delayed CINV. If the oral form of aprepitant is used, doses need to be given for two days after chemotherapy.

Akynzeo® is an oral and intravenous combination product that contains netupitant, a highly selective

NK_1 antagonist, in combination with palonosetron. The combination's effectiveness was established in two clinical trials of 1,720 participants.[7,8] The clinical trials demonstrated that the combination (300 mg of netupitant plus 0.50 mg of palonosetron) significantly improved the prevention of CINV compared to the use of palonosetron alone in patients receiving either highly or moderately emetogenic chemotherapy. One netupitant-and-palonosetron capsule is taken about one hour before the start of chemotherapy, and the intravenous injection is given 30 minutes before. The package labeling also recommends for HEC, the addition of 12 mg of dexamethasone orally 30 minutes before a course of chemotherapy starts and then 8 mg of dexamethasone orally once daily on days two to four. Recipients of anthracycline- or cyclophosphamide-based chemotherapy or chemotherapy not considered highly emetogenic need to take dexamethasone only once per course (12 mg orally before the start on day one).

The response rate to serotonin antagonists is greatly improved when these agents are combined with dexamethasone, which is the standard of care.[9] Dexamethasone is given on the day of HEC administration and for two to four days afterward to prevent both acute and delayed CINV. A meta-analysis of 32 randomized controlled trials with 5,613 patients suggested superiority of dexamethasone over a serotonin antagonist for preventing delayed emesis.[10]

Olanzapine is an atypical antipsychotic that blocks multiple neurotransmitters, including dopamine, serotonin, catecholamines, acetylcholine, and histamine. Olanzapine 10 mg once a day is given on days one to three instead of aprepitant. Combined with a single dose of dexamethasone and a single dose of palonosetron, olanzapine was comparable to aprepitant at controlling acute and delayed CINV in patients receiving HEC.[11] It is also comparable to fosaprepitant.[12] One trial has also examined adding olanzapine to the standard three-drug regimen for HEC, with an improvement in complete response and in the percentage of patients without nausea over placebo.[13] Olanzapine, because it is available generically, is very inexpensive.

Combining the classes of agents just discussed leads to the best control of both acute and delayed CINV.[14] For HEC, a regimen including at least three classes is recommended (Exhibit 2). The option A and B regimens shown in Exhibit 2 are also an option for moderately emetogenic chemotherapy (MEC). The clinician can elect to withhold the NK-$_1$ antagonist for MEC from Option A. The option C regimen is not an option for MEC because it is excessive.

For chemotherapy regimens with low emetic risk, the NCCN guidelines recommend dexamethasone, serotonin antagonist, metoclopramide, or prochlorperazine started before chemotherapy and given daily during therapy.[2] For minimal emetogenic potential chemotherapy, no prophylaxis needs to be given.[2]

Oral chemotherapy is becoming more common and can cause significant CINV. Prophylactic regimens are recommended for moderate or highly emetogenic oral chemotherapy. Because oral chemotherapy is given for a longer duration, only oral or transdermal antiemetics are recommended. Serotonin antagonists are typically the first choice. If the regimen has low or minimal emetogenic potential, metoclopramide, serotonin antagonist, prochlorperazine, or haloperidol can be prescribed for as needed use.

Prevention of CINV with optimal antiemetics is the best way to reduce the incidence of anticipatory CINV. If patients develop anticipatory CINV, they can be taught behavioral techniques, such as relaxation methods, guided imagery, hypnosis, progressive muscle relaxation, biofeedback, and music therapy to manage symptoms. Acupressure performed by the patient is also an option. Antianxiety agents such as alprazolam or lorazepam can be started the night before treatment to lessen this type of CINV.

Breakthrough CINV is treated with a class of agent not previously used on an as-needed basis. There are many different choices to add to the regimen, including benzodiazepines, cannabinoids, metoclopramide, haloperidol, phenothiazines, olanzapine, scopolamine, or gabapentin. When a patient is having breakthrough CNV, it is important that clinicians check that the correct regimens were originally prescribed and that the patient was adherent.

Dronabinol capsules, a cannabinoid, were FDA approved in 1985 for CINV associated with chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. An oral dronabinol solution is also available, which may have a more favorable pharmacokinetic profile. The 2017 American Society of Clinical Oncology (ASCO) antiemetic guidelines state that evidence remains insufficient to recommend medical marijuana for either the prevention or treatment of N/V in patients who receive chemotherapy or radiation therapy.[5] Other nonpharmacologic agents have also been evaluated. Ginger and acupressure have both been studied for CINV and are modestly effective.[15,16]

Conclusion

Because of the substantial costs of uncontrolled CINV, prevention of CINV is the goal. To achieve this goal, the antiemetic guidelines should be followed. Optimal control for highly or moderately

emetogenic chemotherapy will require combination therapy to prevent both acute and delayed CINV.

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Implementing Shared Decision-Making Strategies in the Screening, Diagnosis, and Treatment of Major Depressive Disorder

Michael E. Thase, MD

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

Summary

Major depressive disorder has significant patient and health care system implications. There are many antidepressants which are effective for treatment, especially when combined with psychotherapy. To impact outcomes, shared decision making and measurement-based care should be implemented.

Key Points

- Generic SSRIs, SNRIs, mirtazapine, and bupropion are first-line therapies.
- Newer antidepressants are incremental advances.
- The nonmedication elements of care are more important than the medication.
- Shared decision making and measurement-based care are the new standards of excellence.

MAJOR DEPRESSIVE DISORDER (MDD) IS an important public health issue in the United States (U.S). It is the leading cause of absenteeism and suicide. Having a health care system that can efficiently identify and treat MDD is a necessity.

The percentage of persons treated with antidepressant drugs in the U.S. increased from 5.8 percent to 10.1 percent between 1996 and 2005 and 11 to 13 percent of U.S. adults now take antidepressants.[1] The rate of use increased for anxiety and adjustment disorders in addition to depressive disorders. Increasing rates of use correspond to decreasing rates of counseling and psychotherapy, which is unfortunate. Antidepressants are about twice as likely to be prescribed by primary care providers as they are by psychiatrists.

There has been growing public concern about antidepressants being over prescribed, being overvalued, and contributing to suicide. It is a misperception that antidepressants do not work, but they do not work as well as we might think and they only have about a 10 to 20 percent advantage versus placebo in reducing depression scores in randomized trials. Placebo responses are high in antidepressant trials. True drug responders only account for approximately one-third of responders, the rest are placebo responders.[2] Antidepressants tend to be a better treatment for those with more severe symptoms. Overall, the largest portion of the success of overcoming MDD comes from the process of being taken care of by health care providers, rather than by medication.

Antidepressants modestly increase the risk of suicidal thoughts (~2% above placebo) in youth and (~1%) for young adults. There is no evidence of increased risk of suicide in other adults. The risk of youth suicide is actually reduced by antidepressant use. When the rate of antidepressant prescriptions for youth declined after the addition of an FDA warning about suicidal thoughts, the rate of suicide in youth increased. Overall, antidepressant pharmacotherapy lowers the risk of suicide.[3]

Unfortunately, only about 50 percent of people with MDD receive treatment and only about 50

Exhibit 1: Additive Benefit of Time-Limited Psychotherapy in Major Depression[6]

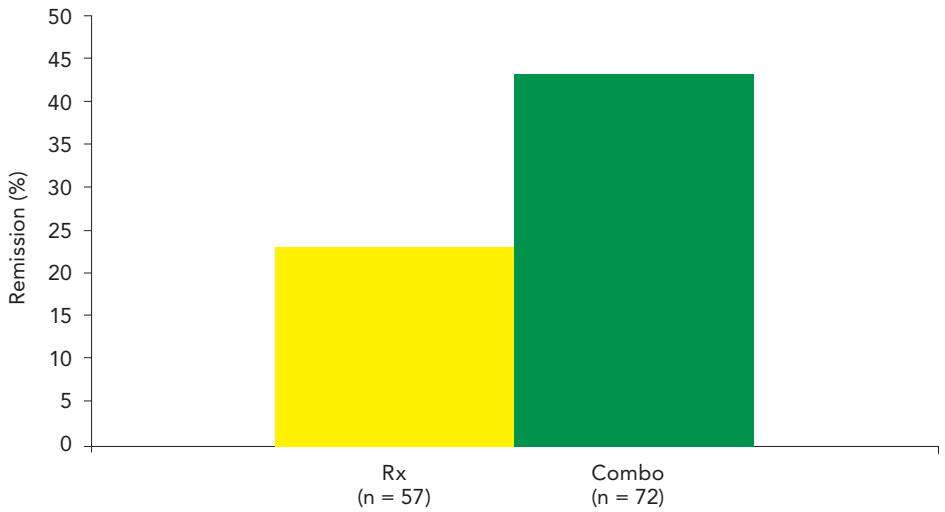


Exhibit 2: Key Elements of Measurement-Based Care

- Assess symptom severity at each visit with a short, accurate self-report scale
- Assess adherence at each visit (review prescription frequency and ask about medication taking)
- Assess adverse effects at each visit AND address those that are getting in the way of adherence

percent of people who are treated receive guideline-concordant care.[4] Guideline-concordant care has a 50 percent chance of success for first-line medication. Even when prescribed, many patients never fill the first prescription nor get refills. Ten percent of initial prescriptions do not get filled and approximately 33 percent of first scripts are not refilled.

What really matters in treating MDD is the care the patient receives – improving care improves outcomes in MDD. In randomized trials, more frequent sessions and longer sessions (25 to 30 minutes) with health care providers are associated with better outcomes. Increased monitoring and patient contact in primary care increase the chance of remission.[5] Additionally, combined psychotherapy and pharmacotherapy regimens typically convey a 10 to 20 percent advantage in response and remission rates over pharmacotherapy alone (Exhibit 1).[6] Because it may not be cost effective to have combination therapy in all patients, combined psychotherapy and pharmacotherapy should be aimed at those with the highest risk of failure with antidepressants alone.

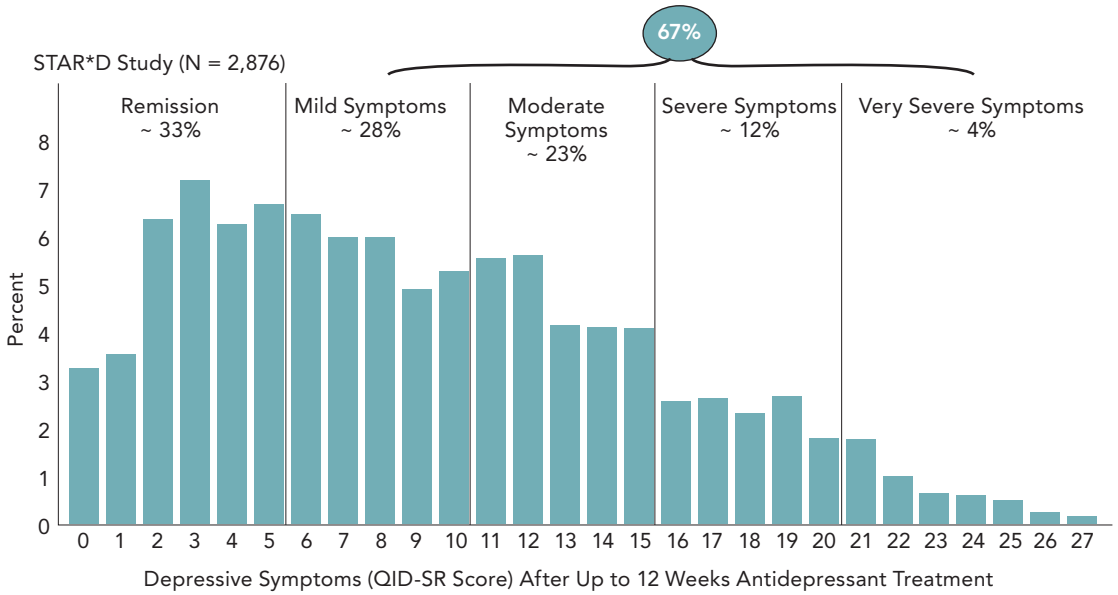
The goal of MDD treatment is to achieve remission of symptoms and improve functioning. Therapy has to be continued for six to nine months after symptoms abate to ensure recovery. Improving adherence with medications also has been shown to improve outcomes.[7] Check in through phone calls or Internet, frequent in person visits, and education about the disease and medication are all interventions to improve adherence in MDD treatment.[8]

Measurement-based care, another way to improve care, has been shown to improve clinician and patient ratings of depression symptoms.[9] Measurement-based care requires assessing symptoms, adherence to medication, and adverse effects at each visit (Exhibit 2). The best symptom scales to use in practice are free to administer (available in public

Exhibit 3: Important Questions and Considerations

- How do these treatments match your own views about what is wrong?
- What experiences do you have with this? (Personal, family and other)
- What are your concerns and worries?
- What information do you need to come to a decision?

Exhibit 4: Response to Antidepressant Therapy is More Dimensional than Categorical



STAR*D = Sequenced Treatment Alternatives to Relieve Depression

domain), take less than five minutes to complete, show acceptable psychometrics, and are sensitive to change. The Patient Health Questionnaire and the Quick Inventory of Depressive Symptomatology (Self-Report) are the two best because they meet all four criteria. These two scales can be used for depression screening and for monitoring efficacy of therapy.

Shared decision making acknowledges shared responsibilities of the prescriber (content expert) and the patient (both as consumer and personal expert based on past experiences). Some important questions and considerations in shared decision making for treating depression are shown in Exhibit 3. The first decision to be made at the time of MDD diagnosis is whether to "wait and see" or treat with medication, psychotherapy, both, or something else.

Some health care systems have a wait and see approach before treating. Waiting before treating is about half as effective as a placebo and one-third as effective as an antidepressant. Odds of benefit improve for "wait and see" when MDD severity is low and there is a transient stressor preceding depression onset. The ethical obligation of wait and see is to try to ensure the person with depression is not lost to follow-up.

Treatment can be either psychotherapy, medication, or a combination. Evidence-based psychotherapy is equally effective as antidepressant treatment in groups of MDD outpatients across 12 to 16 weeks. Chronicity and severity may favor medication. Otherwise, psychotherapy has fewer adverse effects, no discontinuation symptoms, and lower attrition; however, it does have a slower onset of action (8 weeks versus 4 weeks). As noted previously, the combination has the highest rate of remission

success. Patient preference for the treatment option is most important.

Generally, all the antidepressants have similar efficacy. [10] Antidepressant choice depends on personal history, adverse effects and safety issues, family history of response or lack of response, drug interactions, mechanism of action, indication for comorbid disorder, cost, and patient preference. Consensus across guidelines is that selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion (NDRI), and mirtazapine (NaSSA) should be first-line antidepressants. Mirtazapine is first-line only for the elderly. These are available generically and are relatively inexpensive. Most clinicians will choose a SSRI initially.

The newer antidepressants include vilazodone (Viibryd®, 2011), levomilnacipran (Fetzima®, 2013), and vortioxetine (Brintellix®, 2013), which are primarily second- or later-tier agents because they are brand only and offer little in terms of therapeutic advance. Vilazodone, similar in structure to trazodone, blocks serotonin transporters and is a partial agonist of serotonin 5HT1A receptors. Because this agent causes a low incidence of sexual side effects, vilazodone is a second-line agent when someone has sexual side effects from first-line agents. Levomilnacipran is a SNRI with twofold greater selectivity for norepinephrine. Because of the effect on norepinephrine, it causes more adverse effects than other SNRI or SSRI agents. Vortioxetine is a multimodal serotonergic antidepressant. It results in both serotonin reuptake inhibition and antagonism of certain serotonin receptors (5-HT3 and 5-HT7), in addition to complex effects on 5-HT1a, 1b, and 1c. The effects on 5-HT7 may be cognitive enhancing. Despite an advisory panel opinion, the FDA did not approve labeling about positive self-reported effects on cognition in two trials.[11,12] In efficacy trials, it was comparable to duloxetine and may cause fewer sexual side effects than SSRIs. Vortioxetine was superior to escitalopram in improving SSRI-induced treatment-emergent sexual dysfunction while efficacy was maintained.[13] This may be an option for those who have sexual dysfunction with first-line agents or for elderly patients who have pre-existing cognitive issues or are on first-line agents.

One common mistake in treating MDD is waiting too long to change an ineffective treatment. The time to intervention based on response is typically measured in months, and it should be weeks. Clinicians need to act on evidence that a medication is not working. Although clinicians may think of responders and non-responders, the response to antidepressant therapy in MDD is more dimensional than categorical. There will be patients who have remission of symptoms, some residual symptoms, or little relief (Exhibit 4).[14]

Once considered indicative of bad practice, combining antidepressants is now commonly done for treatment-resistant depression. About one-third of patients will have a second antidepressant added to their regimen for inadequate response with bupropion and mirtazapine, the typical agents added. No antidepressant has FDA approval for combination use and only mirtazapine has the support of two positive studies, but the combination of bupropion and mirtazapine with most other commonly used agents is safe.

Second-generation antipsychotics do have a place in the treatment of MDD. Five have established efficacy as adjuncts to antidepressants (aripiprazole, brexpiprazole, olanzapine, quetiapine, risperidone). Quetiapine has established efficacy as a monotherapy in MDD. There are also adverse effect issues, including weight gain, metabolic issues, and tardive dyskinesia, which have to be considered when an antipsychotic is added to the treatment plan. These agents work within two weeks. Whether the addition of the antipsychotic should be early second-line treatment or reserved for later lines of therapy has not been determined. Additionally, issues of cost-effectiveness and the optimal duration of therapy have not been settled.

Conclusion

Generic SSRIs, SNRIs, mirtazapine, and bupropion are first-line therapies for MDD. The newer antidepressants are incremental advances. The nonmedication elements of care are more important than the medications in treatment success. Shared decision making and measurement-based care are the new standards of excellence in MDD treatment.

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Novel Treatment Strategies in Ovarian Cancer: A Closer Look at the Role of PARP Inhibitors

Don S. Dizon, MD, FACP, FASCO

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 introduction of poly ADP ribose polymerase (PARP) inhibitors is changing the treatment landscape of ovarian cancer. These agents are being used after chemotherapy to maintain disease remission and as single-agent treatment after disease progression in selected patients. Since this oral cancer treatment can cause significant adverse effects, clinicians need to work with patients to ensure adherence to therapy.

Key Points

- Genetic evaluation is critical for women at the time of an ovarian cancer diagnosis.
- Genomic testing for recurrent disease should be thoughtfully ordered.
- PARP inhibitors have differing indications for different populations.
- As maintenance, they are used after a treatment response to platinum for women with recurrence.
- As a treatment line, they are for previously treated recurrent ovarian cancer and limited to women with a known mutation in BRCA.

AMONG GYNECOLOGIC CANCER SITES, ovarian cancer is the second most common in incidence and the most common cause of death. In 2017,there were 22,000 new cases and 14,000 deaths.[1] Unlike other cancers, women with ovarian cancer will progress through different disease states (Exhibit 1)[2] When initially diagnosed, primary treatment will lead to remission in most women, and there is a 10 percent five-year survival. Most women will go two years before the disease recurs. At this first recurrence, the disease can be platinum sensitive (>12 months since chemotherapy before recurrence), partially sensitive (6 to 12 months), platinum resistant (1 to 6 months), or platinum refractory (0 to 1 month). What makes ovarian cancer different from other cancers is that if a woman goes 12 months or more without recurrence, the disease will still be platinum sensitive at recurrence. Platinum refractory disease is a cancer that is growing while on platinum- based therapy. Whether after initial therapy or a third recurrence, most women will end up with refractory/persistent disease, which leads to death. In addition to predicting response to platinum treatment, progression-free interval predicts disease outcomes.[3] The median survival for women diagnosed with ovarian cancer has been three years, but that may be improving with newer therapies.

Genetic mutations driving ovarian cancer have been discovered. These are usually mutations in breast cancer gene (BRCA) 1 or 2. In one trial, mutated BRCA1 or 2 (mBRCA) was found in 14.6 percent of participants, and mutation of the BRCA-Fanconi anemia pathway in 3.3 percent.[4] Other DNA damage repair gene mutations (mismatch re-

Exhibit 1: A Disease State Model of Ovarian Cancer[2]

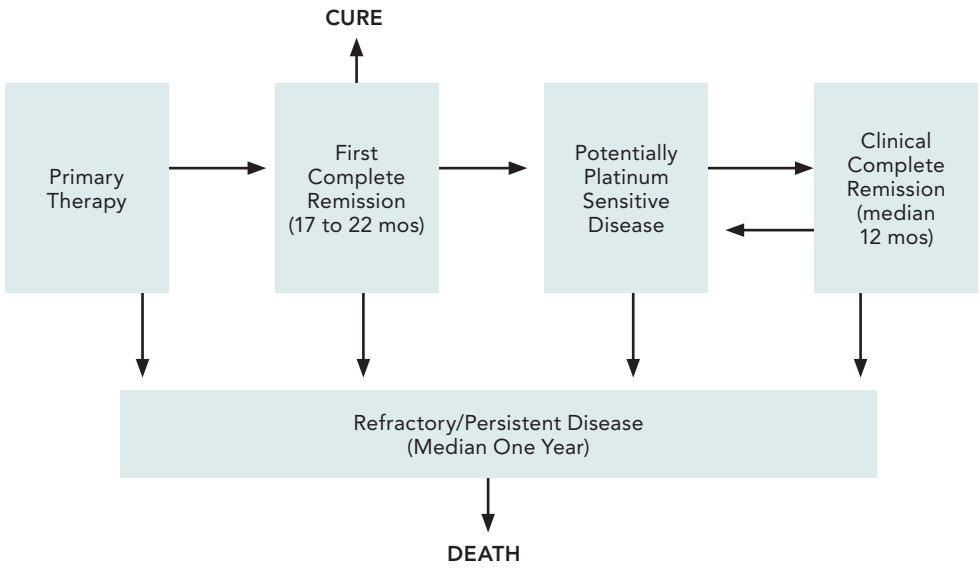

Exhibit 2: Genetic Testing in Ovarian Cancer

Test	Genes in Panel (n)	Turn Around
BRCAplus (Ambry Genetics)	6	1 – 2 weeks
OvaNext (Ambry Genetics)	25	2 – 4 weeks
Breast/Gyn Guidelines panel (Invitae)	19	1 – 3 weeks
Color Genomics	19	4 – 8 weeks
Breast/Ovarian panel (GeneDx)	21	3 weeks
Genetic Health Risk report for BRCA1/2 (23andme)	2	NOTE: only tests for 3 mutations in BRCA 1 or BRCA2
Comprehensive gene panels		
CancerNext (Ambry Genetics)	32	2 – 3 weeks
Comprehensive panel (GeneDx)	32	3 weeks
myRisk (Myriad)	25	2 – 4 weeks
Multi-Cancer Panel (Invitae)	79	1 – 3 weeks

pair deficiency), which predict response to immunotherapy in other cancers, is rarely seen (0.4%) in ovarian cancer.[4]

Selected genetic tests for use in ovarian cancer are shown in Exhibit 2. The Society of Gynecologic Oncologists recommends germline genetic testing at the point of diagnosis for those tumors with high grade histologies (which are the tumors that typically have mBRCA).[5] The National Comprehensive Cancer Network (NCCN) recommends testing all patients.[6] Testing should be done for various reasons, including to select treatment, to identify need for primary prevention of breast and ovarian cancer in family members, and to consider secondary prevention strategies, such as mastectomy to prevent breast cancer. Preventing cases of cancer in family members can save significant health care dollars.

Genomic testing is testing for mutations expressed in a tumor alone (somatic) versus those that are inherited (germline). There are questions whether all

Exhibit 3: Terms in the Treatment of Recurrent Ovarian Cancer

Term	Definition
Consolidation	Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body.
Maintenance	Treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy; it may be given for a long time.
Switch Maintenance	Treatment with an agent with a different mode of action after completion of induction chemotherapy in patients whose tumors have not progressed.
Trealment Line	Therapy administered to achieve an endpoint (i.e., response, durable stability, etc.) after surgery (i.e., adjuvant) or after progression on a prior line (e.g., for control or palliation).

ovarian cancer samples should undergo genomic testing. In two trials, 65 percent and 94 percent of biopsy samples had targetable mutations, but only 18 percent of patients received targeted therapy based on the testing.[7,8] Testing should be driven by data on the frequency of actionable mutations covered by an FDA-approved targeted agent and access to those therapies. If the testing is not going to be used to select treatment, then it should not be ordered. Sites, which are steering patients to clinical trials, may do genomic testing, even if targeted therapies are not available in order to find appropriate trials.

Some terms are used regularly in the treatment of recurrent ovarian cancer (Exhibit 3) First-line agents for recurrent ovarian cancer are platinum-based regimens for platinum-sensitive disease, non-platinum agents for platinum-resistant disease, and single-agent targeted therapy with bevacizumab, olaparib, or rucaparib.[6] Choosing the right treatment for a given patient requires listening to the patient's goals and preferences on dosing interval, administration route, and adverse effects, considering the disease burden (performance status, symptoms, and volume of disease), and knowing the interval since the last platinum-based chemotherapy regimen to determine platinum sensitivity or resistance.

Ovarian cancer cells often have pre-existing defects in DNA damage repair pathways, especially BRCA (mBRCA). The mutation causes defective repair of breaks in double-stranded DNA. Poly ADP ribose polymerase (PARP) is another pathway involved in DNA repair. PARP inhibitors (PARPi) prevent repair of breaks in single-stranded DNA and induce synthetic lethality in tumors deficient in homologous recombination. The concept of synthetic lethality is that cell death occurs when two separate mechanisms for repair of defective DNA are present in a cell and both are incapacitated. If only one DNA repair mechanism is defective, then the cell can remain viable.

There are three FDA-approved PARPi, niraparib (Zejula®), olaparib (Lynparza®), and rucaparib (Rubraca®), which are used for maintenance and treatment in ovarian cancer and are given orally. All three have FDA approval as maintenance-therapy treatment of patients with recurrent epithelial ovarian cancer who are in a complete or partial response after platinum-based chemotherapy. For maintenance therapy, it does not matter if germline mBRCA is present, as these agents still improve progression-free survival by 11 to 15 months.[9-11] There is ongoing investigation to identify biomarkers for response to PARPi other than mBRCA. There is a suggestion from an olaparib trial that giving a PARPi as maintenance may change the tumor to make it sensitive to platinum in future lines of therapy. Maintenance therapy is continued until disease progression.

PARPi have also been studied as a treatment-line, with only olaparib and rucaparib currently approved. Olaparib in patients with mBRCA and platinum-resistant ovarian cancer produced an overall response rate in 31 percent of the subjects and a complete response in six women (n = 193).[12] The median duration of response was 225 days and stable disease was seen in 40 percent. Olaparib is FDA approved as monotherapy for germline-mutated

Exhibit 4: PARP FDA Approvals in Ovarian Cancer

DRUG	INDICATION	POPULATION
Olaparib	Maintenance	Recurrent ovarian cancer, treated with platinum-taxane, no biomarker.
	Treatment	Recurrent ovarian cancer, 3 or more prior lines received, must be gBRCA mutation carrier.
Rucaparib	Maintenance	Recurrent ovarian cancer, treated with platinum-taxane, no biomarker.
	Treatment	Recurrent ovarian cancer, 2 or more prior lines received, must be germline or somatic BRCA mutation carrier.
Niraparib	Maintenance	Recurrent ovarian cancer, treated with platinum-taxane, no biomarker.

Exhibit 5: Cost Effectiveness of PARP Inhibitors Compared to Bevacizumab for Maintenance[16]

	gBRCA		non-gBRCA		HRD	
	PFS difference (months)	ICER	PFS difference (months)	ICER	PFS difference (months)	ICER
Olaparib	13.6	$231,567				
Niraparib	15.5	$244,322	3.1	$304,775	9.1	$255.609
Rucaparib	11.2	$248.992			8.2	$278,552
Bevacizumab*			4.0	$531,151		

gBRCA = germline mutation in breast cancer gene
HRD = homologous recombination deficiency (other than BRCA)
PFS = progression free survival
ICER = incremental cost-effectiveness ratio

BRCA advanced ovarian cancer that has progressed after three or more prior lines of treatment. Rucaparib was studied in 67 women with either germline or somatic mBRCA and produced an objective response rate in 54 percent and a median duration of response of nine months.[13] It is FDA approved with a companion next-generation sequencing diagnostic test for somatic mBRCA. Exhibit 4 summarizes the FDA approvals of the PARPi in ovarian cancer.

Overall, PARPi can be difficult to tolerate. The common adverse effects include nausea, thrombocytopenia, fatigue, diarrhea, constipation, and anemia. Most of these can be managed or even anticipated. A bowel regimen should be started as soon as the medication is started to prevent constipation. Some clinicians also give prophylactic antiemetics because of the high rate of nausea. Frequent blood counts are also necessary to monitor for myelosuppression. Encouraging physical activity is the best way to combat fatigue which can be debilitating.

Several factors have to be considered in selecting patients for PARPi therapy. Patients must have a functioning gastrointestinal tract, good performance status, no history of dose-delays or reductions due to myelosuppression with chemotherapy, and overall good organ function. The ideal patient would have high-grade serous histology and a known genetic mutation impacting homologous recombination. This class of agents has not been studied in low-grade histology. In platinum-responsive disease, PARPi can be used at any point. With platinum resistance, they should be used early on and only in women with genomic or somatic mutation.[14] Women with platinum-resistant disease tend to have

Exhibit 6: Cost-Effectiveness of Niraparib for Maintenance[17]

Strategy	Cost per Patient ($)	PF-QALY Benefit per Patient (years)	Incremental Cost-Effectiveness Ratio ($ per PF-QALY)*	Additional Annual Cost to U.S. health System ($)
Observation	$827	0.29	–	–
gBRCA testing per selective treatment	$44,221	0.48	$225,919 per PF-QALY	$246,000,000
gBRCA testing + HRD per selective treatment	$105,933	0.71	$262,463 per PF-QALY	$590,000,000
Treat all	$165,703	0.74	$2,377,922 per PF-QALY	$922,000,000

gBRCA = germling mutation in breast cancer gene
HRD = homologous recombination deficiency (other than BRCA)
PF-QALY = progression-free quality-adjusted life-year

non-functional bowels by their third- or fourth-line of therapy. At this stage, it is not known if PARPi can be used in subsequent therapy lines if already used earlier.

To be adherent with PARPi therapy, patients must be engaged in their care. The major toxicities of all PARP inhibitors should be anticipated and treated as soon as possible to help patients stay on therapy. Patient-reported outcomes systems and nurse navigation can be used to enhance adherence.

PARPi are expensive; however, cost-effectiveness data are starting to come out for their use, at least for maintenance. There are some data to suggest that a PARPi is more cost effective than bevacizumab for maintenance. [15,16] Exhibit 5 shows data from three decision analysis models generated to compare the cost of observation versus the cost of PARPi therapy for patients with platinum-sensitive recurrent epithelial ovarian cancer with germline BRCA1/2 mutations (gBRCA), evidence of homologous recombination deficiency (HRD), and no germline BRCA1/2 mutation (non-gBRCA). This analysis found that while PARPi demonstrate clinical benefit as maintenance therapy, they are not cost effective at their current average wholesale prices based on a traditional incremental cost-effectiveness ratio (ICER) cutoff. Another decision analysis comparing three strategies for niraparib maintenance treatment of platinum-sensitive recurrent ovarian cancer with observation found similar results of non-cost-effectiveness. (Exhibit 6).[17] The authors of this analysis suggest a preferred strategy of treatment of patients with gBRCA alone or with HRD + tumors with PARPi over global treatment of all ovarian cancer patients.

Conclusion

Ovarian cancer is still the most fatal gynecologic cancer; however, the treatment landscape continues to broaden. Genetic evaluation is critical for women at the time of diagnosis. Genomic testing for recurrent disease should be thoughtfully ordered. PARP inhibitors have differing indications for different populations. As maintenance, they are used after a treatment response to platinum for women with recurrence. As a treatment line, they are for previously treated recurrent ovarian cancer and limited to women with a known mutation in BRCA.

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Optimizing Clinical and Economic Outcomes in the Management of Primary Immunodeficiency Diseases: Taking a Closer Look at the Role of Immunoglobulin Replacement Therapy

Mark Ballow, 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

Patients with primary immunodeficiency diseases (PIDDs) require expensive, lifelong administration of immunoglobulin replacement. Choosing an administration route that works for the patients will result in adherence with therapy. Choosing an appropriate dose can result in an infection-free patient who is less costly than one whose infections are not controlled.

Key Points

- Treatment of PIDD requires immunoglobulin replacement.
- The administration route should be a decision made between the patient and the clinician.
- Subcutaneous administration is favored by most patients.
- Dosing of immunoglobulin should be individualized.

PRIMARY IMMUNODEFICIENCY DISEASES (PIDDs) are a group of more than 300 diseases characterized by defects in the immune system. Recurrent infections and difficult to treat infections are two warning signs of immunodeficiency (Exhibit 1).[1] Primary immunodeficiency affects approximately 500,000 people in the United States (U.S). Exhibit 2 shows the distribution of the various types. PIDDs occur in males twice as often as in females. Most PIDDs are inherited and more than 350 different genetic mutations leading to PIDDs have been identified. There are two age peaks for diagnosis of PIDD. Twenty-seven percent of patients are diagnosed by age 6 and 48 percent are diagnosed between the ages of 30 and 65. It can take years for a pattern of recurrent infections or other symptoms to be apparent before a PIDD is suspected, especially in adults. On average, it currently takes eight years for an adult patient to be diagnosed, whereas, before 1970 it took 14 years

The earlier patients are diagnosed and placed on appropriate replacement therapy, the lower the risk of complications and the lower the treatment costs. Early diagnosis in childhood has been enhanced by newborn screening programs in many states. The delay in diagnosis in adults can lead to complications from multiple infections, such as bronchiectasis from multiple pulmonary infections.

Diagnosis of a suspected PIDD begins with an evaluation of the adaptive immune system. The majority of the diagnostic evaluation should be conducted by an immunology specialist. The first step is a complete blood count with differential to rule out leukemia or other blood disorders and to obtain a serum quantitative immunoglobulin measurement (IgG, IgA, IgM, IgE, and IgG). The second step is to determine if the patient can make natural antibodies after exposure to a pathogen or to vaccines. Vaccine-specific antibody responses to tetanus, *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, and *influ-*

Exhibit 1: 10 Warning Signs of Immunodeficiency[1]

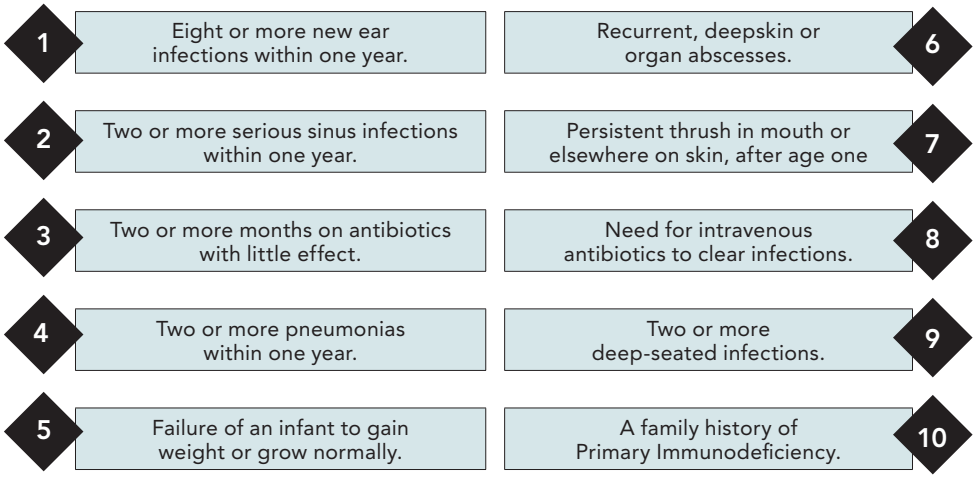
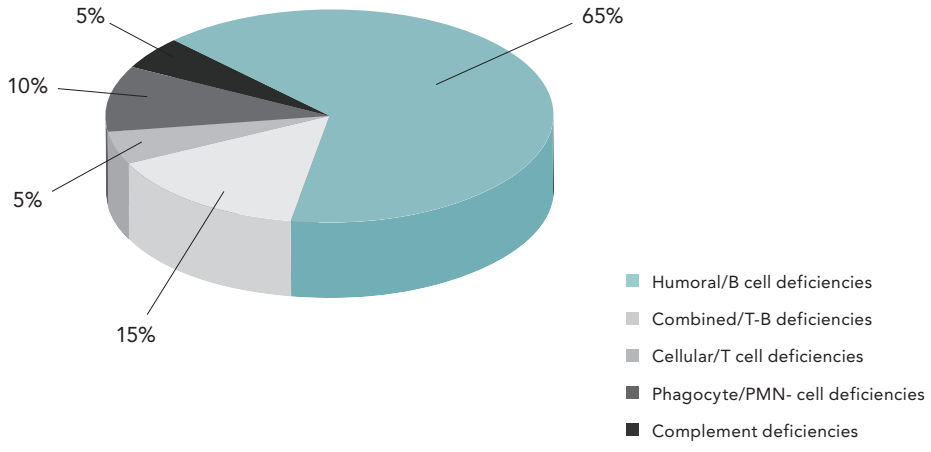


Exhibit 2: Primary Immunodeficiencies

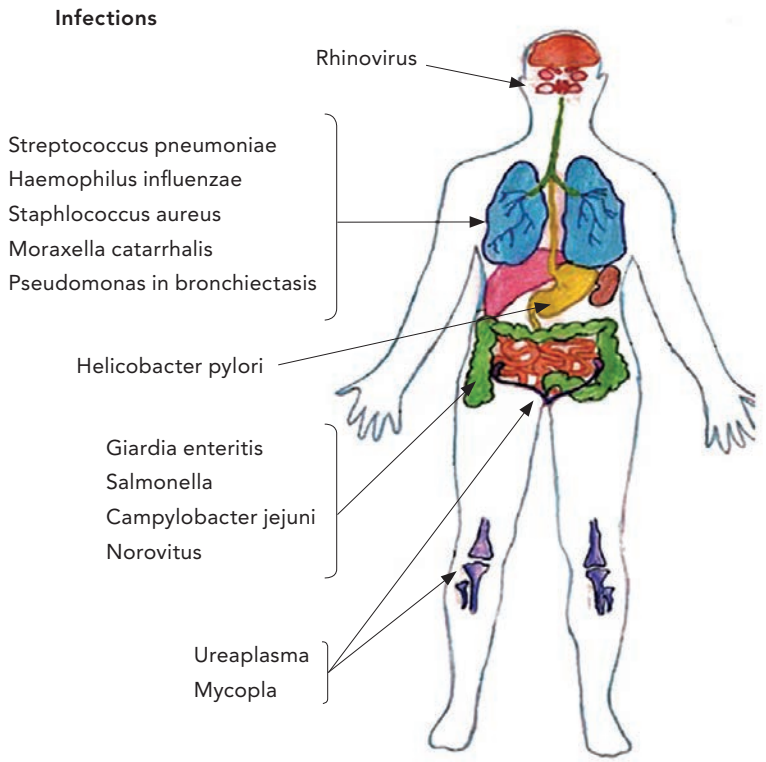


enza virus A and B are measured. Immune phenotyping and lymphocyte subset counts, including T (CD3, CD4, CD8), B (CD19) and natural killer cells (NK) cells, are done. The next stage of testing includes B cell panels (naïve, switched memory, plasma cells), further T cell panels (naïve/memory/effector/activated T cells, naïve recent immigrant T cells, regulatory T cells), and lymphocyte proliferative responses to mitogens/antigens (T cell competence assay). Genetic testing may eventually be a substitute for many of the expensive tests that are currently being used to make a PIDD diagnosis. Multiple specific genes for the various PIDD have been identified.

Infections, especially chronic debilitating ones, are a significant issue in PIDDs (Exhibit 3), but they are not the only issue. For example, when these patients get norovirus they cannot get rid of it. Patients can have many non-infectious manifestations (Exhibit 4) which can significantly impact quality of life and costs-of-care.[2] The non-infectious complications also increase mortality. The risk of death is eleven-fold higher in patients with non-infectious complications compared to those without these complications.[3] Increased mortality is associated with lymphoma, hepatitis, lung disease, and gastrointestinal disease.

Genetic testing is being used to identify those

Exhibit 3: Infections in PIDD[2]



likely to have non-infectious complications.[4] Therapies to target the specific defects of immune dysregulation that lead to many of the non-infectious complications are being developed. For the majority of patients with primary immunodeficiencies, immunoglobulin replacement is the only lifesaving therapy and treatment is lifelong, since the vast majority of primary immunodeficiency patients have primary antibody failure. Various preparations have been used since the 1940s. In 1981, the first intravenous immunoglobulin (IVIG) preparations were approved for primary immune deficiencies which could significantly raise immunoglobulin G (IgG) levels. IgG is the main type of antibody for controlling infection with viruses, bacteria, and fungi. Various problems with the IVIG preparations were identified over the years, including transmission of cytomegalovirus, Creutzfeldt-Jakob disease/new variant prion disease, hepatitis C, renal failure from sucrose containing products, and thromboembolic adverse events (AEs). The safety of these products has been significantly improved with better screening. Testing for and removal of procoagulants has largely eliminated thromboembolic AEs.

The immunoglobulin products are derived from donor pools of 2,000 to 10,000 donors. The composition is primarily monomeric IgG (>95%), with small amounts of dimeric and polymeric IgG and small amounts of IgM and IgA. One gram of an immunoglobulin product contains 4x1018 molecules of antibodies, which have greater than 107 specificities to a broad range of bacterial and viral pathogens. They are stabilized with sugars or amino acids which differ for each product.

The FDA-approved package labeling for immunoglobulin products warns that anaphylaxis, thromboembolism, renal failure, hemolysis, or aseptic meningitis can occur. Although these products have a good safety record, the manufacturers continue to strive for improvements. As these products are derived from human plasma and a potential source of contamination by a variety of blood-borne pathogens, they are capable of disease transmission. Viruses are of particular concern, as bacteria are easy to detect and remove. The production of immunoglobulin products and virus reduction can be broken down into three stages; screening, inactivation, and removal, each designed to complement one another, further reducing the risk of disease transmission. Although the manufacturers of all currently avail-

Exhibit 4: Non-Infectious Problems in PIDD[2]

- Failure to Thrive
- Enteropathy
- Colitis
  - Diarrhea
  - Malabsorption
- Autoimmunity
  - Immune thrombocytopenia purpura
  - Autoimmune hemolytic anemia
  - Alopecia
  - Rheumatoid arthritis
  - Inflammatory bowel disease
  - Celiac like disease
- Hematologic Disorders
  - Neutropenia, anemia, thrombocytopenia
  - Lymphoproliferative disease
  - Splenomegaly
- Atopy
  - Severe eczema, food allergies, environmental allergies
- Endocrinopathies
- Dysmorphic features

able products comply with industry safety standards, some products are subjected to additional testing. Screening involves screening the donors by interview, a questionnaire, and a brief physical examination and testing the plasma for antibodies for a variety of viral diseases. At this stage, some manufacturers will hold the plasma of first-time donors and will discard it if the donor does not appear for a second donation within six months. All plasma will be held in inventory until viral screening of the plasma is complete. Once the plasma is deemed free of pathogenic contamination, the units will be pooled and, in some cases, they may be subjected to a second round of viral marker screening.

Inactivation destroys a virus's ability to infect cells and can be accomplished using physical and/or chemical methods. Currently, available preparations are produced using a number of inactivation methods. Pathogenic agents not destroyed by inactivation are then removed from IGIV preparation by one, or a combination of removal methods. Current products are presumed safe from disease transmission; however, there are differences in each manufacturer's approach to the safety process.[5]

Immunoglobulin replacement products are available for intravenous or subcutaneous infusion. The Immune Deficiency Foundation produces a chart which compares all the available products in terms of production method, administration details, sugar and sodium content, and IgA content (primaryimmune.org). Intravenous administration of these products is well tolerated by most patients and allows for large volumes per infusion, as well as intermittent dosing (every 21-28 days).[6] Additionally, there is also more than 30 years of clinical experience with intravenous administration. A drawback is the requirement for venous access and trained personal to administer, so these products are typically infused in hospitals or infusion centers. In addition, the large shift in IgG levels during dosing may cause adverse effects, such as headaches at or just after peak, and some patients experience fatigue, joint symptoms, or other forms of general malaise at trough levels. If such troughs are avoided by giving fractionated dosing at weekly intervals, these patients may have fewer adverse events. Home intravenous infusion is possible, but it is more technically demanding than subcutaneous administration.

There are over 20 years of international data on subcutaneous immunoglobulin (SCIG) clinical use. These products facilitate self- or home-infusion and venous access is not required. There are also signifi-

cantly fewer adverse effects with SCIG.[7] With subcutaneous administration, gradual absorption leads to more consistent IgG levels. The ability to self-infuse does require a reliable and adherent patient. Disadvantages of SCIG are more frequent dosing and multiple infusion sites may be required.[6] Approximately 60 percent of patients with PIDD are on SCIG compared with 40 percent on IVIG.

SCIG is typically administered weekly, with a recommended dose of 100 to 200 mg/kg/weekly.[8] The weekly dose can be administered in different ways based on patient preference and to reduce adverse effects. It can be administered once weekly or biweekly, with the weekly dose divided by three and given three times per week, or with the weekly dose divided by seven and given daily. Biweekly dosing is possible with the newer 20 percent SCIG products. Infusion generally takes one to two hours if given by a pump and 5 to 15 minutes if given by rapid push.

Patients have many choices for routes of administration of replacement Ig therapy – IVIG, conventional SCIG, and hyaluronidase-facilitated SCIG. The administration route should be a decision made between the patient and the clinician. The goal of immunoglobulin replacement is elimination of infections. Dosing of the products to achieve this goal is somewhat controversial. Managed care plan policies may recommend levels achieving target IgG levels around 500 mg/dL because this level has been shown to significantly reduce the risk of minor infections and infections that required hospitalization, but data supporting higher trough values and individualized trough values are available. A 27 percent reduction in pneumonia incidence for each 100 mg/dL increment in trough IgG was found in another study; the incidence of pneumonia associated with 500 mg/dL trough levels was fivefold that with 1000 mg/dL.[10] A prospective analysis over 22 years found that mean trough levels of 750 to 900 mg/dL were needed to keep patients at low infection rates (< 2.5 infections per year).[11] Those with bronchiectasis need higher trough values. The bottom line is that immunoglobulin replacement doses should be titrated to clinical efficacy for an individual patient (i.e., infection free).[12]

Numerous quality of life (QOL) studies with immunoglobulin replacement in patients with PIDD have been conducted. Approximately one-third of patients are at risk for anxiety and depression related to their disease, with this risk higher in females. A patient's clinical condition rather than treatment strategies with Ig has a major role in causing poor health-related QOL. Multiple QOL studies comparing IVIG and SCIG use show that there is better QOL with SCIG.[13, 14] An adult disease-specific health QOL tool has been developed and is used by several centers to follow patients on replacement.[15]

The nuances of Ig replacement therapy may result in barriers related to appropriate and adequate dosing. Specialty pharmacists may dictate dosing without a full appreciation of the clinical course of the patient. Most clinical immunologists do not use the adjustment factor for SCIG that is in the package insert as a treatment starting point for replacement-therapy. An apparent fixation on trough levels of 500 mg/dL has the potential to limit the appropriate dosing of patients. It is important to treat the patient not the numbers. A payer policy that requires taking patients off of replacement to see if infections recur is inappropriate.

Product selection is paramount, since Ig products are not generic and/or interchangeable. There are a number of differences in manufacturing, safety procedures, stabilizers, and adverse reactions among the products, so they are not interchangeable. Switching products after tolerability has been demonstrated with a given product can result in adverse effects and reduced efficacy. Particular caution is advised when switching IVIG products because a significant portion of patients (15-18%) will have adverse reactions with switching. Adverse effects are the primary reasons why patients prefer a specific product.[16] Formulary restrictions may mandate selection of a 5 percent IVIG product over a 10 percent IVIG product, regardless of clinical appropriateness related to volume considerations and length of infusion.

Beyond appropriate dosing and administration, patient satisfaction and resultant adherence are crucial for treatment success. In a recent survey of individuals with PIDD, most respondents (76%) were satisfied with their current treatment. However, patients remained below the physical and mental well-being norms for health-related quality of life, as determined by the questionnaire. All respondents expressed a desire for once monthly infusions, the ability to administer Ig at home, self-administration, shorter duration of administration, and fewer needle sticks.[17]

There is little data on the cost-effectiveness of PIDD treatment. Total annual costs for infection are reduced after patients start on immunoglobulin replacement.[18] Several studies from Europe and Canada have shown that SCIG therapy results in significant reductions in health care resource utilization and expenditures compared with IVIG when SCIg is dosed 1:1 with IVIG.

Because of the expense of immunotherapy replacement, some have tried reducing doses. There are no studies that have documented procedures of reducing dosages, and this is a practice for which there is no current available guidance. Reducing

doses can potentially put patients in harm's way.

The Immune Deficiency Foundation has developed a model coverage policy which managed care plans can consider adopting (www.primaryimmune.org). They also publish diagnostic and clinical care guidelines for primary immunodeficiency diseases. The American Academy of Allergy, Asthma and Immunology (AAAAI) Primary Immunodeficiency Diseases Committee has created an immunoglobulin replacement toolkit to educate payers and regulators who are responsible for coverage determinations and aid physicians in the safe, effective and appropriate use for patients with primary immunodeficiency diseases. To download the AAAAI IVIG Toolkit, go to www.primaryimmune.org/services/patient-insurance-center/aaaai-ivig-toolkit.

Conclusion

Immunoglobulin replacement therapy is required in patients with certain PIDDs characterized by absent or deficient antibody production: necessary and life-saving. Treatment regimens should be individualized for each patient. The safe and effective use of immunoglobulin requires attention to numerous issues that relate to the site of care, the product and the patient. Numerous studies have demonstrated an enhanced quality of life in patients receiving SCIG compared with IVIG therapy. Greater flexibility now exists in the frequency of SCIG dosing with 20 percent SCIG formulations.

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Exploring Treatment Advances in Epilepsy: Keys to Optimizing Adherence and Patient Outcomes

Carl W. Bazil, MD, PhD

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

Summary

Patients with epilepsy should be seizure free. Obtaining this goal may require trying several different medications and may require referral to specialists for additional testing. Seizure control is possible with medication, surgery, or devices.

Key Points

- Epilepsy is a common, diverse disorder characterized by recurrent unprovoked seizures.
- Seizures can be focal or generalized, and most are controlled with medication.
- The best antiepileptic drug depends on many individual factors.
- Those with refractory disease require specialty evaluation, including video-EEG to verify diagnosis and evaluate for alternatives (surgery or devices).
- Patients can and should be free of all debilitating seizures with no adverse effects.

EPILEPSY IS COMMON AND 1 TO 3 PERCENT of the United States (U.S.) population has active epilepsy. The incidence of epilepsy is 50 per 100,000 person-years. It can begin any time in life, but the rate is higher in the young and elderly. There is still a stigma to having epilepsy, and many people still believe that a patient with the disease has brain damage, despite the fact that most patients have normal cognitive function.

Epilepsy is a disease defined as an enduring predisposition to seizures. A seizure is a symptom and is a paroxysmal change in behavior due to abnormal electrical activity in the brain. Seizures have many causes, only one of which is epilepsy. Ten percent of people will have at least one seizure during their lifetime. Epilepsy is two or more unprovoked seizures or one unprovoked seizure with substantial risk of recurrence.

In making the diagnosis of epilepsy, clinicians need to remember that the patient will usually be normal by the time they are seen, and the patient history will likely be incomplete because the patient does not know what happened, or the event was not witnessed. Causes of seizures are searched for with brain imaging (MRI, CT scan, PET scan) and other tests (lumbar puncture, complete blood count, chemistries, cardiac testing). An electroencephalogram (EEG) can show evidence of epilepsy, while a sleep EEG may be needed to identify seizure activity.

As shown in Exhibit 1, seizures are also very diverse.[1] They can be divided into broad general categories of where the seizure starts – focal or generalized or unknown. Seizures can also be classified by whether they are motor or non-motor. Patients with focal seizures can be aware or unaware that a seizure is occurring.

Focal seizures occur on one side of the brain but can become generalized to bilateral tonic clonic. A partial seizure with frontal onset can be limited or have widespread motor activity. These seizures occur more often in sleep. Focal seizures with temporal

Exhibit 1: Classification of Seizure Types[1]

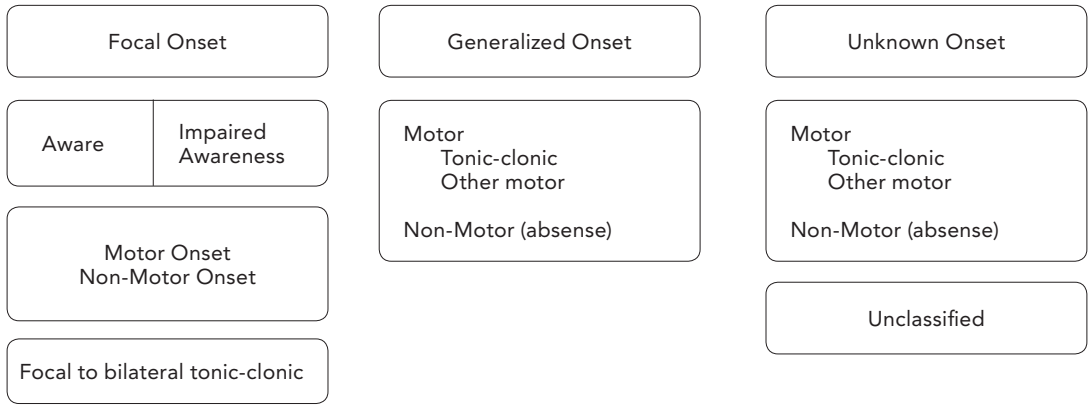


Exhibit 2: Anti-Epileptic Drugs (AEDs)

• phenobarbital	1912	• lamotrigine (Lamicta®)	1994
• phenytoin (Dilantin®)	1938	• fosphenytoin (Cerebyx®)	1996
• trimethadione (Tridione®)	1946	• topiramate (Topamax®)	1996
• mephenytoin (Mesantoin®)	1947	• tiagabine (Gabitril®)	1997
• phenacemide (Phenurone®)	1951	• levetiracetam (Keppra®)	1999
• phensuximide (Milontin®)	1953	• zonisamide (Zonegran®)	2000
• primidone (Mysoline®)	1954	• oxcarbazepine (Trileptal®)	2000
• methsuximide (Celontin®)	1957	• pregabalin (Lyrica®)	2005
• Ethotoin (Peganone®)	1957	• lacosamide (Vimpat®)	2008
• ethosuximide (Zarontin®)	1960	• rufinamide (Banzel®)	2009
• diazepam (Valium®)	1968	• vigabatrin (Sabril®)	2009
• carbamazepine (Tegretol®)	1974	• clobazam (Onfi®)	2010
• clonazepam (Klonopin®)	1975	• ezogabine (Potiga®)	2011
• valproate (Depakene®)	1978	• perampanel (Fycompa®)	2012
• clorazepate (Tranxene®)	1981	• eslicarbazepine (Aptiom®)	2013
• felbamate (Felbatol®)	1993	• brivaracetam (Briviact®)	2016
• gabapentin (Neurontin®)	1993	• cannabidiol (Epidiolex®)	2018

onset are the most common refractory focal epilepsy and are the most suitable for surgical treatment.

Head trauma, stroke, neoplasms, damage from brain infections, congenital lesions, autoimmune diseases, and birth anoxia are all causes of epilepsy. The majority of epilepsy cases used to be considered to have no identifiable cause (idiopathic). With advanced imaging and genetic testing, more causes of epilepsy are being identified. The most common cause that is identified by imaging is cortical dysplasia. There are a few single genes that are known to cause epilepsy; however, most inherited cases are probably the result of numerous genes.

The goal of treatment is complete seizure freedom without adverse effects. Quality of life with people with epilepsy is optimal with zero seizures. Another goal of treatment is reduction in sudden death. The rate of sudden death is 1 percent per year with refractory epilepsy.

There are many available antiepileptic drugs (AEDs) but none are perfect (Exhibit 2). Phenytoin, carbamazepine, eslicarbazepine, gabapentin, oxcarbazepine, pregabalin, and lacosamide are commonly used for focal and generalized tonic clonic seizures. Broad-spectrum agents can be used for all seizure types. Valproic acid, lamotrigine, topiramate, zonisamide, levetiracetam, and clobazam are all broad-spectrum agents.

There are several factors in choosing an AED. Efficacy of AEDs for the given patient's seizure is the

Exhibit 3: Anti-Epileptic Drugs That May Treat Other Disorders

Neuropathic Pain	gabapentin, lamotrigine*, pregabalin
Migraine	valproate, topiramate, lamotrigine*, gabapentin*
Bipolar Disease	valproate, lamotrigine, carbamazepine
Anxiety	gabapentin*, pregabalin*, clobazam
Restless Legs	gabapentin*, gabapentin enacarbil, carbamazepine* , pregabalin*

*not FDA approved for this indication

most important factor. A VA Cooperative Trial was done in 593 older patients, with new onset epilepsy, who were randomized to carbamazepine, gabapentin or lamotrigine. Seizure-free rates were similar for the three agents, but more treated with carbamazepine dropped out due to toxicity.[2] Many other head-to-head trials in partial epilepsy have failed to show differences in focal seizure control. Efficacy results from pivotal trials for FDA approval (in refractory patients) are similar; however, differences in tolerability are often seen.

Patients will be taking these agents for many years; therefore, the impact of adverse effects has to be considered in selecting an AED. For example, carbamazepine is less well tolerated compared to gabapentin or lamotrigine, and phenytoin is no longer a first-line agent because of long-term adverse effects. Central nervous system adverse effects (dizziness, somnolence, diplopia) and cognitive, behavioral effects are common with some of the agents and can impact the patient's quality of life and their ability to work. Some AEDs can cause weight increase (valproate, pregabalin), whereas others cause decreases in weight (topiramate, zonisamide).

Drug interactions are other considerations in selecting treatment. Many epilepsy patients have other conditions requiring drug therapy (including oral contraceptives). AEDs with no appreciable interactions include gabapentin, lacosamide, levetiracetam, and pregabalin. Those with very few interactions are clobazam, lamotrigine, valproate, and zonisamide.

Many women require drug therapy during childbearing years. The best drug during pregnancy is the one that best controls seizures because seizures increase risk of maternal and fetal death. Monotherapy, at the lowest dose that gives complete control, is preferable. Valproate and topiramate are known teratogens and children born of mothers taking valproate have lower IQs.[3,4] Lamotrigine, carbamazepine, and benzodiazepines are considered relatively safe during pregnancy.

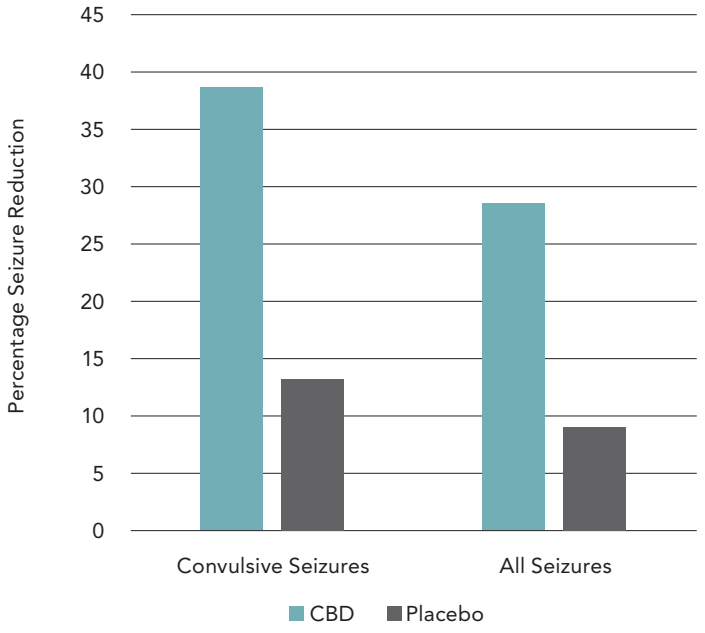
There are also several other considerations in selecting an AED. Half-life affects how often a medication has to be taken. Long half-life agents, which only have to be dosed once or twice a day, are preferred for long-term adherence. Concomitant conditions can also impact choice. Exhibit 3 shows the conditions that various AEDs may treat or worsen concomitant disease. For example, topiramate and levetiracetam can worsen anxiety, while benzodiazepines can worsen sleep apnea.

Cognitive dysfunction is a common complaint in those with epilepsy, and there can be several possible causes. They include unrecognized mood disorders, unrecognized sleep disorder, AED effects (topiramate, zonisamide), uncontrolled seizures (including unrecognized), and attention deficit disorder.[5] Determining the cause of cognitive dysfunction may require formal neuropsychological testing.

Several of the AEDs are available generically. The concern of using generics in epilepsy is that there is a narrower "therapeutic window" than with other conditions. Seizure control can be lost with too low serum levels or adverse effects can be worsened with excessively high levels. Switching between generics can amplify the problem. A bioequivalence study of brand versus generic equivalents of various AEDs found that area under the curve (AUC) was rarely different, but maximum concentration (Cmax) commonly differs.[6] AUC is a measure of how much drug gets into the body and Cmax is a measure of peak concentration. Cmax may be of greater concern with generic sustained-release formulations.

Controlled generic substitution studies in epilepsy

Exhibit 4: Cannabidiol: Clinical Trial[18]



show little risk. In a trial of lamotrigine immediate release comparing brand and generic over four two-week crossover periods, bioequivalence for AUC, Cmax, and minimum concentration (Cmin) was close to 100 percent.[7] In a study of two generic formulations of lamotrigine with the most disparate AUC and Cmax, the two products were found to be within 90 percent of each other.[8] Position statements from the American Epilepsy Society and the American Association of Neurology support the use of bioequivalent generics in epilepsy in most patients.

Uncontrolled seizures may occur because of a wrong epilepsy classification with wrong therapy selected, incorrect diagnosis (not epilepsy), or refractory epilepsy. Identifying the cause of uncontrolled seizures will require verification with video-EEG monitoring. Refractory epilepsy is defined as persistent debilitating seizures despite two appropriately administered AEDs. Overall, about one-third of epilepsy cases are refractory, which is approximately one million patients in the U.S.[9,10]

About one-third of patients referred for evaluation of refractory epilepsy cases actually have psychogenic nonepileptic seizures. It is usually a conversion disorder over which the patient has no control. These seizures do not respond to AEDs, but do respond to psychotherapy; treatment requires a cooperative neurology and psychiatry approach. The difficulty in managing these patients is increased, as about 25 percent also have true epileptic seizures.[11,12]

If a patient has refractory epilepsy, a different AED can be tried. Additional AED trials have a low chance for success; only about 10 percent of people will be seizure free with further drug trials beyond two AEDs. Alternative therapies include diets (ketogenic, modified Atkins), surgery, devices, and marijuana.

Epilepsy surgery can be curative for temporal lobe and extratemporal seizures. Morbidity after surgery corresponds to the surgical site and is primarily cognitive difficulties. Despite proven efficacy, many appropriate patients are not offered treatment. Requirements for surgery include debilitating seizures despite optimal medical treatment; an identifiable, single seizure focus; and a safely resectable focus. Seizure onset localization may remain unclear with noninvasive testing, so invasive monitoring is required. Video-EEG is performed with intracranially implanted electrodes to allow more precise localization of seizure onset and functional mapping.

Stereotactic laser ablation is a less invasive surgery, with faster recovery than larger resections. Patients are sometimes discharged the same day. Efficacy in well-chosen cases appears comparable to larger resection and may cause fewer cognitive deficits.[13]

In randomized trials of surgery, adults with temporal lobe epilepsy, who had surgery, were 58 percent seizure free versus 8 percent in those who were

medically managed. In children who underwent any surgery for epilepsy, 77 percent were seizure free compared with 7 percent.[14,15] In another trial, surgery for temporal lobe epilepsy resulted in 80 percent remission and 40 percent for extra-temporal disease.[16]

Devices that treat seizures are sometimes effective and are an alternative when surgery is not possible. A vagus nerve stimulator is the only device approved by the U.S. FDA with efficacy comparable to AEDs (<10% seizure free). Unfortunately, this is not more effective than AEDs. Deep brain stimulation is a device identical to that used for movement disorders and is only approved for use in Europe. Responsive neurostimulation is technology similar to a cardiac defibrillator, with electrical stimulation to abort a seizure once onset is detected. This device requires a known seizure onset zone and reliable seizure detection algorithms. With the responsive neurostimulator, seizure control improves with time because the device "learns" the patient's seizure pattern; 15 percent of patients are seizure free for at least one year.[17,18]

Medical marijuana for epilepsy is a hot topic. The initial interest came from somewhat misleading anecdotal reports. It is difficult to study the efficacy of marijuana because it is a "dirty" drug with 500 active compounds, 90 cannabinoids, variable dosing from smoking, and is Schedule I. The active compound in epilepsy is likely cannabidiol (CBD). In a double-blind, placebo-controlled trial in 120 children with Dravet syndrome, CBD oil did reduce seizure frequency compared to placebo, but is no better than current AEDs (Exhibit 4).[19] Additionally, the rate of adverse effects was much higher with CBD oil compared to placebo. A proprietary oral solution of highly purified plant-derived CBD oil (Epidiolex®) was approved by the FDA in 2018 for early-onset, treatment-resistant epilepsy syndromes – including Dravet syndrome, Lennox-Gastaut syndrome (LGS) – and is in Phase III trials for Tuberous Sclerosis Complex (TSC).

Conclusion

Epilepsy is a common, diverse disorder characterized by recurrent unprovoked seizures. Seizures can be focal or generalized and most are controlled with medication. The best antiepileptic drug depends on many individual factors. For refractory patients, specialty evaluation including video-EEG should be strongly considered to verify diagnosis and evaluate for alternatives (surgery or devices). Patients can and should be free of all debilitating seizures with no adverse effects. Future treatments may include cortical stimulation devices, prediction devices, and genetic characterization.

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New Options in the Treatment of Hepatitis C (HCV): Economic and Clinical Consideration for Improved Patient Outcomes

Mark S. Sulkowski, 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

Very effective therapies are available to cure hepatitis C viral (HCV) infections. People should be screened according to the guidelines and offered treatment once diagnosed. Curing HCV is not only cost effective, it is cost saving.

Key Points

- HCV infection is a major problem in the U.S.
- Baby boomers with more advanced liver disease and young people who use intravenous drugs are the two major problem groups.
- Treatment is highly effective, with cure rates > 95 percent in all populations, including those who fail the first course.
- At current cost per regimen, treatment is cost saving.

HEPATITIS C VIRUS (HCV) INFECTS HUMAN hepatocytes and was discovered in 1989 as the cause of non-A, non-B hepatitis. It is an enveloped, positive-sense single-stranded RNA virus, which means it can be eliminated from the body. Based on genetic differences, HCV is classified into six genotypes.

HCV is acquired primarily by parenteral transmission; there is a lower risk of sexual or vertical transmission with HCV compared with other infectious agents (Exhibit 1).[1] The United States (U.S.) blood supply was not tested for HCV until 1992, and this led to the infection of many people. The most common mode of infection today is the sharing of needles. Exhibit 2 shows how the rates of HCV infection related to injection drug use have increased over the years among young people.[2]. HCV infection rates actually track along with opioid abuse rates. Individuals typically start with prescription opioids and then move to injected heroin because it is less expensive and easier to obtain with the crackdown on prescription opioid abuse.

After infection with HCV, a patient can have either spontaneous clearance by the immune system (25 – 30%) or develop a chronic infection. Spontaneous clearance is primarily genetically determined. Chronic infection is mostly asymptomatic until the consequences develop. Chronic HCV infection can lead to the development of fibrous scar tissue within the liver.[3] Over time, fibrosis can progress, causing severe scarring of the liver, restricted blood flow, impaired liver function (cirrhosis), and eventually liver failure.[4] Decompensated cirrhosis includes ascites, bleeding gastroesophageal varices, hepatic encephalopathy, and jaundice. Cancer of the liver can develop after years of chronic HCV infection.[1]

HCV infection causes more deaths in the U.S. than 60 other reportable infectious diseases combined.[5] Hepatitis C has been unchecked for many years because of lack of identification, the lack of blood screening, and because of difficult to tolerate therapies like interferon. The National Health and Nutrition Examination Survey (NHANES)

Exhibit 1: Sources of Infection for Persons with Hepatitis C[1]

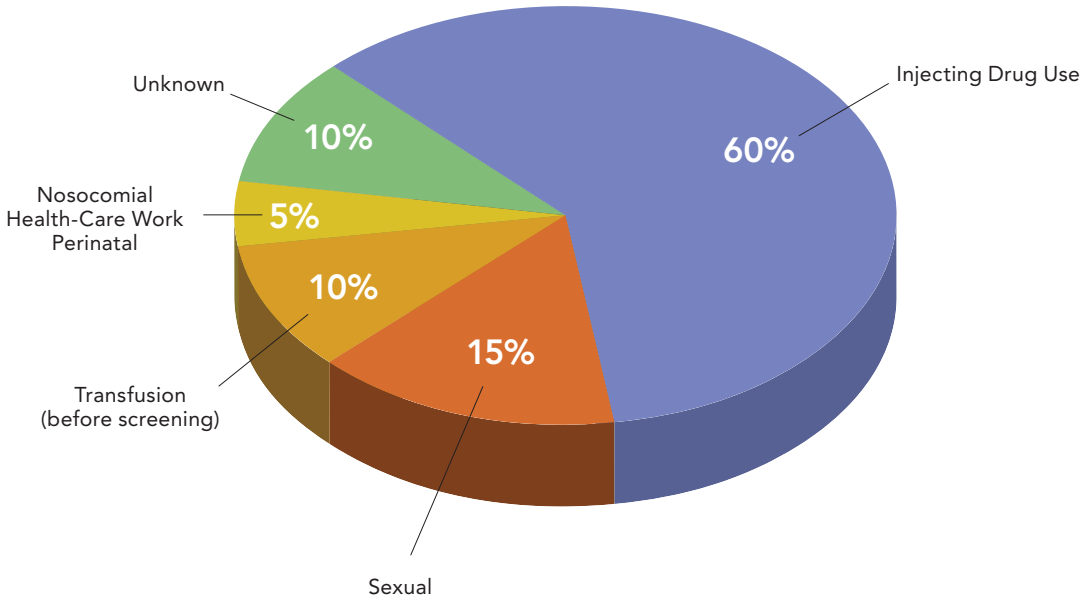
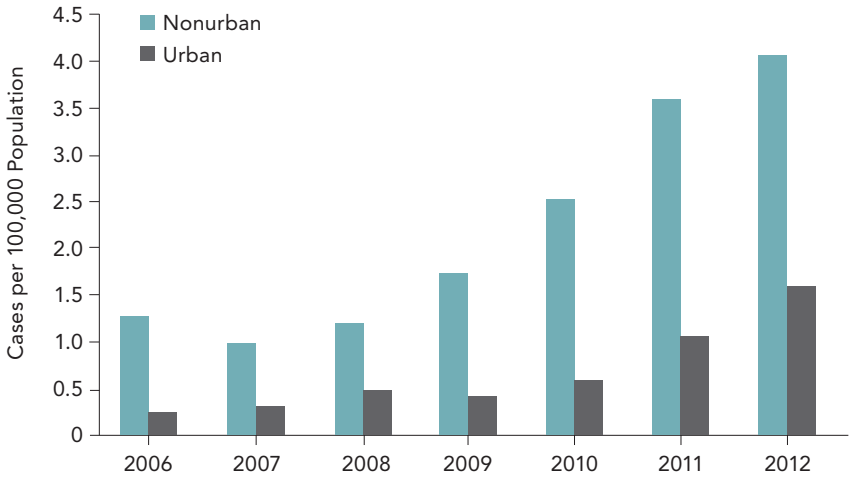


Exhibit 2: Increases in HCV Infection Related to Injection Drug Use Among Persons Aged ≤30 Years[2]



estimated that there are 3.2 million people living with chronic HCV in the U.S. This estimate does not include the homeless (142,761 – 337,610), incarcerated (372,754 – 664,826), veterans (1,237,461 – 2,452,006), active military (6,805), and health care workers (64,809 – 259,234).[6-8] Thus, the prevalence is closer to 5.2 to 7.1 million and unfortunately 45 percent to 60 percent of those infected are unaware of their infection. Over 40,000 new cases occurred in 2016, the most recent year for which data are available.[1] About one million people are estimated to have been treated for HCV so far in the U.S., with the remainder either not linked to care, have complicated psychiatric or social problems, or do not know that they have the disease.

The peak prevalence of HCV infection is in those born in the 1960s, but it is also high for those born between 1945 and 1965 (Baby Boomers). The Cen-

Exhibit 3: U.S. Preventive Services Task Force HCV Screening Recommendations[9]

- Everyone born from 1945 through 1965 (one time)
- Past or present injection drug use
- Sex with an injection drug user; other high-risk sex
- Blood transfusion before 1992
- Persons with hemophilia
- Long-term hemodialysis
- Born to an HCV-infected mother
- Incarceration
- Intranasal drug use
- Receiving an unregulated tattoo
- Occupational percutaneous exposure
- Surgery before implementation of universal precautions

ters for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend that those in this age group should be screened for HCV infection at least once. Birth cohort-based screening has been somewhat successful. Exhibit 3 lists all the groups who should have screening.[9]

The American Association for the Study of Liver Disease/Infectious Disease Society of America (AASLD/IDSA) HCV Guidelines are published online and are frequently updated.[10] The goal of treatment of HCV-infected persons is to reduce all-cause mortality and adverse liver-related health consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure, as evidenced by a sustained virologic response (SVR). With successful treatment and no repeat exposure to HCV, there is a 99 percent probability that the patient will remain HCV free. Treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy.[1]

Prior to starting antiviral therapy, several baseline laboratory tests need to be obtained. This includes a complete blood count, various tests of liver function (albumin, total and direct bilirubin, ALT, AST, alkaline phosphatase levels, and INR), calculated kidney function, HCV genotype and subtype, quantitative HCV RNA (HCV viral load), and HIV serology since coinfection complicates treatment. All patients initiating HCV direct-acting antiviral (DAA) therapy also should be assessed for hepatitis B virus (HBV) coinfection with HBsAg testing and for evidence of prior infection with anti-HBs and anti-HBc testing. It is possible to have a HBV flare when HCV treatment is started. Liver biopsy is no longer recommended to determine cirrhosis status. Noninvasive methods are routine for determining if cirrhosis is present, including blood tests (FIB-4, APRI, or FibroTest®) or liver elastography to measure liver stiffness (FibroScan®). Patients with cirrhosis are harder to cure and are still at risk for liver cancer, even with cure. A less expensive option for predicting fibrosis is the FIB-4 scoring system, which uses a combination of the patient's age, platelet count, and AST and ALT levels; many managed care plans require the more expensive blood or scanning tests before approving HCV therapy.

The HCV life cycle presents multiple targets for direct-acting antiviral (DAA) drugs. Polymerase inhibitors, protease inhibitors, and nonstructural protein 5A (NS5A) inhibitors have all been approved for HCV treatment; however, some of these agents are no longer used or available (Exhibit 4). It is not anticipated that any new agents will be approved for HCV because of the success of the currently available agents.

HCV treatment regimens are selected according to the virus genotype and patient characteristics (Exhibit 5).[10] Most regimens are combination DAA agents given for eight to 12 weeks. Because recommended regimens can change, clinicians should consult the most recent guidelines. The cure rates in practice are 95 percent for the FDA-approved regimens when patients are adherent. The more doses the patient takes, the higher the cure rate. An example of the recommendations for one group, treatment-naïve genotype 1a patients without cirrhosis, is given in Exhibit 6. Genotype 1a is the predominate genotype seen in the U.S. (75%). Genotype 3 is

Exhibit 4: FDA Approved Agents for HCV Treatment

NS3/4A Protease Inhibitors	NS5A Inhibitors	NS5B Polymerase Inhibitors
Boceprevir	Daclatasvir	Fasabuvir
Glecaprevir	Elbasvir	Sofosbuvir
Grazoprevir	Ledipasvir	
Paritaprevir	Ombitasvir	
Simeprevir	Pibrentasvir	
Telaprevvir	Velpatasvir	
Voxilapprevir		

Exhibit 5: Virus and Patient Characteristics for Treatment Selection[10]

- HCV RNA level (< or > 6 million IU/mL)
- HCV genotype; if genotype 1, subtype 1a or 1b
- eGFR (CMP)
- Cirrhosis
  - If cirrhosis, CTP score (albumin, bilirubin, INR) and liver imaging
- HBsAb, HBsAg, HBcAb total, HIV antibody, HAV total
- Concurrent medications
  - PPIs, anti-seizure medications, amiodarone, ART
- Prior HCV treatment

the most difficult to treat and has been spreading in the U.S. among young injection drug users.

HCV replicates very rapidly (billions of viruses daily), and the production of each new virus results in one to three errors per replication cycle, on average. Some of these replication errors result in drug-resistant virus, particularly to NS5A inhibitors. NS5A resistance-associated substitutions (RAS) testing for persons with genotype 1a is recommended prior to use of elbasvir/grazoprevir (EBR/GZR, Zepatier®).[10] An alternative regimen is recommended if RAS is present. Ribavirin can be used in combination with EBR/GZV to overcome resistance, but it requires multiple daily doses, has adverse effects, is teratogenic, accumulates in renal dysfunction, and causes hemolytic anemia.

If a patient does fail the initial treatment regimen which includes a NS5A inhibitor, a rescue regimen (sofosbuvir/velpatasvir/voxilaprevir) is used. Failures are more common in patients with cirrhosis, African American men, and those co-infected with HIV. Cure rates are 99 percent for second-line regimens in those without cirrhosis and 93 percent in those with cirrhosis.[11]

Sofosbuvir, a mainstay of many anti-HCV regimens, is not recommended for use in patients with renal dysfunction (CrCl < 30 mL/min). The combinations of glecaprevir/pibrentasvir or elbasvir/grazoprevir for eight to 16 weeks are recommended. Persons with HCV on dialysis have worse outcomes than persons without HCV, and transmission of HCV in hemodialysis centers is a major concern. Between 2008 and 2016, there were 20 outbreaks in hemodialysis settings. Given the worse outcomes

Exhibit 6: Recommended Regimens for Treatment-Naïve Genotype 1a Patients without Cirrhosis[10]

RECOMMENDED	DURATION
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs for elbasvir.	12 weeks
Daily fixed-dose combination of glecaprevir (300 mg/pibrentasvir (120 mg)	8 weeks
Daily fixed-dose combination of ledipasvir (90 mg/sofosbuvir (400 mg)	12 weeks
Daily fixed-dose combination of ledipasvir (90 mg/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected and whose HCV RNA level is < 6 million IU/mL	8 weeks
Daily fixed-dose combination of sofosbuvir (400 mg/velpatasvir (100 mg)	12 weeks

and risk of transmission, those with HCV on dialysis should be targeted for treatment. There is some controversy in treating HCV infection in those on dialysis awaiting kidney transplant. Patients willing to take an HCV-positive kidney have a much shorter wait for transplant (4 – 6 weeks) than those who want an HCV-negative kidney (4 years). There is a relative abundance of HCV-positive organs available because of the number of young people dying from drug overdoses. An emerging practice pattern is to use the HCV-positive organs and then treat the transplant recipient for HCV infection.

Targeting intravenous drug users for elimination of HCV is another important area. Recent or active intravenous drug use should not be seen as an absolute contraindication to HCV therapy.[10] There is strong evidence from various settings in which persons who inject drugs have demonstrated adherence to treatment, have high cure rates and low rates of reinfection, countering arguments that have been commonly used to limit treatment access in this patient population.[10] A recent study of HCV reinfection and injection risk behavior following EBR/GZR treatment in participants on opiate agonist therapy (methadone or suboxone) found a 2.3 reinfection rate per 100 person years of follow-up.[12] This is a manageable rate of reinfection. Current intravenous drug use does call for a synergistic approach of HCV and addiction treatment.

Many countries are trying to eliminate HCV. Iceland will be the first country to accomplish this by treating its entire population and is able to accomplish this by being a small country with only about 1,000 cases, with universal health insurance, and with no HIPPA laws, so they know who is infected and where they live. To date, they have reduced the prevalence from 43 percent to 12 percent and reduced the incidence of new cases by 53 percent .[13]

In the U.S., the Veterans Administration is also trying to eliminate HCV in the veteran population. This health system has shown that treating HCV reduces overall risk of death and risk of hepatocellular cancer within two years of cure, even among those with cirrhosis.[14]

In addition to mortality and cancer risk, other benefits of cure are now being shown. Within the Medicare population, as use of HCV treatments has increased, the rate of liver transplants secondary to HCV infection has declined after decades of being the number one reason for transplants.[15] Thus, treating older people, even with cirrhosis, has benefits. Interestingly, treating HCV infection can also reduce the risk of developing type 2 diabetes because the liver is involved in gluconeogenesis and the process of developing diabetes.[16,17]

The cost of treating HCV has been a concern for managed care and unlike many other diseases the cost of HCV treatment has decreased substantially since 2013. The wholesale acquisition cost (WAC) for an eight to 12-week course of therapy has declined from $95,000 to $26,000 because of increased competition. Overall, treatment of HCV has been shown to be cost-saving or cost effective by the majority of studies.[18]

Barriers to HCV treatment may be introduced by prescriber requirements, patient requirements, and the prior authorization process. The initial evaluation and the treatment protocols are becoming very streamlined. Many payers still require that treatment be directed by a hepatologist, an infectious disease spe-

cialist, or a gastroenterologist, of which there are insufficient numbers in the U.S. For the new regimens, well-trained internal medicine providers should be able to treat HCV infections. For plans that allow generalists to treat HCV, documentation of consultation support by experts may still be required and is a barrier. Curative treatment may be denied to persons with minimal liver damage, even though the benefits of cure are greater in this group compared with those who have already developed cirrhosis. Curative treatment may be denied to persons with evidence of active drug or alcohol use even though benefits of cure and low rates of reinfection have been demonstrated. Some state Medicaid programs are working to eliminate the disease while other state programs still have significant restrictions on prescribing.

Conclusion

HCV infection is a major problem in the U.S. Baby boomers have had uncontrolled infection for many years and have advanced liver disease and high rates of liver cancer. New cases in younger people who use intravenous drugs continue to increase dramatically. Treatment with DAAs is highly effective, with cure rates greater than 95 percent in all populations, including those who fail the first course and those who already have liver disease. At the current cost per regimen, treatment is cost-saving. Reduced risk of death, liver cancer, and type 2 diabetes have all been shown with curing HCV infection.

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Informed Decision Making in the Management of HIV/AIDS: Expert Strategies for Individualized Treatment

Mary Watson Montgomery, 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

HIV continues to be a public health issue in the United States. Effective once-daily regimens are available for controlling the virus. Because patients are living for many years with HIV infection, they need help with medication adherence, with preventing long-term consequences of the infection, and with the social and financial aspects of the disease.

Key Points

- Universal testing for HIV is still recommended.
- Burden of new diagnoses is concentrated in the southern U.S.
- Life expectancy of HIV patients is improving.
- INSTI-based regimens are recommended as first-line treatment.
- There is data showing there is benefit in starting treatment on the same day as the diagnosis if using an INSTI or a PI-based regimen.
- New regimens are available which are appropriate for certain situations.
- Clinicians need to address with their patients the stigma of HIV, the costs of medical treatment, and the long-term consequences of the disease, such as cancer and cardiovascular disease.

IN THE UNITED STATES (U.S.), THERE ARE approximately 40,000 new cases of human immunodeficiency virus (HIV) infection each year. The southern states bear the greatest burden of HIV, with more than 50 percent of the new infections.[1] Over 1.1 million people are living with HIV in the U.S. Importantly, one in seven infected people do not know they are infected, even with widespread screening.[1] Globally, there were 1.8 million new cases worldwide in 2016 (36.7 million people are living with HIV, and 20.9 million are on HIV medications).[2]

Men who have sex with other men have the highest risk for contracting HIV, followed by women and men who use intravenous drugs, respectively. As shown in Exhibit 1, African American men who have sex with other men have the highest risk.[3] The high risk in African American men is related to the high rate of uncontrolled viremia in that population and not differences in sexual practices. Even though there are risk groups for HIV infection, everyone should be screened at least once for the disease.[4]

A common concern for the newly diagnosed is whether the disease will kill them. Mortality has improved significantly for those infected with HIV. There is still a 13-year gap in life expectancy for those HIV+ compared to those not infected.[6] The gap is eight years for those on antiretroviral therapy (ART) with high CD4. With current therapies, the mortality of those with HIV who are treated with continuous ART, who are not using intravenous drugs, who have CD4 counts greater than 500, and who have undetectable viral load, is the same as the general population.[5] Ongoing inflammation, secondary to the HIV infection in the body which increases risk of cardiovascular disease and cancer, is the likely

Exhibit 1: Lifetime Risk of HIV Diagnosis among Men Who Have Sex with Men (MSM) by Race or Ethnicity[3]

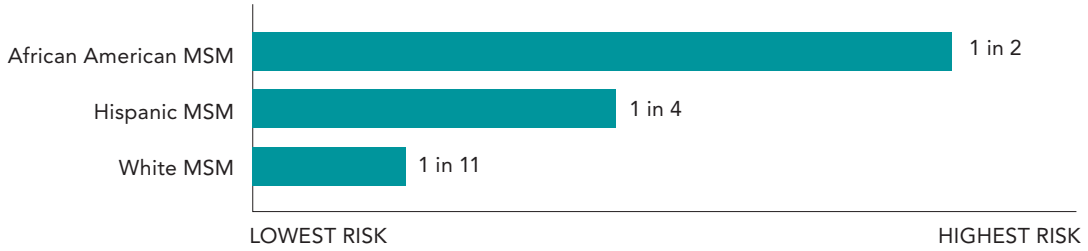
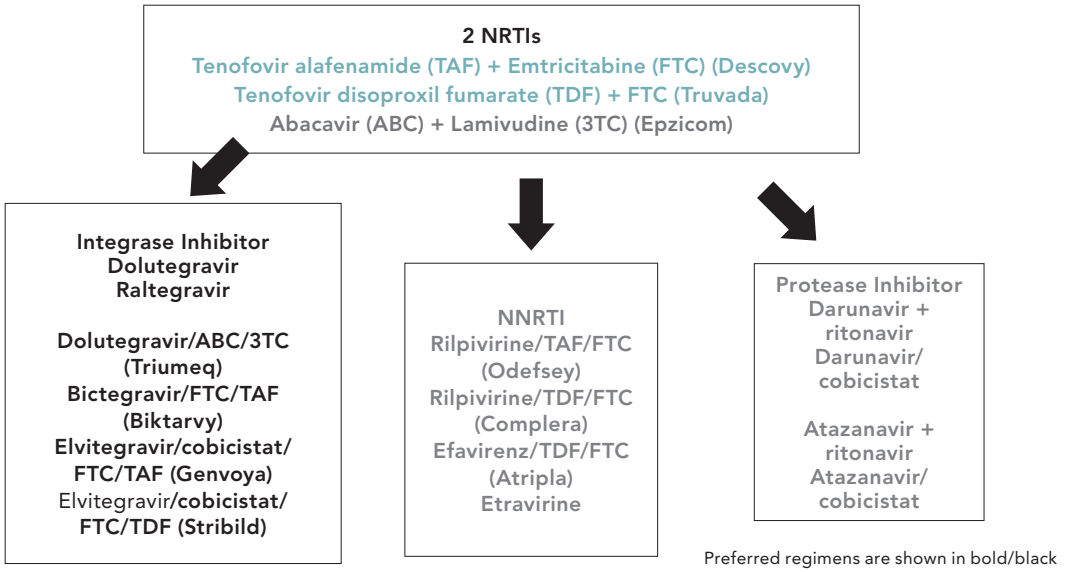


Exhibit 2: Initial DHHS Regimens for Most People with HIV[12]



Preferred regimens are shown in bold/black

cause of the life expectancy gap, even in those who take their medication and have low viral loads.

Traditionally, therapy was not started at the time of the initial diagnosis, but the sooner someone is started on therapy, the lower the risk of transmission to others. There is growing data showing benefits of starting therapy on the same day as the diagnosis. A meta-analysis of four randomized controlled trials, eleven observational studies, and five qualitative studies found that therapy initiated on the same day increased retention in care, remaining on medications at 90 days, and viral suppression at 12 months.[7] There was a non-significant trend toward decreased mortality and loss to follow-up at 12 months. It is better to psychologically engage the patient early in the process. The RAPID trial in the U.S. showed that initiating ART on the same day of the HIV diagnosis shortened time to viral suppression from 4 months to 1.8 months.[8]

Transmitted resistance to drugs may complicate starting therapy on the same day as diagnosis. About 18 percent of patients will have transmitted drug resistance; this will be due to the non-nucleoside reverse transcriptase inhibitors (NNRTI) class in 11.5 percent, nucleoside reverse transcriptase inhibitors (NRTI) in 5.7 percent, protease inhibitors (PI) in 3.9 percent, and integrase inhibitors (INSTI) in 0.04 percent.[9,10] Given the higher rate of resistance,

Exhibit 3: Newer Antiretroviral Medications

	Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)	Dolutegravir/rilpivirine (Juluca)
Indication	• Treatment-naïve patient • Or those with HIV-1 RNA < 50 copies/mL for ≥ 3 mos, no hx treatment failure and no resistance to regimen	• Not for naïve patient, only those virologically suppressed for ≥ 6 mos • No history of treatment failure and no resistance to DTG or RPV
Administration Requirements	• None	• Must take with a meal
Key Drug Interactions	• Can't use with rifampin, dofetilide • May increase metformin concentrations similar to dolutegravir • Antacids may decrease bictegravir concentration	• Separate dose fromantacids • Avoid proton pump inhibitors • Dose adjust metformin
Dose Adjustments	• Not recommended if CrCl < 30 mL/min	• No renal adjustments required

a NNRTI- based regimen would not be a good choice for same-day therapy.

Another question complicating same day therapy is the need for an INSTI genotype at a cost of approximately $150. At least one analysis found that inappropriate and costly therapy changes were made based on the genotype results.[11] Some clinicians are pushing for changes to the treatment guidelines so that INSTI genotype testing is not recommended, as long as the rates of resistance in a given community remain low.

There are numerous ART agents available. A simplified approach to these medications is presented in Exhibit 2.[12] The majority of the time an ART regimen will include two NRTIs and one agent from either the INSTI, NNRTI, or PI categories. The DHHS guidelines recommend two NRTIs and an integrase inhibitor as the first-line regimen for most patients.[12] The already co-formulated combination products are shown in their respective boxes in Exhibit 2. The currently used protease inhibitors need to be boosted with either ritonavir or cobicistat. Elvitegravir, an INSTI, also needs to be boosted with cobicistat. Unfortunately, cobicistat has a great deal of drug interactions, so many clinicians are moving away from ART regimens that require its use. Tenofovir, a commonly used NRTI, is available as tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF). There is reduced risk of renal dysfunction and osteoporosis with TAF, so many clinicians choose this over TDF.

Bictegravir/FTC/TAF (Biktarvy®) is the newest once-daily single-tablet regimen, and it includes a novel, unboosted INSTI. Exhibit 3 shows indication, drug interactions, and special population information for this product. Many patients with HIV have type 2 diabetes and require high doses of metformin. Dolutegravir significantly increases metformin concentrations. The drug interaction trials with bictegravir and metformin showed no increases in metformin concentrations; however, the trials were done in HIV-negative patients, so the package labeling includes a warning about possible metformin increases until further data are available.

Dolutegravir/abacavir (ABC)/lamivudine (3TC) and bictegravir/FTC/TAF have been compared in two trials and appear to be equivalent for efficacy (>90% of subjects had viral suppression).[13,14] No resistance developed in either study. The rates of adverse effects were similar for each regimen, except for nausea, which is more common with dolutegravir/ABC/3TC because of the ABC component. Insomnia and headaches occur in 11 to 14 percent of subjects because of the INSTI component. Clinicians are moving away from abacavir because it increases the risk of developing cardiovascular disease, the most of any of the commonly used ART agents. Switching someone off of abacavir can reduce their risk of cardiovascular disease by 45 percent, which is a much larger benefit than antihypertensive or antihyperlipidemic therapy.[15]

Factors to consider in choosing an INSTI regimen for first-line therapy include one versus two tablets daily, barrier to resistance, food requirement, drug-drug interactions, and medical comorbidities. Agents with a high barrier to resistance are especial-

Exhibit 4: Selecting an INSTI Regimen for First Line Therapy

INSTI	Backbone	STR	Barrier to Resistance	Food Requirement	May be Suboptimal for Pts with:	Key DDIs
BIC	FTC/TAF	✔	High			Metformin
	ABC/3TC	✔	High		High CVD risk, contraindicated with HLA-B*5701	Metformin
DTG	FTC/TAF		High			
	FTC/TDF		High		Osteoporosis, CKD	
EVG/COBI	FTC/TAF	✔	Low/ Moderate	✔	Hyperlipidemia	Statins, steroids
		✔	Low/ Moderate	✔	Hyperlipidemia, osteoporosis, CKD	
RAL	FTC/TAF		Low/ Moderate			
	FTC/TDF		Low/ Moderate		Osteoporosis	

INSTI = integrase inhibitor
STR = single tablet regimen
DDI = drug drug interactions
BIC = bictegravir
DTG = dolutegravir
EVG = elvitegravir
COBI = cobicistat
RAL = raltegravir
FTC = emtricitabine
TAF = tenofovir alafenamide
ABC = abacavir
3TC = lamivudine
TDF = tenofovir disoproxil fumarate
CVD = cardiovascular disease
CKD = chronic kidney disease

ly good for patients with unstable social situations where missing some doses will not significantly decrease the overall efficacy. Exhibit 4 shows these considerations for the available INSTI regimens. Dolutegravir/FTC/TAF and bictegravir/FTC/TAF are the best two regimens for first-line therapy.

Dolutegravir combined with rilpivirine (Juluca®, INSTI/NNRTI) is a newly approved two- drug regimen that is a single daily tablet. Exhibit 3 shows relevant labeling information. The guidelines suggest use of this combination when an NRTI is not desirable in those who have already been virologically suppressed for six months or more.[12] In a switch study of dolutegravir/rilpivirine from baseline ART, there was greater than 90 percent viral suppression, one virologic failure, and a high rate of central nervous system adverse effects, especially those that led to therapy discontinuation, with the two-drug combination compared with baseline ART.[16] The likely population for this dual-drug combination are those with reduced renal function who cannot receive a TAF-based regimen or have cardiovascular disease, so abacavir is contraindicated.

Regimens may need to be switched for various reasons. Reducing tablet burden can be a reason for some patients who are still on older regimens. The regimens have improved dramatically since the 1980s when people had to take 10 to 20 tablets twice a day. Single-tablet or two tablets daily regimens are beneficial for long-term adherence. Adverse effects are another common reason for regimen change. For example, efavirenz causes dramatic nightmares and mood disorders; protease inhibitors (ritonavir and cobicistat) cause nausea and diarrhea; dolutegravir causes insomnia and headaches. The need for a new medication for concomitant disease, such as allergies, that has a drug interaction with current therapy can prompt a change in HIV therapy. For example, corticosteroids in any form (oral, inhaled, injectable) are contraindicated with ritonavir or cobicistat. Patients requiring a proton pump inhibitor should not be receiving rilpivirine and those needing high-dose metformin should not be on dolutegravir or bictegravir. Development of renal dysfunction would also prompt a medication reevaluation.

Doravirine (Pifeltro®) is a next-generation NNRTI that is once daily, has no food requirement, and has no interaction with acid suppressants. It also has activity against multiple NNRTI mutations (K103N, Y181C, G190A, K103N/Y181C, E138K), but the barrier to resistance is not as high as an INSTI-based regimen. It is also available as a single combination of doravirine, lamivudine, and TDF (Delstrigo®), which likely will not be used much because of the TDF component.

Emerging therapies include MK-8591, and inject-

able drugs. MK-8591 is an investigational nucleoside transcriptase translocation inhibitor (NRTTI) with a high barrier to resistance in vitro and a very long half-life. It could possibly be given only once a week. Cabotegravir (INTSI) and rilpivirine (NNRTI) are being studied as long-acting intramuscular injectables (every 4 to 8 weeks).

Overall, HIV patients need affordable medications because they are taken for a lifetime. Many of the may need help from AIDS Drug Assistance Programs and patient assistance programs through pharmaceutical companies to manage the costs. These patients also need high quality care and access to social work and/or AIDS service organizations. Clinicians need to provide counseling around the stigma that patients feel about having the infection – many have isolated themselves because of concerns about transmission. Substance use disorder screening and treatment and preventative care are also important in the care of the person infected with HIV. Preventative care includes cancer screening, appropriate vaccines, cardiovascular risk reduction, and smoking cessation. The rate of lung cancer among smokers with HIV is significantly higher than smokers without HIV.

Conclusion

Universal testing for HIV is still recommended. The burden of new diagnoses is concentrated in the southern U.S. Life expectancy of HIV patients is improving. INSTI-based regimens are recommended as first-line treatment. There are data which support the initiation of treatment on the same day as the diagnosis if using an INSTI or PI-based regimen. New regimens are available which are appropriate for certain situations. Long-acting injectables and long-acting oral agents will likely be coming to market. Clinicians need to address HIV stigma, costs, and long-term consequences, such as cancer and cardiovascular disease, with their patients.

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Redefining Clinical Outcomes in Hemophilia: The Impact of Personalized Treatment Strategies

Christopher E. Walsh MD, PhD

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

Summary

Hepatitis C (HCV) infection and factor inhibitors are two major issues in managing those with hemophilia. With newer therapies, hepatitis C is curable. A new therapy for hemophilia that avoids the problem of inhibitors is now available and will likely revolutionize the treatment of this disease until a cure is found.

Key Points

- Hepatitis C infection is the main cause of death in those with hemophilia and needs to be cured.
- Longer acting factors may play a role in treatment, but factor replacement will likely be succeeded by new non-factor therapies.
- Mimetics and agents that control how blood clots appear to avoid the problem with FVIII inhibitors.
- Genetic therapies are coming and are considered cures.

HEMOPHILIA IS A RARE ORPHAN DISEASE. Hemophilia A (factor 8 [FVIII] deficiency) affects approximately 25,000 patients in the United States (U.S.), whereas only about 4,000 have hemophilia B (factor 9 [FIX] deficiency). Hemophilia A and B are clinically indistinguishable from each other. This is primarily a genetic disease (70% of cases) that is transmitted from mother to son.

A few decades ago the lifespan of a patient with hemophilia was 10 to 20 years; the lifespan is now normal. Untreated, the disease manifests as joint, muscle, and central nervous system bleeding. The clinical phenotype of bleeding correlates with a patient's factor level. Those with less than 1 percent of active factor have severe disease with frequent, spontaneous bleeding. Those with 5 percent or greater have mild disease and bleed less often. Overall, the higher the factor level, the fewer episodes of clinical bleeding.

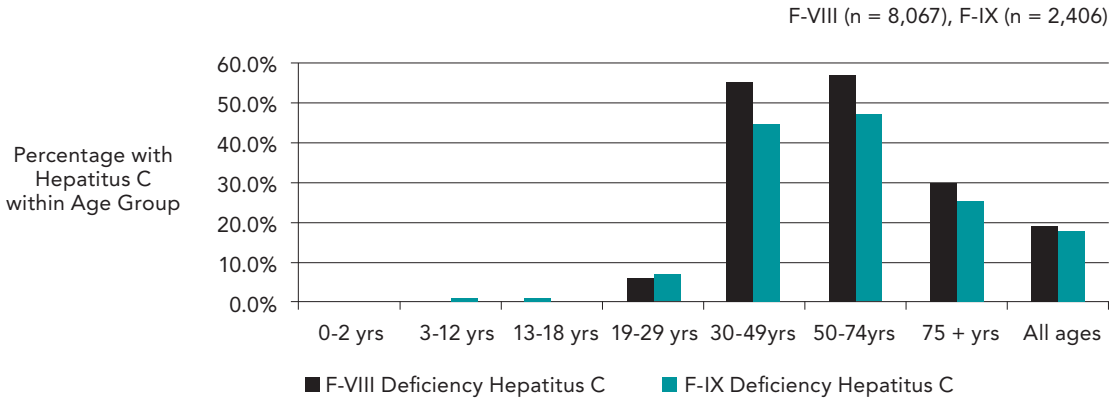
Treatment has been replacement of the missing factor through intravenous infusions. Dosing of factors has been limited by the short half-life of the factors (FVIII T1/2 = 12 hours, FIX T1/2 = 20 hours). Extending the dosing duration of factors has been a goal to improve patient convenience. Enhanced half-life FVIII products modestly extended the half-life to 18 hours (infusion interval improved from every 2 - 3 days to every 4 - 5 days) and modest elevations of trough factor levels (3 - 5%) for a much higher price. These products may help some patients, but they are not a significant advancement. Extended half-life FIX products do significantly improve the dosing interval to allow weekly administration with trough factor levels of 20 to 30 percent.

Overall, treatment of hemophilia in the U.S. has some positives and negatives. The positives of treatment in the U.S. are that overall life expectancy is normal (except for those infected with HCV or

Exhibit 1: Goals of Hemophilia Treatment

1. Eliminate Hepatitus C infection
2. Significantly reduce or eliminate spontaneous bleeding
3. Eliminate factor inhibitors (autoantibodies)
4. Eliminate intravenous infusions
5. Maintain high level of factor or equivalent at all times

Exhibit 2: Hepatitus C Patients by Age



HIV) and factor replacement eliminates greater than 90 percent of bleeding. Negatives of hemophilia treatment include treatment requiring frequent intravenous infusions, development of antibodies to factor VIII (inhibitors), and hepatitis C-related liver disease. HCV and HIV infections are remnants of the earlier days of factor replacement when it was not known that there were contaminants in the products. The Centers for Disease Control and Prevention (CDC) estimate that up to 90 percent of people with hemophilia who used clotting factor prior to 1987 were exposed to HCV through contaminated products. Inhibitors reduce factor efficacy and increase risk of mortality. A recent study showed that mortality is approximately twice as high with inhibitor patients compared to those without inhibitors.[1]

Hemophilia Treatment Centers (HTCs) are a nationwide system of clinics for bleeding disorders that can provide care for those with severe hemophilia. There are approximately 130 HTCs throughout the U.S. that are staffed by physicians, nurses, social workers, physical therapists, and data collectors. The American Thrombosis and Hemostasis Network (ATHN) serves as a central database for patients with bleeding disorders. The National Hemophilia Foundation Medical/Scientific Advisory group (MASAC) produces management guidelines. The goals of treating hemophilia are shown in Exhibit 1. The future is moving toward a cure of the disease with genetic therapies.

HCV liver-related disease is the leading cause of death in hemophilia patients. Exhibit 2 shows the percentage of patients with HCV infection by age groups.[2] Prior to development of direct-acting agents (DAAs), the regimens to eliminate HCV were only 20 to 30 percent effective, and they were very toxic. New daily oral DAAs were developed with few side effects and greater than 98 percent efficacy to eliminate HCV virus. Treatment of hemophilia is effective treatment, with few side effects. Given that HCV is the major killer of those with hemophilia, the money spent to eliminate the virus is worth the cost.

Bleeding into joints leads to synovial, cartilage, and bone destruction. Joint damage in hemophilia is a medical system failure. It is possible to prevent hemophilic arthropathy by giving effective continuous prophylaxis from an early age, and preventing the VIII or IX concentration from falling below 1 percent of normal.[3] The Europeans have been doing continuous prophylaxis since the late 1950s. Numerous studies have shown that prophylaxis produces better outcomes than episodic treatment (only giving factor for a bleed) in those with severe disease.[4,5] The U.S. now gives prophylaxis to both adults and children with severe disease.

Although traditionally factor levels between 1 and 5 percent have been the goal of therapy, accumulating data are suggesting that higher levels should be the target to further reduce the annual bleeding rate.[6] Female carriers of the hemophilia gene with only mild factor deficiencies (5 – 40%) have been shown to have microbleeds into joints and joint damage.[7] Trough levels with factor replacement need to be higher than 5 percent and optimally as high as possible, but clinicians are limited by the current factor technology, which would require almost daily infusions to achieve normal levels.

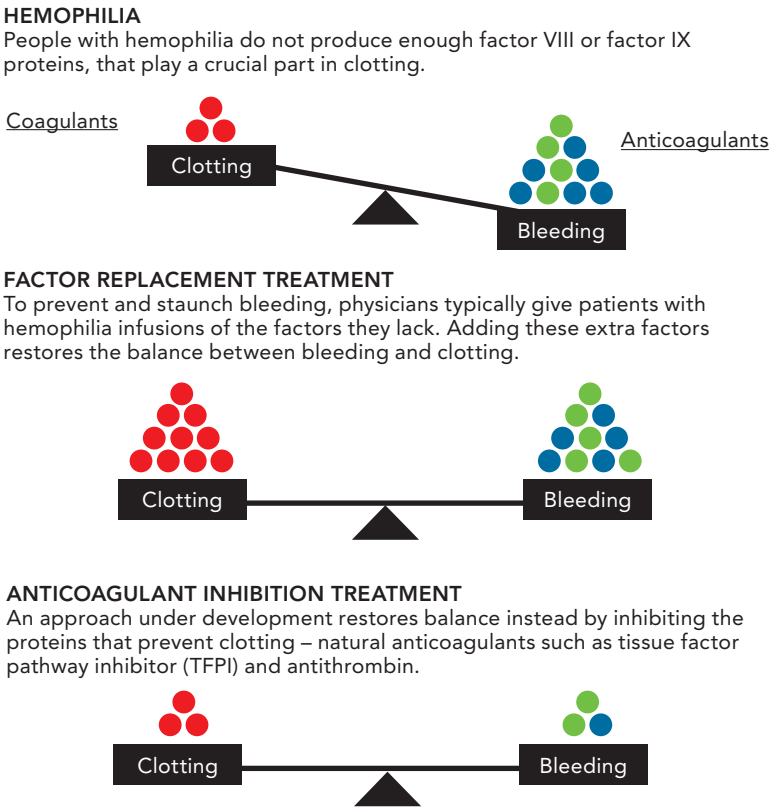
Factor inhibitors, which reduce the efficacy of replacement factor, are a major issue in hemophilia treatment. Approximately 30 to 40 percent of previously untreated patients with hemophilia A will develop antibodies to FVIII. Two to 3 percent of those with hemophilia B will develop FIX inhibitors. Those with factor inhibitors are at higher risk of brain, gastrointestinal tract, and muscle bleeds, in addition to joint bleeds. Treatment of factor inhibitors requires immune tolerance with daily infusions of factor to 'desensitize' patients or the use of bypass agents, FEIBA® (Anti-Inhibitor Coagulant Complex) and NovoSeven® (recombinant factor VIIa). FEIBA® is a freeze-dried sterile human plasma fraction with factor VIII inhibitor bypassing activity. Treatment of those with inhibitors costs millions of dollars per patient. Approximately 60 percent of patients can develop tolerance, but the rest require years of therapy with million- dollar medications.

Many clinicians have switched from plasma-derived factor replacement to recombinant- derived agents to reduce the risk of blood product transmitted diseases, but the recombinant agents may be contributing to the rise in inhibitors. In a study of recombinant-FVIII compared to plasma-derived FVIII in previously untreated patients, there was an 87 percent higher risk of developing inhibitors with r-FVIII and a 69 percent higher risk to develop high-titer inhibitors in those receiving r-FVIII.[8] This raises the question of the role of von Willebrand factor, generally absent from recombinant factors, in protecting against inhibitors. There is no consensus about how to apply these findings to U.S. patients. The MASAC guidance highlighted the limitations of this study and proposed potential actions based on current exposure and the totality of evidence about product classes.[9] There are differences between the results of this study and most of the previous studies that showed no increase or a minimal increase in inhibitor formation with r-FVIII, as well as key differences in the study population from the U.S. population of hemophilia patients. These potentially confounding factors include ethnic differences, gene mutations associated with increased inhibitor risk, and episodic versus prophylactic exposure. The first 50 doses of factor in children are the highest risk point for developing inhibitors, and many clinicians are going back to plasma- derived factors, but these still have at least a 20 percent rate of inhibitor development.

The newest therapy for hemophilia is a medication which mimics the role of FVIII in the clotting cascade and avoids the administration of factor. Emicizumab (Hemlibra®), a bispecific factor IXa- and factor X-directed antibody, was approved by the FDA in October of 2018 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors. Mechanistically, emicizumab simultaneously binds factors IXa and X as it mimics the cofactor function of factor VIII. By doing an end run around FVIII, emicizumab promotes coagulation, even in the presence of FVIII inhibitors. Treatment with this agent resulted in an 87 percent reduction in annualized rate of treated bleeding in adults with inhibitors.[10] The Institute for Clinical and Economic Review (ICER) issued a report concluding that emicizumab is cost-effective, despite its price of $482,000 for the first year and $448,000 susequently.[11] The agency determined that the drug, a weekly subcutaneous injection, would reduce the health care budget in the U.S. by $720,000 per patient annually for children under the age of 12, and by $1.85 million a year for people over 12.

Another new idea for managing hemophilia is controlling how blood clots (Exhibit 3). These approaches are to take the 'brakes' off by reducing tissue factor pathway inhibitor (TFPI) or antithrombin and see if blood clotting returns to normal. TFPI is a single-chain polypeptide which can reversibly inhibit Factor Xa (Xa). While Xa is inhibited, the Xa-TFPI complex can subsequently also inhibit the FVIIa-tissue factor complex. Antithrombin is a small protein molecule that inactivates several enzymes of

Exhibit 3: Control How Blood Clots



the coagulation system. Mimetics and agents that control how blood clots are likely to supplant factor replacement until a cure is found.

Gene-based therapy is the future of a cure. Fixing a genetic disease can be done by inserting a new correct gene, replacing the mutant gene, or editing or repairing the mutant gene. Studies of each approach are ongoing. For example, in one study of 10 patients with hemophilia B, increased factor levels were achieved after one dose of adenovirus-associated virus vector-medicated gene transfer, and the patients are still responding eight years later.[12] The average factor levels with this type of gene-based therapy is 37 percent.

Conclusion

Hepatitis C infection in those with hemophilia is curable and should be treated aggressively to prevent liver disease and liver cancer. Longer acting factors may play a role in treatment; however, factor replacement will likely be replaced by new non-factor therapies, including mimetics that are given by subcutaneous injection monthly. Mimetics and agents that control how blood clots appear to avoid the problem with FVIII inhibitors. Genetic therapies are coming and are considered cures.

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Practical Strategies for Improving Diagnosis and Treatment of PAH

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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 (PAH) is a rare, but deadly, disease of the pulmonary vasculature that leads to right heart failure. Numerous medications are available for treating the disease, but they should only be started in those with proven PAH. Combination therapy with at least two classes of agents is the standard of care for most patients.

Key Points

- The right classification of pulmonary hypertension is important.
- Death from PAH results from right heart failure.
- Combination therapy with ambrisentan and tadalafil is recommended for those in functional Class II and III.
- Intravenous prostacyclin analogues will be needed for Class IV.

PULMONARY HYPERTENSION (PH) REPRESENTS a group of diseases that manifest themselves in increased pressures in the pulmonary arteries. The group that has been subject of the most attention has been pulmonary arterial hypertension (PAH), which is a disease in the vasculature of the lungs.

PAH is a chronic, progressive, cardiopulmonary condition associated with progressive exertional shortness of breath (dyspnea), decreased endurance related to physical activity, and syncope, chest pain or fatigue. Dyspnea is the most frequent symptom of PAH and is slowly progressive. Fatigue, chest pain, edema, and syncope are other presenting symptoms.[1] Because the symptoms are nonspecific, it can take several years for a patient to get an accurate diagnosis. PAH is hemodynamically defined as an abnormal increase in pulmonary artery pressure (PAP), normal pulmonary capillary wedge pressure (PCWP), and increased pulmonary vascular resistance (PVR) on right heart catherterization.[2] PAH results in elevated right ventricular pressure and volume overload, leading to right heart failure and death.

The pathophysiology of PAH includes vasoconstriction and vasoproliferation, leading to eventual right heart failure. The disease is not about hypertension but is about pulmonary vascular constriction and how the right ventricle handles the difficulty of pumping blood through the lungs. Exhibit 1 shows the progression of PAH from presymptomatic and compensated to end- stage disease.[3] PAH can be idiopathic, inherited (BMPR2, ALK-1, endoglin,

Exhibit 1: Progression of PAH[3]

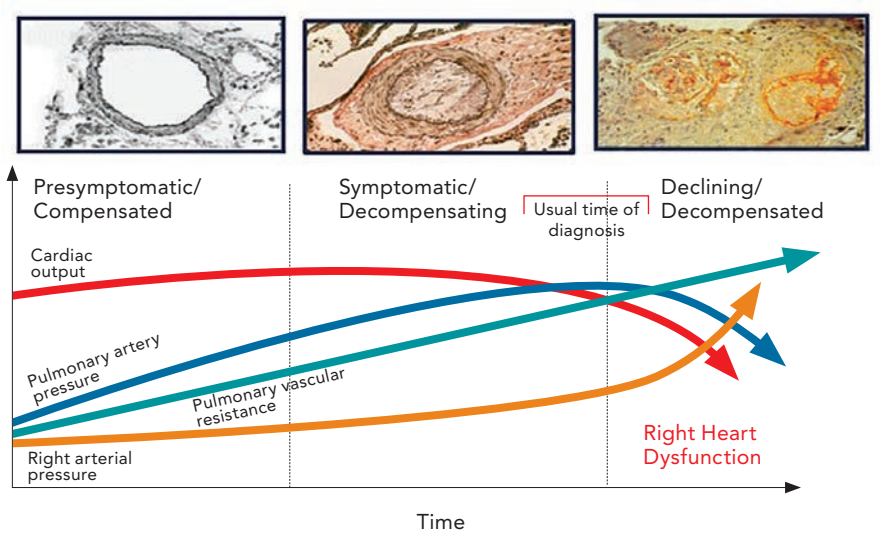

Exhibit 2: Prevalence of PAH in Associated Conditions

Associated Condition	Prevalence of PAH
Systemic sclerosis	7 – 12%
Portal hypertension	2 – 6%
Congenital heart disease Eisenmenger's syndrome	1 – 12 % with systemic to pulmonary shunts 25 – 50%
HIV infection	0.5%
Schistosomiasis	4.6% with hepatic involvement

SMAD9, CAV1, KCNK3, or unknown mutations), drugs and toxins induced (methamphetamine), or associated with connective tissue diseases, HIV infection, portal hypertension, congenital heart diseases, or schistosomiasis (Exhibit 2).

Importantly, the diagnosis of PAH has to rule out the many other types of PH because most of the FDA-approved therapies are for PAH and may be harmful in other types of PH. A major source of misuse of PAH medications is using them in PH secondary to left-sided heart disease. Diagnosing PAH is difficult and should ideally be done only by PH specialists. Overall, PAH is rare and in only a small portion of the patients with PH.

A first-step in evaluation of dyspnea is usually an echocardiogram which can estimate pressure in the heart. On echocardiogram, an estimated right ventricular systolic pressure (RSVP) ≥35 mm Hg should raise concern of PH, especially when accompanied by evidence of right heart pressure overload with right atrial enlargement, right ventricular enlargement, hypertrophy or dysfunction, or significant tricuspid regurgitation. The American College of Cardiology/American Heart Association expert consensus guidelines on PH recommend further evaluation of a patient with dyspnea and an estimated RVSP >40 mm Hg on echocardiogram.[4] Overall, echocardiogram-derived reports of PH are not considered diagnostic and further work-up is required. Right heart cath-

Exhibit 3: NYHA/WHO Functional Classification for PAH[9]

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, or near syncope.
Class II	Slight limitation of physical activity; no discomfort at rest. Ordinary activity causes undue dyspnea, fatigue, chest pain, or near syncope.
Class III	Marked limitation of physical activity; no discomfort at rest. Less than ordinary physical activity causes undue dyspnea, fatigue, chest pain, or near syncope.
Class IV	Inability to perform any physical activity without symptoms; signs of right ventricular failure or syncope; dyspnea and/or fatigue may be present at rest; discomfort is increased by any physical activity.

NYHA = New York Heart Association
WHO = World Heath Association

eterization is required to confirm the diagnosis of PAH and assess its severity for prognosis, exclude left heart disease, and perform vasoreactivity testing. In one trial, only 37 percent of patients had a right heart catheterization prior to initiation of PAH-specific medications.[5] Managed care could limit PAH-specific medications to those patients with evidence from a right heart catheterization.

PAH is a deadly disease. The survival is currently similar to metastatic breast cancer (Stage III) with a five-year survival rate of 57 percent.[6,7] Death is caused by right heart failure, thus the function of the right ventricle matters the most for mortality.[8] PAH needs to be identified as early as possible and treated aggressively upfront like cancer, rather than waiting for the patient to deteriorate.

A patient's functional status and risk for deterioration and death are used to decide on therapeutic interventions. The functional classification of PAH is shown in Exhibit 3.[9] Patients at high risk (>10% risk of death) can be identified by clinical signs of heart failure, progression of symptoms, syncope, functional Class IV, 6- minute walk test less than 165 meters, high brain natriuretic peptide levels, and hemodynamic measurements.[10] The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk score calculator can also be used to determine risk of death.[11] The higher the risk score, the lower the one-year survival rate for a given patient.[12]

Ten agents in four therapeutic classes are currently approved in the United States (U.S.) for the treatment of PAH. These four classes essentially all decrease vascular resistance in the lungs. Recommendations for initial therapy with PAH-specific medications based on functional class are shown in Exhibit 4.[13] Calcium channel blockers (CCBs) are used for vasodilation, but they should only be used on a patient that has had a right heart catheterization with response to vasodilators. The response to CCBs is typically not sustained for more than a few years. This class will worsen disease in anyone without vasodilator response.

Therapy can be sequentially added or started as combination therapy. Combination therapy of ambrisentan/tadalafil reduces risk of events compared to ambrisentan or tadalafil monotherapy.[14] Monotherapy with macitentan has been shown to reduce morbidity and mortality.[15] Those at low risk (functional Class II) should be started on two medications. Patients at high risk (functional Class IV) should be on the intravenous agents. For those in the middle risk group, there is not a consensus of approach, but most clinicians will choose at least two medications. For all functional classes, two agents are better than one. There are studies ongoing with triple oral therapy (selexipag, macitentan, tadalafil) compared to two classes. The 2015 European Society of Cardiology and the European Respiratory Society (ESC/ERS) Guidelines recommend combination therapy with ambrisentan and tadalafil for functional Class II and III.

In addition to therapies targeted for PAH, other care is required for these patients. In general, patients with idiopathic PAH and some with secondary PAH require anticoagulation. Because hypoxia is a potent vasoconstrictor and can raise pulmonary arterial pressure, patients may require oxygen therapy at times. Volume control will also be required once heart failure has occurred. This may include diuretics, fluid restriction, and a low salt diet. Vaccinations to prevent respiratory illness are also important.

Medication persistence and adherence is an issue

Exhibit 4: Initial Therapy for PAH[13]

RED: Clinical trials supporting approval utilized mortality and morbidity endpoints in randomized controlled studies or reduced all-cause mortality. Level of evidence is based on the WHO FC and the majority of patients in supportive trials.

WHO FC II	WHO FC III	WHO FC IV
Ambrisentan	Ambrisentan	Epoprostenol (IV)
Bosentan	Bosentan	Ambrisentan
Macitentan	Macitentan	Bosentan
Riociguat	Riociguat	Macitentan
Sildenafil	Sildenafil	Riociguat
Tadalafil	Tadalafil	Sildenafil
Selexipag	Treprostinil (SC or inhaled)	Tadalafil
	Iloprost (inhaled)	Treprostinil
	Epoprostenol	(SC, IV, inhaled) (oral*)
	Selexipag	
	Iloprost (IV)	
	Treprostinil (IV) (oral*)	

*Oral treprostinil was approved by the FDA in December 2013 for treatment of WHO Group I patients to improve exercise capacity.

in PAH treatment. Fifteen to 30 percent of patients self-discontinue medications, with adverse effects and lack of perceived benefits being the most common reasons. For those who continue taking their medications, about 50 percent have moderate to poor adherence.[16,17] Adverse effects of the PAH-specific therapies are common and include nausea, diarrhea, flushing, and headache. Nonadherence related to adverse effects comes from lack of communication between clinicians and patients regarding expected adverse effects and lack of guidance on prevention and management of adverse effects. Many of the adverse effects can be managed by patient education and proactive management. For example, nausea with oral treprostinil can be managed by taking the medication with food, by downing titration of the dose temporarily, or by utilizing symptomatic medication (i.e., ondansetron). Some clinicians also go ahead and give patients medications to deal with the likely common adverse effects of nausea and diarrhea.[18] Overall, patients with PAH need close follow-up for medication adherence and therapeutic efficacy. Managed care-based adherence programs could be useful in helping patients adhere with therapy, which will reduce their risk of dying, but may be hard to tolerate.

Conclusion

PAH is really right heart failure from high pulmonary vascular resistance and should not be called pulmonary arterial hypertension. Diagnosis is tricky and ideally should be done by a PH specialist. PAH-specific medications are available which can improve patients function and mortality.

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New Horizons in the Treatment and Management of Lymphoma: Novel Therapies for Improved Patient Outcomes

Matthew S. McKinney, 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

The treatment of lymphoma continues to evolve with a better understanding of the genetics, cell markers, and tumor microenvironment which all play a role in the growth and proliferation of the disease. Several targeted and immunotherapies are now available and are improving outcomes in both follicular and Hodgkin lymphoma.

Key Points

- Treatment strategies for lymphoma are targeting both tumor cells and the tumor microenvironment.
- Obinutuzumab, rituximab, PI3 kinase inhibitors, and lenalidomide are all therapeutic options for various stages of follicular lymphoma treatment.
- Brentuximab vedotin and immune checkpoint inhibitors are effective in refractory/relapsed Hodgkin lymphoma.

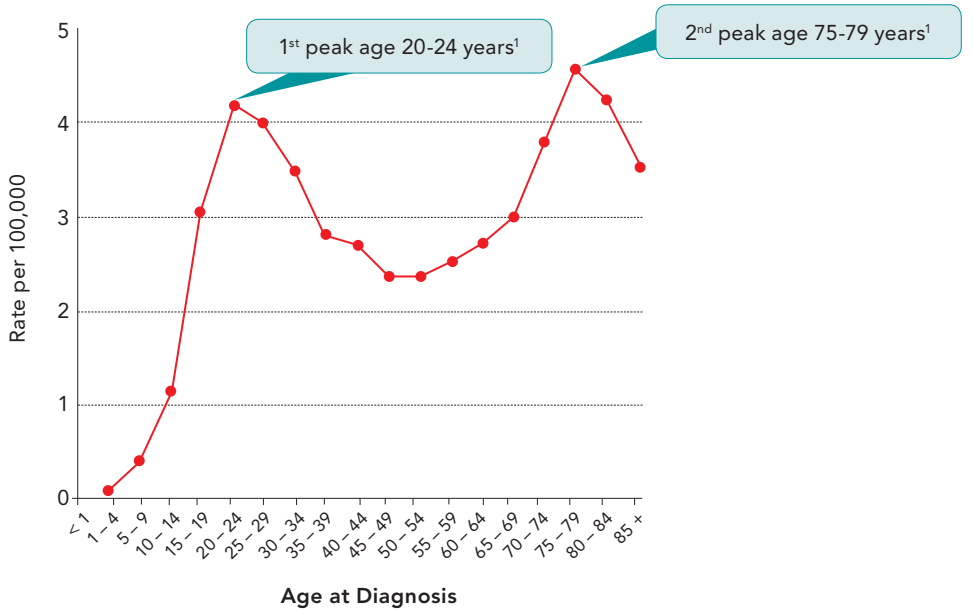
IN 2018, AN ESTIMATED 83,180 NEW CASES of lymphoma and 20,960 deaths from the disease occurred in the United States (U.S.).[1] Lymphoma is a very heterogeneous cancer. Although there are more than 60 subtypes of lymphoma, the focus of this article is follicular and Hodgkin lymphomas.

Follicular lymphoma (FL) is an incurable disease; however, most people live for many years with this cancer. Thirty-year treatment plans are common once the initial diagnosis is made. Because therapy is continually being improved, it is hard to have a definitive median overall survival (OS) in which to communicate to patients. FL is a B-cell lymphoma which expresses CD19, CD20, CD22, and CD79a as cell surface makers. It is thought that FL originates from germinal center B cells that are actively dividing in lymph nodes. Eighty-five percent of cases have a heavy chain rearrangement with juxtaposition of B-cell lymphoma two (Bcl-2) oncogene (position 14) onto the IGH heavy chain locus (position 18), which results in constitutive Bcl-2 expression [t (14;18) (q32; q21)]. Bcl-2 inhibits B-cell apoptosis.

Traditionally, FL has been treated with chemotherapy to induce remission, but no study has shown a survival benefit to upfront chemotherapy compared to waiting for the patient to have symptoms. Once the disease relapses, every line of subsequent chemotherapy produces less of a response.[2] Chemotherapy is still frequently used to impact progression-free survival (PFS).

Novel targeted therapeutics are the latest developments in FL treatment and have the potential of improving survival with "chemotherapy-free" treatment. To understand how novel targeted therapies work in FL, one must understand the environment in which the tumor cells grow and proliferate. With FL, there is an infiltration of cancer cells into the follicles of the lymph nodes or bone marrow. The

Exhibit 1: Bimodal Age Distribution of Hodgkin Lymphoma[14]



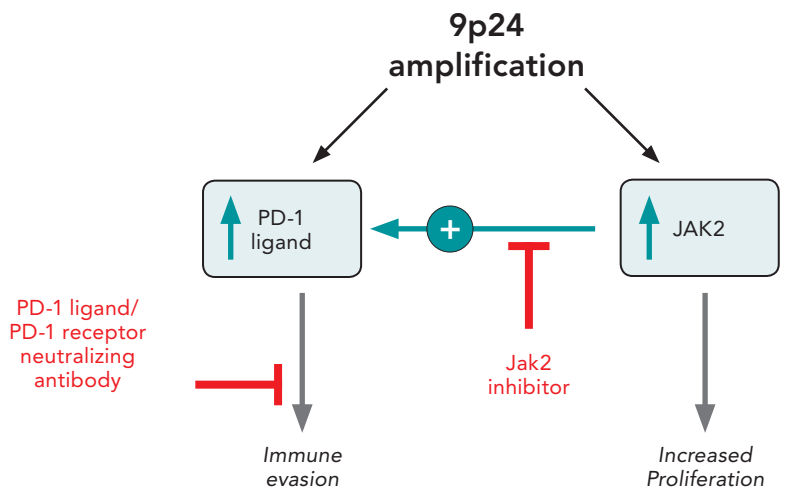
tumor cells interact with other cells around it via cell signaling, which provides for continued tumor cell division and survival (homeostatsis).[3] In the tumor microenvironment, there are now a number of these signals that can be targeted with various therapies.

Because FL cells express CD20 on their surface, anti-CD20 monoclonal antibody biologics were developed and were the first approved therapies to target the immune microenvironment of FL. CD20 is expressed only on B-cell lineage cells and is present in 90 percent of B-cell lymphomas. CD 20 is important for cell cycle initiation and development. Rituximab (Rituxan®) and obinutuzumab (Gazyva®) are the currently approved anti-CD20 biologics, but others are in development.

When rituximab is added to standard chemotherapy regimens, it increases the response rate and the complete remission rate.[4] Rituximab has often been administered as maintenance therapy after a remission that was induced either by single-agent rituximab or by rituximab combined with standard chemotherapy drugs, and it has been shown to prolong the duration of remission.[5] Rituximab maintenance improves median PFS by about a year and a half. It can also be used as retreatment at progression if maintenance was not used.[6] The retreatment approach reduces the amount of rituximab the patient receives, which can reduce costs and adverse effects, but the PFS is greater with maintenance.

Obinutuzumab was developed to try to improve response beyond rituximab. This type II anti-CD20 monoclonal antibody has improved antibody-dependent cellular cytotoxicity and direct lymphoma cell killing effects compared with rituximab.[7] Obinutuzumab and rituximab, in combination with chemotherapy and then as maintenance in previously untreated patients with advanced-stage FL, have been compared in one trial. Patients who achieved complete or partial remission proceeded to maintenance therapy with the same antibody given during induction. Complete response rates were similar with obinutuzumab or rituximab (23.8% and 19.5%, respectively).[8] At a median follow-up of 34.5 months, the three-year PFS rate was superior with obinutuzumab (80.0% vs. 73.3%; P = 0.001); however, the three-year rate of overall survival was similar (94.0% and 92.1%).[8] Grade 3 to 5 toxicity, including cytopenias and infections, was higher with obinutuzumab, especially when combined with bendamustine. Deaths due to adverse effects were similar with obinutuzumab or rituximab (4.0% and 3.4%). Overall, obinutuzumab appears superior to rituximab in FL in the front-line and refractory setting. Compared to rituximab, obinutuzumab causes slightly more toxicity (infusion reactions, cytopenias), but it is generally well tolerated. The cost-effectiveness of choosing obinutuzumab over rituximab, especially in front-line setting, remains to be evaluated.

Exhibit 2: Targeting Chromosome 9p24 Amplification in Hodgkin Lymphoma



Phosphoinositide 3-kinase (PI3K) inhibitors have also been studied in FL, and two agents are currently FDA approved. PI3K coordinates signaling from surface growth factor receptors. Targeting this pathway affects a number of downstream signaling pathways in the tumor cell. There appears to be direct tumor effects and microenvironment effects. Currently, idelalisib (Zydelig®) and copanlisib (Aliqopa®) are FDA approved for relapsed/refractory FL treated with at least two prior systemic therapies. Idelalisib is a once a day oral medication that is a delta PI3K inhibitor. Copanlisib is given by intravenous infusion weekly and is a delta/alpha PI3K inhibitor. Common adverse effects with idelalisib include Grade 3/4 diarrhea, cytopenias, transaminase elevations, and pneumonitis.[9] Its use in front-line therapy, where the patients still have a reasonably robust immune system, led to very high rate of autoimmune-like toxicities. The adverse effects of copanlisib are primarily metabolic (hyperglycemia, hypertension), transaminase elevations, and cytopenias. The toxicities of PI3 kinase inhibitors limit their use in front-line therapy and can make long-term adherence difficult. The place for these agents appears to be in later-line therapy.

Lenalidomide (Revlimid®) is another agent for targeting the microenvironment, but it is not FDA approved for FL. However, it is approved for treating multiple myeloma, mantle cell lymphoma, and myelodysplastic syndromes. This agent impacts T cells, natural killer (NK) cells, and B cells and additionally impacts the tumor microenvironment by decreasing fibroblast growth factor, altering cytokine levels, and increasing immunoglobulin G production. Lenalidomide has been studied in combination with rituximab in front-line FL where it significantly prolongs the time to requiring the next treatment.[10] Rituximab/lenalidomide results in an improved CR/CRu rate versus rituximab in front-line follicular lymphoma (IRR: 61% vs. 36%). Toxicity is manageable (fatigue, arthralgias, GI side effects). Combination therapy failed to show superiority over standard-of-care rituximab-chemo in a Phase III trial.[11] Clinicians are using the combination as second- or third-line therapy. Numerous other targeted therapies are under investigation for FL.

Hodgkin lymphoma (HL) is another B-cell lymphoma characterized by cancerous Reed-Sternberg cells in an inflammatory background.[12] Approximately 8,500 new cases of HL and 1,050 deaths occur annually in the U.S.[1] HL has a bimodal age distribution (Exhibit 1).[13] The younger group is treated more aggressively because of their relative health and life expectancy. About 60 percent of people are in Stage I/II at the time of diagnosis, and 40 percent are Stage III/IV.

Even in advanced-stage disease, HL is highly curable with combination chemotherapy, radiation, or combined-modality treatment. Even patients who are not cured with initial therapy can often be salvaged with alternate chemotherapy combinations, the novel antibody-chemotherapy conjugate brentuximab vedotin, high-dose autologous or allogeneic hematopoietic stem cell transplantation, or

immunotherapy.

Chemotherapy is the standard treatment for HL and leads to 80 percent five-year survival. The goal of research has been to improve the response in those who relapse or are refractory to front-line chemotherapy. Up to 30 percent of Stage III/IV HL patients relapse or are refractory to front-line treatment.[14]

Brentuximab vedotin (Adcetris®) is an antibody-chemotherapy conjugate which selectively targets tumor cells expressing the CD30 antigen, a defining marker of HL. It delivers vedotin, a potent chemotherapy, directly into the tumor cells and improves PFS when used as maintenance therapy post stem cell transplant.[15]

Immune checkpoint inhibitors are the newest therapy for HL and also affect the tumor microenvironment. On biopsy, the majority of cells in HL are immune reaction cells in response to the tumor cells. In searching for what was driving the whole immune invasion process, genomic alterations have been discovered. In HL, the chromosome 9 p24 segment is highly amplified.[16] On this segment, there are several genes that co-occur, including Janus kinase 2 (JAK2) and programmed death 1 and 2 ligands (PD-L1, PD-L2). Amplification of PD-L1 can be targeted with checkpoint inhibitors (Exhibit 2). JAK inhibitors, which are already FDA approved for rheumatoid arthritis and psoriasis, are also a possible treatment for HL.

Treatment with two checkpoint inhibitors ,nivolumab (Opdivo®) and pembrolizumab (Keytruda®), both anti-PD-1 monoclonal antibodies, has shown efficacy in highly refractory HL patients, where few other options are available. Both are FDA approved for HL for the treatment of adult and pediatric patients with refractory HL, or who have relapsed after three or more prior lines of therapy. Nivolumab is also approved for use after stem cell transplant and brentuximab vedotin use. The place of immunotherapy in the application of salvage therapy still needs to be determined. Current trials are also underway to examine the use of checkpoint inhibition earlier in Hodgkin lymphoma treatment.

Conclusion

The treatment of lymphomas is evolving with the development of many treatments that target both tumor cells and the tumor microenvironment. Obinutuzumab, rituximab, PI3 kinase inhibitors, and lenalidomide are all therapeutic options for various stages of FL treatment. Brentuximab vedotin and immune checkpoint inhibitors are effective in refractory/relapsed HL.

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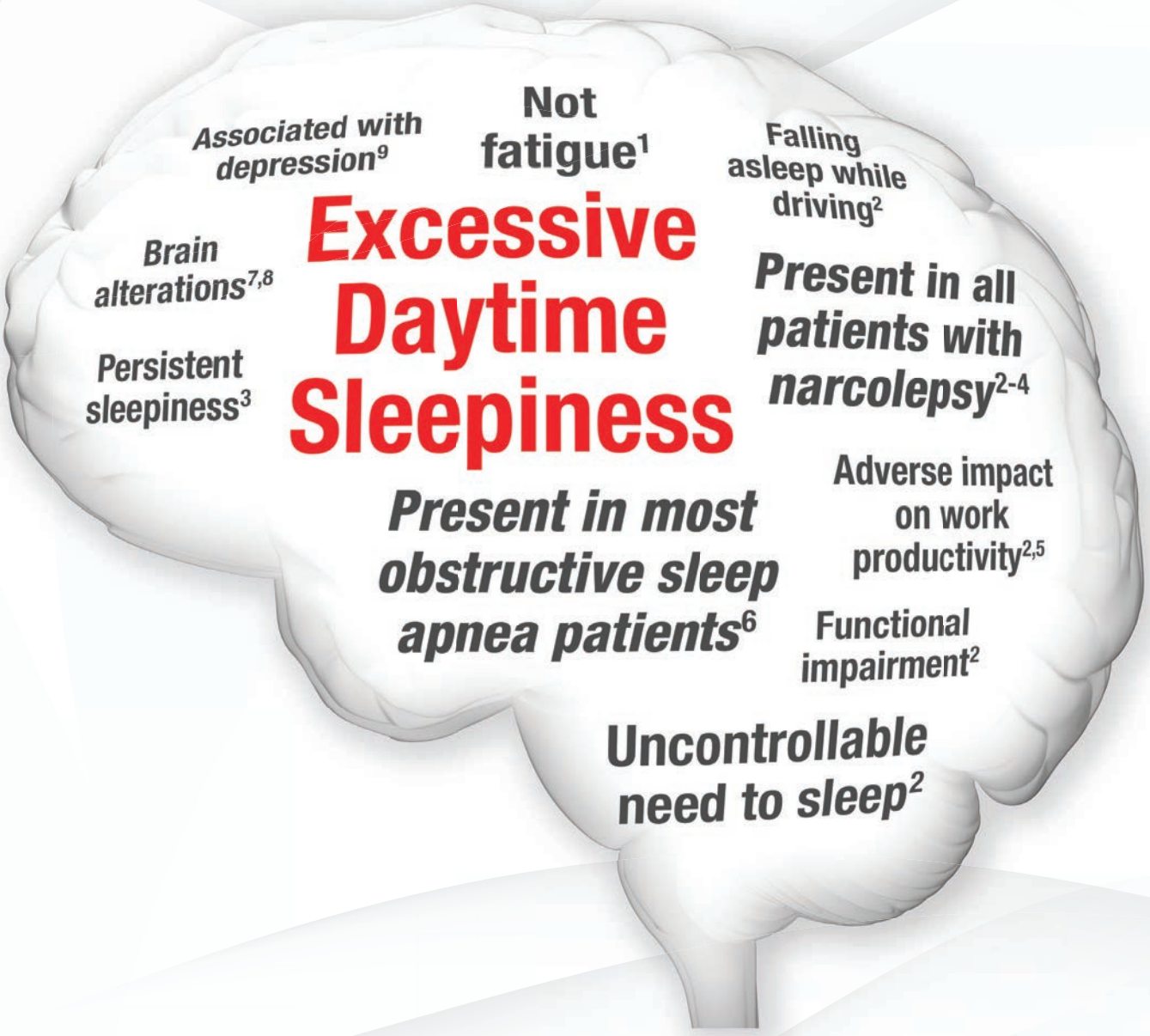

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