Continuing Education

Key Therapeutic Updates:
Breast Cancer, Hepatitis C, Multiple Sclerosis

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Objectives

- Discuss the types of breast cancer the 2017 breast cancer drugs are used to treat.
- List common side effects of the breast cancer drugs.
- Identify the newest agents in the treatment of hepatitis C and how they fit into current guideline recommendations.
- Counsel patients on the new agents when dispensing to patients.
- Discuss the role in therapy of the new agents in treating multiple sclerosis, and how they fit in with current guideline treatments.
- Weigh the risks and benefits of these new treatments and apply them to a population that may benefit from their use.

Introduction

Each year, new drugs are approved by the FDA to treat a variety of disease states. There were 56 new drugs approved in 2016 and 2017. This article will focus on three disease states treated with some of these new medications. Breast cancer, hepatitis C, and multiple sclerosis were selected based off the many new drugs that have been approved each year for their treatment, as well as an average lack of familiarity on the disease states.

New Breast Cancer Drugs of 2017

Three drugs were approved for treatment of breast cancer in 2017 and are Verzenio (abemaciclib), Kisqali (ribociclib), and Nerlynx (neratinib).[1]

Patients Most Likely to Develop Breast Cancer

Breast cancer is the most common cancer and the second most common cause of death due to cancer in the United States.[2] In 2017, an estimated 252,710 women will be diagnosed with breast cancer and 40,610 women will die from breast cancer.[3]

The two most common factors associated with developing breast cancer are age and gender.[4] The likelihood of developing breast cancer increases with age, and the average age of diagnosis is between 60 and 65 years old. Despite breast cancer occurring more frequently in older women, it is still the leading cause of death among females between the ages of 35 to 54 as well.[5]

The most common races to develop breast cancer include women who are white or black.[2] Men have a much lower chance of developing breast cancer, but the mortality rate is higher when compared to women due to an advanced progression of the disease by the time it is typically diagnosed.[6]

Factors that Contribute to the Development of Breast Cancer

Risk factors for developing breast cancer are both hormonal and genetic.[6] Women who start their menstrual cycle before the age of 12, have late onset of menopause occurring after the age of 55, and women who gave birth to their first child after the age of 30 were at higher risk of developing breast cancer.[6] Results from the Women's Health Initiative found that combination estrogen and progestin therapy resulted in a higher rate of breast cancer with each year of therapy.[7] Hormone replacement therapy is contraindicated in women who have a history of breast cancer due to the risk of recurrence outweighing the benefit of therapy.[6]

Women who have had breast cancer in one breast are more likely to develop it in the other breast, and those who have had uterine or ovarian cancer are more likely to develop breast cancer.[6] A women's risk for developing breast cancer is increased by three times if they have a first degree relative who has had breast cancer.[6] A gene mutation that results in an increased incidence of breast cancer involves the BRCA1 and BRCA2 genes. These genes

normally act as tumor suppressors through DNA repair.[6] The risk of a woman that has a BRCA1 or BRCA2 mutation by the age of 70 is 55% and 47% for developing breast cancer, respectively.[8] Testing is available to determine if a BRCA1 or BRCA2 mutation is present, but is only done if there is a family history of breast cancer.[6]

Progression of Breast Cancer

Early breast cancer is generally localized and has a higher cure rate.[6] As disease advances, the cancer cells can metastasize and spread through the lymph and blood to other parts of the body such as skin, bone, liver, lungs and brain. Treatment at this point is usually focused on quality and extension of life as opposed to a cure. Women who are initially diagnosed as having metastatic breast cancer usually had a breast mass that they neglected to seek treatment for months or years.

Staging Breast Cancer

Staging of breast cancer can be broken down into three parts.[6,9] These three parts include:

- Size of the tumor
- Lymph node involvement
- Metastasis

The size of the tumor is the first designator and is defined on a scale of $T_{0\text{-}4}$.[6,9] T_0 means there is no evidence of a tumor. $T_{1\text{-}4}$ generally means the tumor is larger in size the higher the number designator.

The second designator is N and it defines how far the cancer has spread in the lymph nodes.[6,9] A ranking of $N_{0\text{-}3}$ is given where the higher the number implies that more cancer has spread throughout the lymph nodes.

The final part is M and it stands for metastasis.[6,9] M_0 means no distant metastasis detected and M_1 means that distant metastasis have been detected.

The stage of breast cancer is determined based off the combination of these three parts and can range from stage 0 to stage 4.[6,9] Stage 0 is in situ, meaning that localized abnormal cells have been found. Stage I and II are considered early breast cancer. Stage I is used to describe a small, localized tumor. Stage II will encompass tumors that have spread to nearby lymph nodes. Stage III and IV are used for more advanced disease progression. Stage III is used to describe a large tumor that has spread to local lymph nodes. Stage IV describes breast cancers that have metastasized to other organs.

Receptor Based Treatment (Hormone Receptor and HER2)

Breast cancer tissue can contain hormone receptors (HR) that are designated as estrogen receptors (ER) or progesterone receptors (PR).[6,10] These receptors are bound by their respective hormones and the result is cell growth and proliferation. Postmenopausal breast cancer will more likely be hormone receptor positive. Targeted endocrine therapy can be used if a patient is ER+ or PR+. Antiestrogen drugs are used to block estrogen from attaching to estrogen receptors. Tamoxifen is a specific type of antiestrogen called a selective estrogen receptor modulator (SERM).

The HER2 gene encodes for a human epidermal growth factor receptor (HER2).[6,10] This receptor is expressed in breast tissue epithelial cells normally in low amounts. Once bound by growth factors, it sends signals to the cell to grow and divide. When this gene is overexpressed it results in an abnormally high level of HER2 which increases tumor aggressiveness, rate of recurrence, and increased mortality. Monoclonal antibody therapy can be used for patients that are HER2+. These drugs are Herceptin (trastuzumab) and Perjeta (pertuzumab). Both drugs work by binding parts of the HER2 receptor and inhibiting it

from sending growth signals to the cancer cell.

Stage I and II Treatment

The goal of treating stage I or II breast cancer is to cure.[10] A typical treatment path starts with surgery, chemotherapy with HER2 inhibitors, radiation therapy, and finally endocrine therapy. Treatment is divided into localized and adjuvant therapy.

Surgery and radiation are considered localized therapy because they physically target the specific site in the breast containing the cancer.[10] Surgery is performed first and is very successful for stage I and II cancers. Surgical procedures involve removing the tumor as well as part or all of the breast tissue. Radiation therapy is then used on the affected breast following surgery to prevent recurrence.

Adjuvant therapy is used to prevent the cancer cells that remain following localized therapy from growing and spreading.[10] This is done systemically and can contain chemotherapy, endocrine therapy, and HER2 inhibitor therapy. Chemotherapy is used if the tumor is large or if it has spread. HER2 inhibitors and endocrine therapy are used if the cancer is HER2+ or ER/PR+, respectively. Sometimes these drugs can be used prior to surgery to shrink the tumor size. This is designated neoadjuvant therapy.

Stage III Treatment

Stage III treatment is similar to stage I and II treatment in that the patient may still require chemotherapy, surgery, radiation, HER2 treatment, and endocrine therapy.[11] Unlike stage I and II, surgery for stage III treatment will usually remove nearby lymph nodes as well. Chemotherapy will also be more aggressive and usually started before surgery.

Stage IV Treatment

The goals of treating metastatic breast cancer (MBC) are symptom improvement, improving quality of life, and prolonging survival since cure is unlikely.[12] Surgery and radiation can still be used but it is only done for symptom relief to remove painful masses. Systemic treatment is used and based upon the characteristics of the cancer. One treatment is used at a time and it is only replaced if efficacy fails through disease progression or if toxicities become intolerable to the patient.

Drugs Approved in 2017

Verzenio (abemaciclib) was approved in September 2017 for the treatment of HR+, HER- advanced and metastatic breast cancer.[13-15] It can be used alone or in combination with fulvestrant after endocrine therapy. Verzenio is a cyclin-dependent kinase (CDK) inhibitor and works by arresting tumor cells before duplication in the cell cycle to reduce tumor size. There are many side effects associated with treatment and dose is titrated based off the patient's response to these side effects. Neutropenia and diarrhea are the two most common side effects that are dose dependent and may necessitate adjustment. Treatment is continued until it is no longer effective at preventing disease progression or if unacceptable toxicities occur at the lowest dose. The MONARCH 2 trial assessed Verzenio in combination with fulvestrant versus placebo and fulvestrant.[16] There were 669 patients assigned to the trial with 446 patients receiving Verzenio and fulvestrant. The median survival length of patients on Verzenio and fulvestrant was 16.4 months compared to 9.3 months for patients on fulvestrant alone. The common side effects recorded from the patients on Verzenio were diarrhea, neutropenia, nausea, and fatigue.

Kisqali (ribociclib) was approved in March 2017. It is similar to Verzenio in that

it is a CDK inhibitor used to treat advanced and metastatic HR+, HER2- breast cancer.[17-19] However, Kisqali is indicated for postmenopausal women only and it is used combination with letrozole (an aromatase inhibitor) as first-line endocrine therapy. Kisqali is taken as cycle therapy for 21 days on and 7 days off. A phase III trial looked at the efficacy and safety of Kisqali in combination with letrozole as first-line treatment for postmenopausal women with HR+, HER2- advanced breast cancer.[20] The Kisqali and letrozole treated group had 334 patients with an 18-month progression-free survival rate of 63% while the letrozole and placebo group 334 patients with a rate of 42.2%. Common side effects among the Kisqali and letrozole treatment group were neutropenia, nausea, infections, fatigue, and diarrhea. Side effects are similar to Verzenio and therapy should be titrated down if the patient is unable to tolerate them.[17-19] Kisqali therapy should be discontinued if there is disease progression or if the patient is still unable to tolerate side effects at the lowest possible dose.

Nerlynx (neratinib) was approved as extended adjuvant treatment for HER2+, stage I and II breast cancer following adjuvant trastuzumab therapy.[21-23] The length of treatment with Nerlynx following trastuzumab therapy is 12 months. A phase 3 trial compared treatment for 12 months with Nerlynx versus placebo following 12 months of trastuzumab therapy.[24] At the end of treatment, the group on Nerlynx had a two-year invasive disease-free survival rate of 93.9% and the placebo group had a rate of 91.6%. Nerlynx works by reducing activation of HER2 on cancer cells and preventing proliferation.[21-23] Diarrhea is a common side effect and pre-treatment with loperamide is recommended as well monitoring for dehydration.

Hepatitis C Treatment from 2016-2017

Background of Hepatitis

Hepatitis is a viral infection that targets the liver and causes inflammation which can lead to a chronic infection if not treated.[25] Many patients that suffer from hepatitis are unaware that they have the disease, as many times hepatitis is asymptomatic in its early, acute stages.[26] As the disease progresses to a chronic infection, the risk of severe liver damage and future complications are increased. Untreated hepatitis can result in cirrhosis, liver failure, or hepatocarcinoma.[27]

The term “hepatitis” encompasses several different forms/families of hepatitis viruses. Currently, there are five known hepatitis viruses which are classified as hepatitis A-E. The most common forms of hepatitis include hepatitis A, hepatitis B, and hepatitis C.[28] For this article, the focus will be on hepatitis C, but it is important to understand the difference between the viruses.

Routes of Transmission

Although each of the hepatitis viruses affect the liver, they are not all transmitted by the same routes. Table 1 contains each of the hepatitis viruses and their routes of transmission. The hepatitis A and hepatitis E viruses are transmitted through the fecal-oral route.[27] This transmission may occur by consuming undercooked foods such as shellfish, pork, deer meat, or by drinking water that has been contaminated by infected human feces. Hepatitis B and hepatitis D are transmitted through body fluids, including the blood. The hepatitis C virus is transmitted by coming into contact with infected blood, which is primarily done through injection drug use and sharing needles.[26]

Table 1: Routes of Transmission and Progression of Hepatitis[27]

	Routes of Transmission	Progression to Chronic Infection?
Hepatitis A	Fecal-oral	No
Hepatitis B	Body fluids and blood	Yes
Hepatitis C	Blood (percutaneous transmission)	Yes
Hepatitis D	Body fluids and blood	Yes
Hepatitis E	Fecal-oral	No

Effects of Hepatitis in the United States

In the United States, hepatitis affects a large number of individuals. The CDC's most recent report of hepatitis surveillance from 2015 shows that hepatitis infections are on the rise.[28] Hepatitis C remains the most prevalent form of hepatitis infections, followed by hepatitis B and hepatitis A, respectively. The CDC reports that 3.5 million people in the United States are currently living with hepatitis C infections. Another 850,000 cases of hepatitis B were reported as well. Hepatitis A was estimated to have 2,800 new infections in 2015.

Hepatitis C

Hepatitis C is the most prevalent form of hepatitis in the United States. In recent years, hepatitis C infections have steadily increased in prevalence. From 2011 to 2015, the number of new reported cases of acute hepatitis C increased from 29,718 to 33,900 cases, respectively.[28] This current trend is thought to be associated with increased injection drug use.[28]

The hepatitis C virus is broken down into six different genotypes, characterized by genotypes 1-6. The six genotypes can then be further broken down into subcategories such as genotype 1a, genotype 1b, etc.[26,29] In the United States, genotypes 1, 2, and 3 are the most prevalent. Genotypes 1a and 1b are the most common of these three genotypes.[26]

Treating Hepatitis C

In the past, Hepatitis C treatment regimens were associated with extensive drug regimens that had a high pill burden, significant side effects, and relatively low sustained virologic response (SVR) rates.[30] Now, treatment regimens have become available that include one tablet regimens that are taken orally and achieve greater than 95% SVR in patients with hepatitis C. With the recent advances in hepatitis C treatment, many more patients meet the criteria to be treated and are able to finish therapy with much better outcomes and lower rates of serious side effects. These oral treatments are also able to be modified to include some older therapies used, such as ribavirin, for patients with cirrhosis or to extend treatment for 24 weeks.

In patients that undergo treatment with new oral direct-acting antiviral medication, treatment duration can last from 8-24 weeks depending on patient specific parameters. However, to determine treatment success or failure, the follow-up time remains the same. In order to be cured of hepatitis C, patients must have a hepatitis C virus (HCV) RNA that is undetectable 12 weeks after completing therapy.[26] Patients that have an undetectable HCV RNA level are considered to have virologic cure of hepatitis C. If patients do not achieve undetectable levels, other treatment options may be available for future treatment. Table 2 lists the newest medications approved for the treatment of hepatitis C.

All hepatitis C treatment regimens contain the Black Box Warning of hepatitis B reactivation in patients that are co-infected with hepatitis C and hepatitis B. It is thought that the hepatitis C virus suppresses the replication of the HBV virus in co-infected patients that have hepatitis B or that have

been previously treated for hepatitis B.[31] However, when patients are initiated on treatment for hepatitis C, this allows the hepatitis B virus to begin to replicate and progress once again due to the lack of inhibition from the hepatitis C virus. Thus, patients that have previously been treated for hepatitis B should have their hepatitis B antigen levels monitored to ensure that reactivation does not occur while being treated with hepatitis C regimens.

New Drugs/Treatment regimens

Table 2: Indications and Pricing of New Hepatitis C Medications[32-34]

Medication	Indication	Mechanism of Action	Approval Date	Cost for a full treatment course
Mavyret (glecaprevir and pibrentasvir)	Hepatitis C	**Glecaprevir**- NS3/4A protease inhibitor **Pibrentasvir**- NS5A inhibitor	August 3, 2017	$47,520.00
Vosevi (sofosbuvir, velpatasvir, voxilaprevir)	Hepatitis C	**Sofosbuvir**- NS5B polymerase inhibitor **Velpatasvir**- NS5A inhibitor **Voxilaprevir**- NS3/4A protease inhibitor	July 18, 2017	$89,712.00
Epclusa (sofosbuvir and velpatasvir)	Hepatitis C (all 6 genotypes)	**Sofosbuvir**- NS5B polymerase inhibitor **Velpatasvir**- NS5A inhibitor	June 28, 2016	$89,712.00
Zepatier (elbasvir and grazoprevir)	Hepatitis C (genotypes 1 and 4)	**Elbasvir**- NS5A inhibitor **Grazoprevir**- NS3/4A protease inhibitor	January 28, 2016	$65,520.00

Mavyret (glecaprevir and pibrentasvir)

Mavyret is the most recently approved direct-acting antiviral agent used in the treatment of hepatitis C. The direct acting antiviral agent of glecaprevir and pibrentasvir is a combination product containing 100 mg glecaprevir and 40 mg pibrentasvir which is approved by the Food and Drug Administration for the treatment of hepatitis C genotypes 1-6 in patients with or without cirrhosis and regardless if patients are treatment naïve or experienced.[33] Table 3 contains additional information about Mavyret, including dosing options, adverse events, and monitoring parameters.

Table 3: Mavyret (glecaprevir and pibrentasvir)[33-35]

Components	Glecaprevir- 100 mg Pibrentasvir- 40 mg	
Dosing	**3 tablets daily for 8-16 weeks** (300/40 mg total daily dose)	
Adverse Events	**Common Adverse Events**	
	• Headache- 9-17% • Fatigue- 11-14% • Nausea- 6-12%	• Diarrhea- 3-7% • Increased bilirubin- 4%
SVR response rates	**Genotypes 1-2 and 4-6: 96-100%** **Genotype 3: 93-97%**	
Monitoring	• Take medication with food • Hepatitis B Virus • HCV Genotype	• Side effects include headache, fatigue, nausea, diarrhea • HCV-RNA viral load
	Within 12 weeks of beginning therapy	**During Therapy (at weeks 4 and 12)**
	• Baseline CBC • INR • LFTs • GFR	• CBC • Serum creatinine • GFR • LFTs • HCV Viral Load
Black Box Warning	Reactivation of Hepatitis B	

Vosevi (sofosbuvir, velpatasvir, and voxilaprevir)

Vosevi is the only direct-acting, antiviral hepatitis C medication that is approved for re-treatment in patients that have previously been treated with NS5A containing regimens, such as Viekira Pak, Technivie, Harvoni or Epclusa, and failed therapy.[36] The length of treatment for patients with prior treatment of a NS5A inhibitor or sofosbuvir is 12 weeks.[29,33] Table 4 provides information regarding dosing, adverse events and monitoring for Vosevi.

Table 4: Vosevi (sofosbuvir, velpatasvir, and voxilaprevir)[33,34]

Components	Sofosbuvir- 400 mg Velpatasvir- 100 mg Voxilaprevir- 100 mg	
Dosing	One tablet by mouth daily for 12 weeks (400 mg/100 mg/100 mg)	
Adverse Events	**Common Adverse Events**	
	• Headache- 21-23% • Fatigue- 17-19%	• Diarrhea- 13-14% • Nausea- 10-13% • Increased bilirubin- 4-13%
SVR response rates	**Genotypes 1-6: 96% overall SVR**	
Monitoring	• Hepatitis C genotype • HCV-RNA viral load	• Hepatitis B virus • Cardiac monitoring (in an in-patient setting)
	Within 12 weeks of beginning therapy	**During Therapy (at weeks 4 and 12)**
	• Baseline CBC • INR • LFTs • GFR	• CBC • Serum creatinine • GFR • LFTs • HCV Viral Load
Black Box Warning	Hepatitis B Reactivation	

Epclusa (sofosbuvir and velpatasvir)

Epclusa was approved in 2016 as the first direct-acting, antiviral hepatitis C medication that could be used in all genotypes associated with hepatitis C regardless of cirrhosis or prior treatment of hepatitis.[37] Epclusa is provided in a combination tablet that is dosed once daily for 12 weeks in most hepatitis C genotypes and populations. In patients with decompensated cirrhosis, Epclusa is given in combination with ribavirin for a 12-week course of therapy.[29,33] Overall, patients with hepatitis C showed an overall sustained virologic response of 99%. See table 5 for more information regarding Epclusa.

Table 5: Epclusa (sofosbuvir and velpatasvir)[33,34,37]

Components	Sofosbuvir- 400 mg Velpatasvir- 100 mg	
Dosing	**Without cirrhosis/compensated cirrhosis:** one tablet by mouth daily for 12 weeks **Decompensated cirrhosis:** one tablet by mouth daily with ribavirin for 12 weeks	
Adverse Events	**Common Adverse Events**	
	• Headache- 22% • Fatigue- 15%	• Irritability- ≥5% • Insomnia- 5%
SVR response rates	**Genotypes 1-6: 99% overall SVR**	
Monitoring	• Hepatitis C genotype • HCV-RNA viral load	• Hepatitis B virus • Hepatic Function
	Within 12 weeks of beginning therapy	**During Therapy (at weeks 4 and 12)**
	• Baseline CBC • INR • LFTs • GFR	• CBC • Serum creatinine • GFR • LFTs • HCV Viral Load
Black Box Warning	Hepatitis B Reactivation	

Zepatier (elbasvir and grazoprevir)

Zepatier is currently approved for the treatment of hepatitis C genotypes 1 and 4. In recent studies, the combination of elbasvir and grazoprevir have shown significant response rates in SVR in both treatment naïve and treatment experienced patients, with or without NS5A polymorphisms.[38] Treatment duration ranges between 12 and 16 weeks, and is based upon prior treatment or polymorphisms associated with the NS5A protein. Table 6 contains more information regarding dosing, monitoring, and adverse events regarding Zepatier.

Table 6: Zepatier (elbasvir and grazoprevir)[33,34]

Components	Elbasvir- 50 mg Grazoprevir- 100 mg	
Dosing	**Genotype 1a, 1b, 4 treatment naive:** one tablet by mouth daily for 12 weeks **Genotype 1a, 1b treatment experienced:** one tablet by mouth daily for 12 weeks **Genotype 1a with NS5A polymorphisms:** one tablet by mouth daily for 16 weeks with ribavirin **Genotype 4 treatment experienced:** one tablet by mouth daily for 16 weeks with ribavirin	
Adverse Events	**Common Adverse Events**	
	• Fatigue- 7-11% • Headache- 11%	• Nausea- 5-11% • Insomnia 3-5%
SVR response rates	**Genotypes 1 and 4: 92-100%**	
Monitoring	• Hepatitis C genotype • HCV-RNA viral load • NS5A resistance testing in patients with genotype 1a	• Hepatitis B virus • Hepatic Function • HCV-RNA at baseline and weeks 4, 8, 12 • Hepatic Function/LFTs
Black Box Warning	Hepatitis B Reactivation	

New Multiple Sclerosis Drugs

Background

Multiple sclerosis (MS) is an autoimmune disease and is reported to effect around 2.3 million people worldwide.[39] MS is typically diagnosed between the ages of 15 and 45 and is more commonly seen in women than in men by a 2:1 ratio. Risk factors for developing the disease include: age: typically diagnosed between 15-45, environmental influences, genetics, and geography. The risk of developing MS seems to increase the further away from the equator the patient lives. The exact cause of MS remains unknown, but it is more likely to develop in genetically susceptible people who have been exposed to factors or risks resulting in an immune mediated CNS damage response.

Clinical presentation:

The clinical presentation of MS differs from patient to patient. In addition, the symptoms can change in the same patient throughout the progression of the disease.[39] Symptoms can be divided into 3 different categories which are a direct complication of demyelination and neuron damage. This usually reflects the part of the CNS where the damage is occurring. Table 7 contains different categories of symptoms. Secondary symptoms are problems that occur as a result of the primary symptoms. Tertiary symptoms are the effects that the disease has on the patient's everyday quality of life.

Table 7: Symptoms of Multiple Sclerosis[39]

Primary Symptoms	Secondary Symptoms	Tertiary Symptoms
• Visual complaints • Gait problems/falls • Paresthesia • Pain • Spasticity • Weakness • Ataxia • Speech Difficulty • Psychological Changes • Cognitive Changes • Fatigue • Bowel/Bladder dysfunction • Sexual dysfunction • Tremor	• Recurrent UTIs • Urinary Calculi • Decubiti • Osteomyelitis • Osteoporosis • Respiratory Infections • Poor nutrition • Depression	• Financial problems • Personal problems • Social problems • Vocational problems • Emotional problems

Types of MS:

There are 4 different clinical courses of MS and each course progresses differently from each other.[39]

- Relapsing-Remitting MS (RRMS): RRMS is a form of MS where the patient experiences self-limiting periods of exacerbations or flare ups when symptoms appear and/or worsen followed by periods of remission that can be complete or incomplete.
  - This is the most common form of MS occurring in around 85% of all MS patients.
- Primary progressive MS (PPMS): PPMS is a form of MS where there are not periods of remission and periods of relapse. Instead PPMS continually worsen from the time of symptom onset.
  - Only 10 % of MS patients have PPMS
- Secondary progressive MS (SPMS): SPMS is a form of MS where patients start out classified as RRMS and disability tends to accumulate over time until periods of remission and relapse can no longer be differentiated.
  - Most patients that are diagnosed with RRMS will transition to SPMS at some point as the disease progresses.
- Progressive-relapsing MS (PRMS): PRMS is a rare form of MS where patients gradually get worse from diagnosis with periods of relapsing but without remissions.
  - PRMS accounts for about 5% of all MS cases.

Current Treatment:

The overall goal of treatment is to minimize long-term disability and improve the patient's quality of life.[40] When the patient initially presents with MS symptoms they are evaluated and placed in either the induction or escalation category where induction or escalation algorithms are used. The induction algorithm focuses all its therapeutic efforts to the early stages of the disease. In escalation therapy, patients start treatment with safer medications and progress to more effective drugs if the treatments fail. Treatment success is defined as the absence of any clinical evidence of

progression such as relapses, disability progression, or worsening MRI results.

Treatment of Exacerbations

When a relapse is so severe that it affects the patient's ability to function the standard treatment course consists of high dose corticosteroids given IV, typically methylprednisolone for 3-10 days.[41] Corticosteroids have been shown to provide a short-term benefit during an exacerbation in that they speed up functional recovery.[40] The current guidelines say that using corticosteroids long term does not appear to be beneficial.

Disease-Modifying Therapy

To chronically treat MS the goal is to modify the disease so that it either doesn't progress or progresses more slowly.[39] The drugs are referred to as disease modifying therapies and differ from those used to treat exacerbations. When choosing a disease-modifying therapy, (DMT) it is important to consider clinical factors that may represent disease severity. First generation DMTs currently approved by the FDA include four interferon drugs and one non-interferon drug. The first-generation drugs do not immediately begin to relieve symptoms. Symptom relief is often seen 1-2 years after the initiation of therapy, and may be a result of the fact that efficacy is measured by a decrease in annual relapse rates.

New Drugs:

With all the unknown factors surrounding MS as a disease and its treatments, there is a constant search for drugs that can treat previously untreated forms of the disease, such as PPMS, to prevent or delay progression of the disease for as long as possible, and ultimately increase the quality of life of the patient. The addition of these new drugs to the market both improve current treatment options and provide treatment for some previously untreated forms of the disease. Ocrevus (Ocrelizumab) was approved in March 2017 for the treatment of relapsing and primary progressive forms of MS and Zinbryta (Daclizumab) was approved on May 27th, 2016 to treat relapsing forms of MS.[1] These drugs aim to help fill the gaps in MS treatment and provide options to patients to help maintain their quality of life.

Table 8: General Drug Information[39,42,43]

Drug Name:	Brand: Ocrevus Generic: Ocrelizumab	Brand: Zinbryta Generic: Daclizumab
MOA:	Monoclonal antibody that binds to CD-20 surface of B lymphocytes	Monoclonal antibody that binds to CD-25 via IL-2
FDA Indication:	• Relapsing forms of MS • Primary progressive MS	• Relapsing forms of MS
Available Dosage Forms:	IV	Subcutaneous Solution
Cost:	$19,500.00 for 10mL of 30mg/mL	$8683.80 for 1mL of 150mg/mL
Dosing:	• 600mg IV every 24 weeks • Initial dose: 2 300mg doses given 2 weeks apart observe patient for at least 1 hour after infusion completion	150mg SC once a month
Special populations:		Contraindicated if preexisting liver disease, ALT/AST 2x ULN or greater, or history of autoimmune liver disease.
Half-Life:	26 days	21 days

Table 8 contains some generic drug information on the 2 newest MS treatments on the market. It is worth noting that ocrelizumab is the first drug to be approved by the FDA for the primary progressive form of MS.[1] Both these drugs are monoclonal antibodies and are given via IV infusion or subcutaneous injection.[42,43]

Ocrelizumab requires pre-medication prior to infusion to help prevent infusion reactions that may occur, especially with the initial dose.[40] Typical pretreatment consists of an antihistamine, such as diphenhydramine, given 30 to 60 minutes prior to each infusion and methylprednisolone 100 mg IV or an equivalent corticosteroid given 30 minutes prior to each infusion. It is reasonable to consider the addition of an antipyretic such as acetaminophen. Refer to table 8 for standard dosing.

Both ocrelizumab and daclizumab have relatively long half-lives of 26 and 21 days, respectively.[42,43] This provides both drugs with the advantage of longer dosing intervals without reducing efficacy. This is a major selling point to the patients given that clinical trials of MS drugs often report high rates of nonadherence.[39] It is important as pharmacists to talk with the patients and help them manage any problems they may be experiencing. Refer to table 9 for a list of contraindications and side effects regarding these drugs.[42,43]

Table 9: Drug Information, Side Effects, and Patient Counseling[42,43]

Drug Name:	Brand: Ocrevus Generic: Ocrelizumab	Brand: Zinbryta Generic: Daclizumab
Black Box Warning:	None	Hepatic Injury Including Autoimmune Hepatitis, severe liver injury, and liver failure.
Contraindications:	• Active Hepatitis B • Hypersensitivity	• Hypersensitivity • Preexisting liver disease • Autoimmune Disease of the liver.
Pregnancy & Lactation:	Risk cannot be ruled out See recommendations in counseling section.	Risk cannot be ruled out
ADRs:	**Common:** Infection of skin and/or subcutaneous tissue Upper respiratory tract infections **Rare but Serious:** Infusion reaction Depression Increased cancer risk	**Common:** Infections Eczema **Rare but Serious:** Liver failure Disorder of the skin Depression
Monitoring:	**Efficacy**: a reduction in MS relapse rates **Safety:** • S/s of active infection • Screen for Hep B prior to starting S/s of infusion reactions: during infusion and at least 1 hour after completion	**Efficacy:** a reduction in MS relapse rates **Safety:** • Liver function test S/s of immune mediated disorders
Patient Counseling:	• Report S/s of infection • Report S/s of an infusion reaction • Instruct female patients to avoid pregnancy during therapy and for 6 months after last infusion Advise patient to report depression or suicidal thoughts	• Immediately report symptoms of liver dysfunction (eg, pallor, fatigue, dark urine, jaundice) • Report S/s of infection • Teach patient proper technique for injections Advise patient to report depression or suicidal thoughts

In both drugs, it is important to monitor for suicidal thoughts and ideations.[1] The rate of suicide among MS patients is 7 times higher than that seen in the general population. Therefore, it is important to talk with and monitor patients to make sure their safety is maintained.

New Medication Take Home Points

Ocrevus (Ocrelizumab):

- This is the 1st drug approved by the FDA for primary progressive MS (PPMS)[1]
- In 2 phase 3 clinical trials ocrelizumab was shown to decrease the yearly rate of relapse by 47% and decreased MRI lesions by 95% compared to 3 times weekly interferon-b[44]
- Ocrelizumab should be avoided in patients with an active hepatitis B infection[1]
- Do not start ocrelizumab treatment in patients with active infections.
- Vaccines that contain live or live attenuated formulations are not recommended in patients receiving ocrelizumab.
- In clinical trials of ocrelizumab around 35-40% of patients experienced some type of infusion reaction after being given a corticosteroid and an antihistamine 30 minutes prior to the infusion.[44]
    - This reduced the severity of the infusion reactions, but they still occurred.
- Ocrelizumab worked similarly in men and women with RMS, but better in men with PPMS.

Zinbryta (Daclizumab)

- Daclizumab has not been on the market since 2009 due to lack of market demand, it was originally used for prophylaxis against acute rejection in renal transplant recipients.
- Zinbryta (Daclizumab) is a self-administered once monthly long-acting injection.
- This drug has a BLACK BOX WARNING for severe liver injury.
    - Requires liver function test prior to each monthly dose, and for up to 6 months after discontinuation.[45]
- Zinbryta (Daclizumab) should be used only for patients who have experienced an inadequate response to 2 or more MS drugs.
    - This is because Zinbryta (Daclizumab) has serious safety risks, including liver injury and immune conditions
- In a clinical trial conducted in 2010-2012 Zinbryta (Daclizumab) showed a 45% less annual relapse rate than the interferon beta-1a group.[46]
    - However, this is increase in efficacy also came with a slight increase in adverse event frequency. Therefore, a risk vs benefit analysis should always be done when choosing a new MS medication.

Conclusion

Breast cancer, hepatitis C, and multiple sclerosis are diseases that are seen in many Americans. Although not as common as hypertension or hyperlipidemia, these disease states have many new drugs that are being approved in order to improve treatment and even provide a cure. Many of these drugs will be taken by patients in their home setting and they will receive them from their community pharmacies. Pharmacists must be familiar with these drugs as they appear on their shelves in order to provide adequate counseling and ensure the patient's safety.

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