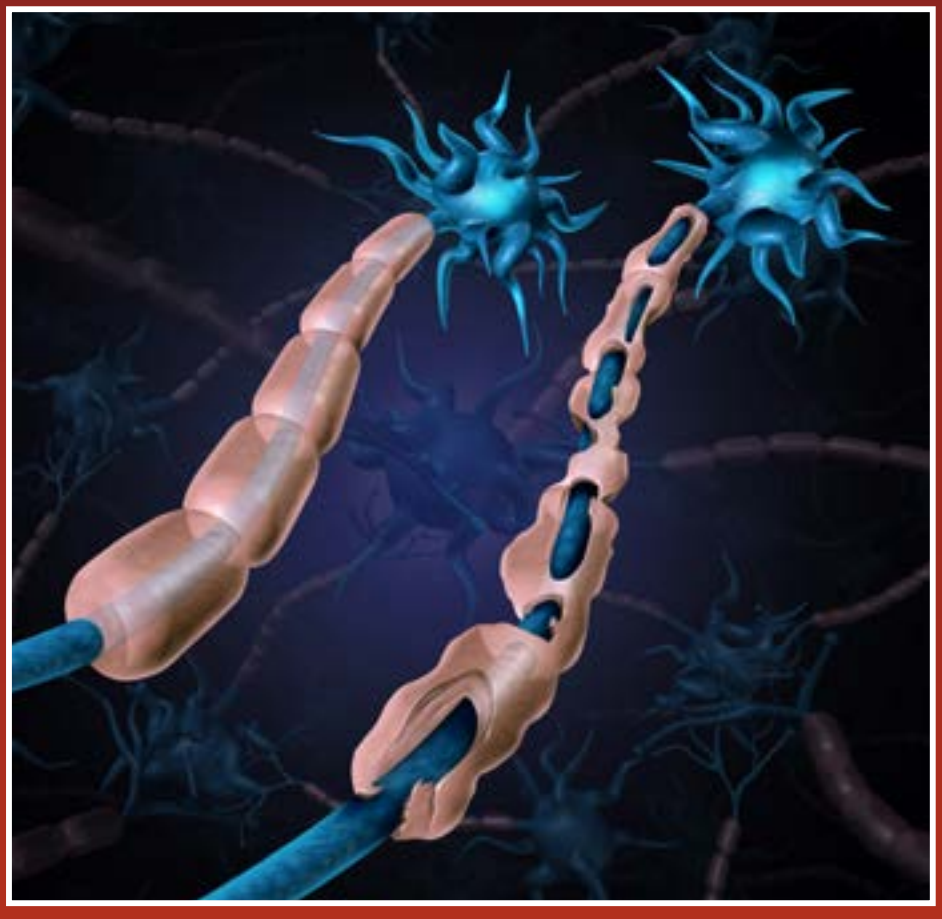
Advances in the Cause And Treatment of Multiple Sclerosis



U.S. Medicine
THE VOICE OF FEDERAL MEDICINE

Federal Medicine Leads the Battle Against MS from Cause to Vaccine

BETHESDA, MD—Researchers with the DoD provided a breakthrough in resolving the mystery surrounding the cause of multiple sclerosis. Now, federal researchers at the National Institutes of Health are undertaking a clinical trial to evaluate a vaccine that could prevent MS, while another team at the Uniformed Services University of Health Sciences (USUHS) is refining a second vaccine candidate.

The massive DoD database provided the key to one of the most puzzling and persistent questions about MS—What starts the disease process? Drawing on blood samples from more than 10 million U.S. servicemembers in the Department of Defense Serum Repository, scientists with the Uniformed Services USUHS and Harvard University were able to determine that Epstein-Barr virus (EBV) starts the cascade that eventually results in the demyelinating disease, though only in a very small percentage of infected patients.[1]

As an active infection, EBV causes mononucleosis. While many people have no symptoms and most others recover in weeks or months, no one fully clears the virus. Studies into the long-term effects of latent infection strongly implicate the virus in a number of other diseases, including myalgic encephalomyelitis or chronic fatigue syndrome, Hodgkin and Burkitt lymphomas, nasopharyngeal and gastric carcinomas, lupus and rheumatoid arthritis. The virus had long been suspected as the culprit in the development of MS as well, but the hypothesis proved extremely challenging to test because nearly 95% of humans contract EBV, also known as herpesvirus 4, during childhood or adolescence.

The size of the DoD database enabled the critical breakthrough. Just 5.3% of the servicemembers with samples in the DoD serum repository had not been infected

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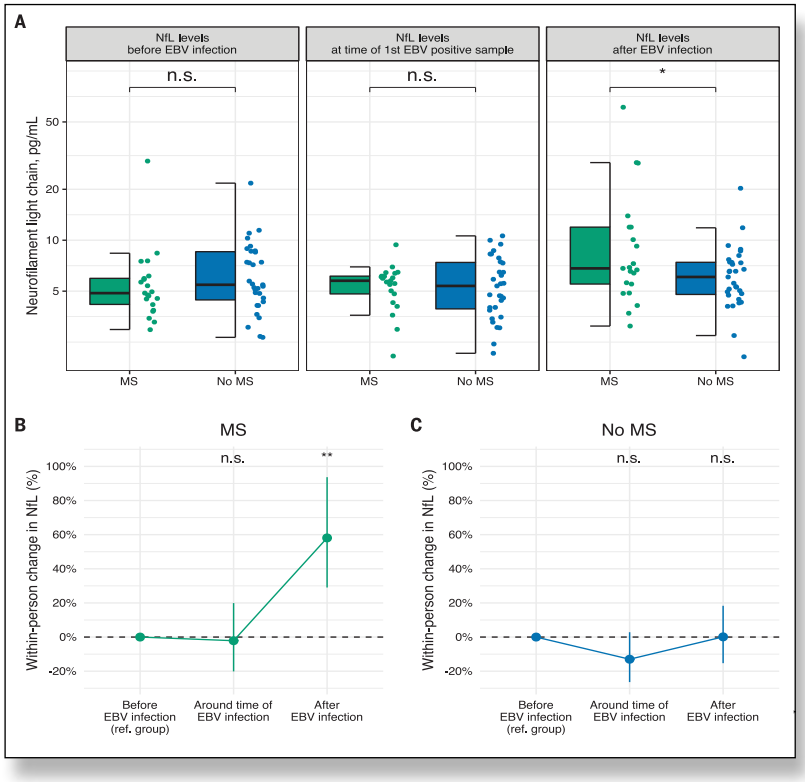


Fig. 3. EBV infection precedes elevation of sNfL before the onset of MS. (**A**) Box plots of sNfL levels before, around, and after the time of EBV infection. *P < 0.05, two-sided multivariable linear regression model adjusted for age and sex. (**B**) Withinperson increase in sNfL levels in MS cases around and after time of EBV infection compared with before EBV infection. **P < 0.01, two-sided linear mixed-effects regression model. (**C**) Within-person increase in sNfL levels in controls around and after time of EBV infection compared with before EBV infection. Error bars in (B) and (C) are 95% CIs. sNfL levels increased significantly more in MS cases than in controls in the sample collected after time of EBV infection compared with before EBV infection (P < 0.001, two-sided linear mixedeffects regression model).

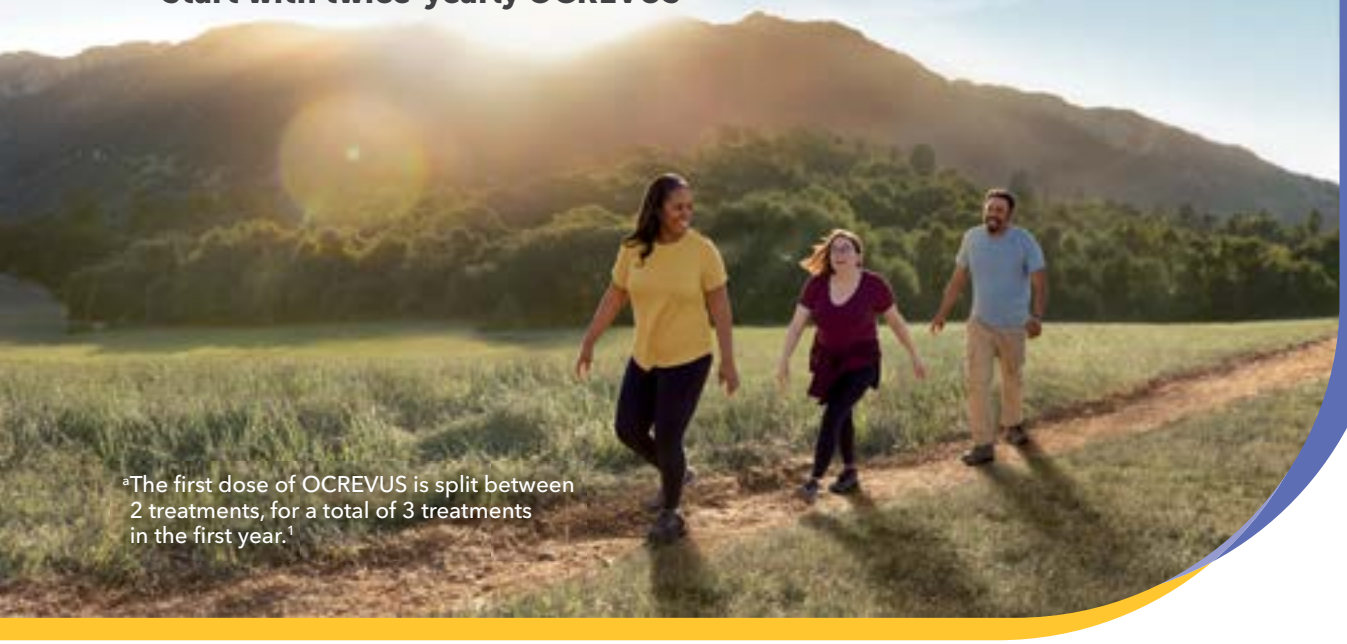
Source: Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, Elledge SJ, Niebuhr DW, Scher AI, Munger KL, Ascherio A. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. *2022 Jan 21;375(6578):296-301. doi: 10.1126/science.abj8222. Epub 2022 Jan 13. PMID: 35025605.*

This is

GENERATION·O

For patients at the start of their MS journey, where they go depends on where you start

Start with twice-yearly OCREVUS[a]



[a]The first dose of OCREVUS is split between 2 treatments, for a total of 3 treatments in the first year.[1]

OCREVUS has the most clinical trial and real-world MS experience in the aCD20 class—including 8+ years of safety data and 250,000+ patients treated globally[2-5]

OCREVUS®
ocrelizumab 300MG/10ML INJECTION FOR IV

Indications

OCREVUS is indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults

Contraindications

OCREVUS is contraindicated in patients with active hepatitis B virus infection and in patients with a history of life-threatening infusion reaction to OCREVUS.

Important Safety Information

Warnings and Precautions

Infusion Reactions

OCREVUS can cause infusion reactions, which can include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis. In multiple sclerosis (MS) clinical trials, the incidence of infusion reactions in OCREVUS-treated patients [who received methylprednisolone (or an equivalent steroid) and possibly other pre-medication to reduce the risk of infusion reactions prior to each infusion] was 34-40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of OCREVUS-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization.

Observe patients treated with OCREVUS for infusion reactions during the infusion and for at least one hour after completion of the infusion. Inform patients that infusion reactions can occur up to 24 hours after the infusion. Administer pre-medication (e.g., methylprednisolone or an equivalent corticosteroid, and an antihistamine) to reduce the frequency and severity of infusion reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered. For life-threatening infusion reactions, immediately and permanently stop OCREVUS and administer appropriate supportive treatment. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

Infections

A higher proportion of OCREVUS-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of OCREVUS-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of OCREVUS-treated patients experienced one or more infections compared to 68% of patients on placebo. OCREVUS increased the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections. OCREVUS was not associated with an increased risk of serious infections in MS patients. Delay OCREVUS administration in patients with an active infection until the infection is resolved.

For additional safety information, please see the following pages and accompanying **Brief Summary** of full **Prescribing Information**.

IN 2 IDENTICAL HEAD-TO-HEAD RMS CLINICAL TRIALS,

OCREVUS WAS SUPERIOR IN REDUCING THE RISK OF DISABILITY PROGRESSION VS REBIF OVER 2 YEARS[1]

SUPERIOR RELAPSE RATE REDUCTIONS VS REBIF[1]

46% OPERA I | **47%** OPERA II

RELATIVE REDUCTIONS $p<0.0001$

PRIMARY ENDPOINT

Annualized relapse rate with OCREVUS vs Rebif® (interferon β-1a):
OPERA I: 0.156 vs 0.292
OPERA II: 0.155 vs 0.290

OPERA I and II (RMS): Two randomized, double-blind, double-dummy, active comparator-controlled clinical trials of identical design vs Rebif in 1656 patients (OCREVUS; OPERA I [n=410], OPERA II [n=417]; Rebif; OPERA I [n=411], OPERA II [n=418]) with RMS treated for 96 weeks. Both studies included patients who had experienced ≥1 relapse within the prior year, or 2 relapses within the prior 2 years, and had an Expanded Disability Status Scale score between 0 and 5.5. The primary outcome of both studies was the annualized relapse rate.[1,6]

Important Safety Information

Respiratory Tract Infections

A higher proportion of OCREVUS-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo and 10% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 9% of patients on placebo. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections and bronchitis.

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in OCREVUS-treated patients than in REBIF-treated patients, including herpes zoster (2.1% vs. 1.0%), herpes simplex (0.7% vs. 0.1%), oral herpes (3.0% vs. 2.2%), genital herpes (0.1% vs. 0%), and herpes virus infection (0.1% vs. 0%). Infections were predominantly mild to moderate in severity. In the placebo-controlled (PPMS) clinical trial, oral herpes was reported more frequently in the OCREVUS-treated patients than in the patients on placebo (2.7% vs 0.8%).

Serious cases of infections caused by herpes simplex virus and varicella zoster virus, including central nervous system infections (encephalitis and meningitis), intraocular infections, and disseminated skin and soft tissue infections, have been reported in the postmarketing setting in multiple sclerosis patients receiving OCREVUS. Serious herpes virus infections may occur at any time during treatment with OCREVUS. Some cases were life-threatening

If serious herpes infections occur, OCREVUS should be discontinued or withheld until the infection has resolved, and appropriate treatment should be administered.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B reactivation has been reported in MS patients treated with OCREVUS in the postmarketing setting. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with OCREVUS. Do not administer OCREVUS to patients with active HBV confirmed by positive results for HBsAg and anti-HB tests. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment.

Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants

When initiating OCREVUS after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS, consider the potential for increased immunosuppressive effect. OCREVUS has not been studied in combination with other MS therapies.

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of OCREVUS for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of OCREVUS for non-live vaccines. OCREVUS may interfere with the effectiveness of non-live vaccines. The safety of immunization with live or live-attenuated vaccines following OCREVUS therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with OCREVUS During Pregnancy

In infants of mothers exposed to OCREVUS during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts as measured by CD19+ B-cells. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

You may administer non-live vaccines, as indicated, prior to recovery from B-cell depletion, but should consider assessing vaccine immune responses, including consultation with a qualified specialist, to assess whether a protective immune response was mounted.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with MS treated with OCREVUS in the postmarketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in OCREVUS-treated patients who had not been treated previously with natalizumab,

ONLY OCREVUS SIGNIFICANTLY IMPACTED DISABILITY
IN 3 ENDPOINTS ACROSS 2 IDENTICAL RMS TRIALS VS AN ACTIVE COMPARATOR[1]

12- AND 24-WEEK CONFIRMED DISABILITY PROGRESSION (PROPORTION OF PATIENTS)[1,6]

40% **reduction in risk of disability progression** vs Rebif, confirmed by 2 different endpoints

PRESPECIFIED, POOLED ANALYSIS:
9.8% OCREVUS vs 15.2% Rebif; *p*=0.0006
7.6% OCREVUS vs 12% Rebif; *p*=0.003

12-WEEK DISABILITY IMPROVEMENT (PROPORTION OF PATIENTS)[6]

33% **more patients experienced disability improvement** vs Rebif

PRESPECIFIED, POOLED ANALYSIS:
20.7% OCREVUS vs 15.6% Rebif; *p*=0.02

Ask your Genentech Clinical Specialist about the 7+ years of clinical data from 2 years of controlled and 5+ years of open-label extension trials[2]

(which has a known association with PML), were not taking any immunosuppressive or immunomodulatory medications, associated with risk of PML prior to or concomitantly with OCREVUS, and did not have any known ongoing systemic medical conditions resulting in compromised immune system function.

JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies.

At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Magnetic resonance imaging (MRI) findings may be apparent before clinical signs or symptoms of PML. Monitoring with MRI for signs consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present.

If PML is confirmed, treatment with OCREVUS should be discontinued.

Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with OCREVUS treatment. The pooled data of OCREVUS clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an association between decreased levels of immunoglobulin G (IgG<LLN) and increased rates of serious infections. Monitor the levels of quantitative serum immunoglobulins during OCREVUS treatment and after discontinuation of treatment, until B-cell repletion, and especially in the setting of recurrent serious infections. Consider discontinuing OCREVUS therapy in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Malignancies

An increased risk of malignancy with OCREVUS may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in OCREVUS-treated patients. Breast cancer occurred in 6 of 781 females treated with OCREVUS and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

Immune-Mediated Colitis

Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving OCREVUS in the postmarketing setting. Some cases of colitis were serious, requiring hospitalization, with a few patients requiring surgical intervention. Systemic corticosteroids were required in many of these patients. The time from treatment initiation to onset of symptoms in these cases ranged from a few weeks to years. Monitor patients for immune-mediated colitis during OCREVUS treatment, and evaluate promptly if signs and symptoms that may indicate immune-mediated colitis, such as new or persistent diarrhea or other gastrointestinal signs and symptoms, occur.

Use in Specific Populations

Pregnancy

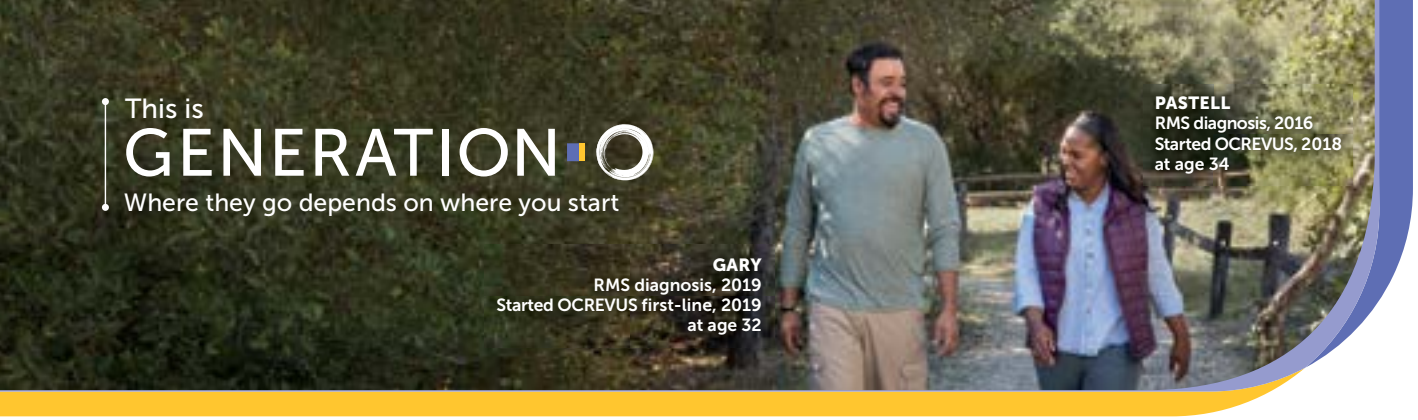
Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to OCREVUS during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-872-4370 or visiting www.ocrevuspregnancyregistry.com.

There are no adequate data on the developmental risk associated with use of OCREVUS in pregnant women. There are no data on B-cell levels in human neonates following maternal exposure to OCREVUS. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. OCREVUS is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier.

For additional safety information, please see the previous and following pages and accompanying **Brief Summary** of full **Prescribing Information**.

OCREVUS®
ocrelizumab 300MG/10ML INJECTION FOR IV



CHOOSE OCREVUS FIRST FOR PATIENTS AT THE START OF THEIR MS JOURNEY

- OCREVUS has the most clinical trial and real-world MS experience in the aCD20 class—including 8+ years of safety data and 250,000+ patients treated globally[2-5]
- **#1 prescribed** MS DMT in the United States[3,a]
- The only **2x-yearly** MS DMT[5,b]

[b]The first dose of OCREVUS is split between 2 treatments, for a total of 3 treatments in the first year.

Genentech provides support to help patients start and stay on OCREVUS: Call 844-OCREVUS (844-627-3887)

Learn more at OCREVUS-hcp.com

[a]From April 2019 to April 2021; IQVIA Claims & IQVIA NSP, rolling 3-month prescriber-based data; includes all patients with an OCREVUS prescription. Includes all patients with an ICD-10-CM of G35 (multiple sclerosis).[3]

Important Safety Information

Lactation
There are no data on the presence of ocrelizumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OCREVUS and any potential adverse effects on the breastfed infant from OCREVUS or from the underlying maternal condition.

Females and Males of Reproductive Potential
Women of childbearing potential should use effective contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS.

Most Common Adverse Reactions

RMS: The most common adverse reactions in RMS trials (incidence ≥10% and >REBIF) were upper respiratory tract infections (40%) and infusion reactions (34%).

PPMS: The most common adverse reactions in PPMS trials (incidence ≥10% and >placebo) were upper respiratory tract infections (49%), infusion reactions (40%), skin infections (14%), and lower respiratory tract infections (10%).

You may report side effects to the FDA at **(800) FDA-1088** or **www.fda.gov/medwatch**. You may also report side effects to Genentech at **(888) 835-2555**.

For additional safety information, please see the previous pages and accompanying **Brief Summary** of full **Prescribing Information**.

References: 1. OCREVUS [prescribing information]. South San Francisco, CA: Genentech, Inc; 2022. **2.** Hauser SL, Kappos L, Montalban X, et al. Safety of ocrelizumab in multiple sclerosis: updated analysis in patients with relapsing and primary progressive multiple sclerosis. Poster presented at: 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), October 13-15, 2021. **3.** Data on file. Genentech, Inc. **4.** Clinicaltrials.gov search results: ofatumumab AND multiple sclerosis. https://clinicaltrials.gov/ct2/results?cond=Multiple+Sclerosis&term=ofatumumab. Accessed January 4, 2022. **5.** Clinicaltrials.gov search results: ocrelizumab AND multiple sclerosis. https://clinicaltrials.gov/ct2/results?cond=Multiple+Sclerosis&term=ocrelizumab. Accessed January 4, 2022. **6.** Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3):221-234.

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OCREVUS®
ocrelizumab 300MG/10ML INJECTION FOR IV

OCREVUS® (ocrelizumab) injection, for intravenous use

Brief Summary of Full Prescribing Information

1 INDICATIONS AND USAGE

OCREVUS is indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults

4 CONTRAINDICATIONS

OCREVUS is contraindicated in patients with:

- Active HBV infection *[see Warnings and Precautions (5.2)]*
- A history of life-threatening infusion reaction to OCREVUS *[see Warnings and Precautions (5.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

OCREVUS can cause infusion reactions, which can include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis. In multiple sclerosis (MS) clinical trials, the incidence of infusion reactions in OCREVUS-treated patients [who received methylprednisolone (or an equivalent steroid) and possibly other pre-medication to reduce the risk of infusion reactions prior to each infusion] was 34 to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of OCREVUS-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization.

Observe patients treated with OCREVUS for infusion reactions during the infusion and for at least one hour after completion of the infusion. Inform patients that infusion reactions can occur up to 24 hours after the infusion.

Reducing the Risk of Infusion Reactions and Managing Infusion Reactions

Administer pre-medication (e.g., methylprednisolone or an equivalent corticosteroid, and an antihistamine) to reduce the frequency and severity of infusion reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered.

Management recommendations for infusion reactions depend on the type and severity of the reaction. For life-threatening infusion reactions, immediately and permanently stop OCREVUS and administer appropriate supportive treatment. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

5.2 Infections

A higher proportion of OCREVUS-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of OCREVUS-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of OCREVUS-treated patients experienced one or more infections compared to 68% of patients on placebo. OCREVUS increased the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections *[see Adverse Reactions (6.1)]*. OCREVUS was not associated with an increased risk of serious infections in MS patients. Delay OCREVUS administration in patients with an active infection until the infection is resolved.

Respiratory Tract Infections

A higher proportion of OCREVUS-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo and 10% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 9% of patients on placebo. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections and bronchitis.

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in OCREVUS-treated patients than in REBIF-treated patients, including herpes zoster (2.1% vs. 1.0%), herpes simplex (0.7% vs. 0.1%), oral herpes (3.0% vs. 2.2%), genital herpes (0.1% vs. 0%), and herpes virus infection (0.1% vs. 0%). Infections were predominantly mild to moderate in severity. In the placebo-controlled (PPMS) clinical trial, oral herpes was reported more frequently in the OCREVUS-treated patients than in the patients on placebo (2.7% vs 0.8%).

Serious cases of infections caused by herpes simplex virus and varicella zoster virus, including central nervous system infections (encephalitis and meningitis), intraocular infections, and disseminated skin and soft tissue infections, have been reported in the postmarketing setting in multiple sclerosis patients receiving OCREVUS. Serious herpes virus infections may occur at any time during treatment with OCREVUS. Some cases were life-threatening.

If serious herpes infections occur, OCREVUS should be discontinued or withheld until the infection has resolved, and appropriate treatment should be administered *[see Patient Counseling Information (17)]*.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B reactivation has been reported in MS patients treated with OCREVUS in the postmarketing setting. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with OCREVUS. Do not administer OCREVUS to patients with active HBV confirmed by positive results for HBsAg and anti-HB tests.

For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment.

Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants

When initiating OCREVUS after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS, consider the potential for increased immunosuppressive effects *[see Drug Interactions (7.1)]*. OCREVUS has not been studied in combination with other MS therapies.

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of OCREVUS for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of OCREVUS for non-live vaccines. OCREVUS may interfere with the effectiveness of non-live vaccines. The safety of immunization with live or live-attenuated vaccines following OCREVUS therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with OCREVUS During Pregnancy

In infants of mothers exposed to OCREVUS during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts as measured by CD19+ B-cells. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines. You may administer non-live vaccines, as indicated, prior to recovery from B-cell depletion, but should consider assessing vaccine immune responses, including consultation with a qualified specialist, to assess whether a protective immune response was mounted *[see Use in Specific Populations (8.1)]*.

5.3 Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with MS treated with OCREVUS in the postmarketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in OCREVUS-treated patients who had not been treated previously with natalizumab (which has a known association with PML), were not taking any immunosuppressive or immunomodulatory medications associated with the risk of PML prior to or concomitantly with OCREVUS, and did not have any known ongoing systemic medical conditions resulting in compromised immune system function.

JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies.

At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

MRI findings may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with other MS medications associated with PML. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Following discontinuation of another MS medication associated with PML, lower PML-related mortality and morbidity have been reported in patients who were initially asymptomatic at diagnosis compared to patients who had characteristic clinical signs and symptoms at diagnosis.

It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

If PML is confirmed, treatment with OCREVUS should be discontinued.

5.4 Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with OCREVUS treatment. The pooled data of OCREVUS clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an association between decreased levels of immunoglobulin G (IgG<LLN) and increased rates of serious infections. Monitor the levels of quantitative serum immunoglobulins during OCREVUS treatment and after discontinuation of treatment, until B-cell repletion, and especially in the setting of recurrent serious infections. Consider discontinuing OCREVUS therapy in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins *[see Adverse Reactions (6.1)]*.

5.5 Malignancies

An increased risk of malignancy with OCREVUS may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in OCREVUS-treated patients. Breast cancer occurred in 6 of 781 females treated with OCREVUS and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

5.6 Immune-Mediated Colitis

Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving OCREVUS in the postmarketing setting. Some cases of colitis were serious, requiring hospitalization, with a few patients requiring surgical intervention. Systemic corticosteroids were required in many of these patients. The time from treatment initiation to onset of symptoms in these cases ranged from a few weeks to years. Monitor patients for immune-mediated colitis during OCREVUS treatment, and evaluate promptly if signs and symptoms that may indicate immune-mediated colitis, such as new or persistent diarrhea or other gastrointestinal signs and symptoms, occur.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Infusion Reactions *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.3)]*
- Reduction in Immunoglobulins *[see Warnings and Precautions (5.4)]*
- Malignancies *[see Warnings and Precautions (5.5)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of OCREVUS has been evaluated in 1311 patients across MS clinical studies, which included 825 patients in active-controlled clinical trials in patients with relapsing forms of MS (RMS) and 486 patients in a placebo-controlled study in patients with primary progressive MS (PPMS).

Adverse Reactions in Patients with Relapsing Forms of MS

In active-controlled clinical trials (Study 1 and Study 2), 825 patients with RMS received OCREVUS 600 mg intravenously every 24 weeks (initial treatment was given as two separate 300 mg infusions at Weeks 0 and 2). The overall exposure in the 96-week controlled treatment periods was 1448 patient-years.

The most common adverse reactions in RMS trials (incidence ≥ 10%) were upper respiratory tract infections and infusion reactions. Table 2 summarizes the adverse reactions that occurred in RMS trials (Study 1 and Study 2).

Table 2 Adverse Reactions in Adult Patients with RMS with an Incidence of at least 5% for OCREVUS and Higher than REBIF

Adverse Reactions	Studies 1 and 2	
	OCREVUS 600 mg IV Every 24 Weeks[1] (n=825) %	REBIF 44 mcg SQ 3 Times per Week (n=826) %
Upper respiratory tract infections	40	33
Infusion reactions	34	10
Depression	8	7
Lower respiratory tract infections	8	5
Back pain	6	5
Herpes virus-associated infections	6	4
Pain in extremity	5	4

[1]The first dose was given as two separate 300 mg infusions at Weeks 0 and 2.

Table 3 Adverse Reactions in Adult Patients with PPMS with an Incidence of at least 5% for OCREVUS and Higher than Placebo

Adverse Reactions	Study 3	
	OCREVUS 600 mg IV Every 24 Weeks[1] (n=486) %	Placebo (n=239) %
Upper respiratory tract infections	49	43
Infusion reactions	40	26
Skin infections	14	11
Lower respiratory tract infections	10	9
Cough	7	3
Diarrhea	6	5
Edema peripheral	6	5
Herpes virus associated infections	5	4

[1]One dose of OCREVUS (600 mg administered as two 300 mg infusions two weeks apart)

Laboratory Abnormalities

Decreased Immunoglobulins

OCREVUS decreased total immunoglobulins with the greatest decline seen in IgM levels; however, a decrease in IgG levels was associated with an increased rate of serious infections.

In the active-controlled (RMS) trials (Study 1 and Study 2), the proportion of patients at baseline reporting IgG, IgA, and IgM below the lower limit of normal (LLN) in OCREVUS-treated patients was 0.5%, 1.5%, and 0.1%, respectively. Following treatment, the proportion of OCREVUS-treated patients reporting IgG, IgA, and IgM below the LLN at 96 weeks was 1.5%, 2.4%, and 16.5%, respectively.

In the placebo-controlled (PPMS) trial (Study 3), the proportion of patients at baseline reporting IgG, IgA, and IgM below the LLN in OCREVUS-treated patients was 0.0%, 0.2%, and 0.2%, respectively. Following treatment, the proportion of OCREVUS-treated patients reporting IgG, IgA, and IgM below the LLN at 120 weeks was 1.1%, 0.5%, and 15.5%, respectively.

The pooled data of OCREVUS clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an association between decreased levels of IgG and increased rates of serious infections. The type, severity, latency, duration, and outcome of SIs observed during episodes of immunoglobulins below LLN were consistent with the overall SIs observed in patients treated with OCREVUS.

Decreased Neutrophil Levels

In the PPMS clinical trial (Study 3), decreased neutrophil counts occurred in 13% of OCREVUS-treated patients compared to 10% in placebo patients. The majority of the decreased neutrophil counts were only observed once for a given patient treated with OCREVUS and were between LLN - 1.5 x 10^9/L and 1.0 x 10^9/L. Overall, 1% of the patients in the OCREVUS group had neutrophil counts less than 1.0 x 10^9/L and these were not associated with an infection.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. Therefore, comparison of the incidence of antibodies to OCREVUS with the incidence of antibodies to other products may be misleading.

Patients in MS trials (Study 1, Study 2, and Study 3) were tested at multiple time points (baseline and every 6 months post-treatment for the duration of the trial) for anti-drug antibodies (ADAs). Out of 1311 patients treated with OCREVUS, 12 (~1%) tested positive for ADAs, of which 2 patients tested positive for neutralizing antibodies. These data are not adequate to assess the impact of ADAs on the safety and efficacy of OCREVUS.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OCREVUS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Immune-mediated colitis *[see Warnings and Precautions (5.6)]*
Infections and Infestations: Serious herpes infections *[see Warnings and Precautions (5.2)]* and progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.3)]*

7 DRUG INTERACTIONS

7.1 Immunosuppressive or Immune-Modulating Therapies

The concomitant use of OCREVUS and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with OCREVUS. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating OCREVUS *[see Warnings and Precautions (5.2)]*.

7.2 Vaccinations

A Phase 3b randomized, open-label study examined the concomitant use of OCREVUS and several non-live vaccines in adults 18-55 years of age with relapsing forms of MS (68 subjects undergoing treatment with OCREVUS at the time of vaccination and 34 subjects not undergoing treatment with OCREVUS at the time of vaccination). Concomitant exposure to OCREVUS attenuated antibody responses to tetanus toxoid-containing vaccine, pneumococcal polysaccharide, pneumococcal conjugate vaccines, and seasonal inactivated influenza vaccines. The impact of the observed attenuation on vaccine effectiveness in this patient population is unknown. The safety and effectiveness of live or live-attenuated vaccines administered concomitantly with OCREVUS have not been assessed *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to OCREVUS during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-872-4370 or visiting www.ocrevuspregnancyregistry.com.

Risk Summary

OCREVUS is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. There are no adequate data on the developmental risk associated with use of OCREVUS in pregnant women. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to OCREVUS have not been studied in clinical trials. The potential duration of B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness, is unknown *[see Warnings and Precautions (5.2)]*.

Following administration of ocrelizumab to pregnant monkeys at doses similar to or greater than those used clinically, increased perinatal mortality, depletion of B-cell populations, renal, bone marrow, and testicular toxicity were observed in the offspring in the absence of maternal toxicity *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Following intravenous administration of OCREVUS to monkeys during organogenesis (loading doses of 15 or 75 mg/kg on gestation days 20, 21, and 22, followed by weekly doses of 20 or 100 mg/kg), depletion of B-lymphocytes in lymphoid tissue (spleen and lymph nodes) was observed in fetuses at both doses.

Intravenous administration of OCREVUS (three daily loading doses of 15 or 75 mg/kg, followed by weekly doses of 20 or 100 mg/kg) to pregnant monkeys throughout the period of organogenesis and continuing through the neonatal period resulted in perinatal deaths (some associated with bacterial infections), renal toxicity (glomerulopathy and inflammation), lymphoid follicle formation in the bone marrow, and severe decreases in circulating B-lymphocytes in neonates. The cause of the neonatal deaths is uncertain; however, both affected neonates were found to have bacterial infections. Reduced testicular weight was observed in neonates at the high dose.

A no-effect dose for adverse developmental effects was not identified; the doses tested in monkey are 2 and 10 times the recommended human dose of 600 mg, on a mg/kg basis.

8.2 Lactation

Risk Summary

There are no data on the presence of ocrelizumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OCREVUS and any potential adverse effects on the breastfed infant from OCREVUS or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Women of childbearing potential should use effective contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS.

8.4 Pediatric Use

Safety and effectiveness of OCREVUS in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of OCREVUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Infusion Reactions

Inform patients about the signs and symptoms of infusion reactions, and that infusion reactions can occur up to 24 hours after infusion. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions *[see Warnings and Precautions (5.1)]*.

Infection

Advise patients to contact their healthcare provider for any signs of infection during treatment or after the last dose. Signs include fever, chills, constant cough, or signs of herpes such as cold sore, shingles, or genital sores *[see Warnings and Precautions (5.2)]*.

Advise patients that OCREVUS may cause reactivation of hepatitis B infection and that monitoring will be required if they are at risk *[see Warnings and Precautions (5.2)]*.

Advise patients that herpes infections, including serious herpes infections affecting the central nervous system, skin, and eyes, have occurred during treatment with OCREVUS. Advise patients to promptly contact their healthcare provider if they experience any signs or symptoms of herpes infections including oral or genital symptoms, fever, skin rash, pain, itching, decreased visual acuity, eye redness, eye pain, headache, neck stiffness, or change in mental status *[see Warnings and Precautions (5.2)]*.

Vaccination

Advise patients to complete any required live or live-attenuated vaccinations at least 4 weeks and, whenever possible, non-live vaccinations at least 2 weeks prior to initiation of OCREVUS. Administration of live-attenuated or live vaccines is not recommended during OCREVUS treatment and until B-cell recovery *[see Warnings and Precautions (5.2)]*.

Progressive Multifocal Leukoencephalopathy

Inform patients that PML has occurred in patients who received OCREVUS. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their healthcare provider if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes *[see Warnings and Precautions (5.3)]*.

Malignancies

Advise patients that an increased risk of malignancy, including breast cancer, may exist with OCREVUS. Advise patients that they should follow standard breast cancer screening guidelines *[see Warnings and Precautions (5.5)]*.

Immune-Mediated Colitis

Advise patients to promptly contact their healthcare provider if they experience any signs and symptoms of colitis, including diarrhea, abdominal pain, and blood in stool *[see Warnings and Precautions (5.6)]*.

Contraception

Females of childbearing potential should use effective contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS.

Pregnancy Registry

Instruct patients that if they are pregnant or plan to become pregnant while taking OCREVUS they should inform their healthcare provider *[see Use in Specific Populations (8.1)]*.

Encourage patients to enroll in the OCREVUS Pregnancy Registry if they become pregnant while taking OCREVUS *[see Use in Specific Populations (8.1)]*.

OCREVUS® [ocrelizumab]
Manufactured by:
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with EBV prior to the first blood sample provided as part of biennial testing. During the 20 years represented by the samples, 955 developed MS while in the service. Of those, 35 had no evidence of EBV infection at first blood collection, and 34 became EBV positive prior to MS diagnosis. Of the 107 initially EBV-free participants used as a control group who did not develop MS, half became EBV positive over the period studied. Servicemembers who remained EBV-free had virtually no chance of developing MS. On the flip side, infection with EBV increased the risk of MS more than 32 times.

"This is a big step, because it suggests that most MS cases could be prevented by stopping EBV infection, and that targeting EBV could lead to the discovery of a cure for MS," said Alberto Ascherio, professor of epidemiology and nutrition at the Harvard Chan School of Public Health and senior author of the study.

Toward a vaccine

A vaccine that prevents infection with EBV could, then, prevent MS. Given the link to a range of other diseases, it could protect health in myriad other ways as well. "A vaccine that could prevent or reduce the severity of infection with the Epstein-Barr virus could reduce the incidence of infectious mononucleosis and might also reduce the incidence of EBV-associated malignancies and autoimmune diseases," said National Institute of Allergy and Infectious Diseases (NIAID) Director Anthony S. Fauci, MD.

NIAID, part of the National Institutes of Health (NIH), recently launched a Phase 1 trial to evaluate an EBV vaccine. The trial is one of just two studies undertaken in more than a decade to assess such a vaccine. Principal investigator Jessica Durkee-Shock, MD, of NIAID's Laboratory of Infectious Diseases (LID) is leading the evaluation of an EBV glycoprotein (gp)350-ferritin nanoparticle vaccine LID developed combined with a saponin-based matrix-M adjuvant developed by Gaithersburg, MD-based Novavax Inc. Gp350 appears on the surface of EBV and on infected cells, while ferritin, which cells use to store iron, enables the protein to be displayed in a dense array on its surface.

The trial will enroll 40 healthy volunteers between the ages of 18 and 29, half of whom have had prior EBV infection and half who have no evidence of EBV infection. Participants will receive three 50 microgram injections of the vaccine, followed by a second dose 30 days later and a third 180 days after the first. The trial is expected to continue for four years.

Moderna recently launched the other phase I vaccine study in process. Its candidate, (mRNA-1189), is an mRNA vaccine that encodes EBV envelope glycoproteins gH, gL, gp42 and gp220. The four glycoproteins are instrumental in controlling entry into the B-cells and epithelial cells EBV targets. The company plans to enroll 272 participants between the ages of 18 and 30, who will receive either a placebo or one of three dosage levels on days 1, 57 and 169.

Researchers at USUHS are investigating another potential vaccine that combines recombinant EBV gH/gL with trimeric gB. The team previously demonstrated that rabbits immunized with either gH/gL or trimeric gB produced 18 to 20 times higher EBV neutralizing antibodies than gp350.

In a more recent study, the researchers showed that "the immune sera from rabbits immunized with EBV gH/gL or trimeric gB conferred strong passive immune protection of humanized mice from lethal dose EBV challenge, partially or completely prevented death respectively, and markedly decreased the EBV load in peripheral blood of humanized mice," they wrote. "These data suggest that the combination of recombinant EBV core fusion machinery envelope proteins gH/gL and trimeric gB could be an ideal EBV prophylactic vaccine, where native epitopes could elicit high titer antibody responses both quantitatively and qualitatively."[2]

[1] Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, Elledge SJ, Niebuhr DW, Scher AI, Munger KL, Ascherio A. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science.* 2022 Jan 21;375(6578):296-301. doi: 10.1126/science.abj8222. Epub 2022 Jan 13. PMID: 35025605.

[2] Cui X, Cao Z, Ishikawa Y, Cui S, Imadome KI, Snapper CM. Immunization with Epstein-Barr Virus Core Fusion Machinery Envelope Proteins Elicit High Titers of Neutralizing Activities and Protect Humanized Mice from Lethal Dose EBV Challenge. *Vaccines* (Basel). 2021 Mar 19;9(3):285. doi: 10.3390/vaccines9030285. PMID: 33808755; PMCID: PMC8003492.

VA Research Finds Disease-Modifying Therapies Protective Against COVID-19

BUFFALO, NY—For veterans with multiple sclerosis, the COVID-19 pandemic increased anxiety. Would the demyelinating disease increase the risk of hospitalization or death in patients infected with SARS-CoV-2? Would the immunomodulating therapies frequently used to slow MS progression make patients even more vulnerable?

VA research provides reassurance for clinicians and their patients that veterans with MS receiving DMTs are not at greater risk; if anything, they appear to do better than patients without MS when hospitalized with COVID-19.

Early analyses demonstrated that immunocompromised patients faced a substantially greater risk of severe disease, with higher rates of hospitalization and death associated with COVID-19 infection. Studies found that patients taking immunosuppressants following organ or stem cell transplants or to treat cancer fared poorly and individuals with weakened immune systems caused by human immunodeficiency virus (HIV) also had higher risk of severe disease and worse outcomes.

In light of these findings, clinicians initially recommended pausing disease-modifying therapies (DMTs) for patients with MS during the pandemic. At the same time, they worried about disease progression without the therapies.

The researchers noted that, far from increasing the risk of severe disease and mortality, DMTs appear to provide protection in MS patients hospitalized with COVID-19.

A study published in August by researchers with the VA Western New York Healthcare System in Buffalo, NY, provided unexpected good news for MS patients. Remarkably, the team found that veterans hospitalized with COVID-19 who had multiple sclerosis and had active DMT prescriptions had better outcomes than patients without MS.[1]

"Results of this study suggest that not only is it safe to initiate or continue DMTs in MS patients during the COVID-19 pandemic, but it is also beneficial in the MS population given the decreased risk of COVID-19 mortality in addition to the established decreased risk of MS disease progression attributed to these therapies," the researchers said.

The Study

The retrospective study analyzed 49,737 cases of veterans hospitalized with COVID-19 at 125 VA facilities between March 3, 2020, and Oct. 1, 2021, using the Corporate Data Warehouse. Of those, 255 had MS. The researchers evaluated all-cause mortality in these patients for 30 days after their initial positive COVID-19 test.

For the comparator component of the study, the team propensity matched the 255 patients with MS to 4,628 veterans without MS on a 1:20 basis. Propensity matching adjusted for age, gender, race, morbidity, use of dexamethasone (as an indicator of COVID-19 severity) and ventilator use.

DMTs analyzed in the study included dimethyl fumarate, fingolimod, glatiramer, interferon 1A and 1B, natalizumab, siponimod, terriflunomide, as well as other, less common, therapies. Ocrelizumab and rituximab were not included as no veterans in the study were prescribed either therapy. Veterans were considered to be on a DMT if they had received a prescription for one within 90 days of a positive COVID-19 test or the record showed an inpatient medication order for a DMT.

Overall, coronary artery disease, heart failure, chronic kidney

Table 2
Unadjusted Outcomes for Inpatients with COVID-19.

	Whole Model			Propensity Matched		
	No MS (N=49,479)	MS (N=258)	P value	No MS (N=4,628)	MS (N=255)	P Value
Readmission within 30 days	5,933 (11.99%)	33 (12.79%)	0.69	292 (6.31%)	33 (12.94%)	<0.0001
ICU within 60 days	15,939 (32.21%)	68 (26.36%)	0.045	1,053 (22.75%)	68 (26.67%)	0.15
Ventilator within 30 days	5,617 (11.35%)	27 (10.47%)	0.65	384 (8.30%)	27 (10.59%)	0.20
LOS	5 (3-11)	6 (3-13)	0.070	2 (1-4)	7 (3-13)	<0.0001
LOS (ICU)	5 (2-10)	4 (2-7.5)	0.022	2 (1-5)	4 (2-7)	0.23
30-day mortality	6,228 (12.59%)	24 (9.3%)	0.11	402 (8.69%)	24 (9.41%)	0.69

MS=multiple sclerosis, LOS=length of stay, ICU=intensive care unit

Source: Fuchs TA, Wattengel BA, Carter MT, El-Solh AA, Lesse AJ, Mergenhagen KA. Outcomes of Multiple Sclerosis Patients Admitted with COVID-19 in a Large Veteran Cohort. Mult Scler Relat Disord. *Published online June 11, 2022. doi:10.1016/j.msard.2022.103964*

disease, cardiovascular disease, diabetes, and hypertension were less common in the MS cohort. Veterans with MS were also more likely to have been vaccinated. In the propensity score matched cohort, vaccination status did not differ between those with and without MS, but the difference in the listed chronic diseases persisted.

On an unadjusted basis, no statistically significant difference in 30-day mortality was found between veterans with MS (9.3%) and those without MS (12.6%), p=0.11. In the propensity score analysis, patients with MS had a 30-day mortality rate of 9.4% compared to 8.7% for those without MS, p=0.69.

Multivariable logistic regression analysis, however, revealed that disease-modifying therapies for MS "consistently reduced the odds of 30-day mortality," the researchers wrote. In the whole model, DMTs reduced the odds of dying within 30 days by 84% (OR: 0.16 [95%CI: 0.01-0.82] p=0.023). In comparison, vaccination reduced the risk of death 59% (OR: 0.41 [95%CI: 0.37-0.44] p<0.0001). Similar results were seen in the propensity score matched cohort and in a subanalysis of unvaccinated veterans.

"Following hospitalization for COVID-19 infection, MS patients who were taking DMTs (excluding anti-CD20 inhibitors) were over 5 times less likely to die from complications relating to COVID-19 infection (OR 0.18), accounting for other relevant factors, such as age, vaccination status, and comorbidities," the VA team found.

While "MS patients were less likely to die than those in the general population when taking DMTs," even without DMTs, MS patients had comparable mortality rates to other hospitalized patients without MS. "In the whole model, hospitalized patients with MS had less severe infection compared to the general population evidenced by the lower rates of ICU admission (26.4% vs 32.2%, p=0.045) and shorter mean length of time in the ICU (4 days vs 5 days, p=0.022)," the team added.

The researchers noted that, far from increasing the risk of severe disease and mortality, DMTs appear to provide protection in MS patients hospitalized with COVID-19. The team cautioned that the findings may not support the use of DMTs for COVID-19 treatment or prevention in patients who do not have MS, however, given the known risks of the therapies.

[1] Fuchs TA, Wattengel BA, Carter MT, El-Solh AA, Lesse AJ, Mergenhagen KA. Outcomes of Multiple Sclerosis Patients Admitted with COVID-19 in a Large Veteran Cohort. *Mult Scler Relat Disord.* Published online June 11, 2022. doi:10.1016/j.msard.2022.103964

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Front page image: Multiple sclerosis damaged myelin or MS autoimmune disease with healthy nerve with exposed fibre with scarred cell sheath loss as a 3-D illustration.

Response to Disease-Modifying Therapy May Differ by Race, Ethnicity

HOUSTON—Disease-modifying therapies have transformed the lives of patients with multiple sclerosis by slowing progression, decreasing relapse rates and reducing brain lesion accumulation since the first approval of interferon beta nearly 30 years ago.

Despite the large number of clinical trials involving the 19 FDA approved disease-modifying therapies (DMTs) for MS, relatively little is known about how—or whether—race and ethnicity affect patients' response to the drugs. Given the potential adverse effects and the cost of these medications, better understanding efficacy and tolerability would benefit both patients and the health care system.

Several post hoc analyses of clinical trials indicated that there may be a difference in response to these powerful medications, with some studies suggesting that Black patients did not fare as well on interferons, glatiramer acetate, and natalizumab as white patients who formed the bulk of clinical trial participants.

Carlos A. Pérez, MD, director of the Multiple Sclerosis Regional Program and Neurology Care Line at the Michael E. DeBakey VAMC and assistant professor of neurology at Baylor College of Medicine and John A. Lincoln, MD, PhD, associate professor of neurology and director of the MRI Analysis Center at the McGovern Medical School, University of Texas Health Science Center at Houston, undertook a study to determine whether those signals were borne out in a more structured analysis.[1]

To do so, Pérez and Lincoln matched 100 self-identified Hispanic patients with MS to an equal number of Black and white patients. All patients were treated at a private clinic affiliated with McGovern Medical School and data were obtained from the MS Comprehensive Care Center's registry. The registry was screened in February 2021 for patients with a diagnosis of MS who were seen at the clinic between January 2000 and December 2020.

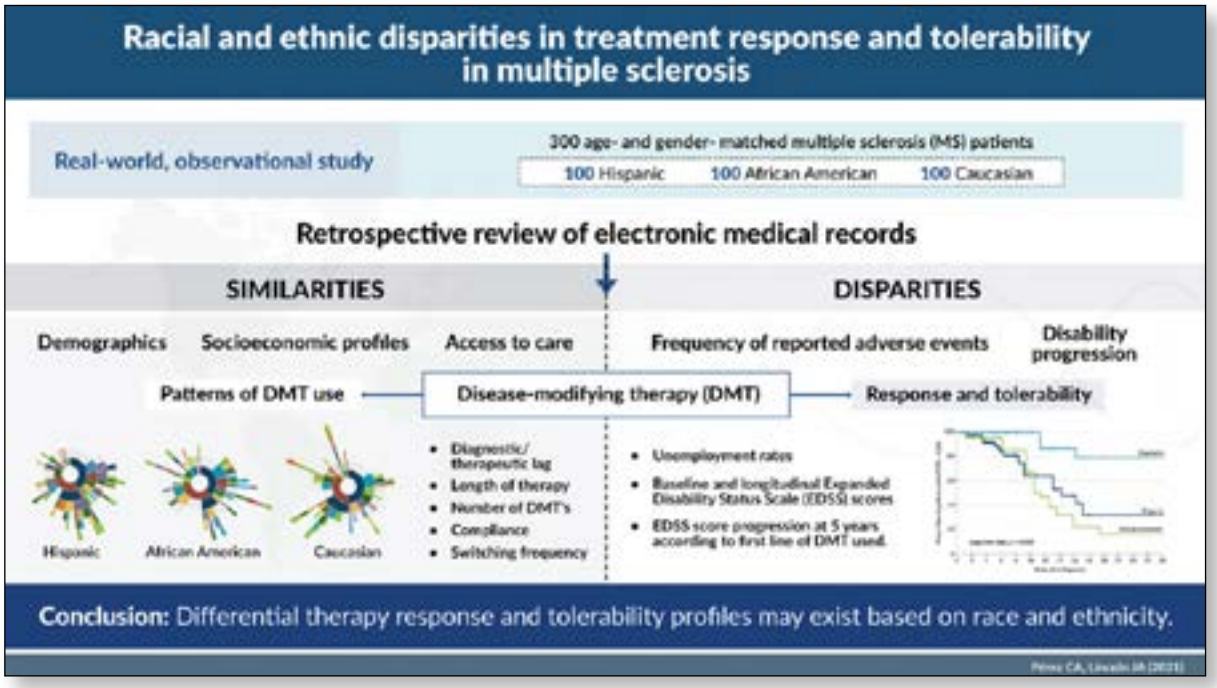
The researchers set as the primary endpoint the proportion of patients with clinical or radiographic evidence of disease activity or Expanded Disability Status Scale (EDSS) score progression. A clinical relapse was defined as a new neurological complaint lasting more than 24 hours with objective physical findings or new lesions seen on a follow-up MRI. Secondary endpoints included time from disease onset to ambulatory disability or EDSS 6.0 and EDSS progression five years from diagnosis (sustained increases of 1.0 point for EDSS scores less than 5.5 and 0.5 points for scores of 6.0 or higher). Other secondary endpoints were the odds of developing ambulatory disability based on first line of DMT used and the reasons for switch or discontinuing treatment.

The study considered monoclonal antibodies and sphingosine-1-phosphate (S1P) inhibitors high-efficacy drugs, while interferons, glatiramer acetate, teriflunomide, and fumarates were categorized as escalation therapies.

DMT Profile

The three groups had no significant differences in average age at onset, lag in diagnosis or receipt of therapy, treatment duration, disease phenotype, smoking status, education, body mass index or number of comorbidities. There were differences in vitamin D levels, household income and insurance type, but none of these had a significant association with clinical outcome. The groups also did not differ in baseline or current DMT profile. About two-thirds of all three groups proceeded to a second line of therapy during the period studied.

Even with all those similarities, the differences in outcomes were stark. Five years after diagnosis, the overall survival of MS patients who did not have ambulatory disability showed far lower survival times for Hispanics and Blacks than whites (survival time ratio [STR] 0.17, $p = 0.004$; and 0.14, $p = 0.002$, respectively). Black patients had a markedly higher rate of disease progression as well as adverse events that led to treatment changes or discontinuation.



Source: 1. Pérez CA, Lincoln JA. Racial and ethnic disparities in treatment response and tolerability in multiple sclerosis: A comparative study. Mult Scler Relat Disord. *2021 Nov;56:103248. doi: 10.1016/j.msard.2021.103248. Epub 2021 Sep 9. PMID: 34536772.*

Hispanic and Black patients also had eight to nine times the risk of ambulatory disability compared to white patients. Black patients accounted for the majority of patients who required therapy escalation and were the least likely to respond to interferon as a first-line therapy. In addition, Black patients had the highest rate of adverse events, which occurred in 46% of cases when Black patients were treated with interferons.

A similar percentage (42.5%) of white patients were unable to tolerate glatiramer acetate, which was particularly notable as 25% more white patients started on glatiramer acetate than Hispanic or Black patients (50.5% vs. 40% and 40.6%, respectively). Patients on CD-20 inhibitors were the least likely to switch therapies across all three groups. Teriflunomide, fumarates, S1P inhibitors and monoclonal antibodies had discontinuation rates of less than 20% across the study groups. Oral medications had higher adherence and lower discontinuation rates than injectables.

Overall, Hispanic patients discontinued therapy at the highest rate (12%). Of the patients switched from escalation therapies to a high efficacy DMT, 40.5% were Black, while 34.3% were Hispanic and 25.2% were white. "Initial treatment with high-efficacy drugs was associated with reduced disability progression as defined by EDSS score increase at 5 years from therapy initiation across racial groups, particularly among Blacks," Pérez and Lincoln found.

"Our findings suggest that race/ethnicity remains a key determinant of health outcome and disparities, and the unequal burden of disease across racial and ethnic groups may not be attributed solely to variations in environmental lifestyle measures and socioeconomic barriers," the authors concluded. "Racial/ethnic disparities in treatment outcome create an unmet need to identify tailored, multifaceted approaches to therapy selection in MS."

[1] Pérez CA, Lincoln JA. Racial and ethnic disparities in treatment response and tolerability in multiple sclerosis: A comparative study. *Mult Scler Relat Disord.* 2021 Nov;56:103248. doi: 10.1016/j.msard.2021.103248. Epub 2021 Sep 9. PMID: 34536772.

VA Researchers, Others Determine That MS Costs the U.S. $85.4 Billion Annually

BALTIMORE—An estimated one million people in the U.S. live with multiple sclerosis today, making understanding the economic impact of the disease a matter of increasing importance.

More than 28,000 veterans receive a diagnosis of MS annually, a number that has risen sharply in recent years. The incidence of the disease among veterans rose from 141 per 100,000 veterans in 1999 to 262 veterans per 100,000 in 2014. With such high and rising numbers of affected veterans, it is little surprise that the VA has been in the forefront of research on the cost of care and identification of the most effective therapies based on expanding knowledge of the pathophysiology of MS.

MS commonly strikes individuals between the ages of 20 and 40 and, for those serving in the military, it often represents a career-ending diagnosis. MS can affect mobility, social interactions, independence, memory and cognitive function, with substantial interpersonal variation in symptoms. For the 85% of patients with relapsing-remitting MS (RRMS), symptoms may wax and wane over time, as well. The 15% with primary progressive MS (PPMS) may have plateau periods but seldom have the remissions seen in RRMS.

Economic Burden

Researchers with the National Multiple Sclerosis Society, The Lewin Group, and Mitchell Wallin, MD, MPH, a neurologist with the VA's Multiple Sclerosis Centers of Excellence, professor of Neurology and Rehabilitation Medicine at University of Maryland and George Washington University, recently estimated that the total economic burden of MS on the U.S. was $85.4 billion per annum. Direct medical costs account for $63.3 billion, with the balance incurred in indirect and nonmedical costs.[1]

"MS is a costly chronic disease, with direct costs of prescription drugs and indirect productivity loss being important cost drivers," the authors said.

Looking ahead, the team estimated that, by 2039, the U.S. will have approximately 1.2 million people with MS with an associated economic burden of $108.1 billion.

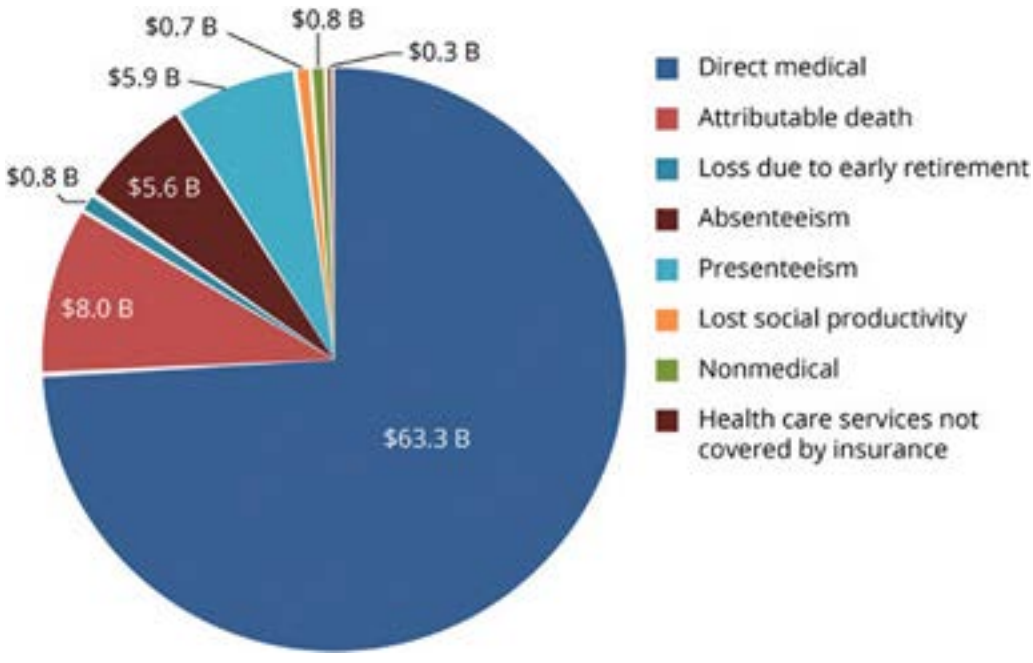
Overall, retail prescription medicine represented 54% of direct costs, with the cost of drugs administered in clinics accounting for another 12% and outpatient care 9%. On a per-person basis, the average excess medical costs exceeded $65,612, with more than half ($35,154) attributed to disease-modifying therapies (DMTs). Indirect costs on a per-person basis, including caregiving costs averaged $22,875. The largest contributors to indirect costs were premature death, presenteeism and absenteeism.

The study used a prevalence-based approach that drew on claims information from the Medicare Current Beneficiary Survey, the Medicare Standard Analytical File and the Optum De-Identified Normative Health Information System for direct costs and compared them to direct costs of matched controls without MS.

"DMT costs accounted for 89% of the total outpatient medication expenditure," the authors noted. "The usage of DMT varied substantially by age group, with about 50% of adults with MS age 18-64 regardless of sex and 21% of men and 40% of women aged ≥65 treated with DMT." The cost per person of DMT ranged from $57,202 to $92,719, depending on patient age and sex.

While DMTs accounted for the majority of medical costs, limiting their use would likely increase

Figure 2



Total Economic Burden of MS in the United States in 2019: $85.4 Billion

Source: Bebo B, Cintina I, LaRocca N, Ritter L, Talente B, Hartung D, Ngorsuraches S, Wallin M, Yang G. The Economic Burden of Multiple Sclerosis in the United States: Estimate of Direct and Indirect Costs. Neurology. *2022 May 3;98(18):e1810-e1817. doi: 10.1212/WNL.0000000000200150. Epub 2022 Apr 13. PMID: 35418457; PMCID: PMC9109149.*

other costs and reduce quality of life. They noted that "studies have shown DMTs to reduce relapses, decrease disability and improve health-related quality of life. In addition, when patients are treated early, DMTs can delay the progression of disease and reduce the number of new lesions and could lead to lower treatment costs, reduced health care utilization, fewer days of work loss, and lower direct and indirect costs."

Some indirect costs were calculated from a survey of 946 patients with MS and included productivity losses, cost of paid and unpaid caregivers (who may have given up paid employment) and environmental adaptations. Others, such as premature death, which accounted for 38% of indirect costs, were calculated based on age and the net current value of future earnings. Paid nonmedical care represented 33% of all nonmedical costs, with special equipment or adaptations of home or vehicle driving the 27% of these costs for $202 million. Nontraditional treatments added $342 million to the cost of care.

Disability payments to individuals with MS, about $6.7 billion, were not included in the calculations, as "transfer payments are often used to pay for both medical and nonmedical services, which would double count costs," the team said.

Looking ahead, the team estimated that, by 2039, the U.S. will have approximately 1.2 million people with MS with an associated economic burden of $108.1 billion.

"The findings of this study help underscore the burden of MS in the United States and potential effects of policy or treatment interventions," the team concluded. "The results suggest a possible role for additional policy initiatives to better support individuals and families affected by MS, in terms of providing treatment and long-term care, worksite support, employment, and occupational training."

[1] Bebo B, Cintina I, LaRocca N, Ritter L, Talente B, Hartung D, Ngorsuraches S, Wallin M, Yang G. The Economic Burden of Multiple Sclerosis in the United States: Estimate of Direct and Indirect Costs. *Neurology.* 2022 May 3;98(18):e1810-e1817. doi: 10.1212/WNL.0000000000200150. Epub 2022 Apr 13. PMID: 35418457; PMCID: PMC9109149.

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