Characterization: incidence of progressive multifocal leukoencephalopathy (PML) during Multiple Sclerosis (MS) biologic exposure

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Research question

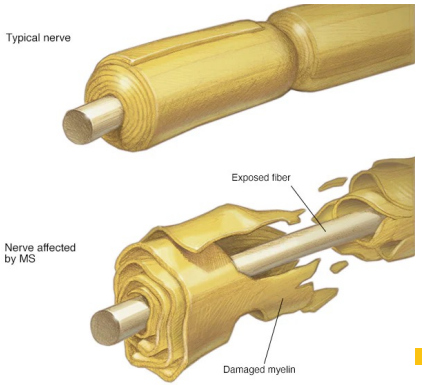
- Amongst patients with MS who are new users of biologic treatment (e.g. Alemtuzumab, Natalizumab, Ocrelizumab, Ofatumumab), how many patients experience PML while on treatment?

Multiple scelrosis

- Multiple sclerosis (MS) is the most common disabling neurological disease of young adults with symptom onset generally occurring between the ages of 20 to 40 years

- Myelin is a substance that makes up the protective sheath (myelin sheath) that coats nerve fibers (axons)

- MS is an immune inflammatory disease that assaults myelinated axons in the central nervous system , damaging the myelin and axon to varying degrees



https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/symptoms-causes/syc-20350269

Multiple scelrosis

- Inflammation, neurodegeneration, and gliosis are hallmarks of MS
- MS is a chronic disease that affects people differently
- A small number of people with MS will have a mild course with little to no disability, whereas others will have a steadily worsening disease that leads to increased disability over time
- Depending on where the nerve damage occurs, MS can affect vision, sensation, coordination, movement, and bladder or bowel control

Risk factors

- Females gender
- Age
  - Onset usually occurs around 20 and 40 years of age. However, younger and older people can be affected
- Genetics
  - A gene on chromosome 6p21
- Family History
- Diseases (viral infection, e.g., Epstein-Barr virus)
- Race
  - White people, particularly those of Northern European descent, are at highest risk of developing MS

Risk factors

- Injury

- Certain autoimmune diseases
  - E.g., thyroid, psoriasis
- Environmental factors
  - Low vitamin D level (who spend more time in the sun and those with relatively **higher levels of vitamin D,** has less risk)

Diagnosis

- No single test used to diagnose MS
- Different tests to rule out or confirm the diagnosis
- MRI scans of the brain and spinal cord to look for the characteristic lesions of MS
- Lumbar puncture (sometimes called a spinal tap) looking for proteins and inflammatory cells associated with the disease
- Evoked potential tests, which use electrodes placed on the skin and painless electric signals

McDonald criteria	
Clinical presentation	**Additional information required**
Attacks: ≥ 2 Clinical evidence ≥ 2 lesions with historical evidence of past attack.	None. Clinical evidence is adequate. Further evidence is desirable.
Attacks: ≥ 2. Clinical evidence of one lesion.	Transmission in space as shown by MRI, or waiting for additional clinical research involving a different site.
Attacks: 1. Clinical evidence ≥ 2 lesions.	Timing of dissemination exhibited by MRI *or* second attack or demonstration of OCBs in the CSF.
Attacks: 1. Clinical evidence of one lesion.	Space dissemination is demonstrated by MRI or waiting for a second attack implicating a different CNS site. and time dissemination confirmed via MRI or a second attack.
Insidious neurologic progression is indicative of MS	Year of disease development and spread in space, demonstrated by1 or more T2 lesions in the brain in areas characterized by MS 2 or more T2 spinal cord focal lesions with positive CSF.

TABLE 1: MS diagnosis according to McDonald's criteria

MS: multiple sclerosis, CSF: cerebrospinal fluid, CNS: central nervous system, MRI: magnetic resonance imaging, OCBs: oligoclonal bands [60,61]

MS types

1. **Clinically isolated syndrome (CIS):** Has a first episode of MS symptoms, HCPs often categorize it as CIS. Not everyone who has CIS goes on to develop multiple sclerosis.
2. **Relapsing-remitting MS (RRMS):** This is the most common form of multiple sclerosis. People with RRMS have flare-ups -- also called relapse or exacerbation -- of new or worsening symptoms. Periods of remission follow (when symptoms stabilize or go away).
3. **Primary progressive MS (PPMS):** People diagnosed with PPMS have symptoms that slowly and gradually worsen without any periods of relapse or remission.
4. **Secondary progressive MS (SPMS):** In many cases, people originally diagnosed with RRMS eventually progress to SPMS. With secondary-progressive multiple sclerosis, you continue to accumulate nerve damage. Your symptoms progressively worsen. While you may still experience some relapses or flares (when symptoms increase), you no longer have periods of remission afterward (when symptoms stabilize or go away).

Treatment

How Biologics Are Shaping Cancer and MS

More takeaways from the Biologic Therapies VI Summit

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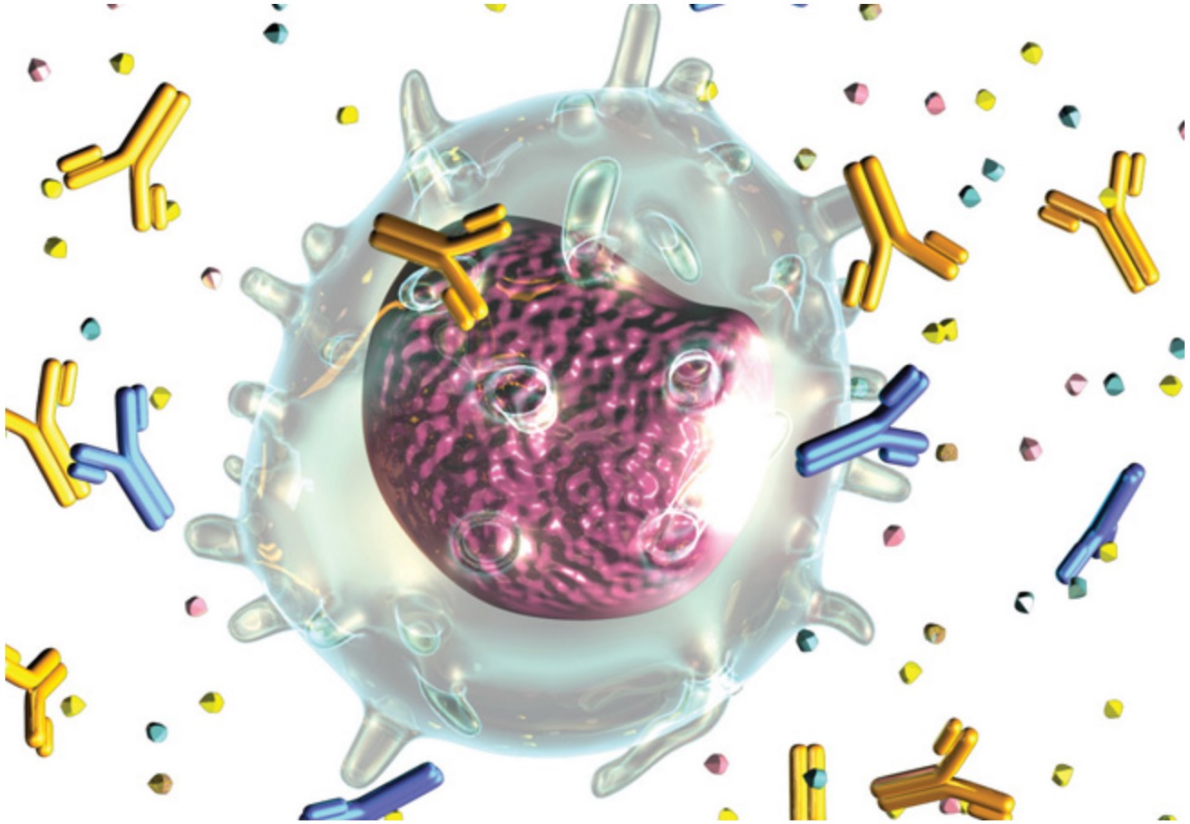
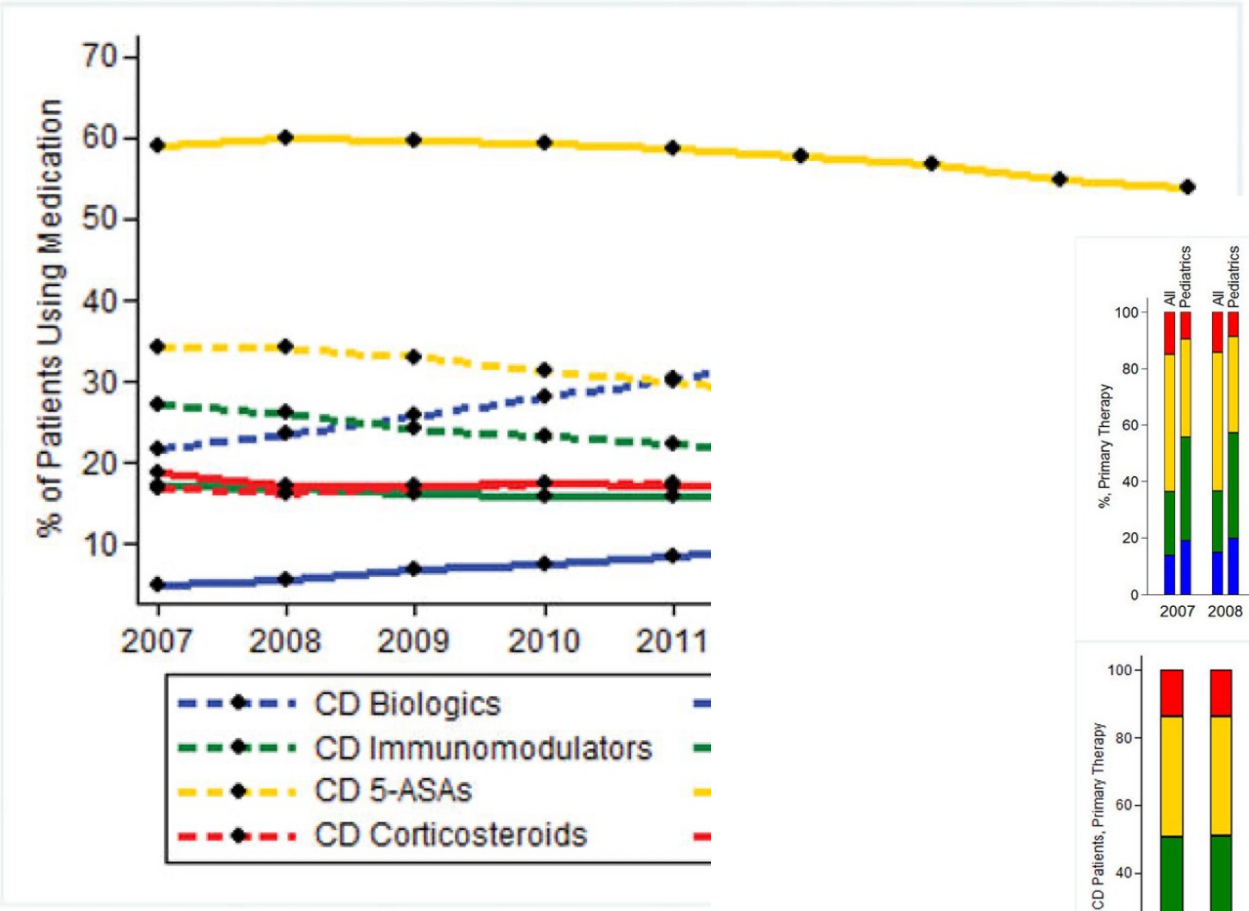


Among the highlights of Cleveland Clinic's Biologic Therapies VI Summit from spring 2015 was an unprecedented session titled "Biological Cross Fire: What Can We Learn From Each Other?" It brought together six expert physicians from diverse disciplines to spotlight how biologics are being used or studied

Increase in biologics therapy use



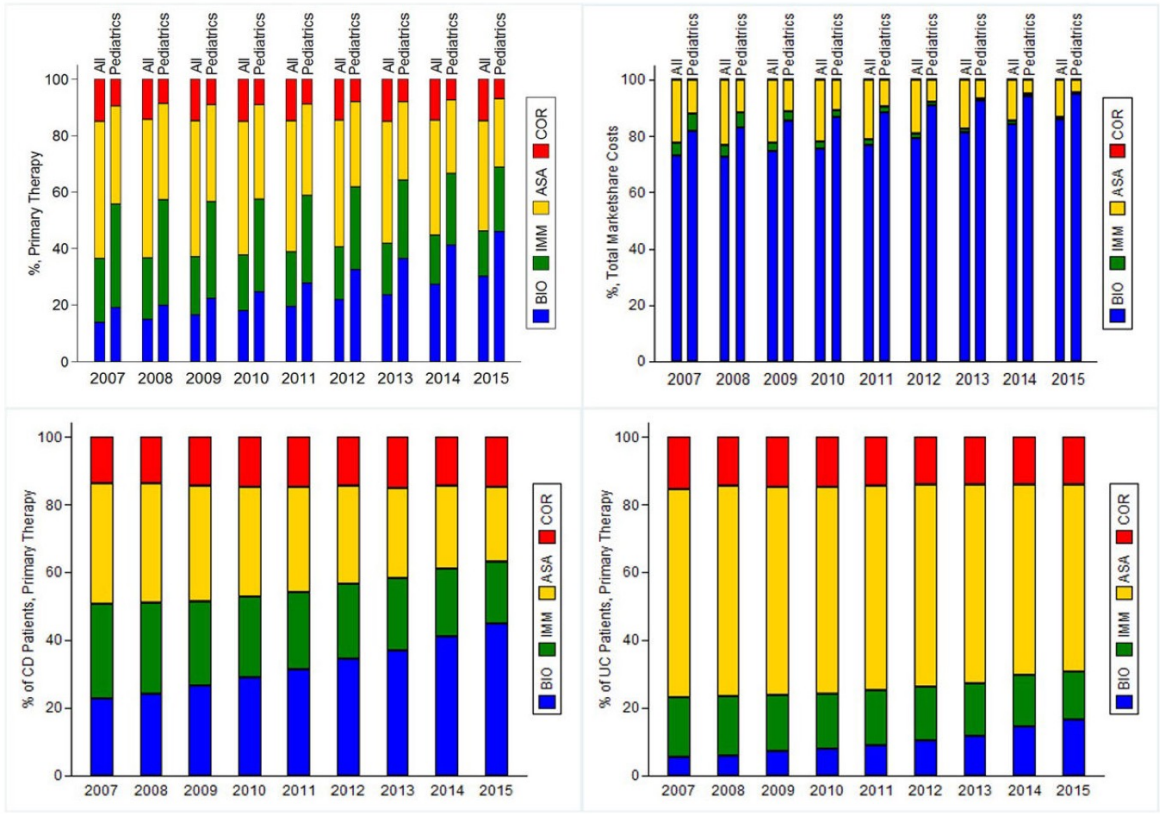


Figure 2. Increasing Market Share of Biologic Therapies
The proportion of patients using biologics and costs allocated to biologics compared to other IBD medications have increased every year from 2007 to 2015.

Treatment

- Treatment of the attacks
  - Corticosteroids
  - Plasma exchange (plasmapheresis)
- Disease-modifying therapies (DMTs)
- Relapse management medications

Treatment

TABLE 1 | Current therapeutic treatments for MS.

	Medication/medication class	Mechanism of action	Route and dosing	Half life	Approved for:	Pivotal clinical trials	Adverse effects	Lab monitoring
Traditional injectables								
Interferons	Interferon beta-1a (Rebif)	Immune modulation	SQ; 44 mcg 3x/week	69 ± 37 h	CIS; RRMS; Active SPMS	PRISMS	**Common**: Injection site reaction Flu-like symptoms Headache **Warnings:** Idiopathic thrombocytopenia Hyper/ hypothyroidism Rarely autoimmune hepatitis	**Baseline**: CBC, LFTs, TSH, TB, T cell subsets. **Routine**: CBC, LFTs q6 months
	Interferon beta-1a (Avonex)	Immune modulation	IM; 30 mcg 1x/week	10 h	CIS; RRMS; Active SPMS			
	Interferon beta-1b; (Betaseron, Extavia)	Immune modulation	SQ; 250 mcg QoD	8 min–4.3 h	CIS; RRMS; Active SPMS	IFNB; BENEFIT		
	Pegylated interferon beta-1a (Plegridy)	Immune modulation	SQ; 125 mcg every 2 weeks	78 h	CIS; RRMS; Active SPMS	ADVANCE		
	Glatiramer acetate; (Copaxone, Glatopa)	Immune modulation	SQ; 20 mg daily or 40 mg TIW	Unknown	CIS; RRMS; Active SPMS	GALA; PRECISE	**Common:** Injection site reaction Chest tightness Anxiety Lipoatrophy Skin necrosis	None required

doi: 10.3389/fneur.2022.824926

	Medication/medication class	Mechanism of action	Route and dosing	Half life	Approved for:	Pivotal clinical trials	Adverse effects	Lab monitoring
S1P receptor modulators	Fingolimod; (Gilenya)	Lymphocyte sequestration and altered cell migration; Binds to S1P receptor subtypes 1,3,4,5	PO; 0.5 mg daily; 0.25 mg daily if <40 kg; First dose observation required	6–9 days	CIS; RRMS; Active SPMS; Pediatric MS	FREEDOMS; TRANSFORMS; PARADIGMS	**Common:** Headache **Warnings:** Rebound syndrome Tumefactive lesions Macular edema Bradycardia/AV block Liver toxicity Hypertension Malignancy risk Seizures Fetal ris	**Baseline**: VZV IgG, OCT, CBC, LFTs, EKG, FEV1 if hx of COPD/asthma **Routine**: CBC, LFTs q6 months, OCT after 3-4 months, skin exams yearly
	Siponimod; (Mayzent)	Binds S1P receptor subtypes 1,5	PO; Titrate to 2 mg daily	30 h	CIS; RRMS; Active SPMS	EXPAND	**Warnings**: CYP2C9*3/*3 genotype	
	Ozanimod; (Zeposia)	Binds S1P receptor subtypes 1, 5	PO; Titrate to 0.92 mg daily	21 h to 11 days	CIS; RRMS; Active SPMS	SUNBEAM	**Common:** Nasopharyngitis headache URI **Warnings:** Untreated sleep apnea Concomintant MAOi use	
	Ponesimod; (Ponvory)	Binds S1P receptor subtype 1	PO; Titrate to 20 mg daily	33 h	CIS; RRMS; Active SPMS	OPTIMUM	**Warnings:** Bradycardia Hepatobiliary disorders Pulmonary events Macular edema Seizures	
	Cladribine (Mavenclad)	Cytotoxic effects on T and B cells by impairing DNA synthesis	PO; 3.5 mg/kg divided into two yearly treatment courses, each with 2 cycles Max 20 mg daily	24 h	RRMS; Active SPMS	CLARITY	**Common:** Headache URI HSV (prophylaxis needed if lymphocyte <200) **Warnings:** Lymphopenia Malignancy risk Fetal risk	**Baseline**: CBC, HIV, HBV, HCV, TB, VZV IgG, LFT, cancer screening **Routine**: CBC 2 and 6 months after each course and before 2nd treatment
Oral medications under investigation								
BTK inhibitors	Evobrutinib	Myeloid and B cell depletion	PO; 25–75 mg daily	2 h	RRMS	Phase 2 completed	**Common:** Headache **Warnings:** Liver toxici	**TBD**

doi: 10.3389/fneur.2022.824926

High efficacy infusion and injectable medications								
B cell depleting therapy	Natalizumab; (Tysabri)	Altered immune cell migration via blocking α-4 β-1 and β-7 integrins	IV; SQ (Europe only); 300 mg q4-6 weeks	11 ± 4 days	CIS; RRMS; Active SPMS	AFFIRM; SENTINEL	**Common:** Headache **Warnings:** PML Rebound syndrome	**Baseline**: JCV Ab, CBC, LFT **Routine**: JCV Ab, CBC, LFT q6 months
	Ocrelizumab; (Ocrevus)	CD20+ B cell depletion	IV; Induction: 300 mg day 1 and day 14; Maintenance: 600 mg q6 months	26 days	CIS; RRMS; Active SPMS; PPMS	OPERA I and II; ORATORIO	**Common:** Infusion reaction URI **Warnings:** Malignancy Hypogammaglobulinemia Infection risk PML	**Baseline**: TB, HBV, HCV, CBC, LFTs, B cell subset, immunoglobulins **Routine**: CBC, LFTs, B cell subset, immunoglobulins,
	Ofatumumab; (Kesimpta)		SQ; Induction: 20 mg weeks 0, 1, 2; Maintenance: 20 mg q4 weeks	16 days	CIS; RRMS; Active SPMS	MIRROR; ASCLEPIOS I and II	**Common:** Injection site reaction URI **Warnings:** Infection Hypogammaglobulinemia	
	Alemtuzumab; (Lemtrada)	CD52+ T and B cells, natural killer cells, monocytes, macrophages	IV; **Year 1:** 12 mg/day daily x 5 days (total 60 mg); **Year 2:** 12 mg/day daily x 3 days (total 36 mg)	14 days	RRMS; Active SPMS	CARE-MS I	**Common:** Infusion reaction Headache **Warnings:** Hypo/hyperthyroidism Risk for autoimmune disease Strokes	**Baseline**: CBC, urinalysis, creatinine, TSH, VZV IgG, TB, HIV, skin exam **Routine**: CBC, creatinine, urinalysis monthly, and TSH q3 months, annual skin exam
	Mitoxantrone; (Novantrone)	Inhibition of cell division	IV; 12mg/m^2 every 3 months; maximum cumulative dose 140 mg/m^2	α: 6-12 min; β: 1–3 h; γ: 23–215 h; Median 75 h	RRMS; SPMS; PRMS	MIMS	**Warnings:** Myocardial toxicity Bone marrow suppression Malignancy risk	**Baseline**: CBC, LFT, echocardiogram, pregnancy testing
FDA-approved oral medications								
Fumarates	Dimethyl fumarate; (Tecfidera)	Immune modulation	PO; Titrate up to 240 mg BID	1 h	CIS; RRMS; Active SPMS	DEFINE; CONFIRM	**Common:** Flushing GI upset **Warnings:** Lymphopenia PML (related to lymphopenia)	**Baseline**: CBC, LFTs, total bilirubin, T cell subsets, TSH, TB, pregnancy screen **Routine**: CBC, LFTs q6-12 months, T cell subsets if needed
	Diroximel fumarate; (Vumerity)	Immune modulation	PO; Titrate up to 462 mg BID	1 h	CIS; RRMS; Active SPMS	EVOLVE-MS2		
	Monomethyl fumarate; (Bafiertam)	Immune modulation	PO; Titrate up to 190 mg BID	0.5 h	CIS; RRMS; Active SPMS			
	Teriflunomide; (Aubagio)	Inhibition of cell division	PO; 7 or 14 mg daily	19 days	CIS; RRMS; Active SPMS	TEMSO; TOWER	**Common:** Headache Hair thinning **Warning:** Hepatotoxicity SJS/TEN Fetal malformations	**Baseline**: TB, pregnancy screen, BP, CBC, LFTs **Routine**: LFTs, CBC, BP monitoring

Oral medications

Drug name	Biologics
Cladribine	
Dimethyl Fumarate	
Fingolimod	
Ozanimod	
Ponesimod	
Siponimod	
Teriflunomide	

Injected Medications

Drug name	Biologics
Glatiramer	
Interferon Beta-1a	✓
Interferon Beta-1b	✓
Ofatumumab	✓
Peginterferon beta-1a	✓

Infused Medications

Drug name	Biologics
Natalizumab	✓
Alemtuzumab	✓
Ocrelizumab	✓
Mitoxantrone	✓

Outcome

- Progressive multifocal leukoencephalopathy (PML)
- PML is a rare, often fatal demyelinating disease of the central nervous system that occurs almost exclusively in immunosuppressed individuals
- This disease is caused by the polyomavirus JC (JCV)

Outcome

- Found in
  - Patients with lymphoproliferative and myeloproliferative diseases
  - Solid organ malignancies
  - Autoimmune diseases, and
  - In patients on antirejection immunosuppressive drugs after organ transplantation or patients treated with immunomodulatory therapies

- There is no specific treatment for PML, which has a high mortality rate

Risk of natalizu with MS is redu

Lana Zhovtis Ryerson, MD,* John Foley, MD,
Ryan R. Metzger, PhD, Judith D. Goldberg, S
Rachna Kasliwal, MPH, Zheng Ren, PhD, Chr
Nolan Campbell, PhD

Neurology® 2019;93:e1452-e1462. doi:10.12

Abstract

Objective

To use the large dataset from the (TOUCH) program to compare progr natalizumab extended interval dosing (multiple sclerosis (MS).

Methods

This retrospective cohort study includ in the TOUCH database as of June 1, 2 planned analyses using Kaplan-Meier r of PML was analyzed by Cox regressio since natalizumab initiation, and cumu

Results

This study included 35,521 patients analysis: 3,331 EID, 15,424 SID; tertia intervals were 35.0 to 43.0 and 29.8 t Hazard ratios (95% confidence interva 0.001) and 0.12 (0.05–0.29, $p < 0.00$1 Relative risk reductions were 94% an analyses, respectively. The tertiary ana

JAMA Neurology | Original Investigation

Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies

Gustavo Luna, MSc; Peter Alping, MD; Joachim Burman, MD, PhD; Katharina Fink, MD, PhD;
Anna Fogdell-Hahn, PhD
Jan Lycke, MD, PhD; Petr
Magnus Vrethem, MD, Pl

IMPORTANCE Alth (MS) have been as interferon beta an well established in with rituximab, wh

OBJECTIVE To exar treatments for MS

DESIGN, SETTING, conducted in Swe prospective data c patients with relap initiating treatmer an age-matched ar

EXPOSURES Treatr

MAIN OUTCOMES A hospitalization. Ac antiviral medicatio

RESULTS A total of fingolimod, and 22 42 645 individuals. treatment start ran The crude rate of ir the general popula person-years), and 10.8-18.5] per 100 person-years), and After confounder a CI, 1.11-2.61]) but nc 0.71-1.77]) compare during rituximab tr natalizumab (HR, 1.

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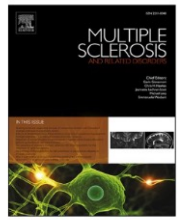
Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Review article

Use of natalizumab in persons with multiple sclerosis: 2022 update

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Natalizumab
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Disease-modifying therapy

ABSTRACT

Background: Natalizumab is a humanized monoclonal antibody used for treatment of highly active relapsing-remitting multiple sclerosis (MS). With more than 15 years of post-marketing experience with natalizumab in Canada, several real-world studies have shown the long-term efficacy and safety of natalizumab. In addition, risk stratification/mitigation strategies for progressive leukoencephalopathy (PML), an adverse effect associated with natalizumab based on the John Cunningham virus (JCV) index; treatment duration beyond 24 months; and prior exposure to immunosuppressant drugs have been developed.

Methods: A group of neurologists from various MS clinics across Canada met in September 2021 to update the 2015 Canadian practice recommendations for the use of natalizumab in persons with MS (PwMS).

Results: The recommendations focused on the long-term efficacy and safety data from real-world studies, patient selection according to JCV index criteria, risk management strategies for PML (including extended interval dosing), and options for switching to currently available disease-modifying therapies for MS.

Conclusions: The recommendations of clinical neurologists seek to optimize the management of PwMS who may benefit from treatment with natalizumab.

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New advice may he

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Dimethyl fumarate (Tecfidera): updated advice on the risk of progressive leukoencepl associated w

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FDA Drug Safety Communication: New risk factor for Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab)

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Drug Safety and Availability

Information about Nitrosamine Impurities in Medications

This information is an update to the FDA Drug Safety Communication: Safety update on Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab) issued on April 22, 2011 and FDA Drug Safety Communication: Risk of Progressive Multifocal Leukoencephalopathy (PML) with the use of Tysabri (natalizumab) issued on February 5, 2010.

Safety Announcement

Content current as of:
02/13/2018

Regulated Product(s)
Drugs

Why we need this

- Most of the publications are reviews
- Most of the conducted studies were focusing on Natalizumab only
- Few studies assessing the PML incidence and patient charactersitcs with these medications
- Single or few databases or one country
- Regulatory safety concern
- HCPs safety concern

Thank you

Backup slides

- These slides for those who are interesred to know more about the disease and the drugs

Table 1 Multiple sclerosis treatments and their mode of action

Table 1 | **Multiple sclerosis treatments and their mode of action**

Drug/treatment	Molecule or therapeutic principle	Mode of action	Effects on the immune system
Relapse treatments			
• Methylprednisolone • Dexamethasone	Glucocorticosteroids	• Genomic and non-genomic effects[181] • Suppression of inflammation by induction of apoptosis and inhibition of migration of immune cells[181,182] • Reduction of inflammatory cytokine levels (IL-2, IFN-γ and tumour necrosis factor)[25] • Inhibition and reduced production of arachidonic metabolites[31] • Restoration of the blood–brain barrier[26]	• Transient leukocytosis (increased neutrophils in particular) • Lymphopenia
Plasmapheresis/plasma exchange	• Removal and treatment of blood plasma, followed by its return to the circulation • Extracorporeal therapy	Rapid removal of pathological substances (autoantibodies, immune complexes and cytokines) from the circulation[183]	Reduction of antibody, complement and cytokine levels
Injectable disease-modifying treatments			
• IFN-β1a/b • Peg-IFN-β1a	• Recombinant cytokine • Pegylation prolongs biological half-life and biological activity[184,185]	• Promotes T_H1 to T_H2 shift in cytokine response (increased production of anti-inflammatory cytokines, suppressed production of proinflammatory cytokines) • Decreases T-cell activation through binding to the interferon receptor • Enhances T-suppressor cell activity • Modulates MHC expression • Reduces inflammatory cell migration across the blood–brain barrier • Decreases T-cell migration • Modulates co-stimulatory molecules on antigen-presenting cells • Blocks activity of matrix metalloproteinases and chemokines • Acts as a secreted ligand for specific cell surface receptors and induces gene transcription, causing antiviral, antimicrobial, antiproliferative/antitumorous and immunomodulatory effects[186–195]	Leukopenia (lymphopenia in particular)
Glatiramer acetate	Synthetic peptide, random polymer of four amino acids (glutamic acid, lysine, alanine, tyrosine) found in MBP[196]	• Increases production of anti-inflammatory cytokines (IL-4, IL-6, IL-10) and decreases production of proinflammatory cytokines (IL-12)[197] • Induces T suppressor cells[198] • Induces T_H1 to T_H2 shift in T-cell responses through effects on dendritic cells[197] • Promotes migration of T_H2 cells into the CNS[197] • Inhibits MBP-specific T-cell responses[199] • Binds promiscuously to MHC antigens with high affinity to prevent presentation of CNS antigens[200] • May exert direct neurotrophic effects and promote remyelination through induction of brain-derived neurotrophic factor[197] • Increases numbers of regulatory $CD8^+$ cells and, via FOXP3, activates the transformation of conventional $CD4^+CD25^-$ T cells to regulatory $CD4^+CD25^+$ T cells[198]	Rare leukocytosis or mild leukopenia
Oral disease-modifying treatments			
Fingolimod	Sphingosine 1-phosphate receptor functional antagonist[201]	• Blocks egress of lymphocytes (mainly $CCR7^+CD4^+$ naive and central memory T cells) from the lymph nodes[201] • Reversibly redistributes lymphocytes into lymphoid tissue, while preserving lymphocyte function • Prevents naive and central memory T cells from circulating to non-lymphoid tissues such as the CNS • Causes lymphoid cell retention in secondary lymphoid tissue • Can exert neuroprotective effects by crossing the blood–brain barrier and binding to neuronal and glial cells[202] • Alters the balance of NK-cell subsets • Could modulate remyelination • Increases astrocyte migration[203–210]	Lymphocyte redistribution

Hartung, H.-P. *et al.* (2016) Disease-modifying therapies and infectious risks in multiple sclerosis *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2016.21

Table 1 Multiple sclerosis treatments and their mode of action

Table 1 (cont.) | **Multiple sclerosis treatments and their mode of action**

Drug/treatment	Molecule or therapeutic principle	Mode of action	Effects on the immune system
Oral disease-modifying treatments (cont.)			
Dimethyl fumarate	Fumaric acid methyl ester	• Inflammatory and cytoprotective effects (mainly through Nrf2 signalling pathway activation)[211,212] • Reduces expression of NF-κB-dependent genes, leading to modulation of inflammatory cytokine, chemokine and adhesion molecule expression[211] • Protects against oxidative stress-induced cellular injury in neurons and astrocytes and cell loss via upregulation of an Nrf2-dependent antioxidant response[213]	Leukopenia (lymphopenia)
Teriflunomide	• Active metabolite of leflunomide • Pyrimidine synthesis inhibitor	• Inhibits *de novo* pyrimidine synthesis in rapidly dividing cells by inhibiting the dihydroorotate dehydrogenase, causing a cytostatic effect on activated/proliferating T and B cells[214] • Does not affect dividing or resting cells[214,215]	Leukopenia (neutropenia)
Azathioprine	Purine analogue	• Blocks *de novo* purine synthesis pathway • Induces apoptosis in stimulated T cells[216]	Leukopenia and lymphopenia
Intravenous disease-modifying treatment			
Natalizumab	Humanized monoclonal anti-α4-integrin antibody	• Prevents immune cells (T and NK cells) from crossing blood vessel walls to reach affected organs[217] • Induces lymphocyte apoptosis[218]	Diminished immune surveillance in the CNS
Alemtuzumab	Monoclonal anti-CD52 antibody	• Binds to $CD52^+$ cells, leading to their depletion • Repopulation of lymphocytes, leading to long-term changes in adaptive immunity and rebalancing of the immune system[121–123,219,220]	Leukopenia and long lasting lymphopenia (T cells affected more than B cells)
Mitoxantrone	• Type II topoisomerase inhibitor • Anthraquinone-derived antineoplastic agent	• Intercalates with DNA and causes single-strand and double-strand breaks[137,221] • Impairs DNA repair[137,221] • Inhibits RNA transcription[222] • Has antiproliferative effects on macrophages, T cells and B cells[222] • Modulates astrocyte activity[223] • Induces suppressive T cells[224]	Leukopenia and lymphopenia

CCR, chemokine receptor; MBP, myelin basic protein; NK, natural killer; Nrf2,nuclear factor erythroid 2-related factor 2; T_H, T-helper.

Hartung, H.-P. & Zettl, U. K. *et al.* (2016) Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2016.21

Table 2 Major infections associated with approved immunomodulatory and immunosuppressive MS treatments

Table 2 | **Major infections associated with approved immunomodulatory and immunosuppressive MS treatments**[225–227]

Drug	Bacterial infections	Viral infections	Fungal infections	Protozoa and parasites
Relapse treatment				
GCS (high-dose pulsed treatment)	• Pyogenic bacteria • Gram-negative rod-shaped bacteria/enterobacteria • Gram-positive rod-shaped bacteria • *Mycobacterium tuberculosis* • Other mycobacteria	• JCV (PML) and HBV reactivation in association with CT • Particular risk of herpesviruses/CMV	• *Pneumocystis jiroveci*, mostly in association with CT • Cryptococcal meningitis	Reported in continuous GCS treatment
Injectable disease-modifying treatments				
• IFN-β1a/b • Peg-IFN-β1a	• No increased risk of infections[52] • Possible increased response against *Mycobacterium avium*[228] • Local infections at injection site possible	• JCV (PML) after intramuscular IFN-β1a monotherapy with combined CVID (+)[54] • Possible antiviral effect on HBV/HCV, no risk of reactivation in chronic viral hepatitis[229–233]	No increased risk of infections[52,234–238]	• NR • Possible protective effect against *Leishmania*[236]
Glatiramer acetate	Local infections at injection site possible	Herpesviruses/CMV (+)	Candidosis +	NR
Oral disease-modifying treatments				
Fingolimod	(+)[18]	• JCV (PML) (+)[239] • Herpesviruses ++	Cryptococcal meningitis/ meningoencephalitis (+)[66,67]	NR
Dimethyl fumarate and fumaric acid esters	(+)	JCV in patients with MS and psoriasis (+)[77,78,83,86] and in patients treated with CT*[78,80–82,240]	NR	NR
Teriflunomide	• Fatal *Klebsiella*-related septicaemia (+)[241] • Gastrointestinal tuberculosis (+)	• JCV (+) • Case reports in patients treated with leflunomide/ CT/PT • Combined CMV + hepatitis C infection (+)	Seen in patients treated with leflunomide or CT	NR
Azathioprine	+	• JCV (+) • Seen in patients treated with CT • Herpesvirus CT/++ • HBV reactivation +[98,242]	Seen in patients treated with CT +	Seen in patients treated with CT +
Intravenous disease-modifying treatments				
Natalizumab	• Gram-negative rod-shaped bacteria/enterobacteriaceae: • *Mycobacterium tuberculosis* (+)[243] atypical mycobacteria[244,245]	• JCV (PML) ++[111,119] • Herpesvirus ++[246–252]	Severe cutaneous *Candida* infection (+)[253]	• Protozoa (+) • Cryptosporidiosis (+)[21,254]
Alemtuzumab	*Listeria* meningitis (+)[125,135,136]	• JCV: not reported for MS • Herpesvirus[133,134]	NR	*Cryptosporidium* infection +[134,255]
Mitoxantrone	+	Herpesvirus ++	+	+

The table includes findings from trials in neurology, haematology and rheumatology. (+), single cases; +, reported association; ++, of particular risk. CMV, cytomegalovirus; CT, under combination therapy; CVID, common variable immunodeficiency syndrome; GCS, glucocorticosteroids; HBV, hepatitis B virus; HCV, hepatitis C virus; JCV, JC virus; MS, multiple sclerosis; NR, no reported risks for MS treatment, or insufficient data; PML, progressive multifocal leukoencephalopathy; PT, immunosuppressive pretreatment. *See main text for details.

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Table 3 Infectious risk-minimizing strategies for disease-modifying drugs in multiple sclerosis

Table 3 | **Infectious risk-minimizing strategies for disease-modifying drugs in multiple sclerosis**

Drug	Recommendations before treatment initiation	Recommendations during treatment	Recommendations after treatment
Glucocorticosteroids (high-dose pulsed treatment)	• Exclusion of active or latent infection (CBC, CRP, ESR) • Check history for systemic mycosis, viral infections, tuberculosis (chest X-ray if patient is from endemic tuberculosis region or risk group) • Delay treatment after live vaccinations	Laboratory testing and search for infectious focus in cases of fever	Delay of subsequent treatment on individual basis
• IFN-β1a/b • Peg-IFN-β1a	None	• Regular checks of injection sites • CBC every 3 months • Standard relapse treatment • No combinations of immunomodulatory drugs beyond clinical trials	None
Glatiramer acetate	None	• Regular checks of injection sites • Standard relapse treatment • No combinations of immunomodulatory drugs beyond clinical trials	None
Fingolimod	• VZV antibody status. If negative, individual decision for active or passive immunization • Exclusion of active or latent infection (CBC, CRP, ESR; HIV/HBV/HCV/tuberculosis testing) • MRI check for PML depending on previous treatment • Leukocyte subpopulations depending on previous treatment	• CBC weeks 2, 4 and 12/every 3 months (more frequent if below 0.6×10^9 lymphocytes per l) • Standard relapse treatment after MRI • Alertness for herpesvirus infections and PML • No combinations of immunomodulatory drugs beyond clinical trials	• CBC and differential blood count until normalization • Delay of subsequent treatment depending on planned drug
Dimethyl fumarate	• Exclusion of active or latent infection (CBC, CRP; HIV/HBV/HCV testing) • MRI check for PML depending on previous treatment • Leukocyte subpopulations depending on previous treatment	• CBC and lymphocyte counts before and every 3 months during treatment • Stop treatment if confirmed leukopenia (cell counts $<3 \times 10^9$ cells per l) or lymphopenia (cell counts $<0.5 \times 10^9$ cells per l) (>6 months) • Standard relapse treatment after MRI • Alertness for PML • No combinations of immunomodulatory drugs beyond clinical trials	• CBC and differential blood count until normalization • Delay of subsequent treatment and laboratory testing depending on planned drug
Teriflunomide	• Exclusion of active or latent infection (CBC; HIV/HBV/HCV/tuberculosis testing) • MRI check for PML depending on previous treatment • Leukocyte subpopulations depending on previous treatment	• CBC months 2, 4 and 6 and subsequently every 3 months • Standard relapse treatment • No combinations of immunomodulatory drugs beyond clinical trials	• CBC and differential blood count until normalization • Delay of subsequent treatment and laboratory testing depending on planned drug
Azathioprine	• Exclusion of active or latent infection • VZV antibody status; if negative, individual decision for active or passive immunization	• CBC and differential blood count weekly for the first 2 months (higher frequency of monitoring in older patients, when using high doses, and if renal or liver function is impaired) • After 2 months, CBC and differential blood count every month or at least every 3 months • Live vaccine contraindicated • Alertness for PML	• CBC and differential blood count until normalization • Delay of subsequent treatment and laboratory testing depending on planned drug
Natalizumab	• Exclusion of active or latent infection (CBC, CRP, ESR; HIV testing), optional HBV/HCV/tuberculosis testing • Check history for herpesvirus infections/systemic mycosis/PML • JCV antibody status • MRI check for PML depending on previous treatment	• Blood count every 6 months • JCV antibody status if negative every 6 months • Standard relapse treatment after MRI • Awareness of PML • Annual MRI first 2 years and every 6 months after 2 years of treatment • No combinations of immunomodulatory drugs beyond clinical trials	• CBC and differential blood count until normalization • Delay of subsequent treatment and laboratory testing depending on planned drug

Table 3 Infectious risk-minimizing strategies for disease-modifying drugs in multiple sclerosis

Table 3 (cont.) | **Infectious risk-minimizing strategies for disease-modifying drugs in multiple sclerosis**

Drug	Recommendations before treatment initiation	Recommendations during treatment	Recommendations after treatment
Alemtuzumab	• Exclusion of active or latent infection (CBC, CRP, ESR; HIV/HBV/HCV/ tuberculosis testing) • MRI check for PML depending on previous treatment • Leukocyte subpopulations depending on previous treatment • VZV antibody status; if negative, individual decision for active or passive immunization • Check history for systemic mycosis, repeated urinary tract and pulmonary infections, pressure ulcers	• Acyclovir treatment (2 × 200mg daily) for the first month of treatment cycle • CBC each month up to 4 years after last treatment cycle • Annual MRI for 4 years after last treatment cycle • Annual HPV screening • Standard relapse treatment after MRI • No combinations of immunomodulatory drugs beyond clinical trials	• CBC and differential blood count and lymphocyte subpopulation until normalization • Delay of subsequent treatment and laboratory testing depending on planned drug
Mitoxantrone	• Exclusion of active or latent infection (CBC, CRP, urine analysis, optional HIV/HBV/ HCV/tuberculosis testing) • Contraindicated if neutropenia is detected (<1.5 × 10^9 cells per l) • Chest X-ray	• Weekly CBC after application until leukocytes are back to normal and before each infusion • Dose adaptation following leukocyte nadir • Exclusion of active or latent infection (CBC, CRP, urinanalysis) before every treatment cycle • Standard relapse treatment • No combinations of immunomodulatory drugs beyond clinical trials	• Delay of subsequent treatment and laboratory testing depending on planned drug • CBC every 3 months for up to 5 years after last infusion

CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papilloma virus; JCV, JC virus; PML, progressive multifocal leukoencephalopathy; VZV, varicella zoster virus.

OBSERVATIONAL HEALTH DATA