APAC Community Call

Training Session #5

September 21, 2023

Agenda

- OHDSI News
  - Global Symposium: Registrations & Agenda
  - Global Symposium: OHDSI Got Talent!
  - APAC Scientific Forum Updates
- Training Session #5: Multiple Sclerosis
  - Characterization: incidence of progressive multifocal leukoencephalopathy (PML) during Multiple Sclerosis (MS) biologic exposure by Thamir M. Alshammari
  - Treatment, utilisation and safety of medicines for Multiple Sclerosis (TELEMUS) by Nicole Pratt

Global Symposium: Registrations & Agenda

- Registrations are now open at https://www.eventbrite.com/e/544413795317!

Friday, October 20

2023 OHDSI GLOBAL SYMPOSIUM

THE 2023 OHDSI SYMPOSIUM WILL TAKE PLACE OCT. 20-22 AT THE HILTON EAST BRUNSWICK HOTEL AND EXEC. MEETING CENTER IN EAST BRUNSWICK, NJ, USA.

$500

Get tickets

Global Symposium: Registrations & Agenda

- Full agenda now available at https://bit.ly/OHDSI2023-Agenda
  - Includes final list of poster presentations, software demonstrations and lightning talks selected

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

OHDSI 2023 Symposium
Oct. 20-22, 2023
Hilton East Brunswick Hotel
& Executive Meeting Center

Agenda · Friday, Oct. 20

Time	Topic
7:30 - 8:30 am East Brunswick Room + Grand Ballroom Foyer	Symposium Registration, Lite Breakfast Buffet, All-Day Exhibits
8:30 - 9:30 am Grand Ballroom	State of the Community OHDSI: Where have we been? Where are we going? George Hripcsak, Columbia Univ. Community Highlights: • OMOP CDM users and the OHDSI data network Clair Blacketer, Johnson & Johnson • OHDSI standardized vocabularies Alexander Davydov, Odysseus Data Services • OHDSI's open-source community Katy Sadowski, Boehringer Ingelheim • OHDSI Europe 2024 Peter Rijnbeek, Erasmus MC • OHDSI Asia-Pacific 2024 Mengling Feng, National Univ. of Singapore

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

OHDSI 2023 Symposium
Oct. 20-22, 2023
Hilton East Brunswick Hotel
& Executive Meeting Center

Agenda · Saturday, Oct. 21

Time	Topic
7:00 - 8:00 am Grand Ballroom Foyer	Lite Breakfast Buffet, All-Day Exhibits
8:00 am - 12:00 pm Various rooms	Introduction to OHDSI Tutorial Common Data Model/Network Data Quality WG Meeting Health Analytics Data-to-Evidence Suite (HADES) Hackathon Health EquityWG Meeting Medical Imaging WG Meeting Natural Language Processing WG Meeting OHDSI Industry WG Kickoff Meeting Oncology WG Meeting Phenotype Development & Evaluation WG Meeting Pregnancy and Reproductive Health Group (PRHeG) WG Meeting

Global Symposium: OHDSI Got Talent!

- First ever OHDSI talent show will take place at this year's global symposium!
- Submissions are due Saturday, September 23, 9 a.m. Korea time
  - Submission form: https://docs.google.com/forms/d/e/1FAIpQLScxU6bNAxCmbphmNOGUfUEqf-SIRnHHi_CZBtXLjped_QAbtA/viewform

2023 OHDSI GOT TALENT SUBMISSION FORM

The success of the OHDSI community rests entirely in the talents of our collaborators. As we have learned, that talent extends well beyond excellence in open community data standards, methodological research, open-source analytic development, and clinical applications.

At the OHDSI Global Symposium on Friday, October 20, at 7:00pmET, we will be holding our first ever 'OHDSI Got Talent' event.

As with the popular television series, we will have a series of contestants perform 4-6 minute routines to showcase their talent, and a panel of judges will share their thoughts on what they have seen. The OHDSI community will vote for their favorite and we will crown a winner!

Do you sing or play a musical instrument? Do you dance? Can you do magic or comedy? Do you have some other unique skill that you can demonstrate in 6 minutes or less? We want to see it!

If you are interested in participating, please fill out the form below. The deadline to submit this form is 8pm ET on Friday, September 22; you will be notified of your acceptance by Friday, September 29.

APAC Scientific Forum Updates

- This month's scientific forum session on OHDSI vocabularies with Anna received a lot of interest from the community!
  - Recording is available on the APAC Scientific Forum Teams channel or https://ohdsi.org/apac/
- Anna will join us again at next month's scientific forum on October 5 to go over use cases and answer any questions the community has
- Please participate in an ongoing survey so that we can have more sessions like this!
  - Support areas follow-up survey: https://forms.office.com/r/sGXSnXV4G3

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

Thamir M. Alshammari, PhD

Research question

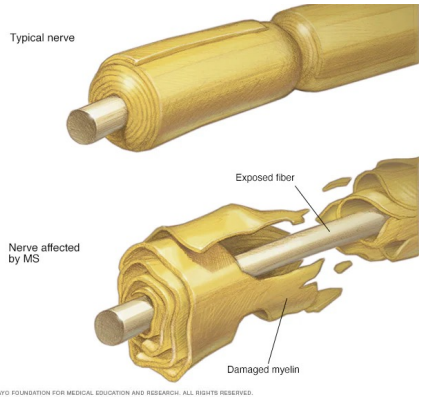
- Amongst patients with MS who are **new users** of biologic treatment (e.g. Alemtuzumab, Natalizumab, Ocrelizumab, Ofatumumab), how many patients experience PML while on treatment?

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

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]

DOI: 10.7759/cureus.33242

MS types

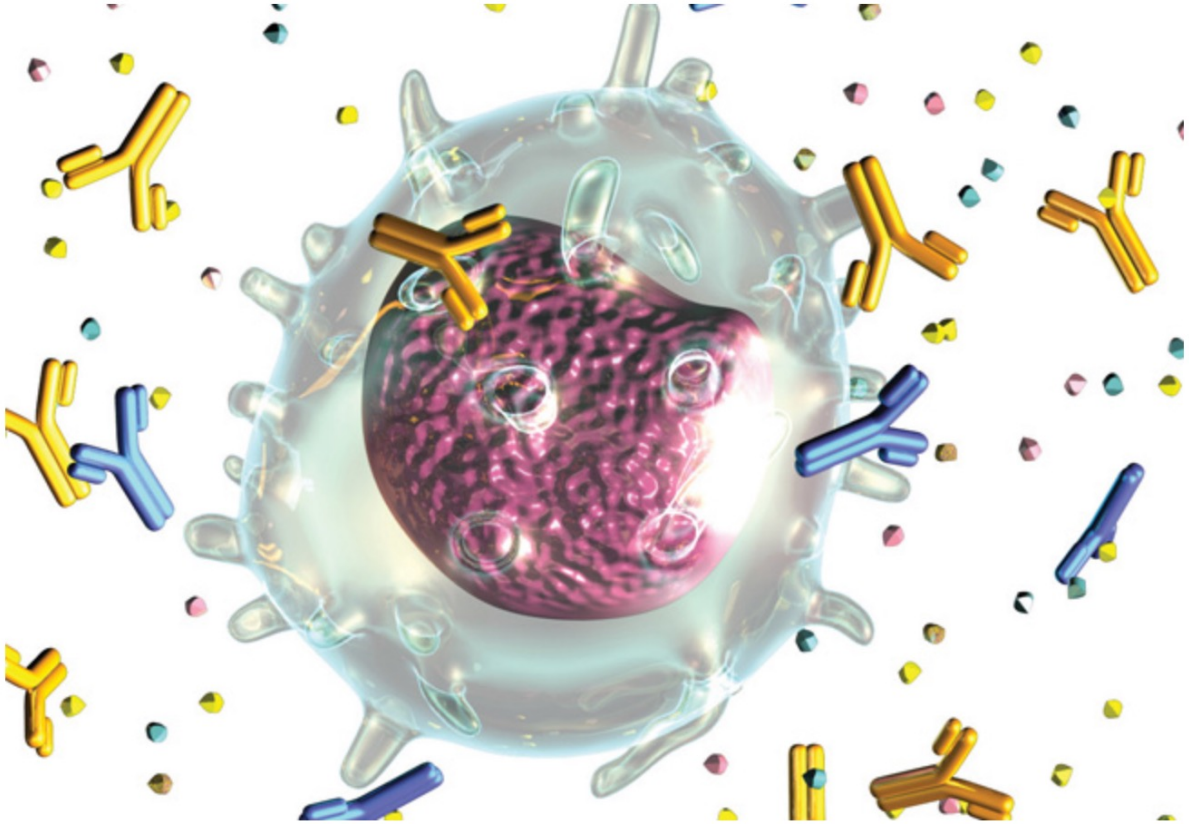
1. **Clinically isolated syndrome (CIS):** Has a first episode of MS symptoms, HCPs often categorize it as CIS. Not everyone who has CIS goes on to develop multiple sclerosis.
2. **Relapsing-remitting MS (RRMS):** This is the most common form of multiple sclerosis. People with RRMS have flare-ups -- 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

SHARE



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

https://consultqd.clevelandclinic.org/biologics-shaping-cancer-ms/

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 a

EXPOSURES Treatr

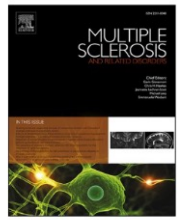
MAIN OUTCOMES A hospitalization. Ac antiviral medicatio

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.

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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



Review article

Use of natalizumab in persons with multiple sclerosis: 2022 update

Sarah A. Morrow [a,*], Fraser Clift [b], Virginia Devonshire [c], Emmanuelle Lapointe [d], Raphael Schneider [e], Mark Stefanelli [b], Reza Vosoughi [e]

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ARTICLE INFO

Keywords:
Multiple sclerosis
Natalizumab
Clinical practice
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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Dimethyl fumarate (Tecfidera): updated advice on the risk of progressive leukoencepha associated w

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Press release 12/02/2

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Published 7 January 2021

U.S. FOOD & DRUG ADMINISTRATION

Search Menu

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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.

Content current as of:
02/13/2018

Regulated Product(s)
Drugs

Safety Announcement

Objectives

- The primary objective of this study is to describe the demographic and clinical characteristics of MS patients who are using high-efficacy infusion and injectable biological medications and developed the outcome of interest (i.e., PML)

- The secondary objectives are to estimate the incidence rate of PML among MS patients using high-efficacy infusion and injectable biological medications.

MS Clinical definition

- One of three MS types will be included in the study (I.e., except CIS MS).
- MS ICD10 code is G35, while the MS ICD9 code is 340.
- In previous work done during phenotype phebruary to phenotype MS, different definitions were used, 1) Culpepper, 2) Widdifield, and 3) Earliest occurrence of Multiple sclerosis diagnosis.
- The Culpepper definition used ICD9 340 and the earliest occurrence of MS diagnosis, requiring ≥3 MS-related occurrences of any combination of inpatient or outpatient diagnosis or MS-specific disease-modifying therapies (DMT) within 1 year. Widdifield definition used ICD9 340 and ICD10 G35, requiring the earliest occurrence of MS diagnosis, 1 hospitalization with MS, or 5+ occurrence of MS diagnosis in 2 years. In contrast, the third method was using the earliest occurrence of MS diagnosis.

Target cohort

- **Target Cohort #1**: Persons with MS will have:
- ≥1 records of MS diagnosis and ≥1 prescription for MS high-efficacy infusion or and injectable biological medications for more than 1 year period.

- **Study population:** Patients diagnosed with MS (except CIS, see below) who meet one of the following criteria: First ever exposure to high-efficacy infusion and injectable biological medications
  - At least 365 days of observation time prior to the index date
  - No diagnosis of PML preceding the index date
  - We will have two groups, natalizumab group and non-natalizumab group (I.e., other biologics)

Exposure group

- Multiple sclerosis patients who are new users of one the following medications, mitoxantrone, natalizumab, alemtuzumab, ocrelizumab, ubilituximab, and ofatumumab.

Index date

- Index date is defined as first exposure to high-efficacy infusion and injectable biological medications

Questions for discussions

- How we solve the problem of "carry-over" cases when we determine the incidence of PML among different medications

- There is a debate about what will be the TAR, 2 years could be more could be less.

Thank you

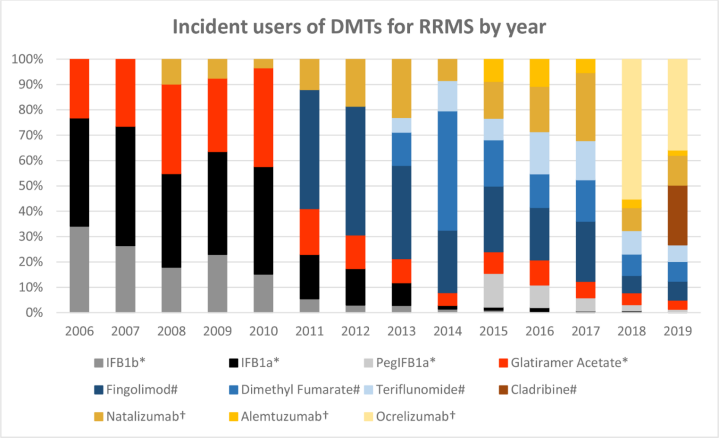
TrEatment, utiLisation and safEty of medicines for MUltiple Sclerosis (TELEMUS)

***Telemus* is *Eurymus'* son, a prophet and a master at reading signs**

nicole.pratt@unisa.edu.au

Objectives

1. Characterisation
   - Incidence and prevalence of MS medicines over time
     - By product
     - Early aggressive v Traditional medicine



2. Cohort Pathways
   - Overall by product and Group
   - By era

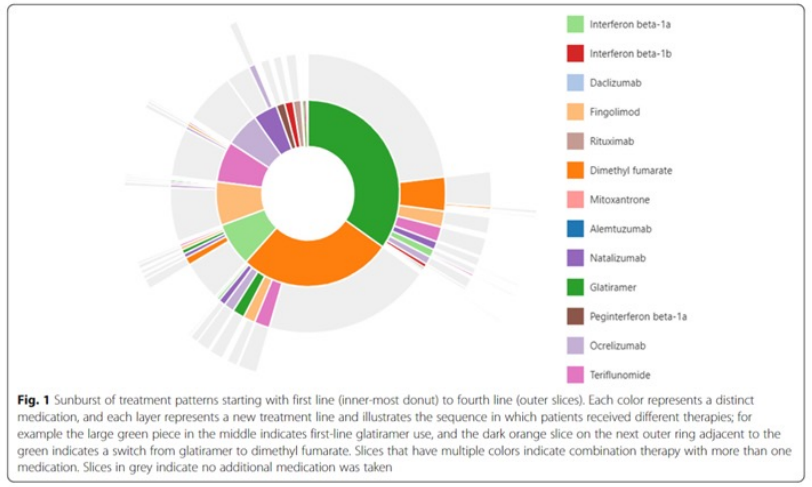


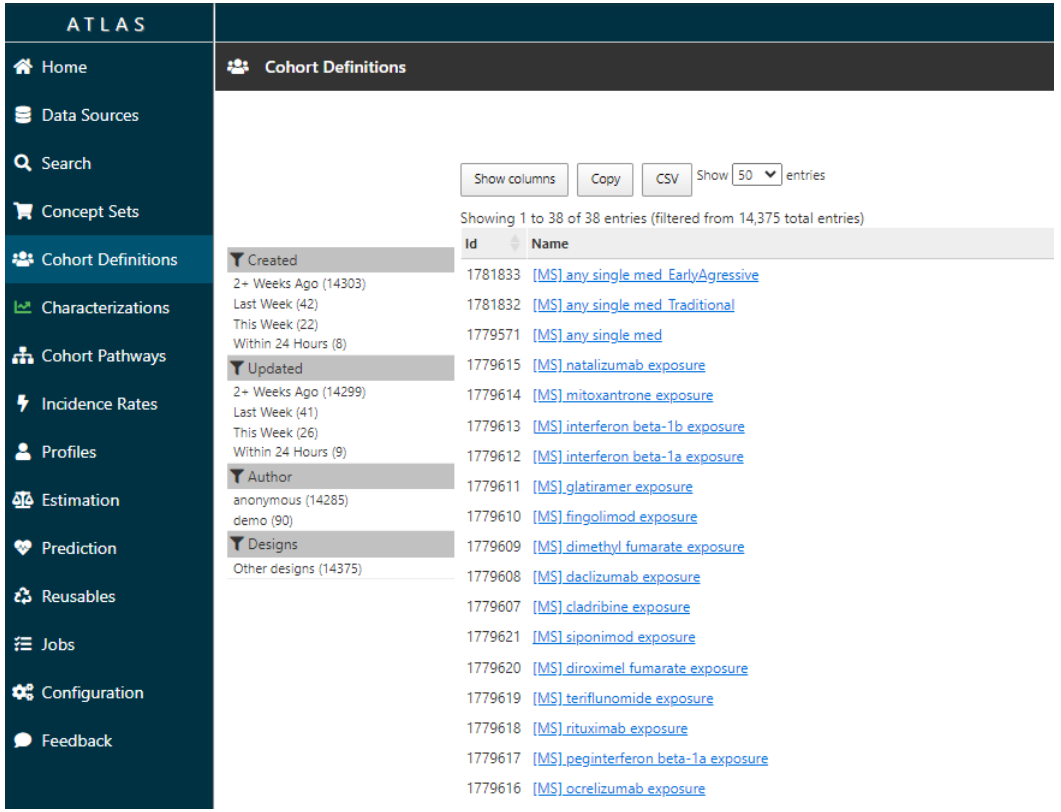
Fig. 1 Sunburst of treatment patterns starting with first line (inner-most donut) to fourth line (outer slices). Each color represents a distinct medication, and each layer represents a new treatment line and illustrates the sequence in which patients received different therapies; for example the large green piece in the middle indicates first-line glatiramer use, and the dark orange slice on the next outer ring adjacent to the green indicates a switch from glatiramer to dimethyl fumarate. Slices that have multiple colors indicate combination therapy with more than one medication. Slices in grey indicate no additional medication was taken

Early aggressive/early highly effective	Concept_ID	Formulation	Treatment	Indication
natalizumab	735843	infusion	Monthly (30)	Potentially used in Crohns
alemtuzumab	1312706	infusion	**12 months**	
Ocrelizumab	1593457	infusion	**6 monthly**	
rituximab	1314273			Potentially used in RA
ofatumumab	40167582	injection	30 days	
cladribine	19054825	Oral (table)	30 days	Also used in cancer (L01BB04 injection)
Traditional/escalation treatments	Concept_ID	Formulation	Treatment	Indication
peginterferon beta-1a	45775146	injection	30 days	
Glatiramer (acetate)	751889	injection	30 days	
teriflunomide	42900584	oral	30 days	
diroximel fumarate	37497593	delayed-release capsules		
dimethyl fumarate	43526424	oral	30 days	
fingolimod	40226579	oral	30 days	
siponimod	1510913	oral	30 days	
ozanimod	37499437	oral	30 days	
Interferon beta-1a	722424	injection	30 days	
interferon beta-1b	713196	injection	30 days	
Other Approved	Concept_ID	Formulation	Treatment	Indication
Daclizumab	19036892	injection	30 days	
Mitoxantrone	1309188		3 months	
ponesimod	740121	oral	?	

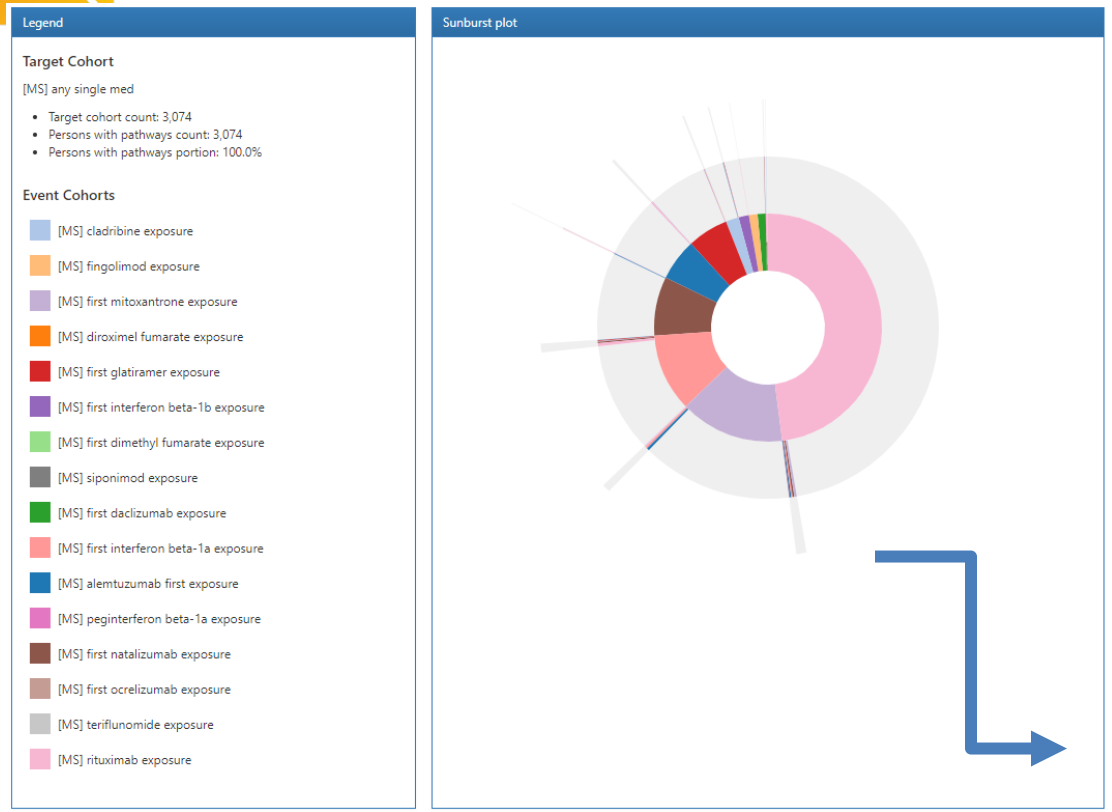
Creating Cohorts

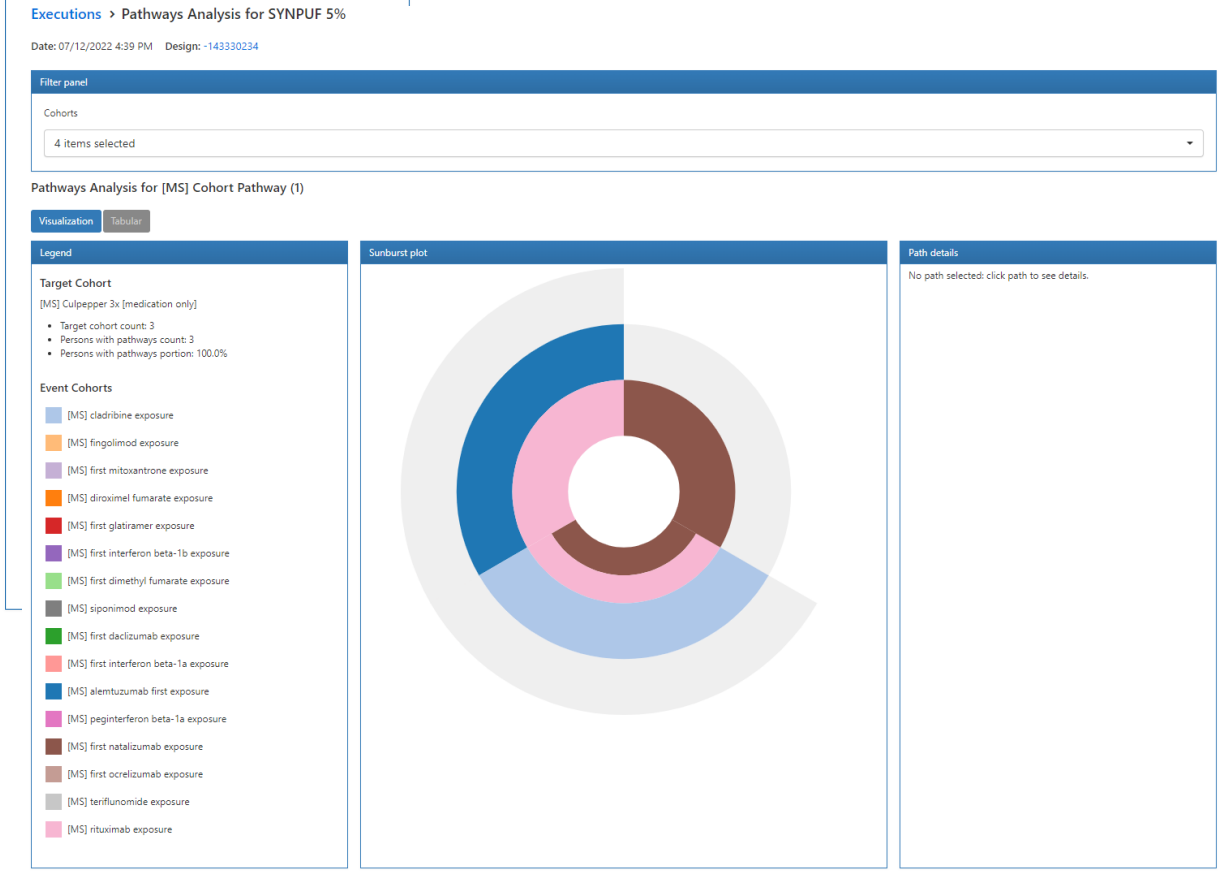
- [ATLAS: Home (ohdsi.org)]
  - https://atlas-demo.ohdsi.org/#/home

- [MS] *Cohorts*



Treatment Pathways





Inclusion of rituximab and mitoxantrone may be problematic if we are unable to use diagnoses as well as rituximab can be used for multiple indications

(Thamer's Study) Incidence of PML in MS treated

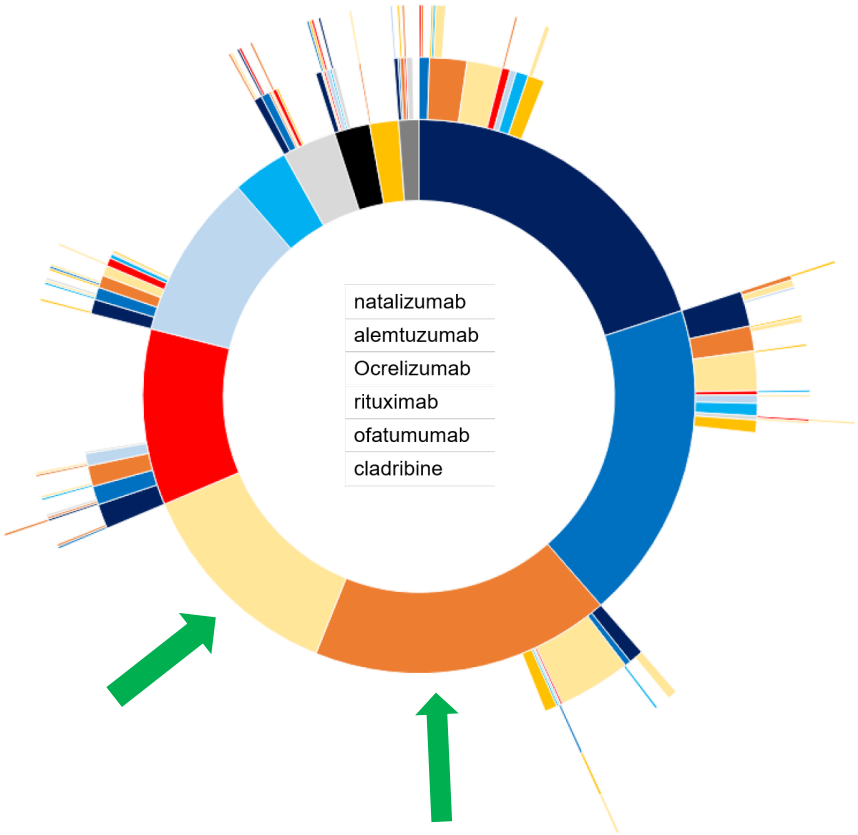
- What is the rate of PML in patients with MS?
  - After diagnosis (see Phenotype)
  - After initiation of any biologic medicines (natalizumab, ocrelizumab, alemtuzumab, ofatumumab)
  - After initiation of other DMTs for MS (traditional)

Culpepper:
Earliest occurrence of MS diagnosis, requiring ≥3
[
MS-related occurrences of any combination of inpatient or outpatient diagnosis
OR
specific disease-modifying therapies (DMT)
]
within a 1-year time period

Why is the treatment pathway so important

Why is the treatment pathway so important?

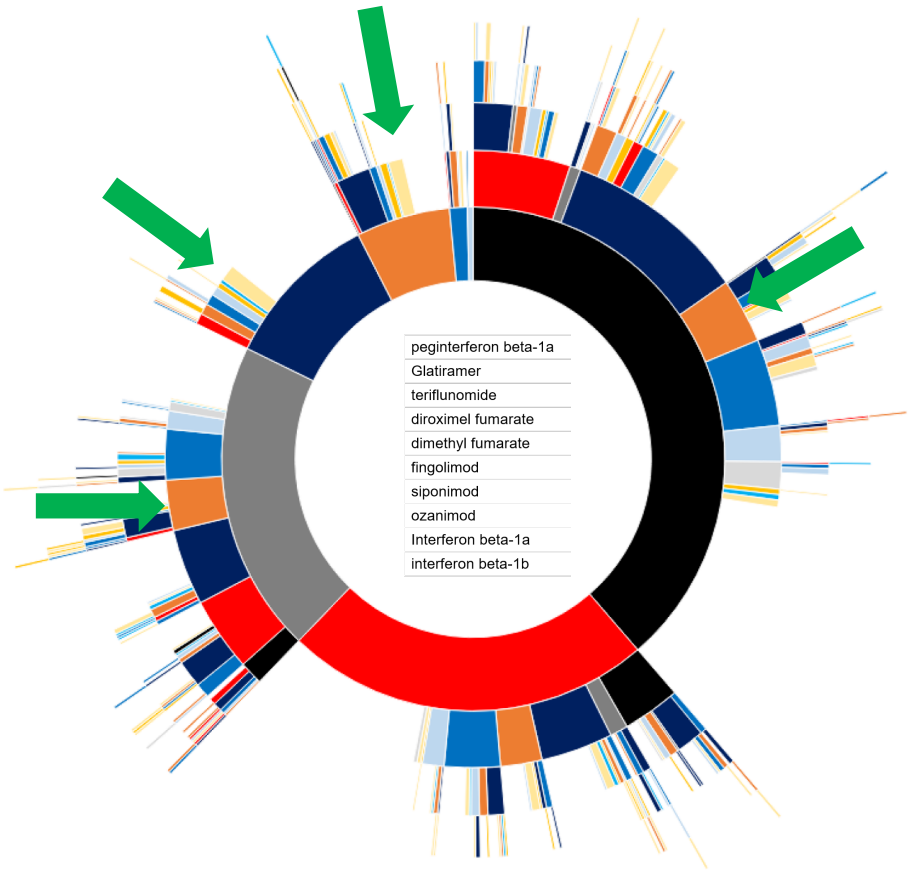
2014-2019



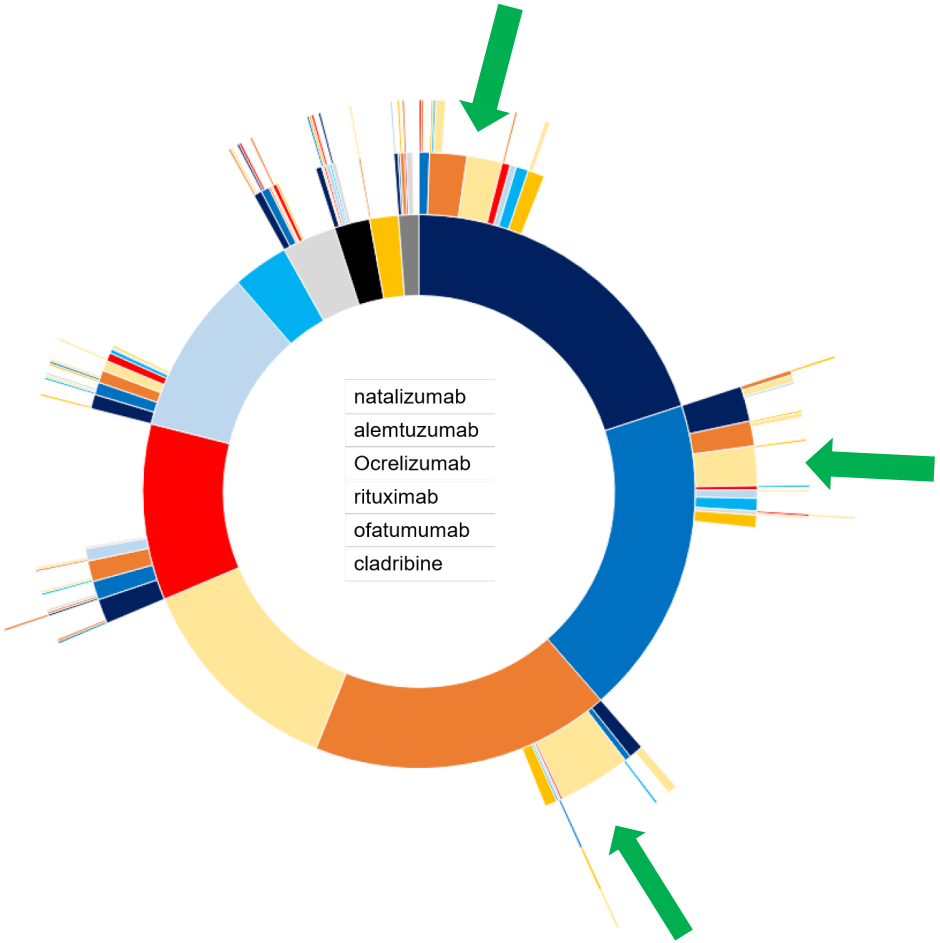
Hillen J, et al. Utilisation of disease modifying treatment and diversity of treatment pathways in relapsing remitting multiple sclerosis. Mult Scler Relat Disord. 2022;57:103412

Prevalent new users

2006-2013



2014-2019



Hillen J, et al. Utilisation of disease modifying treatment and diversity of treatment pathways in relapsing remitting multiple sclerosis. Mult Scler Relat Disord. 2022;57:103412

Incidence of PML in MS treated

- Does the initiation of biologic medicines affect the risk of PML in patients with MS?

- T: Initiation of biologic medicine (natalizumab, ocrelizumab, alemtuzumab, ofatumumab)
- C: Initiation of other DMTs for MS
- O: PML

New user design / prevalent new user

- Active comparator, new-user (ACNU) study
  - starts follow-up at the time of initiation
  - exclude those who have used either the treatment of interest or the active comparator prior.
  - avoids potential bias from
    - confounding by indication, induced by including nonusers,
    - healthy adherer bias (i.e., selection bias) and depletion of susceptibles induced by including prevalent users,

- The prevalent new-user design includes adopters of a new treatment who switched from or previously used standard treatment (i.e., the comparator), expanding study sample size and potentially broadening the study population for inference (webster-clarke)
  - 3 “types” of initiators of a treatment: new users, direct switchers, and delayed switchers.

- ACNU studies exclude patients with recent exposure to the comparator, sample size is reduced, and inference is limited to new users naive to both treatments

- PNU: reduce bias from confounding by indication and healthy-user bias,
  - Match initiators of the treatment of interest to users of the comparator on time or number of prescriptions since initiating the comparator (treat duration or extent of prior comparator use as a confounder).
  - time-conditional propensity score.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Thank you!