

Measuring pharmacodynamics in early clinical drug studies in multiple sclerosis

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Multiple sclerosis (MS) is the most common autoimmune disorder of the central nervous system, estimated to affect 2-3 million individuals worldwide^{1,2}. It is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin (demyelination) and axons³. Direct binding of T lymphocytes to myelin epitopes can lead to activation of macrophages and a subsequent attack of the myelin sheath leading to its phagocytosis⁴. This damage impairs the conduction of signals in the affected nerves. In turn, the reduction in conduction ability causes deficiency in sensation, movement, cognition, or other functions depending on which nerves are involved⁵. Several phenotypes (commonly named types), or patterns of progression, of MS have been described. These phenotypes use the past course of the disease in an attempt to predict the future course. Subtypes that describe the majority of the patients are relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS) and progressive relapsing (PRMS)⁶.

DEMYELINATION In demyelination the myelin sheath of neurons is damaged. Demyelinated axons cannot transmit fast trains of impulse, explaining symptoms resulting from physiological fatigue. Depolarisation might traverse the lesion but at reduced velocity, accounting for the characteristic delay of evoked potentials³. Partially demyelinated axons can discharge spontaneously, producing unpleasant distortions of sensation. Symptom recovery might suggest resolution of conduction block in structurally intact nerve fibres as the episode of inflammation wanes⁷. When structural damage has occurred, sodium channels are redistributed across the demyelinated axonal membrane⁸. Electrical activity is restored, but alterations in sodium and calcium exchange can prove hazardous until normal nodal arrangements are re-established by remyelination⁹. There are many possible biochemical and cellular mechanisms whereby activated immune cells may destroy myelin and oligodendrocytes (table I)⁴.

REMYELINATION Following acute inflammatory episodes, the resolution of the inflammatory process is probably an important factor contributing to the neurological recovery often observed after clinical relapses. Remyelination can occur to a significant extent in lesion areas, and this probably also contributes to functional recovery. Up to 40% of sclerotic plaques show signs of remyelination^{4,10}, and it is unknown what determines the fate of a given lesion¹¹. However, remyelination is generally incomplete, and the myelin is of lower quality, which might be the reason why the original conduction properties are not fully restored¹². Although remyelination is most active during the acute inflammatory process, it also occurs in the progressive phase of MS^{3,13}.

AXONAL LOSS In addition to damage to myelin and oligodendrocytes, axonal loss and injury are characteristic features of sclerotic plaques. In end-state multiple sclerosis, up to 60% of the axons present in sclerotic plaques may have disappeared^{14,15}. As with loss of myelin, neuronal axonal damage is likely to be a multifactorial process. A number of cellular and humoral mediators of the immune response have been shown to be capable of damaging axons, including T lymphocyte, macrophages, antibodies, nitric oxide, glutamate and matrix metalloproteases^{4,16,17}.

PHARMACOLOGICAL TREATMENT OF MS

Current treatment of MS can be divided into disease-modifying treatments and symptomatic treatments. The most common symptoms in MS, such as fatigue, sleep disorders, pain, vestibular symptoms, speech and swallowing, tremors and ataxia, weakness, spasticity, gait, bladder and bowel dysfunction and psychiatric symptoms, are often treated symptomatically with pharmaceutical compounds, physiotherapy and/or psychological help¹⁸. A new symptomatic treatment is discussed in **chapter 2**, where the effects of a new oral formulation of Δ 9-tetrahydrocannabinol (Δ 9-THC) on spasticity and pain in 24 patients with progressive MS is described.

Most registered disease-modifying drugs (DMDS) target the immune system, preventing it from destructing myelin. However, with increasing efficacy and discovery of these compounds over the years², burden due to side effect of these compounds also increases. Figure I shows the different DMDS, of first line treatment (interferons, glatiramer acetate, teriflunomide, dimethylfumarate), second line treatment (natalizumab, fingolimod) and third line treatment (alemtuzumab, mitoxantrone)^{3,19}. A short description of the different pharmacological treatments is listed in table 2.

INTERFERONS Interferons belong to the large class of proteins known as cytokines, molecules used for communication between cells to trigger the protective defences of the immune system that help eradicate pathogens and are divided into type I (α and β interferons) and type 2 (γ or immune interferon)²⁰. Studies show administration of interferon γ increases the exacerbation rate and interferon γ may be involved in the pathogenesis of MS lesions. In contrast, interferon β tends to inhibit the activity of interferon γ and appears to prevent disease activity. Interferon β-Ia and interferon β-Ib are currently used to treat and control the autoimmune process in Ms. The efficacy of subcutaneous interferon β-Ib was demonstrated in a double-blind, placebo-controlled trial of 372 patients with RRMS who were randomly assigned to treatment with either interferon β -Ib 50 mcg every other day, interferon β -Ib 250 mcg every other day, or placebo^{21,22}. A study in which safety and efficacy of PEGylated interferon β-Ia in 1512 patients with RRMS assessed reported PEG interferon β-Ia significantly reduced relapse rate compared with placebo²³. Injection site reactions are common with IFN-β therapy and can include injection site necrosis.²⁴. There is a high prevalence of mainly asymptomatic liver dysfunction associated with IFN-β therapy. However, serious hepatotoxicity associated with IFN-β is rare²⁵.

GLATIRAMER ACETATE Glatiramer acetate (copolymer I) is a mixture of random polymers of four amino acids. The mixture is antigenically similar to myelin basic protein, a component of the myelin sheath of nerves. In experimental models, the immunomodulatory mechanism of action for glatiramer involves binding to major histocompatibility complex molecules and consequent competition with various myelin antigens for their presentation to the T lymphocyte. In addition, glatiramer is a potent inducer of specific T helper 2 type suppressor cells that migrate to the brain and lead to bystander suppression; these cells also express anti-inflammatory cytokines²⁶. In 1995 a double-blind trial with

glatiramer acetate in 251 patients with RRMS was published. Patients treated with glatiramer acetate (20 mg subcutaneously daily) had a significantly lower relapse rate than those receiving placebo (I.19 versus I.68)²⁷. Furthermore, over I40 weeks, a significantly larger proportion of patients in the placebo group experienced increased disability by \geq I.5 steps on the Expanded Disability Status Scale (EDSS) compared with the treatment group (41 versus 22 percent)²⁸. In the clinical trials for glatiramer, the most common adverse reactions reported by those taking glatiramer were skin problems at the injection site (redness, pain, swelling and itching), flushing (vasodilation), rash, shortness of breath and chest pain²⁹.

TERIFLUNOMIDE The immunomodulator teriflunomide is the active metabolite of leflunomide that inhibits pyrimidine biosynthesis what leads to impaired proliferation of T lymphocyte³⁰. The effectiveness of teriflunomide for the treatment of RRMS was demonstrated in several randomized controlled trials. A trial with IO88 adults with relapsing Ms found that teriflunomide significantly reduced the relapse rate by approximately 31 percent compared with placebo³¹. In 2014 a phase 3 trial with over IIO0 adults with relapse rate³². The most common adverse effects of teriflunomide were diarrhoea, nausea, hair thinning, and elevated alanine aminotransferase (ALT) levels³¹.

DIMETHYL FUMARATE Dimethyl fumarate and its primary metabolite, monomethyl fumarate, are cytoprotective of neurons and astrocytes against oxidative stress-induced cellular injury and loss, potentially by up-regulation of a Nrf2-dependent antioxidant response³³. The Nrf2-mediated oxidative stress response mechanisms previously implicated as important for protection of the Central Nervous System (CNS) in a variety of pathological conditions, which can be beneficial for Ms patients³⁴. Two phase 3 studies reported in 2012 significantly reduced relapse rates and the less development of new brain lesions on MRI in patients with active MS, what suggests it might reduce the rate of disability progression. A first study enrolled 1234 patients and compared dimethyl fumarate to placebo³⁵. A second study enrolled 1430 patients and also included glatiramer as treatment³⁶. The most common side effects of dimethyl fumarate are flushing and gastrointestinal symptoms, including diarrhoea, nausea, and abdominal pain. Treatment with dimethyl fumarate may decrease lymphocyte counts, so patients should have a complete blood count checked frequently during treatment and discontinue if lymphocytopenia develops^{35,36}.

NATALIZUMAB Natalizumab is a recombinant monoclonal antibody directed against alpha-4 integrins. Alpha-4 integrin is expressed on the surface of inflammatory lymphocytes and monocytes and may play a critical role in their adhesion to the vascular endothelium and the migration of these cells to the brain³⁷. A decrease in migration of immune cells to the brain will leave less immune cells in the brain to destruct myelin. In 2011 a systematic review of trials evaluating natalizumab for RRMS, pooled efficacy data from two randomized controlled trials, and showed that natalizumab significantly reduced the risk for a relapse during two years of treatment. In addition, natalizumab significantly reduced the risk for experiencing progression at two years³⁸⁻⁴⁰. The JC viral titre is used in the risk

assessment in patients using natalizumab. Natalizumab is one of the most effective treatments for Ms currently available⁴¹. However, progressive multifocal leukoencephalopathy (PML) emerged as a rare adverse event from its treatment, generally occurring late (> 24 months) after initiating treatment⁴². PML is caused by reactivation of a latent JC virus in immunocompromised individuals and leads to a debilitating encephalopathy that is fatal in up to 20-50%⁴³. Determining a JC viral titre is indicated when patients use immunesuppressive medication or use natalizumab for a period of more than 2 years. However, while 50% of Ms patients^{44,45} are JCV Ab seropositive, less than 1% will develop PML⁴⁶, emphasizing the limitations of this biomarker. The risk in sero-negative patients is 6-18 times lower (chances in sero-positive patients increases after two years)⁴⁷. Also, seroconversion rate was reported to be 26.67%⁴⁴.

FINGOLIMOD Fingolimod is sphingosine analogue that modulates the sphingosine-I-phosphate (SIP) receptor, causing internalization of SIP receptors, which sequesters lymphocytes in lymph nodes, preventing them from moving to the central nervous system and cause a relapse in multiple sclerosis.⁴⁸. A 2016 review combined 6 RCTS with a total of 5152 patients, and concluded treatment with fingolimod compared to placebo in RRMS patients is effective in reducing inflammatory disease activity, but it may lead to little or no difference in preventing disability worsening. Also, this benefit is associated with a small increased risk of infection, atrioventricular block, and possibly basal cell carcinoma⁴⁹.

ALEMTUZUMAB Alemtuzumab is a monoclonal antibody that binds to CD52, a protein present on the surface of mature lymphocytes, but not on the stem cells from which these lymphocytes are derived. After treatment with alemtuzumab, these CD52-bearing lymphocytes are targeted for destruction. CD52 has been implicated in the activation and migration of T lymphocytes. Alemtuzumab mediates lysis of these cells, suppressing the neuroinflammatory responses in MS⁵⁰. Combined data from 3 trials, involving I694 patients, concludes there is evidence that annual intravenous cycles of alemtuzumab reduces the proportion of patients with relapses, disease progression, change of EDSS score and developing new T2 lesions on MRI.¹⁰⁰ The main side effects of alemtuzumab were infusion reactions, infections, and autoimmune disorders. Immune thrombocytopenia (ITP) developed in I percent of patients at two years, and in 3 percent at three years.¹⁰¹

MITOXANTRONE Mitoxantrone has immunosuppressive properties by reducing the number of T cells, inhibiting T helper cell function, and augmenting T cell suppressor activity.¹⁰² The largest trial of mitoxantrone in Ms was a single multicenter, double-blind trial of I94 patients with worsening RRMS or SPMS.¹⁰³ Treatment with mitoxantrone was associated with significant clinical benefits compared with placebo on multivariate analysis, reducing progression of disability and clinical exacerbations. Because of cardiac toxicity and possible association with a low risk of developing therapy-related acute leukemia, mitoxantrone should be reserved for patients with rapidly advancing disease who have failed other therapies⁵¹.

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OCRELIZUMAB Ocrelizumab is a chimeric anti-CD20 monoclonal antibody. It selectively depletes CD20-expressing B lymphocytes while preserving the capacity for B lymphocyte reconstitution and pre-existing humoral immunity^{52,53}. A phase 3 trial in 732 patients with primary progressive multiple sclerosis showed that ocrelizumab was associated with lower rates of clinical and MRI progression than placebo. Improvement was reported I2 weeks after the first treatment. Most report adverse events were infusion-related reactions, upper respiratory tract infections, and oral herpes infections⁵⁴.

CLADRIBINE Cladribine is a prodrug, but its active metabolite, cladribine triphosphate, accumulates within the cell, resulting in disruption of cellular metabolism, DNA damage and subsequent apoptosis. Cladribine preferentially targets lymphocytes owing to their relatively high ratio of DCK to 5'-nucleotidase, producing rapid and sustained reductions in CD4+ and CD8+ cells and rapid, though more transient, effects on CD19+ B lymphocyte. Cladribine is relatively sparing of other immune cells⁵⁵. A study in 1326 patients with RRMS, treatment with cladribine tablets significantly reduced relapse rates. Adverse events that were more frequent in the cladribine groups included lymphocytopenia (21.6% in the 3.5-mg group and 31.5% in the 5.25-mg group, vs. 1.8%) and herpes zoster (8 patients and 12 patients, respectively, vs. no patients)⁵⁶.

METHYLPREDNISOLONE Methylprednisolone (MP), an immunosuppressive drug, is prescribed to MS patients as an acute treatment of a relapse, and has been shown to accelerate neurological recovery⁵⁷. **Chapter 3** describes a first in human study with a new formulation of MP, 2B3-201. This compound consists of liposomes containing methylprednisolone. The liposomes have PEG (polyethylene glycol, also known as macrogol) -molecules attached, ensuring a long residence time in the body,^{58,59} and glutathione molecules attached to PEG molecules, improving blood-brain-barrier passage^{60,61}. These characteristics in effect change regular methylprednisolone to a slow-release methylprednisolone, with benefits such as lower dosing frequency because of long residue time and lower peak concentrations and peak concentration related side effects.

Figure I displays the challenge in treatment development: the search for compounds with a high efficacy and limited burden. Remyelinating and neuroprotective therapies are a new class of medication in MS, for which little data is available on efficacy and burden.

FUTURE OF TREATMENTS IN MS

Although a number of DMDS for the treatment of the inflammatory phase are available, the need for treating neurodegeneration and halting the progression of disability remyelinating and neuroprotective therapies is still unmet⁶². Below eight promising drug candidates are discussed that may have the potential to enhance remyelination or positively affect the CNS (table 3).

ANTI-LINGO-I ANTIBODIES LINGO-I, a membrane protein, originally attained prominence as an essential subunit of a tripartite receptor complex containing LINGO-I,

Nogo-66 receptor (NgRI), and TNF receptor superfamily members P75NTR or Troy/Taj⁶³. This complex mediates inhibitory effects of CNS myelin proteins on axon growth⁶⁴. Exposure of mice to an inhibitory monoclonal antibody to LINGO-I was found to promote spinal cord remyelination in an experimental model of MS, the experimental autoimmune encephalitis (EAE) model⁶⁵. This and similar results of subsequent studies motivated development of opicinumab (BIIB033, Biogen), a LINGO-I monoclonal antibody suitable for use in humans. Although a phase 2 study with this compound did demonstrate a difference in remyelination between opicinumab and placebo, this effect was only significant in a subgroup of the study population⁶⁶.

RHIGM22 ANTIBODIES RHIGM22 is a monoclonal IgM antibody that binds myelin tracts and mature oligodendrocytes, induces calcium influx in astrocytes, oligodendrocyte progenitor cells (OPCS) and pre-mature oligodendrocytes in culture. The antibody promotes remyelination in animal studies^{67,68}. One of these animal studies used the cuprizone model, in which the toxin cuprizone leads to demyelination of the central nervous system, demonstrated that treatment with RHIGM22 accelerated remyelination of the demyelinated corpus callosum, and enhancing effects were also accompanied by increased differentiation of OPCS into mature oligodendrocytes⁶⁹. The first clinical studies in humans are ongoing and results are not yet available.

OLESOXIME Olesoxime is an experimental neuroprotective compound that was being developed for amyotrophic lateral sclerosis (ALS)⁷⁰ and spinal muscular atrophy (SMA)⁷¹. It has a number of potentially neuroprotective and neuroregenerative properties, including accelerated maturation of oligodendrocytes and promoting remyelination in cuprizone mouse models of demyelination⁷². A first study in MS patients has started, and preliminary results report olesoxime is safe and well tolerated in patients with MS.

ASICI BLOCKERS Blockade of the neuronal proton-gated acid-sensing ion channel I (ASICI) can support cellular protection, which is increased within axons and oligodendrocytes in acute multiple sclerosis lesions⁷³. Blocking ASICI with amiloride exerts neuroprotective and myeloprotective effects in experimental models of multiple sclerosis⁷⁴. A pilot study suggest that amiloride may exert neuroprotective effects in patients with progressive multiple sclerosis⁷⁵.

BENZTROPINE Benztropine functions by a mechanism that involves direct antagonism of MI and/or M3 muscarinic receptors with subsequent oligodendrocyte maturation. Benztropine has shown to significantly decreases clinical severity in the EAE model⁷⁶. Clinical trials with benztropine have not been announced yet.

GUANABENZ Guanabenz is a $\alpha 2$ adrenergic receptor agonist. It protects oligodendrocytes by preventing dephosphorylation of eIF2, thereby increasing oligodendrocyte survival, and leading to prevention of myelin loss. Preclinical studies demonstrated improvement of deficits in the EAE model⁷⁷. A clinical study has been initiated, but no results have been reported yet.

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QUETIAPINE FUMARATE Quetiapine fumarate stimulates proliferation and maturation of oligodendrocytes, increases neurotrophic factors, and inhibits activated microglia, astrocytes, and T lymphocytes. It was shown to have remyelinating and neuroprotective properties in the EAE mouse model⁷⁸. A clinical study has not been initiated yet.

CLEAN SURFACE GOLD NANOPARTICLES Animal studies with clean-surface gold nanoparticles showed remyelination in the cuprizone model. In **chapter 4** we discuss the first-in-human study with these gold nanoparticles (CNM-AU8), performed in 86 healthy male and female subjects to evaluate safety and pharmacokinetics.

BIOMARKERS IN MULTIPLE SCLEROSIS

Definition

The World Health Organization defined a biomarker as 'any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease'^{79,80}. Biomarkers in multiple sclerosis can be used to assess disease susceptibility, disease progression and response to treatment⁸¹. Biomarkers in response to treatment can be used to assess target engagement, pharmacodynamics, safety and proof-of-concept⁸².

Current biomarkers

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Current frequently used biomarkers in MS diagnosis and treatment management are oligoclonal bands (OCB) in the CSF, neurofilament light, white matter lesions on MRI and JC viral titer⁸¹. While oligoclonal bands may be considered a diagnostic biomarker, white matter lesions on MRI are diagnostic and used as biomarkers for treatment response, and JC viral titer is a biomarker related primarily to risk of side effects. An immunologic abnormality in MS patients is the presence of intrathecal synthesis of immunoglobulin G (IgG) in an oligoclonal pattern, measured in the CSF^{83,84} and it was the first biomarker in the diagnostic criteria of MS in 1983⁸⁵. Although OCBS were removed from the 2010 Mac-Donald criteria for RRMS, they still are a criterion for the diagnosis of primary progressive MS⁸⁶. Results of a recent biomarker study support the value of serum neurofilament light as a sensitive and clinically meaningful blood biomarker to monitor tissue damage and the effects of therapies in MS⁸⁷.

MRI provides a substantial variety of neuroinflammation biomarkers. TI lesions with contrast enhancement can be considered a biomarker of acute neuroinflammation and Blood-Brain-Barrier (BBB) disruption^{88,89}. Hyperintense T2-weighted lesions reflect a combination of mechanisms like inflammation, demyelination, axonal damage and oedema and has a high diagnostic value in MS⁹⁰. Hypotense TI-weighted lesions (black holes) are considered satisfactory biomarkers of axonal damage⁹¹. Both whole brain atrophy and grey matter atrophy are used as prognostic biomarkers in MS^{92,93}. However, MRI

techniques lack in adequate correlation with neurodegeneration and disability progression, the so-called 'clinic-radiological paradox'.⁹⁴⁻⁹⁶

Potential biomarkers

As mentioned earlier, more pharmaceutical compounds will target remyelination and trials with potential neuroreparative or neuroregenerative agents will need appropriate biomarkers. One of the biggest difficulties in the development of remyelination therapies for Ms is the demonstration of remyelination in living patients^{97,98}. Conventional MRI sequences have limited specificity for myelination. Imaging modalities which are potentially more specific to myelin content in vivo are magnetisation transfer ratio (MTR), restricted proton fraction f (from quantitative magnetisation transfer measurements), myelin water fraction and diffusion tensor imaging (DTI) metrics, and positron emission tomography (PET) imaging. Although MTR and DTI measures probably offer the most realistic and feasible outcome measures for such trials, they don't have sufficiently high sensitivity or specificity to myelin, or correlation with clinical features^{94,99}. The inadequacy of imaging biomarkers to quantify the process of myelin formation, and the need for a pharmacodynamic measure that could be used for studies with compounds that enhance remyelination, led us to set up and validate a more accurate method to measure (re)myelination.

In **chapter 5** we describe the development of a method to determine myelin turnover by labelling myelin with deuterium. First, the method was designed with the help of preclinical analyses and modelling. Subsequently the feasibility of the method was assessed in a clinical study subjects. Healthy subjects drank heavy (70% deuterated) water for a period of IO weeks, and deuterium incorporation of myelin breakdown products (beta-galactosylceramide) in the cerebrospinal fluid (CSF) was measured with mass spectrometry, after which the level of incorporation was quantified using modelling techniques. In a second study this labelling experiment was repeated in patients with Ms with the goal to quantify myelin turnover and assess the feasibility of this method to be used in patients with Ms. The results of this study are described in **chapter 6**.

Demyelination of nerves leads to conduction abnormalities and hence to neurological symptoms. Demyelination of the fasciculus longitudinalis medialis in the brainstem leads to slowing of the adducting eye in horizontal eye movements, which, when it leads to clinical symptoms is called an internuclear ophthalmoplegia (INO). We validated a method to accurately measure eye movements in patients with Ms and an INO to be used to demonstrate pharmacological effects of compounds that influence nerve conduction (**chapter** 7). We accurately tracked eye movement in patients with Ms and an internuclear ophthalmoplegia. As validation of a method is best done with a compound that has proven to be effective, we used fampridine (4-Aminopyridine) in this study as treatment. Fampridine caused a significant improvement in eye movements, as measured using a highly sensitive method to use eye movements. This method may also be used to quantify the effects of a compounds that enhance remyelination and thereby improve nerve conduction.

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REFERENCES

- I Annual review of immunology. 2005;23:683-747.
- 2 Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet (London, England). 2018;391(10130):1622-36.
- Compston A, Coles A. Multiple sclerosis. Lancet (London, England). 3 2008;372(9648):1502-17.
- 4 Bruck W. The pathology of multiple sclerosis is the result of focal inflammatory demyelination with axonal damage. Journal of neurology. 2005;252 Suppl 5:v3-9.
- Moore KL, Agur AMR, Dalley AF. Essential clinical anatomy2014.
- Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. Neurology. 1996;46(4):907-11.
- Youl BD, Turano G, Miller DH, Towell AD, MacManus DG, Moore 7 SG, et al. The pathophysiology of acute optic neuritis. An association of gadolinium leakage with clinical and electrophysiological deficits. Brain. 1991;114 (Pt 6):2437-50.
- 8 Black JA, Liu S, Hains BC, Saab CY, Waxman SG. Long-term protection of central axons with phenytoin in monophasic and chronic-relapsing EAE. Brain. 2006;129(Pt 12):3196-208.
- 9 Smith KJ. Axonal protection in multiple sclerosis-a particular need during remyelination? Brain. 2006;129(Pt 12):3147-9.
- 10 Barkhof F, Bruck W, De Groot CJ, Bergers E, Hulshof S, Geurts J, et al. Remyelinated lesions in multiple sclerosis: magnetic resonance image appearance. Archives of neurology. 2003;60(8):1073-81.
- 11 Reich DS, Lucchinetti CF, Calabresi PA, Multiple Sclerosis, The New England journal of medicine. 2018;378(2):169-80.
- 12 Alizadeh A, Dyck SM, Karimi-Abdolrezaee S. Myelin damage and repair in pathologic CNS: challenges and prospects. Frontiers in Molecular Neuroscience. 2015;8:35.
- 13 Bramow S, Frischer JM, Lassmann H, Koch-Henriksen N, Lucchinetti CF, Sørensen PS, et al. Demyelination versus remyelination in progressive multiple sclerosis. Brain. 2010;133(10):2983-98.
- 14 Lovas G, Szilagyi N, Majtenyi K, Palkovits M, Komoly S. Axonal changes in chronic demyelinated cervical spinal cord plaques. Brain. 2000;123 (Pt 2):308-17.
- 15 Mews I, Bergmann M, Bunkowski S, Gullotta F, Bruck W. Oligodendrocyte and axon pathology in clinically silent multiple sclerosis lesions. Multiple sclerosis (Houndmills, Basingstoke, England). 1998;4(2):55-62.
- 16 Mallucci G, Peruzzotti-Jametti L, Bernstock JD, Pluchino S. The role of immune cells, glia and neurons in white and gray matter pathology in multiple sclerosis. Progress in neurobiology. 2015;0:1-22.
- 17 Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain and behavior. 2015;5(9):e00362.
- 18 Shah P. Symptomatic management in multiple sclerosis. Ann Indian Acad Neurol. 2015;18(Suppl 1):S35-42.
- 19 Coles A. Newer therapies for multiple sclerosis. Annals of Indian Academy of Neurology. 2015;18(Suppl 1):S30-S4.
- 20 Parkin J, Cohen B. An overview of the immune system. The Lancet. 2001;357(9270):1777-89.
- 21 listed** na. Interferon beta-1β is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology. 1993;43(4):655-61.
- 22 Paolicelli D, Direnzo V, Trojano M. Review of interferon beta-1ß in the treatment of early and relapsing multiple sclerosis. Biologics: Targets & Therapy. 2009;3:369-76.
- 23 Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. The Lancet Neurology. 2014;13(7):657-65.
- 24 Rio J, Nos C, Bonaventura I, Arroyo R, Genis D, Sureda B, et al. Corticosteroids, ibuprofen, and acetaminophen for IFNbeta-Ia flu symptoms in MS: a randomized trial. Neurology. 2004;63(3):525-8. 25 Tremlett HL, Yoshida EM, Oger J. Liver injury associated with the
- beta-interferons for MS: a comparison between the three products. Neurology. 2004;62(4):628-31.
- 26 Arnon R, Aharoni R. Mechanism of action of glatiramer acetate in multiple sclerosis and its potential for the development of new

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applications. Proceedings of the National Academy of Sciences of the United States of America. 2004;101 Suppl 2:14593-8.

- 27 Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer I Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268-76.
- 28 Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1998;50(3):701-8.
- 29 Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Annals of neurology. 2013;73(6):705-13.
- 30 Zevda M, Poglitsch M, Geveregger R, Smolen JS, Zlabinger GJ, Horl WH, et al. Disruption of the interaction of T cells with antigenpresenting cells by the active leflunomide metabolite teriflunomide: involvement of impaired integrin activation and immunologic synapse formation. Arthritis and rheumatism. 2005;52(9):2730-9.
- 31 O'ConnorP, WolinskyJS, ConfavreuxC, ComiG, KapposL, OlssonTP, et al. Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis. New England Journal of Medicine. 2011;365(14):1293-303.
- 32 Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Neurology.13(3):247-56.
- 33 Scannevin RH, Chollate S, Jung MY, Shackett M, Patel H, Bista P. et al. Fumarates promote cytoprotection of central nervous system cells against oxidative stress via the nuclear factor (erythroid-derived 2)-like 2 pathway. The Journal of pharmacology and experimental therapeutics. 2012;341(1):274-84.
- 34 Linker RA, Lee DH, Ryan S, van Dam AM, Conrad R, Bista P, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain. 2011;134(Pt 3):678-92.
- 35 GoldR, KapposL, ArnoldDL, Bar-OrA, GiovannoniG, SelmajK, et al. Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis. New England Journal of Medicine. 2012;367(12):1098-107.
- 36 Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. The New England journal of medicine. 2012;367(12):1087-97.
- 37 Rice GP, Hartung HP, Calabresi PA. Anti-alpha4 integrin therapy for multiple sclerosis: mechanisms and rationale. Neurology. 2005;64(8);1336-42.
- 38 Pucci E, Giuliani G, Solari A, Simi S, Minozzi S, Di Pietrantonj C, et al. Natalizumab for relapsing remitting multiple sclerosis. The Cochrane database of systematic reviews. 2011(10):Cd007621.
- 39 Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. The New England journal of medicine. 2006;354(9):899-910.
- 40 Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-IG for relapsing multiple sclerosis. The New England journal of medicine. 2006;354(9):911-23.
- 41 Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsingremitting multiple sclerosis: a network meta-analysis. The Cochrane database of systematic reviews. 2015(9):Cd011381.
- 42 Antoniol C, Stankoff B. Immunological Markers for PML Prediction in MS Patients Treated with Natalizumab. Frontiers in immunology. 2014;5:668.
- 43 Brew BJ, Davies NW, Cinque P, Clifford DB, Nath A. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. Nature reviews Neurology. 2010;6(12):667-79.
- 44 Outteryck O, Zephir H, Salleron J, Ongagna JC, Etxeberria A, Collongues N, et al. JC-virus seroconversion in multiple sclerosis patients receiving natalizumab. Multiple sclerosis (Houndmills, Basingstoke, England). 2014;20(7):822-9.

- 45 Olsson T, Achiron A, Alfredsson L, Berger T, Brassat D, Chan A, et al. Anti-JC virus antibody prevalence in a multinational multiple sclerosis cohort. Multiple sclerosis (Houndmills, Basingstoke, England), 2013;19(11);1533-8.
- 46 Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S, 67 et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Annals of neurology. 2014;76(6):802-12.
- 47 Berger JR, Houff SA, Gurwell J, Vega N, Miller CS, Danaher RJ. JC virus antibody status underestimates infection rates. Annals of neurology. 2013;74(1):84-90.
- 48 Cohen JA, Chun J. Mechanisms of fingolimod's efficacy and adverse effects in multiple sclerosis. Annals of neurology. 2011;69(5):759-77.
- 49 La Mantia L, Tramacere I, Firwana B, Pacchetti I, Palumbo R, Filippini G. Fingolimod for relapsing-remitting multiple sclerosis. The Cochrane database of systematic reviews. 2016:4:Cd009371.
- 50 Ruck T, Bittner S, Wiendl H, Meuth SG. Alemtuzumab in Multiple Sclerosis: Mechanism of Action and Beyond. International journal of molecular sciences. 2015;16(7):16414-39.
- 51 Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003;61(10):1332-8.
- 52 McGinley MP, Moss BP, Cohen JA. Safety of monoclonal antibodies for the treatment of multiple sclerosis. Expert Opinion on Drug Safety. 2017;16(1):89-100.
- 53 DiLillo DJ, Hamaguchi Y, Ueda Y, Yang K, Uchida J, Haas KM, et al. Maintenance of Long-Lived Plasma Cells and Serological Memory Despite Mature and Memory B Cell Depletion during CD20 Immunotherapy in Mice. The Journal of Immunology. 2008;180(1):361-71.
- 54 Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. The New England journal of medicine. 2017;376(3):209-20.
- 55 Beutler E. Cladribine (2-chlorodeoxyadenosine). Lancet (London, England). 1992;340(8825):952-6.
- 56 Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sorensen P, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. The New England journal of medicine. 2010;362(5):416-26.
- 57 Nos C, Sastre-Garriga J, Borrlàs C, Río j, Tintoré M, Montalban X. Clinical impact of intravenous methylprednisolone in attacks of multiple sclerosis. Multiple Sclerosis Journal. 2004;10(4):413-6.
- 58 Linker RA, Weller C, Luhder F, Mohr A, Schmidt J, Knauth M, et al. Liposomal glucocorticosteroids in treatment of chronic autoimmune demyelination: long-term protective effects and enhanced efficacy of methylprednisolone formulations. Experimental neurology. 2008;211(2):397-406.
- 59 Schmidt J, Metselaar JM, Wauben MH, Toyka KV, Storm G, Gold R. Drug targeting by long-circulating liposomal glucocorticosteroids increases therapeutic efficacy in a model of multiple sclerosis. Brain. 2003;126(Pt 8):1895-904.
- 60 Gaillard PJ, Visser CC, Appeldoorn CCM, Rip J. Enhanced brain drug delivery: safely crossing the blood-brain barrier. Drug Discovery Today: Technologies. 2012;9(2):e155-e60.
- 61 Kannan R, Chakrabarti R, Tang D, Kim KJ, Kaplowitz N. GSH transport in human cerebrovascular endothelial cells and human astrocytes: evidence for luminal localization of Na+-dependent GSH 83 Correale J, de los Milagros Bassani Molinas M. Oligoclonal bands transport in HCEC. Brain research. 2000;852(2):374-82.
- 62 Coclitu C. Constantinescu CS. Tanasescu R. The future of multiple sclerosis treatments. Expert Review of Neurotherapeutics. 2016 10/21/2016:1341-56.
- 63 Mi S, Lee X, Shao Z, Thill G, Ji B, Relton J, et al. LINGO-I is a component of the Nogo-66 receptor/p75 signaling complex. Nat Neurosci. 2004;7(3):221-8.
- 64 Shao Z, Browning JL, Lee X, Scott ML, Shulga-Morskaya S, Allaire N, et al. TAJ/TROY, an Orphan TNF Receptor Family Member, Binds Nogo-66 Receptor 1 and Regulates Axonal Regeneration. Neuron. 2005;45(3):353-9.
- 65 Mi S, Hu B, Hahm K, Luo Y, Kam Hui ES, Yuan Q, et al. LINGO-I antagonist promotes spinal cord remyelination and axonal integrity in MOG-induced experimental autoimmune encephalomvelitis. Nat Med. 2007;13(10):1228-33.

- 66 Cadavid D, Balcer L, Galetta S, Aktas O, Ziemssen T, Vanopdenbosch L, et al. Safety and efficacy of opicinumab in acute optic neuritis (RENEW): a randomised, placebo-controlled, phase 2 trial. The Lancet Neurology. 2017;16(3):189-99.
- Watzlawik J, Holicky E, Edberg DD, Marks DL, Warrington AE, Wright BR, et al. Human remyelination promoting antibody inhibits apoptotic signaling and differentiation through Lyn kinase in primary rat oligodendrocytes. Glia. 2010;58(15):1782-93.
- 68 Watzlawik JO, Warrington AE, Rodriguez M. PDGF is required for remyelination-promoting IgM stimulation of oligodendrocyte progenitor cell proliferation. PloS one. 2013;8(2):e55149.
- 69 Mullin AP, Cui C, Wang Y, Wang J, Troy E, Caggiano AO, et al. RHIGM22 enhances remyelination in the brain of the cuprizone mouse model of demyelination. Neurobiology of disease. 2017;105:142-55.
- 70 Martin LJ. Olesoxime, a cholesterol-like neuroprotectant for the potential treatment of amyotrophic lateral sclerosis. IDrugs: the investigational drugs journal. 2010;13(8):568-80.
- 71 Bertini E, Dessaud E, Mercuri E, Muntoni F, Kirschner J, Reid C, et al. Safety and efficacy of olesoxime in patients with type 2 or nonambulatory type 3 spinal muscular atrophy: a randomised, doubleblind, placebo-controlled phase 2 trial. The Lancet Neurology. 2017;16(7):513-22.
- 72 Magalon K, Zimmer C, Cayre M, Khaldi J, Bourbon C, Robles I, et al. Olesoxime accelerates myelination and promotes repair in models of demyelination. Annals of neurology. 2012;71(2):213-26.
- 73 Vergo S, Craner MJ, Etzensperger R, Attfield K, Friese MA, Newcombe J, et al. Acid-sensing ion channel I is involved in both axonal injury and demyelination in multiple sclerosis and its animal model. Brain. 2011;134(2):571-84.
- 74 Friese MA, Craner MJ, Etzensperger R, Vergo S, Wemmie JA, Welsh MJ, et al. Acid-sensing ion channel-I contributes to axonal degeneration in autoimmune inflammation of the central nervous system. Nat Med. 2007;13(12):1483-9.
- 75 Arun T, Tomassini V, Sbardella E, de Ruiter MB, Matthews L, Leite MI, et al. Targeting ASICI in primary progressive multiple sclerosis: evidence of neuroprotection with amiloride. Brain. 2013;136(Pt 1):106-15.
- 76 Deshmukh VA, Tardif V, Lyssiotis CA, Green CC, Kerman B, Kim HJ, et al. A regenerative approach to the treatment of multiple sclerosis. Nature, 2013;502(7471);327-32.
- 77 Way SW, Podojil JR, Clayton BL, Zaremba A, Collins TL, Kunjamma RB, et al. Pharmaceutical integrated stress response enhancement protects oligodendrocytes and provides a potential multiple sclerosis therapeutic. Nature communications. 2015;6:6532.
- 78 Zhornitsky S, Wee Yong V, Koch MW, Mackie A, Potvin S, Patten SB, et al. Quetiapine fumarate for the treatment of multiple sclerosis: focus on myelin repair. CNS neuroscience & therapeutics. 2013:19(10):737-44.
- 79 Organisation WH. WHO International Programme on Chemical Safety. Biomarkers in Risk Assessment: Validity and Validation. 2001.
- 80 Strimbu K, Tavel JA. What are biomarkers? Current opinion in HIV and AIDS. 2010;5(6):463-6.
- 81 Housley WJ, Pitt D, Hafler DA. Biomarkers in multiple sclerosis. Clinical immunology (Orlando, Fla). 2015;161(1):51-8.
- 82 Zhao X, Modur V, Carayannopoulos LN, Laterza OF. Biomarkers in Pharmaceutical Research. Clinical chemistry. 2015;61(11):1343-53.
- and antibody responses in Multiple Sclerosis. Journal of neurology. 2002;249(4);375-89.
- 84 Davenport RD, Keren DF. Oligoclonal bands in cerebrospinal fluids: significance of corresponding bands in serum for diagnosis of multiple sclerosis. Clinical chemistry. 1988;34(4):764-5.
- 85 Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Annals of neurology. 1983;13(3):227-31.
- 86 Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Annals of neurology. 2011;69(2):292-302.
- 87 Disanto G, Barro C, Benkert P, Naegelin Y, Schadelin S, Giardiello A, et al. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. Annals of neurology. 2017;81(6):857-70.

- 88 Shinohara RT, Goldsmith J, Mateen FJ, Crainiceanu C, Reich DS. Predicting breakdown of the blood-brain barrier in multiple sclerosis without contrast agents. AJNR American journal of neuroradiology. 2012;33(8):1586-90.
- 89 Katsavos S, Anagnostouli M. Biomarkers in Multiple Sclerosis: An Up-to-Date Overview. Multiple sclerosis international. 2013;2013;340508.
- 90 Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. The New England journal of medicine. 2002;346(3):158-64.
- 91 Brex PA, Parker GJ, Leary SM, Molyneux PD, Barker GJ, Davie CA, et al. Lesion heterogeneity in multiple sclerosis: a study of the relations between appearances on TI weighted images, TI relaxation times, and metabolite concentrations. Journal of neurology, neurosurgery, and psychiatry. 2000;68(5):627-32.
- 92 Dalton CM, Chard DT, Davies GR, Miszkiel KA, Altmann DR, Fernando K, et al. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. Brain. 2004;127 (Pt 5):1101-7.
- 93 Fisher E, Rudick RA, Simon JH, Cutter G, Baier M, Lee JC, et al. Eightyear follow-up study of brain atrophy in patients with MS. Neurology. 2002;59(9):1412-20.
- 94 Dekker I, Wattjes MP. Brain and Spinal Cord MR Imaging Features in Multiple Sclerosis and Variants. Neuroimaging clinics of North America. 2017;27(2):205-27.
- 95 Hackmack K, Weygandt M, Wuerfel J, Pfueller CF, Bellmann-Strobl J, Paul F, et al. Can we overcome the 'clinico-radiological paradox' in multiple sclerosis? Journal of neurology. 2012;259(10):2151-60.
- 96 Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited. Current Opinion in Neurology. 2002;15(3):239-45.
- 97 Bothwell M. Mechanisms and Medicines for Remyelination. Annual review of medicine. 2017;68:431-43.
- 98 Harlow DE, Honce JM, Miravalle AA. Remyelination Therapy in Multiple Sclerosis. Frontiers in Neurology. 2015;6:2257.
- 99 Mallik S, Samson RS, Wheeler-Kingshott CA, Miller DH. Imaging outcomes for trials of remyelination in multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2014 2014:1396-404.
- 100 Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, Yang X. alemtuzumab versus interferon beta Ia for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews 2017, Issue II. Art. No.: CDDI0968. DOI: 10.1002/14651858.CDDI0968.pub2.
- 101 A.J. Coles, E. Fox, A. Vladic, S.K. Gazda, V. Brinar, K.W. Selmaj, A. Skoromets, I. Stolyarov, A. Bass, H. Sullivan, D.H. Margolin, S.L. Lake, S. Moran, J. Palmer, M.S. Smith, D.A.S. Compston 'Alemtuzumab more effective than interferon β-Ia at 5-year follow-up of CAMMS223 Clinical Trial', Neurology Apr 2012, 78 (14) 1069-1078; DOI: 10.1212/WNL.ob013e31824e8ee7
- 102 Martinelli Boneschi F, Vacchi L, Rovaris M, Capra R, Comi G. Mitoxantrone for multiple sclerosis. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD002127. DOI: 10.1002/14651858.CD002127.PUB3.
- 103 Hartung, Hans-Peter et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial The Lancet, Volume 360, Issue 9350, 2018 - 2025

TABLE I - Mechanisms of demyelination in multiple sclerosis, derived from Bruck, 2005⁴.

Primary immune mechanisms	Secondary mechanisms
т lymphocytes	Excitotoxicity
Cytotoxins	Free radicals
Nitric oxide	Death ligands and receptors
Antibodies	Toxins
Complement	Viruses

TABLE 2 - Disease Modifying Drugs, registered in the Netherlands.

Compound	Target	Development phase
Interferons	Immunomodulatory cytokine	Registered compound
Glatiramer acetate	Immunomodulatory: competition with various myelin antigens presentation to τ lymphocyte	Registered compound
Teriflunomide	Inhibits pyrimidine biosynthesis what leads to impaired proliferation of τ lymphocyte	Registered compound
Dimethyl fumarate	Neuroprotective effect through Nrf2-mediated oxidative stress response	Registered compound
Natalizumab	Antibody against alpha-4 integrins, decreases migration of immune cells	Registered compound
Fingolimod	Prevents lymphocytes from moving to the CNS	Registered compound
Alemtuzumab	Mediates lysis of immune cells, suppressing the neuroinflammatory responses in MS	Registered compound
Ocrelizumab	Selectively depletes CD20-expressing B lymphocytes	Registered compound
Cladribine	Causes apoptosis of T lymphocyte	Registered compound
Mitoxantrone	Immunosuppressive properties: reducing the number of B lymphocyte, inhibiting T helper cell function, and augmenting T lymphocyte suppressor activity	Registered compound

TABLE 3 - Compounds in developmental phase, selected on those that influence CNS.

Compound	Target	Development phase
Anti-LINGO-1 antibodies	Promotes remyelination	Phase II
RHIGM22 antibodies	Promotes remyelination	Phase I-II
Olesoxime	Neuroprotective and neuroregenerative properties	Phase I
ASICI blockers	Neuroprotective and myeloprotective effects	Pilot study
Benztropine	Oligodendrocyte maturation	Animal studies
Guanabenz	Increasing oligodendrocyte survival	Phase I
Quetiapine fumarate	Remyelinating and neuroprotective properties	Animal studies
Clean surface gold nanoparticles	Enhance remyelination	Phase I

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FIGURE I – Frequently used medication in multiple sclerosis, modified from Coles 2015¹⁹. Ocrelizumab and cladribine are not in this figure.

