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Review

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Current immunotherapies for multiple sclerosis and neuromyelitis optica spectrum disorders: the similarities and differences

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Abstract

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are autoimmune demyelinating diseases of the central nervous system. Neuromyelitis optica was considered a variant of MS until the discovery of NMO-IgG in 2004, which changed our understanding of the pathophysiology of NMOSD. This review focuses on the similarities and differences in the immune treatments of MS and NMOSD.

Keywords: Multiple sclerosis, neuromyelitis optica spectrum disorders, pathophysiology, treatment, disease-modifying drugs

INTRODUCTION

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are chronic immune-mediated demyelinating diseases of the central nervous system (CNS) with distinct immunological and pathological features[1-3]. MS is common in Western countries (incidence, > 100 per 100,000 in the European and North American populations), where it is the most common non-traumatic disabling disease among young people. However, MS is not common in Asia (incidence, 0-20 per 100,000 in Asian populations)[4]. Interestingly, the farther away one goes from the equator, the higher is the prevalence of MS[5]. MS generally progresses from a period of relapses and remissions to progressive disability. The pathogenetic mechanism

underlying MS is an autoimmune reaction to myelin or oligodendrocytes, but no MS-specific autoantigen has been identified.

NMO/NMOSD typically manifest as optic neuritis and longitudinally extensive transverse myelitis, and can lead to severe disability. The prevalence of NMOSD rarely exceeds 5/100,000, and is comparatively similar globally[4]. In 2004, Lennon *et al.*[6] discovered NMO autoantibodies, which clearly differentiated NMO from MS. Up to 80% of NMO patients test positive for antibodies against aquaporin4 (AQP4), which is a water channel protein found in many organs of the body[7]. In the CNS, AQP4 is expressed in a perivascular distribution on astrocytic foot processes[6]. The distinctive immunopathology of NMO lesions supports a central role for AQP4-IgG in the pathogenesis of this disease. AQP4-IgG damages the blood-brain barrier (BBB) through complement-dependent astrocytic damage. AQP4-IgG-positive NMOSD is not a classic demyelinating disease as MS, marked by secondary demyelination due to astrocyte loss[8,9]. In addition to the optic nerve and spinal cord, areas of high AQP4 expression around the ventricles are often involved, such as the area postrema of the medulla oblongata, thalamus, peripheral area of the third and fourth ventricles, corpus callosum, and white matter of the cerebral hemisphere. The high specificity of AQP4-IgG extends the study of NMO and its related diseases. Previously, the diagnostic criteria for NMO required optic nerve and spinal cord involvement. In 2007, Wingerchuk proposed the concept of NMOSD[10]. In 2015, the International Panel for NMO Diagnosis removed the separate definition of NMO and integrated NMO into the broader term of NMOSD[11]. NMOSD are a class of antigen-antibody-mediated CNS inflammatory demyelinating diseases that are primarily mediated by humoral immunity, with or without AQP4 positivity[12].

PATHOGENESIS OF MS AND NMOSD

MS is considered a classic autoimmune disease mediated by autoreactive T-lymphocytes, specifically CD4+ T-helper (Th)1 cells and Th17 cells. Th1 cells produce interferon (IFN)-γ, while Th17 cells are a T-cell subgroup producing IFN-γ and interleukin (IL)-17[13,14]. Activated T-cells can express a variety of adhesion molecules that combine with receptors on the vessel wall. Furthermore, vascular endothelial cells express selectins that bind to T-cells, and chemokines can induce T-cells to enter the CNS. Additionally, T-cells secrete matrix metalloproteinases that degrade the collagen component of blood-vessel walls, destroying the BBB and facilitating the entry of T- and B-lymphocytes and monocytes into the brain. In the CNS, T-cells secrete inflammatory cytokines and chemokines, which cause the activation of other inflammatory cells, resulting in a series of complex cascades of immune responses that finally lead to damage to the myelin sheath and even axons[13-16]. IL-4 stimulates the differentiation of CD4+ T-cells into anti-inflammatory Th2 cells and inhibits Th1 and Th17 cells. IL-2 and transforming growth factor (TGF)-β stimulate the production of regulatory T cells, which can inhibit Th17, Th1, and CD8+ T-cells in the CNS[17]. Th1 cells can recognize major histocompatibility complex (MHC) class II molecules, cross the BBB, and induce CNS autoimmunity. And Th17 lymphocytes are capable of crossing the BBB, and their secretion damages the BBB and promotes the entry of other inflammatory cells into the CNS[18]. In recent years, it has been found that B-cells also play an important role in the pathogenesis of MS. In most MS patients, oligoclonal bands and B-cell clonal proliferation occur in the CSF, and B-cell proliferation and germinal-center formation may occur in the meningeal follicles[19].

NMOSD are humoral immune-mediated autoimmune diseases. B-lymphocytes secrete specific antibodies that bind to complement, then deposit and destroy AQP4, which is expressed on the surface of astrocytes. However, the role of B-cells in the pathogenesis of NMOSD may not be limited to the production of AQP4-IgG, and an imbalance between pro-inflammatory and anti-inflammatory B-cell functions may also be involved[20]. Other inflammatory cells such as macrophages, eosinophils, and neutrophils are then attracted towards the injured tissue and secrete inflammatory factors that cause myelin loss and axonal damage[21]. A study has shown that peripheral blood neutrophils show a primed phenotype in NMOSD[22]. In some

NMOSD patients, antibodies against myelin-oligodendrocyte-glycoprotein (MOG) rather than AQP4 antibodies are detectable. The clinical features of MOG-IgG-positive NMOSD are different from those of the classic AQP4-IgG-positive NMOSD, and the underlying pathogenesis of the two conditions may also be different. MOG is a glycoprotein localized on the myelin surface as well as in the cell bodies and processes of oligodendrocytes. The MOG antibody is a subtype of IgG1, which is effective in regulating complement-dependent cytotoxicity. MOG antibodies target myelin-forming oligodendrocytes, whereas AQP4 antibodies damage astrocytes leading to secondary demyelination[23,24]. In terms of clinical features, MOG-IgG-positive NMOSD tends to be monophasic, more common among men, and have a younger onset age and a better prognosis[25]. At present, it is unclear whether CNS demyelinating diseases mediated by MOG antibodies should be independent of MS and NMOSD[26,27]. However, according to the revised NMOSD diagnostic criteria in 2015, AQP4-IgG positive or negative diseases and MOG-IgG positive diseases can be classified as NMOSD[11]. AQP4 antibodies and MOG antibodies are mainly produced extrathecally and are therefore less frequently found in the CSF than in the serum. AQP4 antibodies can be detected in the CSF in only 70% of patients who are seropositive for AQP4 antibodies and in none of the patients who are seronegative for AQP4 antibodies[28,29]. Furthermore, the levels of AQP4 and MOG antibodies may vary during the course of the disease. However, AQP4 antibody titers do not seem to predict long-term disease duration, and the serum AQP4 antibody status does not predict immunotherapy response[30,31].

TREATMENT OF ACUTE ATTACKS

At present, there is no cure for MS and NMOSD. The primary goal of therapy in the acute phase is to alleviate symptoms, shorten the disease course, and prevent complications. Currently available treatments only act on the inflammatory components of the disease process, and no therapy that can directly reverse myelin loss or neuronal damage exists. As in other autoimmune diseases, the recommended management strategy for patients with MS or NMOSD during the acute phase includes intravenous methylprednisolone (IVMP) pulse therapy, plasma exchange (PE), and intravenous immunoglobulin (IVIG)[32,33]. The treatment of acute attacks shortens the duration of relapses and reduces symptoms, but does not have long-term neuroprotective effects[34,35]. IVMP is considered the standard treatment for acute attacks[36,37]. Mainly in patients with contraindications to IVMP or disease that is refractory to IVMP, PE and IVIG are alternative therapies. NMOSD lesions are associated with IgG, IgM, and complement deposition; all of these are targeted by PE, which has a good therapeutic effect in NMOSD[38]. Immunoadsorption (IA) can remove immunoglobulins from the circulation, and is an alternative treatment for acute attacks[39,40]. For severe attacks, PE and IA can be used as initial therapies[41]. IVIG is a safe and well-tolerated immunotherapy that could also be used as a treatment alternative for MS and NMOSD[42,43]. However, this recommendation is based mostly on clinical experience, because of a lack of trials on IVIG monotherapy in the treatment of acute attacks. Furthermore, IVIG probably confers no advantage over IVMP and PE[44]. For MS, IVIG is usually only used for patients with contraindications to IVMP and PE, as the efficacy of IVIG is uncertain. NMOSD are humoral-mediated diseases, and therefore, therapeutic agents that inhibit B-cells or antibody production may be effective[45]. IVIG can reduce anti-AQP4 levels[46]; however, the efficacy of IVIG for acute attacks still needs to be proven.

Corticosteroids are an important therapy in the acute phase of relapse. High-dose methylprednisolone (0.5-1.0 g intravenously for 3-5 days) is recommended in the acute phase. The mechanisms of action of IVMP include dampening the inflammatory cytokine cascade, inhibiting the activation of T-cells, decreasing the expression of MHC-II molecules on antigen-presenting cells and the entry of immune cells into the CNS, and facilitating the apoptosis of activated immune cells[47]. Some studies have shown that oral methylprednisolone is no worse than IVMP in terms of the clinical and radiological outcomes of MS relapses[48-51]. The European Federation of Neurological Societies guidelines recommend an oral methylprednisolone dose of at least 0.5 g/day for 5 days (cumulative dose, 2.5 g)[52]. Several studies have

shown the safety of stopping a short course of high-dose corticosteroids without a tapering regimen[53,54]. In addition, one study showed that in MS, IVMP combined with low-dose oral hormones did not improve disability progression compared with IVMP alone[55]. However, low-dose oral corticosteroids may help prevent relapses in NMOSD[56]. In some patients with NMOSD, a rebound effect may occur if corticosteroids are stopped quickly. A study of 59 patients with relapsing MOG antibody-associated demyelination showed that most cases of relapse occurred within 2 months of prednisolone cessation and in patients who had been administered daily doses of < 10 mg[57]. Therefore, an oral weaning course of prednisolone over 2-6 months and long-term maintenance with low-dose oral prednisolone is recommended[58,59]. Compared with MS, NMOSD relapse is often more severe and less responsive to IVMP[60,61]. A retrospective study showed that IVMP has a significant effect on acute relapses in both MS and NMOSD patients, but the effects in MS were slightly better than those in NMOSD based on the changes in the Expanded Disability Status Scale score before and after IVMP[62].

PE can remove circulating autoantibodies, macromolecular immune complexes, inflammatory cytokines, and other mediators. It can also affect lymphocyte proliferation and activation[63]. Common side effects of PE include hypocalcemia, bleeding, and infections. When remission is absent or insufficient, PE every other day is recommended, with removal of 1-1.5 plasma volumes each time (30-40 mL/kg). A total of 5-7 treatments are recommended. Studies have found that the exchanged molecules will drop to less than 20% of their initial level after 5 exchanges[64,65]. In addition, IA is a more selective method that eliminates certain proteins, such as antibodies, while retaining other plasma proteins. The effects of IA and PE are comparable in the treatment of MS- or NMOSD-relapses[66]. Patients with a suboptimal response to methylprednisolone and those who present with severe symptoms should be treated with PE/IA. Some results support the use of PE in severe relapses of MS unresponsive to corticosteroids[67]. PE and IA can clear AQP4-IgG and are effective therapies for NMOSD. The results of a retrospective cohort study suggest early use of PE/IA in NMOSD attacks[68]. And no superiority was shown for one of the 2 apheresis techniques[68]. PE/IA combined with IVMP is more effective than IVMP alone in NMOSD[69,70]. In addition to steroids, it is recommended that PE/IA be started as soon as possible[71,72]. A study showed that the early initiation of PE (≤ 5 days) is more beneficial than delayed PE for cases that are refractory to IVMP[71].

IVIG is another important therapy that can affect a variety of immunomodulatory and antigenic-recognition pathways, including humoral and cellular immunity. It interacts with various subsets of B- and T-cells, modulates cytokines, scavenges complement, and blocks idiotypic antibodies[73]. Patients should be given IVIG at a dose of 0.4 g/kg/day for 5 days[74]. In MS, studies have shown that IVIG combined with IVMP is not superior to IVMP alone[75,76]. Few studies have assessed the efficacy of IVIG monotherapy for MS relapses. IVIG has a good effect in other humoral immune-mediated neuroimmunological diseases. IVIG may affect certain steps of pathological processes in NMOSD. Clinical experience suggests that this therapy may be of benefit in NMOSD patients[44]. A retrospective study with a small sample size has shown the efficacy of IVIG treatment for NMOSD relapses[43]. Furthermore, it has been shown that regular IVIG could prevent relapses in both MS and NMOSD[77-80].

TREATMENTS IN THE REMISSION PERIOD

In most instances, the initial course of MS consists of relapses and remissions, known as relapsing-remitting MS (RRMS), with disability progression over the course of the disease. Most patients eventually enter a secondary phase of progressive disease, i.e., secondary progressive MS (SPMS). In a few patients, the initial course is progressive with no relapsing-remitting phase; that is known as primary progressive MS (PPMS)[81]. The relationship between disability progression and relapses in MS is not yet clear. Unlike MS, in NMOSD, disability is the result of cumulative inflammatory damage caused by acute attacks[58]. The purpose of treatment during the remission period is reducing the risk of relapse and disability progression. In both MS and NMOSD, treatment during remission should be started as soon as possible[58,59,82,83]. Therapeutic drugs

in the remission period include conventional immunosuppressants and some new immunomodulators as well as biological agents. The latest guidelines in the United States and Europe recommend disease-modifying drugs (DMDs) to regulate MS[82,83]. Most recommendations for NMOSD are still based on expert advice because of the lack of clinical evidence, as until recently, most studies reporting treatment outcomes were conducted in a non-random and often retrospective environment[84-86]. There exist differences in the mechanisms of action, routes of administration, and approved indications of different drugs. The various medications are presented in Table 1. Table 2 lists the results of some important trials.

Attack prevention in MS

The pathogenesis of MS includes focal inflammatory demyelination and axonal loss. The available DMDs are mainly beneficial for controlling inflammation and have a poor effect on the degenerative component of the disease[173]. Since the first DMD, IFN-β1b became available in 1993, the US Food and Drug Administration has approved more than a dozen DMDs for MS: IFN-β1b, IFN-β1a, glatiramer acetate (GA), mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate (DMF), alemtuzumab, pegylated IFN-β1a, daclizumab, ocrelizumab, cladribine and siponimod. The mechanisms of action of these DMDs have been depicted in [Figure 1].

Currently, three types of IFNs have been approved for RRMS: IFN-β1b, IFN-β1a, and pegylated IFN-β1a. The biological activity of IFN-β1a is 10 times higher than that of IFN-β1b. However, pegylated IFN-β1a, which consists of covalently linked IFN and polyethylene glycol, has a long half-life, which decreases the required frequency of administration[99,100]. IFN-β and GA, which were approved more than 20 years ago, are safe and effective. Both drugs are often considered as standard therapies in clinical trials of new DMDs. Among the DMDs for MS, mitoxantrone is not recommended firstly because of its cardiac toxicity. The cardiotoxicity of anthracyclines is thought to be dose dependent and irreversible, leading to a reduction in left ventricular ejection fraction and congestive heart failure. Regular and frequent cardiac monitoring is required during mitoxantrone therapy[174]. Daclizumab was delisted because of its high risk of serious inflammatory brain disorders, including encephalitis and meningoencephalitis[175,176]. Ocrelizumab, which has an anti-CD20 action, is the only drug approved for PPMS. Last month, siponimod has been approved by FDA. It may reduce the activity of the disease and has a modest effect on the gradual disability accrual in SPMS[156].

Monoclonal antibodies are more effective than other immunomodulators and can reduce the annual relapse rate by almost 50%[82]. Alemtuzumab (anti-CD52), fingolimod, or natalizumab (α4-integrin inhibitor) are recommended for patients with highly active MS[83]. Patients who use fingolimod, DMF, natalizumab, ocrelizumab, or rituximab should be evaluated for their risk of progressive multifocal leukoencephalopathy (PML). Cases of PML due to the use of fingolimod or DMF are fortunately rare[177,178]. However, the overall risk of PML with natalizumab use is high (4 per 1000)[179-181]. Patients with MS taking natalizumab should be switched to another DMD with a lower PML risk, if the anti-JC virus antibody index exceeds 0.9 during treatment. High-dose steroid and maraviroc (1000-3000 mg/day, po) may be beneficial for natalizumab-associated PML, and are lacking in experience[182,183]. The advent of oral DMDs has greatly facilitated the daily management of MS patients and improved compliance to treatment. Rituximab, which is usually used to treat NMOSD, has also been used for MS since the discovery of the role of B-cells in the pathogenesis of MS[160-162].

Attack prevention in NMOSD

Since the cumulative inflammatory damage caused by acute attacks leads to disability in NMOSD, attack prevention is crucial for long-term efficacy. It is accepted that first-line immunotherapies for the prevention of relapses in NMOSD include azathioprine, mycophenolate mofetil, and rituximab[41,84-86]. It should be noted that most studies on this topic were not well-controlled or randomized, and may have some bias in their results. Azathioprine antagonizes purine metabolism, and was the first immunosuppressant drug that was found to be effective in preventing NMOSD relapses[165]. Mycophenolate mofetil blocks lymphocyte

Table 1. Disease-modifying drugs for multiple sclerosis and neuromyelitis optica spectrum disorders

DMD	Trade name, available since	Dosage	Mechanism of action	Clinical trials
IFN-β1b	Betaseron, 1993 Extavia, 2009	250 μg, every other day, sc	Reduces Th1 and Th17 production; promotes Th2 proliferation; regulates T-, B-, natural killer, and dendritic cells; blocks leukocyte migration to the central nervous system[99-101]	RRMS[87-93], SPMS[94-96], PPMS[97,98]
IFN-β1a	Avonex, 1996 Rebif, 2002	30 μg, once a week, im 22 or 44 μg, three times a week, sc		
Pegylated IFN-β1a	Plegridy, 2014	125 μg, once 2 weeks, sc		
GA	Copaxone, 1996	20 mg, once a day, sc 40 mg, 3 times a week, sc	Binds MHC class II; interferes with development of self-reactive proinflammatory T-cells; promotes Th2 proliferation; regulates various immune cells[102-104]	RRMS[105-109], PPMS[110]
Mitoxantrone	Novantrone, 2000	12 mg/m^2, once every 3 months, iv	Inhibits type-II topoisomerase; disrupts DNA synthesis	RRMS[111,112], SPMS[113-115], PPMS[114]
Fingolimod	Gilenya, 2010	0.5 mg, once a day, po	Sphingosin-1 phosphate receptor agonist; induces lymphocytes to enter secondary lymphoid organs[116-118]	RRMS[119-124], PPMS[125]
Teriflunomide	Aubagio, 2012	7 or 14 mg, once a day, po	Prevents dihydroorotate dehydrogenase activation; suppresses activated T-lymphocyte proliferation[126,127]	RRMS[128-131]
Dimethyl fumarate	Tecfidera, 2013	240 mg, twice a day, po	Th1-Th2 shift, lymphocyte apoptosis[132,133]	RRMS[134-136]
Natalizumab	Tysabri, 2006	300 mg, once every 4 weeks, iv	Inhibits α4-integrin; prevents activated CD4+ T-cells from crossing the blood-brain barrier[137-139]	RRMS[140-145], SPMS[146]
Alemtuzumab	Lemtrada, 2013	12 mg, once a day for 5 days, then for 3 days one year later, iv	Anti-CD52; depletes CD52-positive lymphocytes[147]	RRMS[148-150]
Ocrelizumab	Ocrevus, 2017	600 mg, every 6 months, iv	Anti-CD20, depletes a large part of the B-cell lineage	PPMS[151], RRMS[152,153]
Cladribine	Mavenclad, 2017	Cumulative doses: 3.5 mg/kg or 5.25 mg/kg, po	Synthetic purine nucleoside analogue, disrupts DNA repair and synthesis, achieves therapeutic depletion of lymphocytes	RRMS[154,155]
Siponimod	Mayzent, 2019	2 mg, once a day, po	A new sphingosine 1-phosphate receptor modulator, depletes circulating lymphocytes, promotes CNS repair by modulating S1P1 on astrocytes and S1P5 on oligodentrocytes[157]	SPMS[156] RRMS[157,158]
Rituximab	Mabthera 1997	Two sessions of slow iv infusion of 1 g rituximab 14 days apart or 375 mg/m^2 each week for 4 weeks	Anti-CD20, attacks B-cells and plasmoblasts	NMOSD[159], RRMS[160,161], PPMS[162]
Azathioprine		2-3 mg/(kg·day) , po	Inhibits purine nucleotide synthesis; activates mitochondrial apoptotic pathway; activated T-cell apoptosis[163,164]	NMOSD[159,165,166], RRMS[167]
Mycophenolate mofetil	CellCept	1000-3000 mg/day, po	Blocks guanine nucleotide production; inhibits lymphocyte proliferation[168,169]	NMOSD[170-172]

DMD: disease-modifying drug; IFN: interferon; sc: subcutaneous; iv: intravenous; im: intramuscular; po: per os; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; MHC: major histocompatibility complex; NMOSD: neuromyelitis optica spectrum disorders

proliferation by inhibiting the synthesis of guanine. It causes fewer adverse reactions, so it is a safe and generally well tolerated drug for NMOSD[169]. The efficacy of rituximab is better than that of azathioprine

Table 2. Clinical trials of multiple sclerosis and neuromyelitis optica spectrum disorders

Drug	Comparator	Trial	Disease	Duration	Sample size	Findings
IFN-β1b[87]	Placebo	Randomized, double-blind	RRMS	2 years	*n* = 372, 1:1:1 ratio of placebo, 1.6 million IU, and 8 million IU	Annual exacerbation rate: Placebo, 1.27; 1.6 million IU, 1.17; 8 million IU, 0.84
IFN-β1a[89]	Placebo	Randomized, phase III, double-blind	RRMS	104 weeks	*n* = 301, 1:1 ratio of placebo and 30 μg IFN-β1a	Annual exacerbation rate: Placebo, 0.9; interferon β-1a 0.61; Patients with disability progression: Placebo, 34.9%; IFN-β1a, 21.9%
PegIFN-β1a, ADVANCE trial[93]	Placebo	Randomized, phase III, double-blind	RRMS	2 years	Placebo (*n* = 500), PegIFN every 2 weeks (*n* = 512), PegIFN every 4 weeks (*n* = 500)	Annual relapse rate: Placebo, 0.397 (95%CI: 0.328-0.481); PegIFN every 2 weeks, 0.256 (95%CI: 0.206-0.318); PegIFN every 4 weeks, 0.288 (95%CI: 0.234-0.355)
GA[105]	Placebo	Randomized, phase III, double-blind	RRMS	2 years	GA (*n* = 125), placebo (*n* = 126)	Annual relapse rate: Placebo, 0.84; GA, 0.59
GA[109]	Placebo	Randomized, double-blind	RRMS	1 year	GA (*n* = 943), placebo (*n* = 461)	Annual relapse rate: Placebo, 0.505; GA, 0.331
Teriflunomide, TOWER trial[128]	Placebo	Randomized, phase III, double-blind	RRMS	48 weeks	Placebo (*n* = 388), 7 mg (*n* = 407), 14 mg (*n* = 370)	Annual relapse rate: Placebo, 0.50 (95%CI: 0.43-0.58); 7 mg, 0.39 (95%CI: 0.33-0.46); 14 mg, 0.32 (95%CI: 0.27-0.38) No effect on sustained accumulation of disability (7 mg) (HR: 0.95, 95%CI: 0.68-1.35)
Teriflunomide, TEMSO[129]	Placebo	Randomized trial	RRMS	108 weeks	*n* = 1088 1:1:1 ratio of placebo, 7 mg, and 14 mg	Annual relapse rate: Placebo, 0.54; 7 mg, 0.37; 14 mg, 0.37 Patients with confirmed disability progression: Placebo, 27.3%; 7 mg, 21.7%; 14 mg, 20.2%
DMF[135]	Placebo, GA	Randomized, phase III, double-blind	RRMS	96 weeks	Placebo (*n* = 363) Twice-daily DMF (*n* = 359), Thrice-daily DMF (*n* = 345), GA (*n* = 350)	Annual relapse rate: Placebo, 0.40; Twice-daily DMF, 0.22; Thrice-daily DMF, 0.20; GA, 0.29 Fewer new or enlarging hyperintense lesions on T2-weighted images ($P < 0.001$)
DMF[134]	Placebo	Randomized, phase III, double-blind	RRMS	2 years	Placebo (*n* = 408), Twice-daily DMF (*n* = 410), Thrice-daily DMF (*n* = 416)	Annual relapse rate: Placebo, 0.36; Twice-daily DMF, 0.17; Thrice-daily DMF, 0.19 Confirmed disability progression: Placebo, 27%; Twice-daily DMF, 16%; Thrice-daily DMF, 18%
Fingolimod, FREEDOMS II trial[120]	Placebo	Randomized, phase III, double-blind	RRMS	24 months	Placebo (*n* = 355), 0.5 mg (*n* = 358),	Annual relapse rate: Placebo, 0.40 (95%CI: 0.34-0.48); 0.5 mg, 0.21 (95%CI: 0.17-0.25); Percentage brain volume change: Placebo, -1.28 (SD, 1.50); 0.5 mg, -0.86 (SD, 1.22)

Fingolimod[119]	Placebo	Randomized, phase III, double-blind	RRMS	24 months	Placebo (*n* = 355), 0.5 mg (*n* = 358), 1.25 mg (*n* = 370)	Annual relapse rate: Placebo, 0.40; 0.5 mg, 0.18; 1.25 mg 0.16 Cumulative probability of disability progression (confirmed after 3 months): Placebo, 24.1%; 0.5 mg, 17.7%; 1.25 mg, 16.6%
Cladribine, CLARITY study[154]	Placebo	Randomized, phase III, double-blind	RRMS	96 weeks	Placebo (*n* = 437), 3.5 mg/kg (*n* = 433), 5.25 mg/kg (*n* = 456)	Annual relapse rate: Placebo, 0.33; 3.5 mg/kg, 0.14; 5.25 mg/kg, 0.13
Natalizumab, AFFIRM trial[140]	Placebo	Randomized, phase III, double-blind	RRMS	2 years	Placebo (*n* = 627), Natalizumab (*n* = 315)	Cumulative probability of progression: Placebo, 29%; Natalizumab, 17% Rate of relapse at 1 year reduced by 68%
Alemtuzumab[148]	IFN-β1a	Randomized, phase III, double-blind	RRMS	2 years	IFN-β1a (*n* = 231) Alemtuzumab (12mg) (*n* = 436)	Patients with relapse: IFN-β1a, 51%; Alemtuzumab, 35% Cumulative disability: IFN-β1a, 20%; Alemtuzumab, 13%
Ocrelizumab[151]	Placebo	Randomized, phase III, double-blind	PPMS	120 weeks	Placebo (*n* = 244), Ocrelizumab (*n* = 488)	Worse performance on timed 25-foot walk: Placebo, 55.1%; Ocrelizumab, 38.9%
Siponimod[156]	Placebo	Randomized, phase III, double-blind	SPMS	3 years	Placebo (*n* = 546), Siponimod (*n* = 1099)	Patients with 3-month confirmed disability progression: Placebo, 32%; Siponimod, 26%
Rituximab[161]	Self	Phase II	RRMS	52 weeks	*n* = 30	Median GdE lesions reduced from 1.0 to 0; MSFC improved (*P* = 0.02)
Rituximab[162]	Placebo	Randomized, double-blind	PPMS	96 weeks	Placebo (*n* = 147), Rituximab (*n* = 292)	Patients with CDP: Placebo, 38.5%; Rituximab, 30.2% (*P* = 0.14) Mean (SD) T2 volume change: Placebo, 2,205 (4306); Rituximab, 1,507 (3739)
Rituximab[159]	AZA	Randomized clinical trial	NMOSD	12 months	Rituximab (*n* = 33), AZA (*n* = 35)	Decreased annual relapse rate: Rituximab, 1.09; AZA, 0.49 Relapse-free disease: Rituximab, 78.8%; AZA, 54.3%
AZA[167]	IFN-β	Randomized, phase III, single-blind	RRMS	2 years	AZA (*n* = 77), IFN-β (*n* = 73)	Annual relapse rate: AZA, 0.26; IFN-β, 0.39 Annualized new T2 lesion rate: AZA, 0.76; IFN-β, 0.69

IFN: interferon; PegIFN: pegylated interferon; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; AZA: azathioprine; DMF: dimethyl fumarate; GA: glatiramer acetate; MSFC: multiple sclerosis functional composite; CDP: confirmed disease progression; GdE: gadolinium enhanced; CI: confidence interval; HR: hazard ratio; SD: standard deviation

and mycophenolate mofetil, and is probably the best choice at present[184-187]. Rituximab is a human-mouse chimeric monoclonal antibody against CD20, which is a regulatory factor for the early activation and differentiation of B-cells. It acts on B-cells and plasmablasts. After a single dose of rituximab, the number of B-cells typically decreases to their minimum value by 2 weeks, and this effect is generally maintained for 6 months. Studies have found that long-term rituximab treatment often leads to significant reduction in immunoglobulins[188]. There have been reports of infections with long-term rituximab treatment. It is important to monitor CD19+ B-cell counts, the total and specific Ig levels before and during treatment with

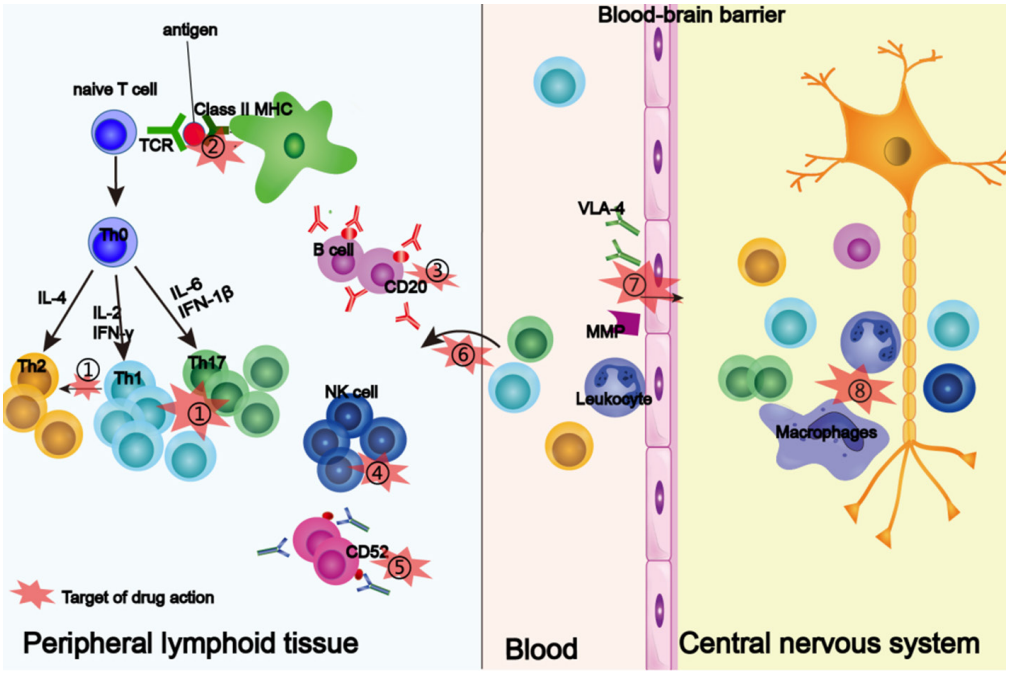

Figure 1. Pathogenesis of multiple sclerosis and targets of drug action. ① Reduced production of Th1 and Th17 cells and Th1-Th2 shift (interferon-β, teriflunomide, dimethyl fumarate); ② Competitive binding of MHC class II molecules (glatiramer acetate); ③ Depletion of CD20-positive lymphocytes (ocrelizumab, rituximab); ④ Regulation of T-cells, B-cells, NK cells, and dendritic cells (interferon-b, glatiramer acetate); ⑤ Depletion of CD52-positive lymphocytes (alemtuzumab); ⑥ Alteration of lymphocyte distribution (fingolimod); ⑦ Preventing activated CD4+ T-cells from crossing the blood-brain barrier (natalizumab, interferon-β); ⑧ Promoting leukocyte migration to the central nervous system (glatiramer acetate). VLA-4: very late antigen-4; MMP: matrix metalloproteinase; MHC: major histocompatibility complex; IFN: interferon; IL: interleukin; NK: natural killer; TCR: T-cell receptor; Th: T helper

rituximab to prevent complications[188,189]. Other immunosuppressants that have been used to treat NMOSD include tacrolimus, cyclophosphamide, methotrexate, and cyclosporin A. Tacrolimus and cyclosporin A produce good selective inhibition of Th cells, and methotrexate inhibits folate metabolism. However, these drugs have not been used frequently because of their uncertain effects[84-86]. Some studies have found that some new DMDs for MS, such as fingolimod, DMF, alemtuzumab, and natalizumab, may cause the disease to worsen, mainly in patients with AQP4-IgG-positive NMOSD[190-194]. There are insufficient data to support or discourage the use of GA and IFN-β in NMOSD[195,196]. Currently, experience in the treatment of MOG-IgG-positive NMOSD is still lacking, and long-term immunosuppression may be effective[197,198].

CONCLUSION

Currently, MS and NMOSD are incurable diseases. There is no consensus on the best treatment strategy or treatment target. Early, conventional immunosuppressive agents, such as azathioprine and cyclophosphamide, have been used for the treatment of MS and NMOSD. Various immunosuppressive agents have different degrees of efficacy in MS or NMOSD. Among them, only azathioprine and mycophenolate mofetil are currently recommended for the treatment of NMOSD, but no credible randomized controlled trial has yet proved their effects. Now, more than a dozen DMDs are available for MS, with varying levels of efficacy and safety. Immunomodulators against MS have been marketed since 1993, and conventional immunosuppressive agents have rarely been used in this condition. Compared with new immunomodulators, conventional immunosuppressants have more side effects and worse drug targeting. However, in some countries and regions, due to economic reasons or a lack of DMDs, cyclophosphamide, tacrolimus, and other drugs are still used to treat MS and have some therapeutic effect[199-201]. Despite the use of DMDs, some patients still have exacerbations and develop progressive disease. Few DMDs are available for NMOSD, and there is a lack of

large-scale clinical trials.Several new drugs are currently undergoing clinical trials, including tocilizumab (IL-6 receptor blocker), eculizumab (C5 complement inhibitor), and inebilizumab (CD19 B-cell depletion)[202].

More efficacious therapies that alter the disease course are therefore required. Additional research on neuroprotection and repair is urgently needed. Many therapies are currently under study, including hematopoietic stem cell transplantation, neural stem cell-based regenerative approaches, and exosomes derived from bone marrow mesenchymal stem cells. The future of MS and NMOSD treatment is extremely promising as more effective treatments are being developed.

DECLARATIONS

Authors' contributions

Summarized the references and wrote the manuscript: Zhang L
Discussed paper writing and revised the manuscript: Zhang L, Tian JY, Li B
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