Minireview

Recent developments in multiple sclerosis therapeutics
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Abstract
Multiple sclerosis, the most common neurologic disorder of young adults, is traditionally considered to be an inflammatory, autoimmune, demyelinating disease of the central nervous system. Based on this understanding, the initial therapeutic strategies were directed at immune modulation and inflammation control. These approaches, including high-dose corticosteroids for acute relapses and long-term use of parenteral interferon-β, glatiramer acetate or natalizumab for disease modification, are at best moderately effective. Growing evidence supports that, while an inflammatory pathology characterizes the early relapsing stage of multiple sclerosis, neurodegenerative pathology dominates the later progressive stage of the disease. Multiple sclerosis disease-modifying therapies currently in development attempt to specifically target the underlying pathology at each stage of the disease, while avoiding frequent self-injection. These include a variety of oral medications and monoclonal antibodies to reduce inflammation in relapsing multiple sclerosis and agents intended to promote neuroprotection and neurorepair in progressive multiple sclerosis. Although newer therapies for relapsing MS have the potential to be more effective and easier to administer than current therapies, they also carry greater risks. Effective treatments for progressive multiple sclerosis are still being sought.

Introduction
Multiple sclerosis (MS) is a chronic progressive disorder of the central nervous system (CNS). It is traditionally considered to be an inflammatory disorder characterized by episodic CNS demyelination. However, current understanding is that neurodegeneration dominates the progressive stages of the disease. This article summarizes the pathogenesis of MS, reviews approved MS therapies and discusses the proposed mechanisms and likely benefits and risks of new MS therapeutics.

Disease pathogenesis and disease subtypes
MS presents in most people (80%) with clinical relapses characterized by fully or partially-reversible focal neurologic deficits [1]. Relapsing-remitting MS (RRMS) is dominated by inflammation, oedema and the physiologic actions of cytokines [2]. Active inflammation of the brain and spinal cord is visualized as gadolinium enhancing white matter lesions on magnetic resonance imaging (MRI). After 10-20 years, or median age 39.1 years, about half of those with RRMS gradually accumulate irreversible neurologic deficits in the absence of clinical relapses or new white matter lesions by MRI [3]. This stage is known as secondary progressive MS (SPMS). The remaining 20% with progressive clinical deterioration from the onset of the disease have primary progressive MS (PPMS) [1]. PPMS and SPMS are thought to be dominated by axonal degeneration in the absence of overt inflammation [4].
which is most likely a result of oxidative damage and/or increased susceptibility to injury caused by the loss of the myelin sheath.

**Current MS therapeutics**

Clinically significant acute MS relapses are usually treated with high-dose, short-term, intravenous corticosteroids (methylprednisolone 1 g/day for 3-5 days). This shortens relapse duration but does not improve the degree of recovery or the long-term course of the disease [5-7]. Disease-modifying therapies (DMT) for MS alter the course of the disease. They lower the clinical relapse rate, extend the time to next relapse and reduce the accumulation of new lesions on MRI, all of which are intended to decrease the long-term accumulation of disability. The first approved DMT for MS, subcutaneous interferon beta-1b (IFNβ-1b, marketed as Betaseron in the USA and as Betaferon in Europe), was approved by the US Food and Drug Administration (FDA) for RRMS in 1993. This was based on the pivotal placebo-controlled trial in which treated subjects had significantly lower annualised relapse rates and more subjects were relapse-free after 2 years [8]. IFNβ (interferon beta) acts as an anti-inflammatory and has several mechanisms of action, including a reduction in the production of pro-inflammatory IFNγ and TNFα, inhibition of T-cell activation and clonal expansion, modulation of cytokine and matrix metalloproteinase production and the release and inhibition of T-cell migration and entry into the CNS [9].

Since the release of IFNβ-1b, five other parenteral medications have been approved for the treatment of MS: IFNβ-1a (Avonex®, Biogen Idec, North Carolina, USA), IFNβ-1a (Rebif®, EMD Serono, Geneva, Switzerland), glatiramer acetate (GA, Copaxone®, Teva Pharmaceuticals, Petah Tikva, Israel), mitoxantrone (Novantrone®, OSI Pharmaceuticals, New York, USA) and natalizumab (Tysabri®, Biogen Idec, Massachusetts, USA). The IFN products are thought to all have similar mechanisms of action although they differ in the route of administration, rapidity of onset of action and risk of induction of neutralizing antibodies [10]. In contrast, GA - a synthetic copolymer of glutamic acid, lysine, alanine and tyrosine - is believed to activate Th2 regulatory cells in the periphery. These activated Th2 cells cross the blood brain barrier (BBB) and enter the CNS where they shift the immune response from pro-inflammatory to anti-inflammatory by secreting cytokines that down-regulate the inflammatory response and inhibit pro-inflammatory Th1 cells. Mitoxantrone is an antineoplastic agent that inhibits DNA and RNA synthesis of B and T-cells. While approved for the treatment of RRMS and SPMS [11-13], it has only shown a clear benefit for patients still experiencing relapses and developing new MRI lesions. Increasing recognition of short and long-term risks of cardiotoxicity, acute leukaemia and bone marrow suppression limit its use [14-16]. Natalizumab is the first monoclonal antibody (MAB) therapy approved for the treatment of MS. It binds to VLA-4 on the surface of leukocytes, preventing T-cells from crossing the BBB into the CNS [17]. Natalizumab was found to reduce MS relapses by 68% compared to placebo [18] but its use is limited by its association with the development of progressive multifocal leukoencephalopathy (24 patients at the time of this writing) [19], as well as melanoma [20] and primary CNS lymphoma [21] which are all probably due to an altered immune surveillance. In response, the FDA limited approval of natalizumab to patients failing other MS therapies and requires patients to be enrolled in a safety monitoring programme.

**Future directions**

DMT development for MS is an area of active research and many potential agents are in various phases of investigation. Most of these are oral medications or MABs that target specific aspects of inflammation in RRMS. Others are designed to have neuroprotective and neurorestorative effects in PPMS and SPMS (Figure 1).

**Oral anti-inflammatory agents for RRMS (Table 1)**

Fingolimod (FTY720), a small molecule derived from a fungus and chemically related to sphingosine, causes internalization of sphingosine-1-phosphate (S1P) receptors on lymphocytes, thereby blocking their egress from lymph nodes and thymus. The reversible lymphocytopenia-
niation prevents activated T cells from crossing the BBB and causing inflammation [22]. Fingolimod may also have direct effects via the S1P receptors present on all CNS cells types. A phase II clinical trial in RRMS found that fingolimod significantly reduced gadolinium-enhancing lesions and relapse rates compared to placebo [23] and a second trial demonstrated fingolimod's superiority to IFNβ-1a [24]. A European phase III clinical trial of fingolimod for RRMS has been completed, and a USA phase III trial is underway [http://www.clinicaltrials.gov]. Frequent adverse events associated with fingolimod include nasopharyngitis, dyspnea, headache and nausea. Rare serious adverse events in the trials were skin cancers and two deaths, one each from herpes encephalitis and disseminated varicella, all suggesting an inadequate immune surveillance.

The antimitabolite cladribine, an adenosine analogue, incorporates into DNA and causes the death of rapidly proliferating inflammatory B and T cells, thus resulting in selective and long-lasting lymphocyte depletion. Approved as a therapy for use in hairy-cell leukaemia, early trials indicated that cladribine was effective for RRMS but not SPMS [25,26]. A recent phase III trial in RRMS (CLARITY) demonstrated a significant benefit of cladribine over placebo with a reduction in annualized relapse rate of over 50% at 96 weeks [27]. Based on this trial, the manufacturers are applying for FDA registration for cladribine. Cladribine has an appealing short administration schedule and is generally well-tolerated, but there were some serious adverse events in the trial including herpes zoster in 2% of subjects, three cancers and four deaths in the cladribine groups [27].

There are three oral agents in phase III trials in RRMS, laquinimod, teriflunomide and BG00012. Laquinimod and teriflunomide are thought to work in part by shifting the T-cell balance from pro-inflammatory Th1 cells to anti-inflammatory Th2 cells. Laquinimod is a chemically and pharmacologically distinct derivative of the drug roquinimex, the study of which in RRMS was halted due to significant pulmonary and cardiac toxicity [28]. A 24 week phase II trial of laquinimod demonstrated a significant reduction of gadolinium-enhancing lesions on MRI over placebo [29]. Based on these promising early results, two phase III trials are underway in patients with RRMS. Teriflunomide is the active metabolite of leflunomide, a drug used in rheumatoid arthritis. It also inhibits dihydro- orotate dehydrogenase, the enzyme necessary for de novo synthesis of pyrimidine, thus reducing activated B and T cell proliferation [30]. A promising phase II trial [31] has led to phase III placebo-controlled trials of teriflunomide RRMS and clinically isolated syndrome (CIS). Need for pre-treatment with cholestyramine or activated charcoal and the frequent association of hypertension, alopecia and rash could potentially limit its use. BG00012 probably affects MS primarily through its anti-oxidant effects. It is an oral formulation of dimethyl fumarate, a topical agent used to treat psoriasis. Promising early studies [32] led to a phase III trial now underway.

Based on the observation that there is a reduction in MS relapses during pregnancy, a condition associated with high levels of and progesterone, it is thought that or progesterone may benefit patients with MS and progesterone have potent anti-inflammatory effects and may also provide neuroprotective benefits by increasing oligodendrocyte precursor cell number [33] and promoting oligodendrocyte process formation [34]. Phase III trials of oral estriol in conjunction with glatiramer acetate in RRMS are ongoing.

**Monoclonal antibodies for RRMS (Table 2)**

Alemtuzumab targets the CD52 antigen present on T cells, B cells, monocytes, macrophages and eosinophils, but not stem cells, and causes reversible leukocyte depletion. Alemtuzumab is approved for chronic lymphocytic leukaemia and showed promise in early trials for RRMS [35] but not SPMS [36]. Patients with RRMS treated with alemtuzumab compared to IFNβ-1a had significantly lower risk for relapse (75%) and reduction in sustained disability (65%) over 2 years [35]. Safety concerns included three cases of immune thrombocytopenic purpura with one fatality, Grave’s disease, autoimmune anaemias and neutropenias and Guillain-Barre syndrome. Phase III trials are ongoing. Daclizumab depletes leukocytes by binding to the α-chain of the IL-2 receptor (CD25) required for T cell

| Agent | Proposed mechanisms of action | Stage of development* |
|-------|------------------------------|-----------------------|
| Fingolimod (FTY 720) | Binds sphingosine-1-phosphate on T cells preventing circulation and CNS entry | Phase III for RRMS |
| Cladribine | Selectively depletes B and T cells by causing DNA damage | Phase III for RRMS and CIS |
| Laquinimod | Shifts T cells from TH1 (pro-inflammatory) to TH2 (anti-inflammatory) | Phase III for RRMS and CIS |
| Teriflunomide | Shifts T cells from TH1 (pro-inflammatory) to TH2 (anti-inflammatory); Blocks pyrimidine and reproduction of rapidly dividing B and T cells | Phase III for RRMS and CIS |
| BG00012 (dimethyl fumarate) | Antioxidant | Phase III |

*a compiled from clinicaltrials.gov
CIS, clinically isolated syndrome; CNS, central nervous system

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**Table 1: Oral anti-inflammatory agents for relapsing-remitting multiple sclerosis (RRMS).**

| Agent Proposed mechanisms of action | Stage of development* |
|-----------------------------------|-----------------------|
| Fingolimod (FTY 720) Binds sphingosine-1-phosphate on T cells preventing circulation and CNS entry | Phase III for RRMS |
| Cladribine Selectively depletes B and T cells by causing DNA damage | Phase III for RRMS and CIS |
| Laquinimod Shifts T cells from TH1 (pro-inflammatory) to TH2 (anti-inflammatory) | Phase III for RRMS and CIS |
| Teriflunomide Shifts T cells from TH1 (pro-inflammatory) to TH2 (anti-inflammatory); Blocks pyrimidine and reproduction of rapidly dividing B and T cells | Phase III for RRMS and CIS |
| BG00012 (dimethyl fumarate) Antioxidant | Phase III |
proliferation and activation. Daclizumab, approved for treatment of renal transplant rejection, appears to stabilize disease in RRMS patients who have failed IFN therapy [37,38] and is in Phase II clinical trials for RRMS. Adverse events associated with daclizumab include thromboses, lymphoproliferative disorders, and infections. Rituximab, a MAB that depletes CD20+ B cells, is an approved therapy for haematological malignancies, rheumatoid arthritis and thrombocytopenic purpura. B-cell dependent mechanisms such as antigen presentation, antibody secretion and demyelination, are increasingly implicated in the pathogenesis of MS [39,40]. A phase II trial [41] and case reports [42] show promise for its use in RRMS [43]. Adverse effects of rituximab include progressive multifocal leukoencephalopathy, pancytopenias, Stevens-Johnson syndrome and rare infections.

**Neuroprotective and neurorestorative agents for PPMS and SPMS**

Thus far, all of the anti-inflammatory therapies that are effective in RRMS have had minimal or no effect in controlling progressive MS. There is a growing belief that SPMS and PPMS will not respond to anti-inflammatory therapies and that neuroprotective and neurorestorative therapies that affect neuronal integrity will be required for progressive MS. A variety of existing and novel approaches are under investigation as neuroprotective and neurorestorative therapies in progressive as well as relapsing MS (Table 3). Therapeutic strategies include protecting demyelinated axons as well as oligodendrocytes (the CNS myelin-producing cells) from oxidative injury, promoting neuronal remyelination and restoring neuronal growth and function with neurotrophic factors [44]. Lipoic acid, a fatty acid present in certain foods and available as an oral supplement, may protect oligodendrocytes by antioxidant mechanisms and effects on microglia. Lipoic acid is well tolerated [45] and phase II trials of this compound in RRMS and SPMS are being planned. Drugs that block glutamate receptors present on demyelinated axons may prevent oxidative injury [46]. Riluzole, an oral glutamate NMDA receptor antagonist approved for use in amyotrophic lateral sclerosis [47], is being evaluated in conjunction with IFNβ-1a in a phase II trial for early MS. Another strategy for neuroprotection in MS is selective sodium channel blockade with antiepileptic medications including phenytoin, topiramate and lamotrigine [48,49].

### Table 2: Monoclonal antibodies for relapsing-remitting multiple sclerosis (RRMS)

| Agent       | Proposed mechanisms of action                                                                 | Stage of development* |
|-------------|------------------------------------------------------------------------------------------------|-----------------------|
| Alemtuzamab | Leukocyte depletion; Depletes CD52 B and T cell populations, monocytes, macrophages and eosinophils | Phase III for RRMS    |
| Daclizumab  | Leukocyte depletion; Binds cell-surface receptor IL2; reduces T cell proliferation and activation | Phase II for RRMS     |
| Rituximab   | B cell-directed therapy; Depletes CD20 B cell population                                       | Phase III for RRMS    |

*Compiled from [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

### Table 3: Oral and parenteral neuroprotective and neurorestorative agents for primary progressive multiple sclerosis (MS) and secondary progressive MS.

| Strategy                                      | Drug class                  | Agents *                          |
|-----------------------------------------------|-----------------------------|-----------------------------------|
| Protection of oligodendrocytes/axons from oxidative injury | Antioxidants | Lipoic acid                       |
| Protection of demyelinated axons from injury  | Glutamate receptor antagonists | Riluzole, NBQX, GYKI-52466        |
|                                               | NMDA                        |                                   |
|                                               | AMPA/Kainate                |                                   |
|                                               | Sodium channel blockers     | Phenytoin, Topiramate, Lamotrigine|
| Promotion of remyelination                    | Stem cells                  | Embryonic, autologous             |
|                                               | LINGO-I                     | Anti-LINGO-I antibodies           |
| Neurotrophic factors to help restore neuronal function | Pregnancy hormones | Estradiol                         |
|                                               | Neurotrophic factors        | GDNF, IGF, CNTF, neurvtin, artemin, persephin |
|                                               | GDNF, BDNF, NT3/4           |                                   |

*oral agents are indicated in italics

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; GYKI-52466, a 2, 3-benzodiazepine; IGF, insulin-like growth factor; LINGO-1, leucine rich repeat and Ig domain-containing, Nogo Receptor-interacting protein 1; NBXX, 2, 3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione; NMDA, N-methyl-D-aspartic acid; NGF, nerve growth factor; NT3/4, neurtophin 3 and 4.
A recent phase II trial of lamotrigine in SPMS, however, failed to meet its primary endpoint of reducing the rate of central cerebral volume loss [50,51].

Trials of stem cell transplantation, with the goal of repopulating oligodendrocytes, are underway in people with MS. Remyelination may also be promoted by blocking leucine rich repeat and Ig domain-containing, Nogo Receptor-interacting protein 1 (LINGO-1), a protein on the surface of neurons that inhibits differentiation of precursor oligodendrocytes into mature cells. Antibody blockade of LINGO-1 has shown promise in an animal model of MS [51]. Neurotrophins are protein factors produced by CNS cells that support neuronal growth, survival and differentiation [52]. In MS, secretion of the neurotrophin brain-derived neurotrophic factor (BDNF) is low and dysregulated [53] and BDNF is therefore also being considered as a therapeutic target.

Conclusion
Current MS therapeutics are moderately effective for modifying disease during its relapsing-remitting phase. There are a number of oral and parenteral agents that target inflammation in development and several are likely to be approved for treatment of RRMS within the next few years. These therapies will likely more effectively control RRMS but will also carry greater known and, as yet, unknown safety risks. These risks and benefits will have to be weighed carefully against the efficacy and proven safety of the IFNs and GA. Furthermore, none of the anti-inflammatory therapies currently in late stage of development are likely to benefit patients with SPMS and PPMS. Development of effective neuroprotective and neurorestrative therapies are needed in order to benefit patients with progressive MS.

Abbreviations
BBB: blood brain barrier; BDNF: brain-derived neurotrophic; CIS: clinically isolated syndrome; CNS: central nervous system; DMT: disease-modifying therapy; FDA: US Food and Drug Administration; GA: glatiramer acetate; IFN: interferon; LINGO-1: leucine rich repeat and Ig domain-containing, Nogo Receptor-interacting protein 1; MB: monoclonal antibody; MRI: magnetic resonance imaging; MS: multiple sclerosis; PPMS: primary progressive MS; RRMS: relapsing-remitting MS; SIP: sphingosine-1-phosphate; SPMS: secondary progressive MS.

Competing interests
RIS has no competing interests. MHC has received honoraria for speaking from Teva Neuroscience. DB has research grants from the National Institutes of Health, the Department of Veterans Affairs and the National Multiple Sclerosis Society. DB has also received honoraria for speaking/consulting or unrestricted educational grants, from Teva Neuroscience, Biogen Idec, EMD Serono and Bayer USA.

Authors’ contributions
RIS and MHC contributed equally to the paper. All authors were involved in the drafting of the manuscript and revision for important intellectual content. All authors read and approved the final manuscript and have given their approval of final published version.

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References
1. Compton A, Coles A: Multiple sclerosis. Lancet 2008, 372:1502-1517.
2. Frohman EP, Racke MK, Raine CS: Multiple sclerosis - the plaque and its pathogenesis. N Engl J Med 2006:942-955.
3. Confavreux C, Vukusic S: Natural history of multiple sclerosis: a unifying concept. Brain 2006, 129:606-616.
4. Kezele IB, Arnold DL, Collins DL: Atrophy in white matter fiber tracts in multiple sclerosis is not dependent on tract length or local white matter lesions. Mult Scler 2008, 14:779-785.
5. Milligan NM, Newcombe R, Compton DA: A double-blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: I. Clinical effects. J Neurol Neurosurg Psychiatry 1987, 50:11-516.
6. Zivadinov R, Rudicik RA, De Masi R, Nasuelli D, Ukkara M, Pozzi-Mucelli RS, Grop A, Cazzato G, Zorzon M: Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. Neurology 2001, 57:1239-1247.
7. Beck RW: The Optic Neuritis Treatment Trial. Arch Ophthalmal 1998, 106:1051-1053.
8. The IFNB Multiple Sclerosis Study Group: Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. In Neurology Volume 43. The IFNb Multiple Sclerosis Study Group; 1993:655-661.
9. Goodkin D: Interferon beta-1b. Lancet 1994, 344:1057-1060.
10. Schwid SR, Panitch HS: Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. Clin Ther 2007, 29:2031-2048.
11. Mauch E, Korinhiber HH, Kraf H, Fezzer U, Laufen H: Treatment of multiple sclerosis with mitoxantrone. Eur Arch Psychiatry Clin Neurosci 1992, 242:96-102.
12. Noseworthy JH, Hopkins MB, Vandervoot MK, Karlik SJ, Lee DH, Pennan M, Rice GP, Grinwich KD, Cauvier H, Harris BJ: An open trial evaluation of mitoxantrone in the treatment of progressive MS. Neurology 1993, 43:1401-1406.
13. Edan G, Miller D, Clanet M, Confavreux C, Lyon-Caen O, Lubetzki C, Gandon JM, Lai HM, Moseley I, Sabouraud O: Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. J Neurol Neurosurg Psychiatry 1997, 62:112-118.
14. Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology: 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, 61:1332-1338.
15. Ghalee RG, Mauch E, Edan G, Hartung HP, Gonsette RE, Eisenmann S, Le Page E, Butine MD, De Goodkin DE: A study of therapy-related acute leukemia after mitoxantrone therapy for multiple sclerosis.[see comment]. Mult Scler 2002:441-445.
16. Veltz R, Stark M, Zingler V, Strupp M, Kolb HJ: Mitoxantrone therapy in multiple sclerosis and acute leukemia: a case report out of 4 treated patients. Mult Scler 2004, 10:472-474.

17. Radzioch RM: Natalizumab for multiple sclerosis. N Engl J Med 2007, 356:2622-2629.

18. Polman CH, O’Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Waight A, Toal M, Lynn F, Panzara MA, Sandrock AW, AFFIRM Investigators: A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006, 354:899-910.

19. Berger JR, Houff SA, Major EO: Monoclonal antibodies and progressive multifocal leukoencephalopathy. mAbs 2009, 1:1-7.

20. Jacob A, Kempnick B: Melanoma complicating treatment with Natalizumab (Tysabri) for multiple sclerosis. J Neurol 2009, 256:1711-1722.

21. Schweikert A, Kremer M, Ringel F, Liebig T, Duyster J, Stuve O, Hemmer B, Berthele A: Primary central nervous system lymphoma in a patient treated with natalizumab. Ann Neurol 2009, 66:403-406.

22. Hiestand PC, Rausch M, Meier DP, Foster CA: Ascomycete derivative to MS therapeutic: SIP receptor modulator FTY770. Prog Drug Res 2008, 66:361.

23. Kappos L, Montalban X, O’Connor P, Polman CH, Haas T, Korn AA, Karlsson G, Radue EW, FTY720 D2201 Study Group: Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med 2006, 355:1124-1140.

24. Cohen J, Pelleiter J, Kappos L, Barkhof F, Comi G, Hartung HP, Montalban X, Kinkel T, Tiel-Wiklicki K, Izquierdo G, et al: Oral fingolimod (FTY720) significantly reduced relapse rate compared with intramuscular interferon beta-1a in relapsing-remitting multiple sclerosis: clinical results from a 12-month phase III study (TRANSFORMS). ECTRIMS 2009.

25. Costelloi KGC: Cladribine tablets’ potential in multiple sclerosis treatment. J Neurosci Nurs 2008, 40:275-280.

26. Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J: Ismail A, Kemp J, Sharrack B: Monoclonal antibodies and progressive multifocal leukoencephalopathy. mAbs 2009, 1:1-7.

27. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann K, Barkhof F, Sandrock AW, AFFIRM Investigators: A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. Neurology 2007; 69:483-489.

28. Noseworthy JH, Wolinsky JS, Neuhaus SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, Bar-Or A, Panzara M, Sarkar N, Agarwal S, Langer-Gould A, Smith CH, HERMES Trial Group: B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008, 358:676-688.

29. Stadie O, Lesinski V, Frohlich R, Hemmer B, Hartung HP, Menge T, Kieseir BC: Long-term B-lymphocyte depletion with rituximab in patients with relapsing-remitting multiple sclerosis. Arch Neurol 2009, 66:259-261.

30. Jacob A, Weinshenker BG, Violich I, McLinskey N, Krupp L, Fox RJ, Wardlaw JM, Montaner J, Sandrock AW, O’Neill GN, BG-12 Trial Group: Oral fingolimod (FTY720) for relapsing multiple sclerosis: preliminary results from a phase IIb study. Neurology 2009, 73:1716-1720.

31. Killestein J, Kalkers NF, Polman CH: Glutamate inhibition in MS: the neuroprotective properties of riluzole. J Neural Transm 2005, 112:13-15.

32. Black JA, Waxman SG: Prevention and repair by neurotrophic and gliotrophic factors in multiple sclerosis. Lancet Neurol 2008, 7:635-645.

33. Loeb JA: Neuroprotection and repair by neurotrophic and gliotrophic factors in multiple sclerosis. Neurology 2007, 68(Suppl 3):S3-S4.

34. Azzouly D, Urshansky N, Karni A: Low and dysregulated BDNF secretion from immune cells of MS patients is related to reduced neuroprotection. J Neuroimmunol 2008, 195:186-193.

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