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Emerging Therapies in Multiple Sclerosis: Current Concepts and Future Perspectives

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SUMMARY

Multiple Sclerosis (MS) represents the main cause of neurological disability in young adults of Caucasian ancestry. However for more than a decade the only therapies available were two immunomodulatory drugs, interferon beta and glatiramer acetate, and the immunosuppressant mitoxantrone. Although the etiology of MS remains obscure, the immunopathogenesis appears to involve both the cell- and humorally-mediated arms of the immune system acting in concert with genetic and environmental factors. In that respect, natalizumab, a humanized monoclonal antibody (mAb) raised against α4-integrin, showed increased efficacy compared to existing therapies, which led to its recent approval in Europe and the USA as second-tier treatment of Relapsing Remitting MS. Natalizumab acts by blocking lymphocyte adhesion to endothelium and thus prevents the transmigration of autoreactive T cells across the blood brain barrier into the CNS. However treatment with natalizumab was associated with JC virus reactivation and development of progressive multifocal leucoencephalopathy (PML). In addition, 2 recently completed phase III trials showed significant reduction in both MRI and clinical markers of disease activity with the orally administered fingolimod, a sphingosine-1-phosphate (S1P) modulator that prevents lymphocyte egress from lymph nodes. Cladibrine is an adenosine deaminase-resistant purine nucleoside analogue that causes longlasting lymphocyte depletion preferentially affecting$CD4^+$ T cells.A short treatment course (8-20 days per year) with cladribine tablets provided a significant benefit for patients withRRMS. Very promising results were obtained with alemtuzumab, a humanised mAb that targets CD52, a cell-surface glycoprotein abundantly expressed on T and B lymphocytes, monocytes, and eosinophils, thus resulting in depletion of both T and B cells. In a phase II trial, alemtuzumab administered yearly demonstrated superior to interferon efficacy, with respect to the relapse rate, disability progression and MRI activity, albeit with an excess risk of developing an antibody-mediated autoimmune disease (Graves disease, idiopathic thrombocytopenia). The growing evidence that humoral immunity is operative in MS pathogenesis prompted the use of Rituximab, a chimeric murine/ human mAb directed against CD20, a surface antigen expressed on pre–B cells and mature B cells. A phase II trial confirmed the efficacy of rituximab in RRMS without significant adverse effects or opportunistic infections. However recent reports of PML occuring in patients with lymphoproliferative and other autoimmune disorders treated with rituximab cause an increasing concern over its safety. Recently daclizumab, a humanized mAb directed against IL-2Rα (CD25) was tested either as monotherapy or in combination with interferon-β in RRMS patients, showing benefit in both clinical and MRI parameters. Although the exact mechanism of action has not fully been elucidated, an expansion of the immunoregulatory $CD56^{bright}$ natural killer cells is postulated. Finally clinical trials are under way with three oral immuno-modulatory drugs: Teriflunomide, Laquinimod and Dimethyl Fumarate (BG00012).