Emerging therapies for the treatment of ms

Currently, there are six new drugs that are being assessed by clinical scientists and some of these drugs have entered or completed phase 2 level and phase 3 level clinical trials. Three of these drugs are oral drugs and they include Lanquinimod, Teriflumomide and Di-methyl fumarate. The other three are monoclonal antibodies (mAb) namely Alemtuzumab, Daclizumab and Rituximab (Borrero et al, 2012). All of these drugs target the immune system in different ways but some of them still present with some side effects as well which are discussed below.

Starting with Lanquinimod, it is an immunomodulator that is currently being trialled in patients with RRMS and SPMS. It has a very small recommended dose of 0. 6 mg daily and it exhibits anti-inflammatory properties. These properties are believed to support the downregulation of MHC class II transcription factors, stimulation of neurotrophic factors, activation and up-regulation of the IL-4 pathway in CD4+ T cell for anti-inflammatory effects. It also promotes apoptosis in Cytotoxic T-cells (CD8+) and B-cells and also suppresses metabolism in CD14+ and natural killer cells (Thöne et al., 2016). It is currently undergoing Phase III trials and has resulted in 23% reduction in the rate of relapse of MS while there has been a 37% reduction in contrast enhancing lesions in volunteers (Borrero et al, 2012). Its side effect is only the upregulation of Liver Function Tests (LFTs)

The second oral drug that is undergoing phase III clinical trials is Teriflunomide and it is being trialled for patients with RRMS and SPMS. Doses ranging from 7 to 14 mgs daily are recommended to be administered orally in patients. Its mode of action depends on sequestering the production of DNA pyrimidine bases by acting as an inhibitor for the enzyme

dihydroorotate dehydrogenase, which is essential in de novo pyrimidine synthesis in T and B cells that are rapidly dividing. This reduces any inflammation that would've been caused by those cells and thus immune suppression is achieved. According to Borrero et al, it has a success rate of 61% in reducing contrast enhancing lesions, a rate of 30% in reducing Annualized relapse rates (ARRs) and disability progression was observed to be reduced to 23-30%. Terfilunomides's side effects include Nasopharyngitis; which is the inflammation of the nasopharyngeal duct, diarrhoea, back pain, fatigue, hair thinning, influenza, Urinary Tract Infection (UTI), nausea and elevated LFTs (Borrero et al, 2012).

The third oral drug is Di-methyl fumarate (DMF) or BG-12. It is also undergoing type III clinical trials for patients with RRMS. Its suggested dose is 120-24 mg three times a day. It has shown a decrease of 69% in contrast enhancing lesions in its phase II trial and its phase III trials have so far showed 53% reduction in ARR, 38% reduction in disability progression and in 2 years, by 49% (Borrero et al, 2012). Di-methyl fumarate's mode of action is still being debated but it is believed that it can regulate oxidative pathways which may in turn affect other signalling pathways that are responsible for inducing tissue damage. Studies by Moharregh -Khiabani et al in 2009 showed that DMF had an inhibitory effect on the nuclear factor NFκB dependant, TNF α induced gene transcription in endothelial cells. It is also believed that DMF can stimulate cells to secrete cytokines such as IL-10, IL-4 and IL_5 which have anti-inflammatory properties thus allowing a more Th2 focused response than a Th1 one (Wierinckx et al., 2005). Moreover, DMF is believed to have a neuroprotective therapeutic effect as well. This occurs as

it causes an upregulation in the levels of the detoxification enzyme; NADPH but like other emerging drugs, it has side effects. These side effects include diarrhoea, cramps, elevated LFT, nausea and can cause flushing and in very rare cases, Progressive multifocal leukoencephalopathy (PML) (MS Society 2016).

Other novel therapies include the use of monoclonal antibodies (mAb) for the treatment of MS. As of now, there are three that are undergoing phase II and III trials respectively. Alemtuzumab is one such mAb that is in its phase III clinical trial for patients with RRMS and SPMS. Its recommended dosage is Intravenous infusion of 12- 24 mg daily for a course of 5 days every month if it's a 1 year course and this can be increased to 24mg on the 12 th month. Its mode of action is causing the destruction of circulating immune cells by binding on to CD52 on mature leukocytes which results in the lysis of CD4+ and CD8+ T cells, B cells, eosinophils, NK cells, monocytes and macrophages as well (Hart and Bainbridge 2016). In phase III trials, it has so far shown up to 75% reduction in sustained accumulation disability and up to 74% reduction in relapse rate but has been associated with potentially increasing the risk of autoimmunity which included thyroiditis, idiopathic thrombocytopenic purpura, autoimmune thyroid-related problems, Goodpasture's syndrome and also, can cause flushing and headaches (Borrero et al, 2012) . As of yet, it has not been approved by the FDA as it is still undergoing trials but it is used as a medication for treating a form of blood cancer called B-cell chronic lymphocytic leukaemia (B-CLL) (FDA 2016).

References

https://www. researchgate. net/profile/Anne_Wierinckx/publication/7750124_Detoxication_enzyme_inducers_modify_cytokine_production_in_rat_mixed_glial_cells/links/0c960534be656953a2000000/Detoxication-enzyme-inducers-modify-cytokine-production-in-rat-mixed-glial-cells. pdf

https://www. ncbi. nlm. nih. gov/pmc/articles/PMC2724664/

http://journals. sagepub. com/doi/pdf/10. 1177/1756285612450936

https://www. fda. gov/Drugs/DrugSafety/ucm082681. htm

http://www. ajmc. com/journals/supplement/2016/cost-effectiveness-multiple-sclerosis/cost-effectiveness-multiple-sclerosis-current-emerging-treatment/P-3

https://www. mssociety. org. uk/what-is-ms/treatments-and-therapies/licensed-disease-modifying-drugs/Tecfidera