Multiple sclerosis: therapeutic options effectiveness

Effectiveness and Controversies of Disease Modifying Treatments (DMTs)

Pharmacists consider Type I Interferons (IFNs) a safe long-term treatment option for RRMS and they have widely used IFNs in the past two decades. The activity of Interferon-Beta (IFNB) is similar to that of the interferon produced by the body. Studies indicate that they have the ability to reduce the rate of relapse compared to placebos. However, based on comparisons of historical data, scientists also report that the β-Interferons contribute significantly to the progression of multiple sclerosis (Buzzard, Broadley, & Butzkueven, 2012). Incomplete recovery from MS episodes can lead to permanent disability, especially during the relapsing remitting stage of MS.

Two types of interferon-beta occur and include Interferon beta-1a and non-glycosylated interferon beta-1b. Initially, medics used the type-1 Interferons for the treatment of the MS because of their antiviral nature. This was because of the tendency of viral infections to prompt the relapse of the disease (Compston & Coles, 2002). One of the arguments toward the mechanism of the type 1 interferon revolves around the down regulation of the expression of the MCH class II antigens. However, researchers believe that other complex mechanisms are associated with the activity of the type-1 interferon. The side effects associated with the administration of the β-Interferons are dependent the frequency, route, and dose of administration. Acyclovir can nullify the side effects before the treatment with the β-Interferons (Buzzard, Broadley, & Butzkueven, 2012).

Another DMT approved for the treatment of RRMS is Glatiramer Acetate (GA). Initial experiments showed it suppressed MS in animals. Several clinical trials

indicated that GA reduced the rate of relapse of the MS compared to the placebo and this led to its approval in 1996. Medics administer the polymer through a subcutaneous injection. Reports show that the route of administration reduces the number of parameters of the disease shown during MRI (Buzzard, Broadley, & Butzkueven, 2012). Additionally, recent studies have reported a balance in the treatment of both GA and Interferon Beta. Since experiments show that GA lacks long-term side effects, significant in the progression of the MS, its use in the routine treatment of MS has been ongoing for over 15 years. Experiments show that the immunomodulatory activity of the GA improves the cells of the inborn and adaptive resistant system.

In 2004, the FDA approved the use of Natalizumab for the treatment of RRMS. Natalizumab is a monoclonal antibody that directs its activity towards the α-4 subunit of the integrin α-4 beta 1 and the lymphocyte receptors of the α-4 beta 7 lymphocytes (Buzzard, Broadley, & Butzkueven, 2012). The drug blocks the interaction between the VCAM-1 ligand and the VLA-4 receptor by binding to the α-4 integrin on lymphocytes. Prior to its approval, different clinical studies demonstrated remarkable activity on the relapse of MS. Of all the approved treatment, the FDA reports Natalizumab to be the most efficacious, though it has some side effects. Buzzard, Broadley, and Butzkueven, (2012) report that Progressive Multifocal Leukoencephalopathy (PML) occurs in over 200 patients treated with Natalizumab some of which have been fatal.

Fingolimod is a drug administered orally. In 2004, the FDA approved it for the treatment of MS. The drug is a lysophospholipid original used in organ

transplantation. Initially, medics used Fingolimod in combination with cyclosporine, but the drug was not efficacious in the prevention of organ rejection after renal transplant (Buzzard, Broadley, & Butzkueven, 2012). Despite this setback, clinical trials conducted later demonstrated that it reduced the progression of MS. Since the route of administering the drug is oral, it has an advantage over all the agents administered through an injection. The activity of the Fingolimod occurs through the interaction with G-protein-coupled sphingosine-1-phosphate receptors. However, no study has been done to prove the immunomodulation activity of the drug.

Alemtuzumab is another monoclonal antibody whose activity gears toward CD52, found on the surface of natural killer cells, and B and T lymphocytes (Azzopardi & Coles, 2011). The CD52 also exists in some dendritic cells and monocytes. In addition, the Alemtuzumab is involved in the lysis of cells that express the CD52. One of the clinical trials that researched on the activity of the agent on MS patients was the CARE-MS 1 study and the researchers compared the activity to µg beta-IFN. The scientists reported a reduction in the occurrence of RRMS at the rate of 54% (Cross & Naismith, 2013). The CARE-MS II study compared the agent with beta-IFN 1a in relapsed patients and reported a reduction in the rate or relapse (49%). However, the drug was reported to have adverse side effects in the two different clinical trials. The side effects reported ranged from mildly to moderately severe and the most common was the development of secondary autoimmune diseases. Additionally, scientists reported cases of thyroid carcinoma in the CARE-MS 1 trial.

As the result of the increased interest in the use of oral therapy, in an effort to improve the compliance of the MS patients, medics are using a number of emerging agents as DMTs (Buzzard, Broadley, & Butzkueven, 2012). Fumaric acid is one of the emerging agents. It is administered as Dimethyl Fumarate, which is a product of the citric cycle. Medics have used Dimethyl Fumarate for many decades in the treatment of Psoriasis, especially in Germany. Studies have suggested that the agent is effective against pro inflammatory mediators, such as adhesion factors, cytokines, and chemokine in MS. Its activity is directed toward reducing NF-Kb activity and thus reducing the expressions of molecules that cause inflammation. The progression of the MS is associated with damage to cells in the central nervous system and researchers report that Fumaric acid esters offers protection against damage to these cells. Several clinical trials have used BG-12, which is a derivative of the Fumaric acid as it contains DMF. Researchers report a reduction in the rate of relapse. Lastly, medics have used other emerging agents as DMTs for MS that include Teriflunomide, Laquinimod, Alemtuzamab, Daclizumab, and B-Cell therapies.

Effectiveness and Controversies of Symptomatic Treatments

A collective symptom reported in patients with MS is fatigue. According to Kaminska, Kimoff, Schwartzman, and Trojan (2013), there has been an inconsistent finding in the correlation between fatigue and the extent of disability. The Expanded Disability Status Scale (EDSS) measures the physical fatigue attributed to physical impairment. Depression and pain in the MS patient is also considered an indicator of the level of fatigue in the patients. The treatment used for the management of the fatigue is non-

pharmacologically based CBT therapy. In addition, medics have used drugs, such as amantadine, modafinil, and pemoline in the management of the fatigue. However, the presence of undiagnosed sleep disturbance disorders is one of the confounding factors reported in testing the efficacy of these drugs. Other non-pharmacological treatments involve energy-conservation techniques and exercise, such as pacing and spacing activities (Ben-Zacharia, 2011). In cases where medics use pharmacological interventions in fatigued MS patients, the tolerance levels and effectiveness should determine the doses.

Although walking impairment occurs gradually in patients with MS, it may be characterized with a gradual onset in some patients (Ben-Zacharia, 2011). This affects the patients balance and gait and could have emotional effect on the patients. Medics administer Dalfampridine (Ampyra) to patients with walking impairments but it is contraindicative in patients with history of renal diseases and seizures. Its activity acts toward the repair of damaged nerves as it acts as a blocker for the potassium channel and medics administer it orally. The recommended dosage for the drug is one tablet (10 mg) taken two times in day. Moreover, in two randomized controlled trials, the conclusions made by the researchers were that the dosage of 10 mg taken twice a day improved the walking speed of MS patients. However, the drug has side effects that include dizziness, nausea and nervousness (Patti, et al., 2009).

The occurrence of tremors and ataxia occurs in patients with MS and the treatment is challenging. Medics manage Ataxia through rehabilitation or pharmacology through the administration of Levetiracetam, Clonazepam,

Topiramate, Propranolol, and Clonazepam. Researchers report the medications to have modest effects on the Ataxia. In addition, surgical interventions that involve deep brain stimulation have been reported to be effective in some patients (Ben-Zacharia, 2011). Spasticity occurs in patients with MS and it is dependent on the increase in velocity of the muscle tissues, because of increase in tone and rigidity of the motor pathway. The symptom occurs in about 75 % of the MS patients and medics can manage it through conservative techniques or drugs; either injected into the patient or administered orally (Pappalardo, Castiglione, Restivo, Calabrese, Cimino, & Patti, 2006). The conservative methods involve bracing, casting, and stretching exercises (Mori, et al., 2011). Baclofen and tizanidine are the most common form of first line treatment for spasticity but are associated with side effects, such as weakness and sedation (Rizzo, Hadjimichael, Preiningerova, & Vollmer, 2004). The second and third line treatments used for spasticity include dantrolene, gabapentin, and benzodiazepines.

Another common system in MS is pain and it is usually because of the loss of inhibitory pathways in the spine. Demyelination or axonal loss cause acute pain in the MS patients while bladder spasms and vertebral compression cause sub-acute pain. The drugs used for the management of pain include gabapentin, pregabalin, antiepileptics and carbamazepine and they are first line treatment forms for neuropathic pains (Ben-Zacharia, 2011). Cannabinoids are also efficient in pain management and medics use them to manage spinal injury and spasticity (Pertwee, 2002). Clinical depression affects about 50% of MS patients and the available treatments regimes

include serotonin, norepinephrine, and dopamine reuptake inhibitors, which are all anti-depressants (Ben-Zacharia, 2011).

Pseudo Bulbar Affect (PBA) is a neurologic disorder that presents with symptoms such as laughing and crying and researchers report it in about 10% of the patients. The management of PBA involves the administration of quinidine sulfate, and dextromethorphan hydrobromide (Ben-Zacharia, 2011). Cognitive dysfunction occurs in 50% of MS patients and it affects the speed at which the patient processes information, losses memory and vision, reduces verbal fluent, and reduces the attention span (Patti, et al., 2009). Researchers have tested Acetylcholinesterase in MS patients with promising results. However, a recent clinical trial disputed the efficacy of the drug. The FDA has approved other drugs, such as memantine and rivastigmine for use on Alzheimer’s patients but not MS. The conservative management of this dysfunction involves use of methods that retrain and improve on the memory and visual ability of the patients.

Conclusion

Current Research Strength

For over two decades, researchers have conducted research on MS and the available treatments. However, even with all the research the currently available treatments have been unable to reduce the occurrence of symptoms in all the patients. The immunopathogenic factors in different patients determine their responses to the different treatments. Research conducted on the current forms of treatment shows that immunopathogenic factors have varying and unexpected results in different patients.

Researchers have also been unable to determine the exact mechanisms that affect the disease process of MS. Additionally, several studies done regarding the disease reported disparities between clinical trials and animal models. Researchers agree that no single intervention is effective for halting the disease or reversing the effects of axonal degeneration and demyelination. This is an indicator that more research about MS is still in need to establish the mechanisms associated with the progression.

Future Perspective

Although there has been progress in research on the pathological, clinical and treatment of MS, some aspects remain unsolved. Researchers have based current research on the effort to repair the damage caused by the MS. Future researchers should aim at determining the treatments intended at healing the disease or reversing the disability attributed to MS.

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