

Monoclonal Antibodies in the Treatment of Multiple Sclerosis

Nivaasini Sivarajah

Saveetha Dental College and Hospitals, Vellapan Chavadi

Abstract: Multiple Sclerosis is a chronic inflammatory disease of the central nervous system, which causes demyelination and variable axon loss in the brain stem or spinal cord. Multiple Sclerosis is one of the most common causes of non-traumatic disability in young adults and women (2). 30% of these patients with clinically isolated syndrome will have progression to clinically definite multiple sclerosis within 12 months after presentation (3). The course of disease in multiple sclerosis is hard to predict ranging from benign course to classic relapsing-remitting, chronic progressive, rare fulminant course, relapsing-remitting with progression into a secondary progressive form after varying period of time or primary progressive right from the start(2). A combination of environmental and genetic factors which lead to autoimmune reaction against CNS structure which in turn results in CNS tissue damage and neurological impairment. (2). Depending on the localization and characteristics of the morphological changes in both white and grey brain matter, different symptoms and signs may occur(2). Relapsing phases of ms are usually heralded by focal burst of inflammation in the white matter of the spinal cord and brain, while in the progressive phase there is a slow relentless axonal and neuronal loss. The focal burst of inflammation not only results in demyelination but also incomplete remyelination. (4). Main course of reduces mobility in multiple sclerosis is lack of physical activity, the progression of the disease which leads to a secondary sequel (2). Drugs and interferon's are strikingly effective (4). The autoimmune etiopathology, immune modulator drugs are treatment of choice, if this drugs are not effective monoclonal antibodies (2). They are two routes that the monoclonal antibody treatment can be given which is through IV infusion or through Oral route (1).

Keywords: alemtizumab, daclizumab, orcelizumab, ofatumumab, natalizumab

1. Monoclonal Antibodies

Monoclonal antibodies are now the emerging treatment used in relapsing multiple sclerosis. Monoclonal antibodies such as alemtizumab, daclizumab, orcelizumab, ofatumumab, natalizumab are used for the treatment of multiple sclerosis. The two most common antibodies used in the treatment are Alemtizumab and Natalizumab.

Alemtizumab

Humanized monoclonal antibody which targets CD52 an epitope which is expressed on T and B lymphocytes(1). This antibody was initially developed for the treatment of lymphoid malignancies but trial have proven that it has a potent role in treatment of multiple sclerosis(6). The treatment of multiple sclerosis with alemtizumab results in rapid depletion of CD52 which has antibody dependent cellular toxicity(1). Following the treatment the cell population staggered with return to the baseline for monocyte and B cell at 3 months(6). The most common adverse effects of alemtizumab include early infusion related effects such as fever, headache, rash nausea and vomiting, this side effects may be managed by administration of glucocorticoids or acetaminophen prior to the infusion of alemtizumab(1). The most common side effects encountered after the infusion of Alemtizumab are auto immune disease, thyroid disease Good pasture's disease(6).

Natalizumab

Humanized IgG4 monoclonal antibody (mAb) against the alpha 4 integrin(5). Natalizumab is a monoclonal antibody which antagonizes the alpha4beta1 integrin expressed on the surface of activated lymphocytes(1). It is the first licensed mAb for the treatment of relapsing-remitting

multiple sclerosis. The drug was developed by Georges Kohler and Cesar Milstein in the year 1975 and it was granted a noble prize in the year 1984(5). Natalizumab has a selective adhesion molecule subunit which prevents the leukocyte from adhering and migrating across the blood brain barrier (bbb) yielding in its therapeutic effect(1). Natalizumab is a fused antibody which produces a B cell line with an immortalised myeloma cell line and generates an immortalised cell line that produces a specific antibody derived from one clone(5).

Mode of Action of Natalizumab (5)

- Binds to alpha 4 subunit and alpha4beta1 integrin which is known as a crucial transmigration of immune cell response across the BBB.
- VLA-4 is expressed primarily on T cells and monocyte
- VLA-4 inhibits interaction with VCAM-1 and prevents infiltration of T cell into the CNS
- Inhibition of leukocyte migration and extravasations the main mode of action although there is an additional mode that might modulate the therapeutic and the adverse effect.

The side effects of natalizumab are headache and fatigue after the mAb has been infused. Allergic reaction occurs in about 4% of the patient treated with this mAb. Most allergic reaction occurs after the second infusion – headache, hot flush and hypotonia. The presence of all this allergic reaction occurs due to the presence of anti-natalizumab antibody(5). Severe side effects of this mAb are relapse of multiple sclerosis and hypersensitivity reaction(1).

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Daclizumab

Humanized monoclonal antibody against the alpha subunit of the IL-2 receptor on T and B cells and natural killer cells. Interleukin -2 plays a very important role in the activation and proliferation of T cell. Daclizumab has been demonstrated to increase the quantity of CD56 which is a natural killer cell. (1) Adverse effects of daclizumab are urinary tract and respiratory tract infection, liver abnormalities and altered sensation (7).

Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody which targets the CD20 receptor and suppresses the B cell. It has been shown to enhance the antibody dependent cell mediated cytotoxicity which leads to reduction in complement dependent cytotoxicity which is similar to Rituximab. This mAb is given through IV infusion (1). A side effect of this mAb is that it causes systemic inflammatory response syndrome (5).

Ofatumumab

Type 1 humanized monoclonal antibody which acts against a novel epitope of CD 20 on B lymphocytes. To mediate a B cell lysis by complement-dependent cytotoxicity and antibody-dependent cell mediated cytotoxicity. It targets a CD20 epitope which is distinct from the targeted rituximab (1).

2. Conclusion

Despite all the research done for this disease, there is still no cure. The treatments currently available are oral agents, monoclonal antibodies and hormonal therapies. These treatments are currently and continuously being evaluated in clinical trials (6). Selection of an appropriate disease modifying therapy will become increasingly more complex as more therapies become available. The risk to benefit ratio should be considered in each individual (1). Neurologist will need to carefully match each individual's disease profile with an appropriate therapy while weighing the risk and the benefit of the therapy to the individual (1). The development of biomarkers to help prognosticate a given individual's likely disease severity and help predict the treatment (5). mAb's has proved to be a potent treatment option for Multiple Sclerosis. They target very specific molecules derails the autoimmune process by influencing a specific target cell or receptor. They have ability to reduce inflammation and mAb's have potential disadvantages which should be taken into consideration (7)

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