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REVIEW ON MONOCLONAL ANTIBODIES TREATMENT FOR MULTIPLE SCLEROSIS

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ABSTRACT

Monoclonal antibodies (MABs) are attractive immunological tools with applications in the fields of immunology, biotechnology, biochemistry and applied biology. Production of MABs using hybridoma technology was discovered in 1975 by George Kohler of West Germany and Cesar Milstein of Argentina. Recently MABs have been widely applied in the fields of clinical medicine. Currently MABs account for one-third of all the new therapy treatments for breast cancer, leukemia, arthritis, transplant rejection and asthma with many more late-stage clinical trials been conducted. Mab therapies for relapsing and remitting multiple sclerosis target the immune cells are other molecules involved in pathogenic pathway with many extraordinary specificity. Some antibodies had been demonstrated significant reduction in clinical and magnetic resonance imaging disease activity and stability in clinical studies. These monoclonal antibodies have distinct structural characteristics and unique targets conferring different mechanism of action in multiple sclerosis. Because of structural difference monoclonal antibodies for multiple sclerosis do not constitute a single treatment class, each must be considered individually when selecting appropriate therapy. Multiple sclerosis is a potentially disabling chronic autoimmune neurological disease that mainly affects young adults. So far there is no drug available that can completely halt all the neuro degenerative changes associated with the disease. In this review, we outline the production, application, antibody engineering, mechanism of action, indication, side effects, safety and pharmaceutical application of various monoclonal antibodies used in the treatment for multiple sclerosis as a molecule for understanding and monitoring the biology of disease and its role in research, clinical, diagnostic and pharmaceutical applications.

KEYWORDS: Monoclonal Antibodies, Multiple Sclerosis, Autoimmunity, Therapy, Remitting, Clinical research.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease which affects the central nervous system (CNS) that includes the brain, spinal cord of the human body. MS is a predominantly white matter disease and a neurodegenerative disorder. The inflammation is caused when the body's own immune cells attack the nervous system while the demyelination takes place when the myelin (protective covering of the nervous) is destroyed leaving multiple area of scar tissue or sclerosis which causes progressive diseases. The earliest description of MS was recorded in Holland on august 4, 1421 but the history of the disease really begins in the 19 the century with the first clear illustration and clinical description of the disease beginning to appear in 1838. They are 4 types of MS.

1) Relapsing-remitting MS(RR-MS)
2) Primary-progressive MS (PP-MS)
3) Progressive-relapsing MS(PR-MS)
4) Secondary-progressive MS (SP-MS).

RRMS -the most common disease is characterized by clearly defined attack of new or increasing neurological symptoms. These attacks- also called relapses or exacerbation-are followed by period of partial or complete recovery. During reemission, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no apparent progression of the disease during the periods of remission.

According to their way of generation, Mab's can be classified by as

- Momab: mouse monoclonal antibody
- Ximab: chimeric monoclonal antibody
- Zumab: humanized monoclonal antibody
- Humab: completely humanized monoclonal antibody.

In young adults MS is a most common disease, which causes neurological disability. The known prevalence of MS is increasing, which is most likely due to greater awareness and improved imaging techniques. In clinical presentation MS is extremely variable and it is largely unpredictable. [1]

Regarding pathogenesis of MS, both genetic and environmental factors are thought to play a role. Several causative factors appear to affect risk of developing MS, such as previous viral infections; distance from the equator prior to age 15 (ie, above the 37th parallel); family history (primarily first-degree relatives); cigarette smoking; and decreased sunlight exposure/vitamin D levels. Multiple studies of sunlight exposure and vitamin D levels suggest that increased vitamin D consumption in early life may decrease likelihood of MS.

Although the disease can affect any ethnic group, individuals of Northern European descent are more likely to be affected than other ethnicities.MS typically presents in adults 20 to 45 years of age, but occasionally it presents in childhood or in later middle age. Women are more frequently diagnosed with MS compared with men by at least a 2:1 ratio and as high as 3:1.

MS is characterized by destruction of the myelin on neurons (demyelination) and subsequent damage to the underlying axon. The demyelinating plaque, the main pathologic hallmark of MS, contains a prominent immunologic response dominated by CD8+ and CD4+ T cells. When activated, these T cells (primarily TH1 cells) cross the blood–brain barrier into the CNS and attack the myelin sheath on the axons. The resulting inflammation deteriorates the myelin, which slows or interrupts the conduction of nerve impulses along the axons.

Demyelination leads to axonal damage, which can affect both white and gray matter. The Recent data have highlighted that the involvement of gray matter, which is relevant to the irreversible disability that occurs in MS. Over time, demyelination can leave the underlying axon exposed and susceptible to damage Axon loss is believed to be the major cause of permanent disability in patients with MS. B cells and their products were also contribute to the pathogenesis of MS. B cells produce proinflammatory and anti-inflammatory cytokines, where proinflammatory cytokines activate T cells for T cell mediated demyelination.

Diagnosing Multiple Sclerosis

MS is a diagnosis of exclusion. The diagnosis is based on clinical expertise and involves obtaining evidence from a clinical examination, medical history, laboratory tests, and magnetic resonance imaging (MRI) scans of the brain and spinal cord. These tests are intended to gather data consistent with MS, while ruling out other possible causes not consistent with the disease.

Despite the lack of a diagnostic test for MS, MRI scans is essential for investigation the suspected disease. MRI scans show high sensitivity .The detection of focal white matter lesions in the CNS and particularly for the lesions disseminated in time and space. Dissemination in space is fulfilled by the presence of 1 or more lesions in 2 of 4 characteristic anatomic locations, while dissemination in time is demonstrated by simultaneous presence of gadolinium (Gd) .Gray matter lesions are associated with cognitive impairment and are present in the brains of patients with MS. MRI sensitivity is much lower in detecting gray matter lesions when compared to white matter lesions. There is currently a lack of standardized image acquisition and analysis for gray matter.

For diagnosing MS the Mc Donald criteria is mostly used. The goal of the McDonald criteria is to diagnose MS by allowing MRI-detected brain lesions, cerebrospinal fluid abnormalities, and visual-evoked potentials (VEPs) to replace the clinical lesions by defining "separated by time and space." The original criteria were released in 2001, updated in 2005and 2010, and revisions to the McDonald criteria in 2017 have further simplified the diagnosis of MS.

The immune system in vertebrates is continuously evolving to protect itself from different intruding pathogens. The immune responses rotate around some innate mechanisms, including adaptive processes such as producing antibody (Ab) molecules that can bind to all molecular structures of the microbial pathogen (bacteria, viruses, fungi, nematodes, and other parasites) and can keep pace with the diversified mutations in an organism. An antigen is defined as a molecule or part of a molecule that can be recognized by the immune system as a foreign entity. The challenge of the immune system is thus combated in two ways. First, the B lymphocytes produce varied antibodies specific for a new antigen (epitope) expressed by a pathogen by shuffling and reshuffling its genetic constituents. Second, paratope-encoding genes of the antibody are mutated rapidly to cope and bind strongly with the epitope of the antigen. Thus, these generated antibodies are better at binding with the antigen with greater affinity and high specificity.

The Polyclonal antibodies mixtures contain different antibodies developed in the blood of immunized animals from different cell types. As most antigens bear multiple epitopes, they can stimulate the proliferation and differentiation of a variety of B-cell clones.Specificity for particular epitope(s) of the antigen are also produced with heterogeneous pool of serum antibodies.

In contrast, monoclonal antibodies (MAb(s)) are a mixture of homogenous antibody molecules with affinity towards a specific antigen, often generated using a hybridoma by fusing a B-cell with a single lineage of the cells containing an definite antibody. Finally, a population of identical cells (or clones) is produced that

secrete the same antibody. Due to their specificity and high reproducibility using culture techniques, MABs offer advantage over polyclonal antibodies. MABs are increasingly used in applications such as research and diagnosis, therapeutic tools in cancer and immunological disorders, and pharmacy, thus generating a great demand in industry. The essential characteristics that confer the clinical applicability of MABs include their specificity of binding and homogeneity, as well as their ability to be produced in unlimited quantities. This also enables to screen an antibody of choice from a mixture of antibody population with a purified antigen; thus, a single cell clone can be isolated. For these reasons, the objective of this review was to dissect the diverse facets of applicability of MABs in disease monitoring and diagnosis.

Natalizumab

Natalizumab (NTZ), targeting the α-4 integrin receptor, is an efficacious treatment for relapsing-remitting multiple sclerosis (RRMS)[2]

1) In a phase-I trial, NTZ stayed detectable in the serum for 3−8weeks after infusion with dosing of 1−3mg/kg.
2) Based on the different therapeutic dosages of 3−6mg/kg in phase-II, a fixed dose of 3 mg once in 4weeks was chosen for phase-III trials so the majority of patients (with weights ranging between 50 and 100 kg) would fall between a dose of 3 and 6mg/kg.
3) Nowadays, a dose of 300mg every 4weeks has been approved by the European Medicines Agency (EMA)/Food and Drug Administration (FDA) for the treatment of RRMS. In this treatment regimen, NTZ concentrations may stay detectable in serum up to 200 days after cessation of therapy.
4) Serum NTZ concentration corresponds with the percentage of α-4 integrin receptor saturation.5Desaturation of the α-4 integrin receptor occurs when the serum NTZ concentration falls under 1−2μg/mL.
5) Above this threshold of 2μg/mL, NTZ receptor saturation will roughly fall between 70% and 100%.5An adequate receptor saturation is

Estimated as ⩾70%−80% saturation, although prospective data confirming this assumption are lacking.[3] Based on a model with results from a large phase-II trial, approximately 90% of patients showed NTZ trough concentrations largely exceeding 2.5μg/mL. Levels exceeding 2.5μg/mL could indicate that the approved treatment regimen of NTZ for RRMS results in a relative over-treatment, that is, the patient receives more NTZ than necessary for optimal drug efficacy.[4]

Furthermore, it is suggested that higher NTZ receptor saturation could increase the risk of progressive multifocal leukoencephalopathy (PML), the feared complication of NTZ treatment. This unconfirmed hypothesis leads to clinicians extending dose intervals in NTZ treatment with the aim of reducing the PML risk by decreasing NTZ exposure.[5]

Daclizumab

Daclizumab (DAC), a humanized monoclonal antibody targeting the α subunit (CD25) of the high-affinity IL-2R expressed on activated T cells, has multiple effects on MS pathology.[6,7] This review summarizes the development of and clinical experience with DAC high yield process (DAC HYP) as a new treatment option for MS. History of daclizumab development. Investigations of DAC in MS continued to be carried out by an intramural National Institutes of Health (NIH) team which also discovered its novel mechanism of action (MOA). The CHOICE study (Study of Subcutaneous DAC in Patients with Active Relapsing Forms of MS; a phase II[8,] randomized, double-blind, placebo-controlled, add-on trial with interferon β, sponsored by PDL BioPharma, Incline Village, NV, USA) used a subcutaneous formulation of DAC produced in penzberg.[9] The final formulation of the humanized monoclonal antibody against CD25 called DAC HYP was developed jointly by Biogen Idec (Cambridge, MA, USA) and Abbott Bio therapeutics Corporation (Redwood City, CA, USA).[8,10] It shares an identical amino acid sequence with the original Zenapax preparation, but a different production process resulted in a different glycosylation pattern of the molecule, which affects the binding of DAC to Fc receptors and decreases antibody-dependent cellular toxicity. DAC HYP and former Zenapax also differ in pharmacokinetics.

Ocrilzumab

The CD20 molecule is a transmembrane protein with an incompletely understood function. It is expressed on most cells of the human B-cell lineage but not on stem cells, pro-B cells or differentiated plasma cells. A small subset of T cells also express CD20.[27,28]

Ocrelizumab is an anti-CD20 antibody which depletes the circulating immature and mature B cells but spares the CD20-negative plasma cells. The effector mechanisms of anti-CD20 antibodies are complement-dependent cytotoxicity and antibody-dependent6 cellular cytotoxicity. Ocrelizumab completely decreased the CD19+ B-cells count (CD19+ cells represent a measure of B-cell counts in anti-CD20-treated patients) in the blood after 2 weeks of treatment in two phase, III studies of patients with RRMS.[29] The median time to B-cell replenishment was 72 weeks after the last ocrelizumab infusion in a phase II study of patients with RRMS.[30]

Ocrelizumab is associated with increased antibody-dependent, cell-mediated cytotoxic effects and reduced complement-dependent cytotoxic effects *in vitro*, when compared to rituximab. After several phase II clinical trials.[31,32] reported encouraging results for the efficacy of the anti-CD20 antibody rituximab in patients

with MS, trials testing ocrelizumab as a treatment for RRMS were launched.

Phase II

Ocrelizumab was first tested in patients with MS in a phase II trial.[33] This placebo-controlled trial was designed to assess the efficacy and safety of two dose regimens of ocrelizumab (500mg and 1700 mg) in patients with RRMS. The primary objective was to investigate the effect of ocrelizumab compared with placebo on the total number of gadolinium-enhanced T1 lesions observed on brain magnetic resonance imaging (MRI) scans at weeks 12, 16, 20 and 24.

A total of 230 patients completed this 26-week study, and highly significant differences in the total number of gadolinium-enhanced T1 lesions were observed in both ocrelizumab groups ($p < 0.0001$) at weeks 11, 15, 21 and 25 when compared with the placebo group. Overall, the relative reductions were 89% in the 600 mg ocrelizumab group and 96% in the 2000 mg group compared with those in the placebo group. As a secondary objective, annualized relapse rates over 26 weeks were reduced by 75% in the 600 mg ocrelizumab group and 76% in the 2000 mg group compared with the placebo group.

Rituximab

A little more than a decade ago the mouse-human chimeric monoclonal antibody to CD20, rituximab, was approved by the US Food and Drug Administration (FDA) for the treatment of some forms of lymphoma. Rituximab targets cells are express in the surface CD20, which were found on pre-B and mature B cells. Rituximab, a complement binding IgG1 κ monoclonal antibody, which lyses circulating B cells while the restricting of the stem cells and mature plasma cells. Initially approved for therapy of non-Hodgkin's lymphoma in the USA in 1997, its FDA approval has expanded to encompass chronic lymphocytic leukemia and, in 2006, rheumatoid arthritis. Most recently, in 2011 it was approved for Wegener's granulomatosis and microscopic polyangiitis, two rare types of vasculitis.[11] The advent and availability of rituximab allowed for the first time the ability to determine the effects of B-cell depletion on the course of MS. The results have been beneficial in relapsing MS.

A phase II, double-blind clinical trial in 104 patients with RRMS randomized to receive a single course of rituximab or placebo showed that patients who received rituximab had reduced inflammatory brain lesions as evaluated by gadolinium-enhanced magnetic resonance imaging (MRI), and a lower number of clinical relapses that was sustained for 48 weeks after treatment.[11,12] Another smaller open-label phase I study was performed in patients with RRMS. This was a 72-week clinical trial to evaluate as primary outcome the safety of two courses of rituximab (administered at week 0 and week 24). No serious adverse events were observed. The majority of adverse events were infusion-associated events known to be due to cytokine release during B-cell lysis.[13]

In this cohort of RRMS, B-cell depletion was accompanied by a sustained reduction of relapses and magnetic resonance activity throughout the 72-week study duration_Rituximab has also been tried as a single agent in PPMS .In a 96-week multicenter trial, 439 patients swith PPMS received two 1000 mg infusions of rituximab or placebo every 24 weeks for four courses. The primary endpoint was time to confirmed disability progression based on sustained 12-week increase in the Expanded Disability Status Scale (EDSS) score.[14] That is, a diminished increase in T2 lesion volume was observed with rituximab therapy. Of note, pre-planned subgroup analyses showed that time to confirm disability was significantly delayed by rituximab in patients under 51 years old and in those with gadolinium-enhanced (GDE) lesions, with the greatest effect in those who were aged under 51 years and had GDE lesions.[15] The duration of shorter diseases has a better improvement. This study had two important conclusions: first the study indicated a critical role for B cells in the disability progression of at least a subset of patients with PPMS; second that PPMS may be more heterogeneous and with greater inflammation (as evinced by GDE lesions) than previously realized.

Alemtuzumab

Alemtuzumab is a MAb directed against the antigen expressed on the cell surface of both T and B lymphocytes monocytes, macrophages, and eosinophil, but not stem cells. Alemtuzumab is a humanized derivative of the rat MAb Campath-1, named after the Cambridge University Department of Pathology.[19] Like rituximab, alemtuzumab depletes target antigen carrying cells through complement-mediated lysis, antibody-dependent cell toxicity, and induction of apoptosis, although the exact mechanisms of action in humans have not yet been clarified. At present, alemtuzumab is FDA approved for the treatment of refractory chronic lymphocytic leukemia, it may also have a role in T-prolymphocytic leukemia, mycosis fungoid, and Sezary syndrome.[20] In a preliminary study in MS patients, treatment with alemtuzumab resulted in profound lymphopenia and led to reduction of disease activity in MRI scans. This observation nourished the hope that during subsequent reconstitution of the T-cell repertoire, autoreactive T-cell clones may be excluded. In an open label study, alemtuzumab was then tested in 25 patients with secondary progressive MS.

After a single dose of alemtuzumab, patients were followed for 18 months with serial MRI scans. Although there was a significant decline in the number and volume of contrast-enhancing lesions over 18 months.[21] most patients suffered from disease progression and an increase in brain atrophy despite the suppression of inflammatory activity. Alemtuzumab was then investigated in a second open-label study, mostly with

treatment naive patients.[22] The relapsing remitting MS patients in this cohort were characterized by a very active disease (annualized relapse rate of 2.2) and a relatively high EDSS score. After treatment with alemtuzumab, the relapse rate decreased by 94% from 2.2 relapses to 0.14 relapses per year during the two years of follow up. In parallel, the mean EDSS score decreased from 4.8 to 2.1. The striking discrepancy between the relapsing-remitting and progressive MS patient cohorts also provided clues for the pathophysiology of the disease implying that in chronic MS courses, ongoing disease progression is rather not caused by active inflammation, but mediated by a neurodegenerative process independent of active inflammation.[23]

Thus chronic progressive MS patients may rather benefit from protective strategies than anti-inflammatory medications alone. In view of these preliminary results, a phase II, randomized, open-label, randomized study was initiated. In three arms including 334 patients, this study designed for an observational period of three years compared high and low-dose alemtuzu mab versus high-dose IFN-beta in patients with early, active relapsing-remitting MS. The primary outcome measure was defined as time to sustained accumulation of disability; secondary read-outs include relapse rate and MRI markers of disease activity. Preliminary results were reported at the American Academy of Neurology 2007.[24] In comparison to IFNbeta-1a, two treatment cycles of alemtuzumab with an annual interval led to a highly significant 75% reduction in relapse rate and a 60% reduction in sustained disability. These data including a more comprehensive safety analysis were also presented at the American Academy of Neurology 2008. Currently, two large multi-center phase III trial are initiated (CARE I/II trial, sponsor: Bayer Schering Pharma/Genzyme). Although alemtuzumab was generally well tolerated in the MS studies, some documented side effects exist. These include a possible infusion reaction characterized by fever, rigors, rash, nausea, and hypotension, which may be mediated by cytokine release during lymphocyte lysis, e.g., via TNF- and interleukin (IL)-6.[25] and may lead to transient worsening of MS symptoms. This infusion reaction can be prevented by pretreatment with glucocorticosteroids, diphenhydramine, and acetaminophen.

Moreover, the lymphocyte depletion puts alemtuzumab-treated individuals at risk for infections. In the initial MS studies, possibly treatment-related infections included cases of measles, spirochete, gingivitis, herpes zoster, varicella zoster recurrent oralaphthous ulcers, and pyogenic granuloma. Unexpectedly, in the secondary progressive MS cohort, alemtuzumab treatment resulted in Development of Grave's disease was associated with a faster reappearance of CD8 positive lymphocytes, which are implicated in the pathogenesis of autoimmune thyroiditis.[26] Interestingly, Grave's disease was not reported after alemtuzumab treatment in hematologic patients thus suggesting a special disposition for this condition in MS patients. In the subsequent phase II study, no further cases of Grave's disease were reported. However, alemtuzumab treatment resulted in six individuals in autoimmune idiopathic thrombocytopenic purput leading to fatal intracranial hemorrhage in one patient. Another patient suffered acute glomerulonephritis finally requiring kidney transplantation. In view of the occurrence of these autoimmune diseases, it seems conceivable that alemtuzumab-mediated lymphocyte depletion may result in disturbed regulatory circuits, e.g. via depletion of regulatory T-cells. Thus, future studies with alemtuzumab are of high interest given its outstanding efficacy, but also need special attention regarding unexpected (autoimmune) side effect.

LIMITATIONS

When compared with chemotherapy the MAB s have less side effects. A mild allergic reaction (rash) may be occurs with first administration of the drugs. Common side effects are fever, headache, weakness, chills, nausea with vomiting and diarrhea, and low blood pressure. Inhalational anthrax (potential biological terrorism) is caused by breathing the bacterial spores of bacillus anthracic.

The FDA-approved drug raxibacumab (MABs) injection is used to treat infectious inhalational anthrax when alternative therapies have failed.[16,17,18] More effective MAB drugs resulting from advancements in MAB engineering along with the development of cell biomarkers for characterizing the patient subpopulations may lead to more cost-effective use of treatment responding drugs. MABs therapies are financial burden on patients, and with some health plans and step-wise therapies the problems can be resolved.[16, 17]

MABs drug doses is needed for the treatment that is highly significant than other drugs. Thus, large scale production that is cost- effective in manufacturing processes are required. However the huge demand for production of these drugs and the drive to lower the cost of these expensive medicines is a continuous challenge to the present industry. This will further improve the efficiency of manufacturing process.

CONCLUSION

MS is a chronic disease of CNS that is characterized by progressive loss of function and it's influenced by genetics, epigenetics, and environmental factors. The immune system is central to its pathogenesis, with the disease probably initiated and perpetuated by its self are foreign antigens. Experiences with monoclonal antibodies has shown that early, effective treatment of MS has the potential to prevent or delay disability. Physicians and patients need to carefully weight of the benefits and the risk of monoclonal antibody therapy.

The devastating clinical and social consequents of this disease, however, should not be underestimated.

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