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Review Article

Therapeutic Applications of Monoclonal Antibodies in Multiple Sclerosis

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ABSTRACT

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Despite the various therapies available, the use of monoclonal antibodies is a highly specific approach that has only recently been of interest to researchers. The properties of antibodies have led to their use in the treatment of various diseases, including cancer, Alzheimer's disease, diabetes and multiple sclerosis (MS). MS, a chronic inflammatory disease, occurs commonly in young adults. The disease is one of the attractive options for monoclonal antibody therapy because it has no definitive drug for its treatment. Antibodies, by targeting different molecules, have different mechanisms to improve the disease. Treatment with monoclonal antibody has culminated in a clear divergence in paradigm and concentration in MS therapeutics. Application of monoclonal antibody in early inflammatory phases can inhibit or postpone the disability in MS subjects. Ocrelizumab and daclizumab are currently under investigation by late phase III trials, and some other monoclonal antibodies are in the early stages of clinical trials. Monoclonal antibodies are of special structural features (including chimeric, humanized, or fully humanized) as well as specific targets (such as stimulation of signal transduction by binding to receptors, blocking interactions, antibody-dependent cell cytotoxicity, complement-dependent cytotoxicity), thus providing various mechanisms of actions during MS therapy. In the present paper, we reviewed different monoclonal antibodies used in MS, their mechanism of action and theirs target molecules.

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Introduction

Multiple sclerosis (MS) is considered as an autoimmune, chronic and inflammatory condition that leads to degeneration of neurons and abnormal immune responses occurred in the central nervous system (CNS). The disease is regarded as the most common non-traumatic cause of CNS injury in young and adult subjects. The immune system has critical role in the pathogenesis of MS [1-4]. During most of the MS cases, the disease form is relapsing-remitting (RRMS) in initial disease course with periods of relapse, which is then followed by periods of remission [5]. Over the course of last decades, huge progress has been made in the therapy of MS. After several decades of treatment with disease-modifying treatments (DMTs), including interferon (IFN)-β and glatiramer acetate. Currently, effective therapies for MS are available. The first oral DMT was fingolimod, which was approved in 2010 in the United States. Afterwards, several other oral drugs have been approved or are in the process of phase III clinical trials [6]. To date, three monoclonal antibodies have been approved for treatment of MS and some other antibodies in the final state of developing. Despite a promising advancement in therapeutic approaches of MS, the current approaches could not meet the future needs because of the complicated etiopathogenesis of the disease. In this review, we have discussed the monoclonal antibodies developed for therapy of MS.

Etiology of MS

MS is a multifactorial disease the exact causes of which are unknown; scientists believe that MS is probably due to a change in the immune system or contact with environmental factors (infectious agents) or both. The immune system plays an important role in creating MS disease in which macrophages, killer T cells, lymphokines and antibodies attack their own myelin or oligo-dendritic antigens in case of penetration into the brain [7].

The MS susceptibility is associated with a very complicated interaction between environmental and genetic factors. The simultaneous effects of certain factors have been reportedly observed in the onset of MS. Among these, some previous studies have indicated that the branching of Asn (N)-linked glycans can be changed by the modulators of the MS risk such as a variety of genetic factors in interleukin-7 receptor-α (IL7RA*C), interleukin-2 receptor-α (IL2RA*T), MGAT1 (IVAVT-T) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) (Thr17Ala) environmental factors affecting vitamin D3 levels [8]. According to the studies on the animal model of MS, decreased branching can lead to the hyperactivity of T-cell, demyelination of spontaneous inflammatory and development of neurodegeneration [9].

The hypothesis of developing MS introduced by Putnam (1933), chronic cerebrospinal venous insufficiency (CCSVI), was confirmed and scrutinized by Zamboni et al. in the recent years. Based on this hypothesis, a vascular condition is defined as abnormalities of the leading extracranial cerebrospinal veins involved in normal cerebrospinal outflow that in turn results in retrograde blood flow, inducing

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lysis of erythrocytes, iron sludge stimulation, inflammation, and hence pathology of MS [10].

The shear stress in endothelial cells which is induced from blood flow stopped in narrow vessel leads to synthesis of NO and $O^{\cdot}$. Subsequently, CuZnSOD mediates the conversion of $O^{\cdot}$ to H_2O_2. Then, two redox loops, intersected in mitochondria, are activated in the astrocytes following the penetration of H_2O_2 and endothelial and circulating NO. The degeneration of oligodendrocyte in early lesions has been shown to happen due to the astrocyte dysfunction [11]. 4-Hydroxy-2-nonenal (HNE), NO and H_2O_2 leaked from activated macrophages and astrocytes influence other CNS cells, especially oligodendrocyte. The oligodendrocyte death has been reported following the overexpression of NO on iNOS in the syncytin (human endogenous retrovirus glycoprotein)-producing astrocytes [12]. The electron transfer chain is impeded by NO, thereby elevating H_2O_2 production, activating NF-κB and expressing iNOS and cyclo-oxygenase 2 [13]. The macrophage/microglia can also be activated by NO, and H_2O_2 and NO can in turn be released increasingly from these cells [14].

Mitochondrial dysfunction, inflammation-driven oxidative stress, and the presence of divalent metal ions (which catalyse the generation of highly toxic OH– radicals from H_2O_2) all result in generation of oxygen free radicals [15]. Free radicals interfere with de novo synthesis of respiratory chain components and can directly induce mitochondrial DNA damage [16]. The expression of enzymes involved in free radical production markedly increases in active MS lesions, most prominently in areas of initial tissue injury [17]. Oxidized DNA and lipids, as well as nitrotyrosine, a marker of peroxynitrite-induced tissue injury, are all abundantly present in active MS lesions [18].

A study found the nitrotyrosine accumulation in oligodendrocyte in a young patient suffering from early MS, which then contributed to $ONOO^{-}$ mediated damage [17]. The $ONOO^{-}$ is unable to induce the oligodendrocyte apoptosis; and necrosis has been reported as the active cause of the cell death [19]. It should be noted that the astrocytes show intermediate resistance to $ONOO^{-}$. The $ONOO^{-}$ may indirectly stimulate the key pathophysiological consequences of high level of NO. DNA single-strand is cleaved by peroxynitrite that then activates poly (ADP-ribose) polymerase (PARP) [13].

The apoptosis-inducing factor is released due to the damaged mitochondria in oligodendrocytes, followed by translocation into the nucleus to activate PARP that is an in vivo mechanism proven in the cuprizone intoxication-induced model of oligo dendrocyte destruction and demyelination [20]. Age in human leads to the accumulation of iron in the brain, mostly in oligodendrocytes. It is detoxified through binding to ferritin and increases during young adulthood with a plateau of 40 to 50 years of age which shows elevated cerebral iron loading [21]. Fe^{2+} accumulation in the extracellular space can occur because of oligodendrocyte destruction, hence possibly amplifying oxidative damage in axons and other cells. The

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activated macrophages and microglia take up Fe^{2+} in MS lesions [22].

The myelin fragments and vesicles have been shown to accumulate at the site of an early lesion through non-apoptotic and so incomplete controlled oligodendrocyte death occurrs simultaneously along with macrophages and microglia's decreased capability of removing myelin [23]. Interleukin (IL)-23, IL-12, and IL-12R in antigen presenting cell (APC) have shown an increase in the mice exposed to malondialdehyde (MDA)-myelin oligodendrocyte glycoprotein (MOG) expression, which in turn induces the differentiation of T helper (Th)17 and Th1 cells [24]. The residual lysine, histidine, or cysteine in proteins have stable adducts through HNE, resulting in the accumulation in MS lesions and the induction of potent immune response [25].

In a study by Veto et al., potential PARP immunoreactivity was seen in astrocytes and oligodendrocyte in pattern III lesions in MS patients within 6 to 60 days, and the highest activity of PARP was in the very early lesions. The MS pathogenesis is strongly associated with the activation of PARP [20]. Further MS processes can be organized due to astrocyte-derived NO. The iNOS overexpression in macrophages early during the disease and before demyelization has also been reported [26]. Moreover, the arginine injection (acting as either iNOS substrate or up-regulator of iNOS mRNA) [27] into the rat brain induces demyelination, indicating the role of iNOS expression in developing MS [14]. The oligodendrocyte death is triggered by the NO, HNE and H_2O_2 leaked from astrocytes and macrophages. In additin, the mice with eNOS-deficient experience a delayed experimental autoimmune encephalomyelitis (EAE) initiation, which indicates the importance of eNOS in the onset of MS; it relates with delayed blood-brain barrier (BBB) breakdown [28].

Pathophysiology

The most frequent cells found in the human brain are the astrocytes that establish an optimal physical and metabolic environment for neuronal activities and play an important role in the neuronal redox homeostasis, potassium balance, BBB regulation, myelination, neuro-transmitter uptake, and synapse formation and function. Electrical signaling in the neurons is responsible for transmitting information. The myelination of long processes in axons and neurites is necessary to efficiently conduct signals. Among these, the oligodendrocytes support and insulate the axons through myelin sheath formation [29].

Myelin is a protective coating that is made of fat and protein and helps the nerve fiber forward the message. In MS disease, plaques (sclerosis) are formed on the myelin coating of the nerve fibers in the CNS. When the protective myelin of nerve fibers is destroyed as the result of plaques (demyelination), this phenomenon causes disruption of the nerve messages sent from the brain. Some nerve fibers or axons never recover from the effect of demyelination and then hurt thus leading to axonal damage. Demyelination and axonal damage can affect multiple systems and cause to outbreak of the disease factors [30].

The axonal ion homeostasis imbalance has been demonstrated during the neurodegeneration.

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Dystrophic or demyelinated axons have shown aberrant expression of Na^+ channels, acid-sensing Na^+ channels, glutamate receptors [31], and voltage-gated Ca^{2+} channels. Intra-axonal Ca^{2+} accumulation and axonal degeneration simultaneously directly or indirectly have been found following the changes in the expression and activity of these ion channels.

Immunopathogenesis of MS

The genetic and environmental factors obviously affect the MS as an immune-pathologic disease (probably an autoimmune disease). BBB consisting endothelial cells create strong interconnections-tight junctions [32]. BBB formation and function require essentially the astrocytes and pericytes [33]. The immune cell infiltration into the CNS are associated with blood vessels of postcapillary venules.

To enter perivascular space [Virchow-Robin space (VRS)], the immune cells need to cross the endothelial cell layer and endothelial basal lamina [34], limited by endothelial basal lamina and glial basal lamina. Astrocytic end-feet is found beyond glial basal lamina, making glia limitans. The infiltration of immune cells into the VRS does not occur classically; and they need to pass the glia limitans and penetrate into the CNS parenchyma infiltrating into the CNS [34]. The macrophages and activated T cells of any specificity are able to pass BBB and blood-cerebrospinal fluid barrier and penetrate into the CNS in spite of inhibiting the immune cell entry into the CNS [35].

There are two different types of inflammation involved in the activation of plaques including the initial response mainly T $CD8^+$ cells and highly activation of micro glial; and myelin destruction-induced secondary recruitment of T cells, B cells and macrophages. The inflammatory cell infiltration into the CNS is a marker of inflammation in the relapsing-remitting stage of MS, which causes serious damage to the BBB demonstrated with gadolinium-enhanced magnetic resonance imaging of lesions [36]. Activated demyelination and neurodegeneration are invariably related to inflammation in primary progressive MS (PPMS) and SPMS [37]. The inflammatory process in the brains of PPMS or SPMS patients is also dissociated from BBB damage, resulting in inflammatory infiltration encountered around small veins and venules without evidence of loss of BBB integrity [38].

The cortical demyelination has been shown to be significantly and strongly associated with diffuse meningeal inflammation. A majority of lesions contain $CD3^+$ cells (as a key immunohistochemical marker for T cells in general) and $CD8^+$ T cells, but not the $CD4^+$ T ones [39]. In a study, $CCR6^+$ T cells were found in early cortical lesions indicating that T cells infiltrate CSF using choroid plexus/CCL20 route and proceed to the cortex by provoking IL-17-dependent redistribution of CCL20 on the walls of blood vessels [40].

The memory T cells are able to penetrate into the CSF in the subarachnoid space across the choroid plexus epithelium or transvascular route. The CSF of the patients suffering from MS, and non-inflammatory neurological disease, and even healthy CSF have reported $CD4^+$ and $CD8^+$ memory T cells [41]. The pathogenesis of MS disease is associated with

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the autoimmune responses of T and B cells against CNS antigens [42].

Immune-pathologic cascade is probably organized by self-activated T cells [reactive to myelin). Different kinds of T cells participate in this scenario (T cells helping CD4, suppressor T cells, inflammatory T cells, regulatory T cells, and CD8 effectors) [43]. The $CD14^+$ monocytes have been indicated to have the capacity to migrate across the inflamed human BBB and to differentiate into $CD83^+CD209^+$ dendritic cell (DC) through BBB-secreted transforming growth factor-b and granulocyte-macrophage colony-stimulating factor. The proliferation and expansion of Th1 and Th17 lymphocytes can be induced by $CD209^+$ DC and be related to lymphocytes in the activated MS lesions [44].

T cells can migrate into the CNS after initial activation where they are reactivated. The CNS-resident phagocytes are activated to present antigens on major histocompatibility complex (MHC) class II molecules due to redox-imposed damage to nervous tissue. Interaction of these cells leads to reactivation of autoreactive $CD4^+$ T cells resulting in differentiation into effector IFN-c-producing Th1 cells and/or IL-17-producing Th17 cells [45]. The proinflammatory cytokines are released by the stimulated effector Th cells locally, which can lead to an inflammatory reaction thus likely resulting in demyelination [46]. NO-promoted development of Treg cells can hamper Th1 proliferation and differentiation, and by NOX2-related inhibition of IL-12 release from DC. reactive oxygen species (ROS) generation in mitochondria can induce Th17 cell differentiation [47]. IL-17 is associated with tumor necrosis factor (TNF) in the induction of oxidative stress-dependent death of oligodendrocyte. The BBB disruption can induce IL-17 by inducing NOX- or XO-dependent ROS production [48].

The stimulated T-cell receptor (TCR) activates $CD4^+$ and $CD8^+$ T cells to express NOX2, dual oxidase 1 (Duox1) and eNOS (on cellular and outer mitochondrial membrane) [49, 50]. The TCR stimulation can results in the production of H_2O_2 and calcium influx. Two-minute stimulation develops H_2O_2 production, resulting in suppression by rotenone, the inhibitor of electron transfer chain complex I [51]. Consistent with the findings on several cell types, TNF and IFN-c released from T cells can be induced by H_2O_2 [52]. On the other hand, the effector T cell suppression avcand the Treg cell induction are strongly associated with extracellular ROS production, especially by NOX2 [53]. The stimulated $CD4^+$ and $CD8^`$ T cells can produce extracellular O° by cellular membrane-bound NOX2 for self-regulation [50]. The reactivity threshold increases by the activity of NOX2 resulting in the suppression of T cell proliferation by provoking oxidation of specific thiol groups (-SH) on T-cell membranes [54]. In the study by Yan et al., DC induced the activation and proliferation of T cells by releasing GSH after the contact with T cells or antigens thereby cleaving to cysteine [55]. TCR-triggered proliferation of myelin-reactive T cells impede myelin-laden macrophages inhibit in an antigen-independent manner by iNOS-mediated NO production [56], indicating the importance of

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S-nitrosylation of thiol switches in regulation of the activity of T cells.

There is evidence on the major molecular targets in the immune response in MS and its different models. Many myelin proteins, such as MOG, myelin basic protein (MBP), and proteolipid protein (PLP); lipids, such as sulfatide, sphingomyelin, and oxidized lipids; and glycans [e.g.,Glc(a1,4)Glc(a)] have been reported. There are also significant molecular targets axo-glialproteins, including neurofascin and contactin-2, in MS [57].

A number of therapeutic targets involving in these functions such as deletion or inhibition of effector and T cells, seem as a rational treatment for the disease. Moreover, because antibody reactive to myelin and B cells plays a role in pathogenesis, migration of immune cells, chemokine and cytokine networks can also be considered as additional therapeutic targets [43].

The designed monoclonal antibodies for MS

Today, the exact mechanism of MS has not been known, hence the existing treatments are not entirely specific. Of course, for possible mechanisms involved in the disease, many drugs have been designed and manufactured. Among these, monoclonal antibodies have been considered as the best option because of their high specificity. INF-β has been accepted as the first immune-modulatory therapy for relapsing MS in 1993 [58]. Since then, other drugs have been approved for MS including two combinations of INF-β1b as well as gelayteramerestat and mitoxantrone [59]. Several antibodies are also under investigation and development for treating MS. Natalizumab drug is the first monoclonal antibody that bears the capacity to get the Food and Drug Administration confirmation for this disease [60]. In the following, a number of the latest monoclonal antibodies designed for MS that have gone or are going through clinical trials have been briefly listed by relying on the type, target molecule, and mechanism of action.

Monoclonal antibodies that are designed for MS are in some categories based on target molecules including monoclonal antibodies targeting cytokines or chemokines, monoclonal antibodies targeting B cells, and monoclonal antibodies targeting different CNS antigens.

A. Approved monoclonal antibody

Natalizumab

Natalizumab is a humanized monoclonal antibody immunoglobulin G4 (IgG4) which targets α-4 chain in α4β1 integrin and in other adhesion molecules containing α4 integrin. T cells need integrin α-4 to pass the BBB and reach the site of the brain lesion. Dimmer integrin α4β1 is also known by the name of very late activated antigen 4 (VLA-4); VLA-4 is expressed at leukocytes surface. After natalizumab connection, VLA-4 ability is destroyed in connection to vascular cell adhesion molecule-1 and other ligands like fibronectin; therefore, leukocytes are unable to connect to the innermost layer of cerebrovascular wall and subsequently cannot pass BBB and do not reach the CNS [61].

Alemtuzumab (Campath, MabCampath, Lemtrada)

Alemtuzumab is a humanized monoclonal antibody kappa IgG1. This antibody is a combination of rat immunoglobulin G2b CAMPATH-1G (six hypervariable loops) and

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human IgG1 (κ light chain of the Bence-Jones protein REI and the heavy chain of a new immunoglobulin). Alemtuzumab targets a glycosyl-phosphatidyl-inositol-anchored glycoprotein (CD52 antigen) which it mostly expressed on the surface of epididymis epithelial cells, mature spermatozoa and lymphocytes, eosinophils, monocytes, dendritic cells and granulocytes. CD52 antigen is not expressed on the hematopoietic stem cells [62]. The most important effects of this antibody are antibody dependent cell cytotoxicity, complement dependent cytotoxicity, and apoptosis [63].

B. Monoclonal antibodies targeting cytokines or chemokines

Daclizumab (Zenapax)

Daclizumab is a humanized monoclonal antibody IgG1. The mechanism of action of this drug is through binding to the α-chain of interleukin-2 receptor (CD25) on activated T-cells and inhibition of IL-2 binding [64]. Through the saturation of the receptor, it can inhibit lymphocyte T activation and consequently improve the disease [65]. This antibody has had different effects *in vitro* and *ex vivo*. Kircher et al. have reported its inhibitory effects on T-cell proliferation and differentiation *in vitro*. However, the effects of this antibody on the proliferation of T-cells in the ex vivo environment have not been identified [66].

Secukinumab (AIN457)

Secukinumab is a human monoclonal antibody IgG1κ. The mechanism of action of this drug is through the inhibition of proinflammatory cytokine IL-17A [67], that are produced by Th17 cells, as well as by macrophages, neutrophils, natural killer cells, dendritic cells, mast cells, and γδ-T cells.

MOR103

MOR103 is a human monoclonal antibody IgG1. The mechanism of action of this drug is through interfering the interaction between granulocyte-macrophage colony-stimulating factor (GM-CSF) and its receptor that in turn leads to turning off its signaling pathway [68]. Macrophages and dendritic cells activation, maturation and differentiation are provoked by GM-CSF, so it is a pro-inflammatory factor in cell-mediated immune responses [69].

GNbAC1

GNbAC1 is a recombinant DNA-derived humanized monoclonal antibody (IgG4/κ isotype) that contains framework regions and complementarity-determining regions from human and parent murine antibodies, respectively. The mechanism of action of this antibody is through direct binding to extracellular domain of MS-associated retro-virus envelope protein (MSRV-Env) [70]. No physiological role is known for the MSRV-Env protein, but it is over-expressed in brain of MS patients [71]. As it is mentioned, proinflammatory agents are involved in the pathogenesis of MS. MSRV-Env Protein plays a pro-inflammatory role by interacting with toll-like receptor 4.

Ustekinumab

Ustekinumab is a human monoclonal antibody IgG1 which, throughtargeting the p40 subunit of Interleukin 12 and 23, inhibits their binding to the beta1 subunit of the receptor [72]. IL-12 and IL-23 are pro-inflammatory cytokines which induce the differentiation of Th1 cells

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and IFNγ, IL17 and IL-17-producing Th17 $CD4^+$ cells, respectively [73].

Lovett-Racke et al. demonstrated significant relation between dysregulation of the Th1/Th17 pathways and MS disease [74]. These results created ideas for the use of drugs against these cytokines. In line with these results, some research confirmed that administration of IL-12 leads to an increase in EAE in rodents and marmosets [75]. They also showed that anti-IL-12 antibodies result in decreasing the EAE.

C. Monoclonal antibodies targeting B cells

The role of B cells has long been debatable in MS pathogenesis; there are some signs (B cells existence, plasma blasts and immunoglobulin in MS lesions, and also immunoglobulin and oligoclonal connections in CNS that B cells are involved in MS disease pathogenesis [76]. It seems that B cells play some role in T cells activation, cytokines production, demyelination, and re-myelination [77]. Therefore, it seems reasonable that there are antibodies that target CD20 in the surface of B cells. Wootla et al. have proven that B cells play a significant role in the initiation and propagation of MS [78]. Therefore, targeting CD20 [79] or CD19 [80] by monoclonal antibody can help improve MS disease.

Rituximab

Rituximab is the first anti-CD20 monoclonal antibody. Rituximab is a chimeric monoclonal antibody IgG1 that targets CD20 in the surface of B cells line; the effect of this drug is applied by antibody dependent cell cytotoxicity and complement dependent cytotoxicity apoptosis. This monoclonal antibody has been designed for B cells lymphoma treatment at first [81].

Ocrelizumab

Ocrelizumab like rituximab targets the CD20 containing cells line with the exception of plasma cells. Both mentioned monoclonal antibodies induce apoptosis and reduce B lymphocytes. Ocrelizumab is a humanized monoclonal antibody IgG1, unlike rituximab; therefore, it seems that ocrelizumab may have less allergic reactions and also less anti-idiotype antibodies. Contrary to rituximab, its efficiency is more likely revealed by antibody dependent cell cytotoxicity and complement dependent cytotoxicity [82].

Ofatumumab (Arzerra)

Ofatumumab is a fully human monoclonal antibody IgG1 that targets CD20 in the surface of B cell line. The mechanism of the action of Ofatumumab is different from the two previous ones. This antibody inhibits B cell activation by attaching to a different position of the CD20 receptor.

Initially, this antibody was made by transgenic mice; however, by using genetic engineering techniques, human's heavy and light chains genes are transfected to mouse myeloma cell line. It seems that its decreasing effect on B cell by complement dependent cytotoxicity is more than rituximab.

Tabalumab

Tabalumab is a human monoclonal antibody. The mechanism of action of this antibody is not exerted by binding to CD19 and 20, but it binds to BAFF and CD257 [83] and suppresses the activation of the B cells. BAFF is a member of TNF super family which, by binding to the receptor on the mature B cells, has a key role in survival and maturation of B cells [84].

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D. Monoclonal antibodies targeting different CNS antigens

Anti-LINGO-1 antibody

leucine-rich repeat and immunoglobulin domain containing NOGO receptor interacting protein-1 (LINGO-1) works with Nogo receptor-signaling complex as a co-receptor and reacts to NogoR ligand-binding Nogo-66 receptor. In both embryonic and postnatal stages, the LINGO-1 is over expressed in oligodendrocytes and neurons localized in CNS [85-89]. In the EAE animal model, the use of antibody against LINGO-1 leads to stimulation of remyelination in spinal cord. The monoclonal antibodies for MS treatment are shown in table 1.

Table 1. The commonly used/tested monoclonal antibodies for MS disease

	Name	Kind	Target molecule	IgG sub-group	Clinical status	Side effects	Ref
Approved	Natalizumab	Humanized	α 4-integrin	IgG4	Approved	Increased risk of CNS virus infections leading to progressive multifocal leukoencephaolpathy	[90]
	Alemtuzumab	Humanized	CD52	IgG1 kappa	Approved	Intense depletion of lymphocyte and monocyte populations in the bloodstream, autoimmune thyroid disease developing	[91]
Cytokines or chemokines	Daclizumab	Humanized	CD25	IgG1	Off-label, Phase III	Hepatotoxicity and autoimmune hepatitis, infections, mood disorder/suicidal thoughts, rash, lymphadenopathy	[92]
	Secukinumab	Human	IL-17A	IgG1k	Phase II	Not reported	[67]
	Tocilizumab	Humanized	interleukin-6 receptor	IgG1k		May cause secondary auto-immunity in CNS	[93]
	MOR103	Human	GM-CSF	IgG1	Phase I	Not reported	[68]
	GNbAC1	Humanized	Multiple Sclerosis-Associated Retrovirus	IgG4/κ		Not reported	[94]
	Ustekinumab	Human	IL-12p40+IL-23p40	IgG1	Phase II	Not reported	[95]
B cell	Rituximab	Chimeric	CD20	IgG1	Off-label, Phases II/III	Progressive multifocal leukoencephaolpathy, reactivation of dormant prior infections like hepatitis B	[96]
	Ocrelizumab	Humanized	CD20	IgG1	Phase III	Not reported	[97]
	MEDI-551	Humanized	CD19	IgG1k	Phases I/II	Neutropenia, nausea, pyrexia, cytokine release syndrome and fatigue	[98, 99]
	Tabalumab	Human	BAFF, CD257		Phase II	Not reported	
	Oftamumab	Human	CD20	IgG1	Phase II	Not reported	[100]
CNS antigens	Anti-LINGO-1 antibody	Human	ligand-binding Nogo-66 receptor	IgG1	Phase II	Not reported	[88]

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Conclusion

With respect to monoclonal antibody the best treatment option for MS therapy is still a matter of controversy. Selection of the treatment approach should comply with the inflammatory condition of the patients. Alemtuzumab and natalizumab are the preferred options in subjects who suffer from active MS. During the last years, the substantial influence of these therapeutic approaches on promoting the life expectancy in the MS patients is due to prevention of the disease in the initial steps of development. Therapy of the right patient with the best option in early stages of the disease development and before occurrence of the disability, can culminate favorable outcomes in the long run. The future of MS therapy would greatly rely on apprehensive knowledge of the disease immunopathogenesis.

Conflict of Interest

We have no conflict of interest to declare.

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