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"Advancements in Monoclonal Antibody Therapy for Multiple Sclerosis: Targeting Genetic Abnormalities to Safeguard Neural Integrity"

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A B S T R A C T

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS), characterized by demyelination and neuroinflammation. Over the years, significant progress has been made in understanding its pathogenesis and developing targeted therapies, particularly with monoclonal antibodies (mAbs). This review provides a comprehensive overview of the role of mAbs in MS treatment, highlighting their evolution from murine to humanized and fully human forms. The advent of hybridoma technology in 1975 revolutionized mAb production, enabling the development of therapies such as alemtuzumab, rituximab, ocrelizumab, and others, which selectively target immune cells or molecules involved in MS pathogenesis.The review discusses the mechanisms of action of these mAbs, including B-cell and T-cell targeting, and their impact on disease progression. It explores recent advancements in the field, including the use of novel mAbs targeting CNS antigens and immune modulators like IL-17 and IL-6 receptors. Additionally, the safety profiles and clinical outcomes of these therapies are examined, with insights into ongoing research and future directions in MS treatment.Through a comprehensive analysis of current literature and clinical trials, this review underscores the pivotal role of mAbs in reshaping MS therapy, offering insights into their efficacy, safety, and potential for personalized treatment approaches. The evolving landscape of monoclonal antibody therapies promises continued advancements in managing MS and improving patient outcomes.

Keywords:Monoclonal antibodies (mAbs),B-cell lymphoma,Rituximab,Anti-LINGO-1 antibody,Alemtuzumab,Chimeric antibodies.

1. Introduction

Medication study on cancer using compounds that selectively target the genetic abnormality without endangering the organism. It wasn't until Köhler and Milstein developed hybridoma technology (mAbs) in 19752 that Ehrlich's dream came true. Monoclonal antibodies (mAbs) with the required specificity might now be produced in infinite quantities thanks to this technique[1]. The development of chimeric, humanized, and ultimately fully human mAbs was made possible by recent technological advancements, starting with murine antibodies[2]. B-cell lymphoma patient was the first to demonstrate the therapeutic potential of monoclonal antibodies. An anti-idiotype antibody and an anti-CD3 mAb (OKT3, Muromonab-CD3) were administered to the patient in order of treatment. The US Food and Drug Administration (FDA) initially authorized muromonab-CD3 for clinical usage in humans[3]. We will first provide an overview of MS in this review, and then we will go over an overview of monoclonal antibodies used in MS treatment. We will review immunotherapies utilizing traditional monoclonal antibodies and talk about the characteristics and modes of action of monoclonal antibodies that are being utilized in clinical trials and by MS patients at this time. We'll also talk about the most recent developments in MS treatments and emphasize natural autoantibodies, or Nabs, which specifically target CNS cells[4].

1.1. An inflammatory CNS disorder called multiple sclerosis

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MS is a demyelinating CNS disease with an uncertain etiology that advances in the white (and grey) matter of the CNS and is frequently relapsing. As of right now, MS patients have no known way to reverse their current disability or stop the disease's progression. According to data from the MS Foundation, there are an estimated 400,000 or more people in the US. Relapsing-remitting MS (RRMS), the most prevalent subtype of MS, affects 80–85% of individuals. It usually manifests in the second or third decade of life, with a 2:1 or, more recently, 3:1 female preponderance. Individuals usually show improvement on their own or react well to intravenous corticosteroids. Moses Rodriguez established a treatment paradigm at the Mayo Clinic in 1983 that involved injecting 1 gram of methylprednisolone intravenously for each of three consecutive days without the use of an oral corticosteroid taper (referred to as the "Rodriguez protocol"). Over time, this treatment plan has evolved into the accepted method for managing acute MS exacerbations globally. Regretfully, the patient's corticosteroid reactivity usually wanes over time. Between relapses, a certain degree of CNS impairment may continue or worsen over time (secondary progressive MS). Plasma exchange may help some of these deficiencies that endure following methylprednisolone medication. In a double blind, placebo-controlled study, it was demonstrated that this was the case, with genuine exchange improving 40% of patients[5]. Primary progressive MS, which advances gradually without evident relapses and remissions, affects about 15-20 percent of MS patients. Men and women experience primary progressive MS at similar rates, and the condition is not responsive to the approved treatments for MS at this time). There is currently no recognized cause (or causes) for multiple sclerosis (MS), therefore a cure is unattainable[6]. Nonetheless, a number of approaches to managing multiple sclerosis were devised, commencing in 1993 with the approval of interferon-β1b (Betaseron®). This was succeeded by other FDA-approved treatments, including glatiramer acetate (Copaxone®), mitoxantrone, and interferon (IFN)-β1a (Avonex® and Rebif®). But none of these authorized medications significantly slow down the MS disease's progression. Every medication also has an own profile of possible negative side effects. The regular use of magnetic resonance imaging (MRI) of the brain and spinal cord for MS patient diagnosis and follow-up has greatly increased our knowledge of the disease's etiology[7]. As a result, several medications that reduce inflammatory MRI readouts were developed. But these medications came at a heavy cost: the medication's safety was compromised. The more potent the drug's ability to suppress the immune system (and thus, immune-mediated attacks during early disease stages), the more severe and even fatal were its side effects. We think there has to be a paradigm change in MS treatment from immunosuppressive/immunomodulatory approaches, which try to stop the illness from becoming worse, to active regenerative approaches, which try to heal demyelinated brain and spinal cord lesions[8].

2. Monoclonal antibodies licensed by the US Food and Drug Administration (FDA) for the treatment of multiple sclerosis

The only monoclonal antibodies approved by the US Food and Drug Administration (FDA) to treat multiple sclerosis are alemtuzumab and natalizumab.

2.1 Natalizumab (Tysabri)

A humanized monoclonal antibody called nabilizazumab targets T lymphocytes and other immune cells' focal adhesion molecule, integrin α-4. For T cells to penetrate the BBB and reach the CNS lesion site, integrin α-4 is necessary. In an immune-mediated animal model of multiple sclerosis, natalizumab is effective in preventing T cells from reducing the illness by penetrating the CNS lesions[9]. In a phase III trial, natalizumab decreased the exacerbation rate by almost 68% when given every four weeks[10]. An further reduction in disease activity was observed when beta-interferon and natalizumab were combined[11]. On the other hand, natalizumab increases the risk of CNS viral infections, which can result in PML, or progressive multifocal leukoencephalitis. There were 588 cases of natalizumab-associated PML among 142,000 patients as of August 31, 2015[12].

2.2 Alemtuzumab (Campath-1H)

Alemtuzumab (CAMPATH-1H) is a humanized monoclonal antibody specific to CD52 that consists of six hypervariable loops derived from the rat immunoglobulin (Ig)G2b CAMPATH-1G coupled to a human IgG1 (which is composed of the heavy chain of a novel immunoglobulin and the κ light chain of the Bence Jones protein REI)[13]. The cell-surface molecule CD52 glycosylphosphatidylinositol-anchored glycoprotein that is expressed on mature spermatozoa, epididymis epithelial cells, human lymphocytes, monocytes, and eosinophils. The treatment of chronic lymphocytic leukemia is the main indication for alemtuzumab. Within minutes of the first dosage, the medication significantly reduces the number of lymphocyte and monocytes in the blood, and this impact lasts for up to a year after treatment. In MS patients treated with alemtuzumab, peripheral blood monocytes reverted to baseline levels after one month[14], and B cell populations within three to seven months after treatment[15]. Patients with RRMS showed reduced relapse rates in a phase III trial when compared to controls, but the degree of disability remained unchanged. Three patients in an earlier phase II trial had idiopathic thrombocytopenia, which led to the experiment's termination. Alemtuzumab-treated patients experience autoimmune thyroid disease in about 23% of cases. They may also be susceptible to PML or other potentially deadly opportunistic infections. The primary safety concerns include idiopathic thrombocytopenic purpura (ITP), which requires patient monitoring, and autoimmune thyroid issues[16].

3. Immune cells and their constituent parts in the central nervous system

3.1 Role of B cells in MS pathogenesis

Histologically, an MS plaque is characterized by gliosis, demyelination, and inflammation. Acute MS lesion infiltration is commonly characterized by the presence of mononuclear cells, specifically macrophages and T cells. According to earlier findings, postmortem material from MS patients' brains and spinal cords included more Ig-containing cells inside the plaques than outsidemore prevalent in modern plaques than in older ones[17]. Following this, it was revealed that during CNS inflammatory reactions, B cells can make up as much as 25% of the leukocytes that infiltrate CSF. Other authors proposed that the immunological response against CNS structures involves a reaction akin to that of a germinal center (GC)19. It was demonstrated that trafficking of activated antigen-specific B cells into the brain, retention, and antibody production was possible using a rodent model with an intact blood brain barrier, indicating that the brain microenvironment supports the development of antigen-directed humoral immunity[18]. This idea was validated by Corcione et al., who demonstrated that the CSF of MS patients contained each B-cell subgroup involved in the GC reaction. The precise target antigens of pathogenic B-cell responses in multiple sclerosis are yet unclear. It is evident that not all B-cells in MS patients contribute to harmful autoimmunity, hence it is critical to be able to distinguish between normal B-cells and pathologically relevant cells. Thus, the rationale for targeting specific B cell populations in MS22 is highlighted by the pro-inflammatory GM-CSF-producing B cell subset that co-expresses high levels of TNFα and IL-6, induces pro-inflammatory myeloid cell activation in a GM-CSF-dependent manner, and is abnormally increased in MS patients[19].

3.2 The CNS contains immunoglobulins

The continuous detection of oligoclonal bands in CSF23 indicated intrathecal generation of antibodies following clonal expansion in MS patients. The notion that the degree of B-cell involvement in MS24 is correlated with CSF oligoclonal bands has been substantiated by several studies over the past two decades. Subsequent research revealed that these oligoclonal bands in MS were typically associated with a poorer prognosis or impairment in MS[20].

3.3 Role of T cells in MS pathogenesis

The mouse model of MS that is most commonly utilized is called experimental autoimmune encephalomyelitis (EAE). This illness model is determined by Th-1 CD4+ T cells. This is why CD8+ T cells were overlooked for several decades in MS research, whereas this fraction of T cells was the focus. The EAE model made autoimmunity more understandable for MS researchers[21]. immunological monitoring, central nervous system inflammation, and immune-mediated tissue damage and resulted in the creation of three drugs that are now authorized for the treatment of MS[22]. The focus has switched to the involvement of CD8+ T cells after it was reported that, in all samples from MS patients, independent of the MS subtype, duration, or pace of disease progression, CD8+ T cells exceed the CD4+ T-cell subset[23]. There was also conclusive proof of the clonal proliferation of CD8+ T lymphocytes in MS lesionsand patients [24]. Tzartos et al.'s research revealed a crucial role for IL-17 in MS pathogenesis as well as an elevation of both IL-17+ CD4+ and CD8+ T cells in active MS lesions[25].Lastly, pro-inflammatory (Th1 and Th17) responses of CD4+ and CD8+ T cells are markedly reduced upon B cell depletion, both ex vivo and in vivo[26]. When combined, the research mentioned above show that B- and T-cells play a part in the pathophysiology of MS, opening the door to treating the disease by targeting these immune cells and slowing or stopping its progression.

4. MS treatment using non-FDA-approved monoclonal antibodies: B-cell-reactive mAbs

A number of FDA-approved medications exhibit some degree of immunogenicity in patients, supporting the search for further therapeutic medications with minimal human toxicity profiles. As was previously mentioned, new research suggests that B cells and immunoglobulins play a larger role in the development and spread of MS lesions during various phases of their ontogeny[27]. Antibodies against CD2034 or CD1935 may be more effective in treating multiple sclerosis (MS) since they target all stages of B-cell development, including fractions of plasma cells.

4.1 Rituximab

B lymphocytes are bound and destroyed by the chimeric monoclonal antibody Rituximab (Rituxan®) when it binds to a phosphorylated glycoprotein (CD20). The majority of disorders for which rituximab was prescribed were those with hyperactive B lymphocytes. Based on the presumed predictive value for relapsing based on antibody-mediated damage observed in an immune-mediated animal model of multiple sclerosis (EAE)[28]. Rituximab was investigated further as a potential alternative treatment for MS and progressive MS. According to data collected 48 weeks after treatment, rituximab reduces the likelihood of relapses in MS patients by 50%[29]. Nonetheless, there was no discernible difference in the clinical outcome between patients with main progressive illness[30]. Furthermore, Rituximab has been linked to the reactivation of latent past illnesses such as hepatitis B37 and can potentially induce PML. Neuromyelitis optica (NMO) is an inflammatory autoimmune condition of the central nervous system that typically relapses and results in varying degrees of disability due to attacks. The disease's response to available treatments, which primarily involve immunosuppression, varies. Although rituximab was once included in consensus statements as a possible treatment for NMO, a growing body of research has shown that not all NMO[31].patients respond well to this medication. Rituximab has occasionally been seen to quickly exacerbate NMO after treatment[32].

4.2 Ocrelizumab

Ocrelizumab, a fully humanized monoclonal antibody, targets phosphorylated glycoprotein CD20 on circulating B-lymphocytes but not plasma cells (see to Rituximab). Ocrelizumab, like Rituximab, depletes B-lymphocytes by stimulating apoptosis and cytotoxic effects that are dependent on complement and antibodies.Finding anti-chimeric neutralizing antibodies against the chimeric antibody Rituximab in 24% of patients was a development. Patients receiving treatment with the humanized antibody ocrelizumab are probably going to have a decrease in this unsettling result. A phase III research in primary progressive MS and RRMS40 was initiated as a result of the positive outcome of a phase II trial comparing Ocrelizumab against interferon beta-1a and placebo. Ocrelizumab safety concerns, however, stem from the phase II MS experiment mentioned above, in which a patient, 41 years old, passed away due to brain edema 14 weeks into the treatment. Opportunistic infections following methotrexate exposure led to the termination of a phase III Ocrelizumab trial in patients with systemic lupus erythematosus[33]. Genentech reported encouraging findings from a pivotal Phase III research evaluating Ocrelizumab in patients with primary progressive multiple sclerosis (PPMS) in September 2015 (http://j.mp/ocrelizumab_1509). The Expanded Disability Status Scale (EDSS) demonstrated that therapy with ocrelizumab significantly reduced the progression of clinical disability sustained for at least 12 weeks when compared with placebo in the ORATORIO study, which achieved its primary goal. Researchers randomized 1,656 individuals with RRMS in the recently completed OPERA trials (October 2015) to receive interferon beta-1a (Rebif) as 44-mg subcutaneous injections three times a week or a 600-mg IV infusion of Ocrelizumab every six months. Comparing ocrelizumab to interferon over a 2-year period, the annualized relapse rate was lowered by around 50% ($P<0.0001$ for both studies; 0.292 versus 0.156 in OPERA I and 0.290 versus 0.155 in OPERA II). In both studies, the overall rate of adverse events was around 83% for both groups. However, as anticipated, the Ocrelizumab group experienced more infusion-related responses (34.3% compared to 9.7%). Serious adverse event rates were comparable (6.9% and 8.7%), and there were no documented incidences of PML (http://bit.ly/OPERA_Trial)[34].

4.3 Ofatumumab

Ofatumumab is a completely human monoclonal antibody that targets CD20. It is also known as Arzerra® or HuMax-CD20. Compared to the other two CD20-specific monoclonal antibodies, ocrelizumab and ritaximab, this one binds to a different area of the CD20 molecule. It now has FDA approval for inhibiting B-lymphocyte activation. Treatment of some cases of chronic lymphocytic leukemia that have not responded to alemtuzumab and fludarabine therapy; this medication has also been used in experimental settings to treat RRMS. Phase I/II trials for RRMS that compared the efficacy of ofatumumab with placebo yielded no significant safety concerns. For all Ofatumumab dosages more than 30 mg ($P <.001$)42, the number of new T1 gadolinium-enhancing lesions decreased by almost 90% after therapy[35].

4.4 MEDI-551

Targeting CD19, MEDI-551 is a humanized IgG1k mAb. In vitro, the antibody had strong effects in the deletion of multiple B-cell lines taken from individuals suffering from B-cell malignancies. Patients with RRMS are presently being studied in a Phase I/II trial (NCT01585766) that is randomized, double-blind, placebo-controlled, and focuses on the mAb. Additionally, MEDI-551 is being looked into in individuals with B-cell cancers and scleroderma. Phase II clinical trials showed a satisfactory safety profile. The adverse effects that were reported the most frequently were fatigue, pyrexia, cytokine release syndrome, nausea, and neutropenia[36].

4.5 Tabalumab

High-affinity human antibodies like tabalumab (LY2127399) have the ability to neutralize soluble and membrane-bound B-cell activating factor (BAFF, CD257). For B cells, BAFF is a survival and maturation factor that is a member of the TNF superfamily[38]. The expression of BAFF is dysregulated, which leads to autoimmune disorders or B-cell cancers by impacts on aberrant B-lymphocyte survival, activation, proliferation, and production of immunoglobulins. As BAFF binds to three distinct receptors, most of which are present on mature B cells, it is essential for both B-cell survival and activation. Patients with RRMS participated in a phase II clinical trial conducted by Eli Lilly and Company (NCT00882999) that involved several subcutaneous doses of Tabalumab. Examining the decrease in MRI lesions at 12, 16, 20, and 24 weeks in comparison to a placebo was the study's main goal. As of now, no data from this June 2012-completed study has been released.

5. Unapproved monoclonal antibodies by the FDA to treat multiple sclerosis: mAbs that react with chemokines, cytokines, or their receptors

5.1 Daclizumab

Zenapax® Daclizumab (anti-CD25) is an IgG1 class humanized monoclonal antibody that binds to the Tac epitope on the α-chain of CD25 (interleukin-2 receptor). Daclizumab effectively stops the high affinity Il-2 receptor from being generated. When the high affinity Il-2 receptor is triggered, signaling via it promotes the growth of activated T lymphocytes[39]. The main purpose of daclizumab was to stop organ rejection after transplantation. The suppression of the Il-2 receptor is thought to be the mechanism of action in MS, as it prevents T lymphocyte activation and growth, which ameliorates the condition. Regarding processes associated with disease, CD25 is also expressed by lymphocytes that infiltrate tumors, neoplastic B cells, and neuroblastomas. When

daclizumab was used alone or in conjunction with β-interferon, it enhanced the MRI results and clinical scores in MS patients[40]. There have been no reports of opportunistic infections or other potentially fatal side effects associated with daclizumab to date. This is different from the adverse effects observed with Rituximab and Natalizumab, and it could be due to its immunomodulatory rather than immune suppressive properties. Daclizumab was thought to eliminate certain populations of CD4+ and CD8+ T lymphocytes by raising the concentration of CD56+ natural killer cells[41]. Daclizumab was found to reduce annual relapses in individuals with RRMS49 by 45% as compared to interferon beta-1a in a phase III trial. Daclizumab's safety profile matched the results of the earlier phase II trials. The medication resulted in a higher incidence of significant cutaneous events (eczema, drug eruption, pityriasis rubra pilaris, and urticaria) (2% versus 1%), serious infections (4% versus 2%), and cutaneous adverse events (37% versus 19%) as compared to IFN. Compared to 3% of individuals receiving IFN, 6% of patients receiving daclizumab experienced elevations in liver function tests greater than five times the upper limit of normal. Two deaths occurred in the phase II studies, one from autoimmune hepatitis and one from a psoas abscess whose connection to the drug could not be ruled out[42]. There was one death in the group receiving daclizumab treatment that was determined not to be related to the drug.

5.2 Secukinumab

Targeting IL-17A50, secukinumab (AIN457) is a completely human IgG1k mAb. Th17 cells also produce other effector cytokines, including as IL-17F and IL-22, in addition to the proinflammatory cytokine IL-17A. Several innate immune system lineages, such as mast cells, neutrophils, dendritic cells, γδ-T cells, macrophages, and others, also express IL-17A. natural killer cells. As a therapeutic target, inhibiting IL-17A would have different physiological effects than suppressing Th17 cell activity. Patients treated with secukinumab have shown rapid and prolonged symptom reductions in psoriasis, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, with no overt safety signals[43]. Many investigations on humans and animals have demonstrated the significant role that Th17 cells and IL-17A play in the etiology of multiple sclerosis (MS).RRMS were enrolled in a first proof-of-concept research (NCT01051817) and were randomized 1:1 to receive intravenous secukinumab (10 mg/kg) or a placebo for a duration of 20 weeks. Initial findings indicated that the Secukinumab-treated group had a significant decrease in the total number of distinct active lesions during weeks 24–48 (the primary endpoint). Early termination occurred from a phase II adaptive dosage ranging research (NCT01874340) that assessed the safety and effectiveness of secukinumab in patients with RRMS. This resulted from the creation of a completely human anti-IL17 monoclonal antibody that has improved therapeutic potential for MS patients[44].

5.3 Tocilizumab

A humanized IgG1k mAb that targets the interleukin-6 receptor (IL-6Ra) is called tocilizumab (TCZ). It is presently approved in the US for RA patients who have not improved with at least one anti-TNF therapy[45]. It is a treatment method for people with rheumatoid arthritis (RA). Utilizing a double-label immunohistochemistry method, the IL-6 was found in the brains of six MS patients' acute and chronic active plaques[46]. Increased levels of IL-6 ($p<0.05$) were discovered in the CSF of patients with RRMS when a panel of Th1/Th2 cytokines and the chemokine CCL2 were evaluated in serum and CSF from MS patients and healthy controls. In a case study, a 53-year-old Japanese woman with RA and MS found that tocilizumab treatment for the RA55 caused her MS to stabilize. Tocilizumab clinical studies for MS patients are presently being organized. According to a fairly recent study, a 48-year-old lady receiving tocilizumab treatment for RA56 developed multiple sclerosis. This case study demonstrates how tocilizumab may result in CNS secondary autoimmunity. As a result, anti-IL6 medication needs to be used carefully[47].

5.4 MOR103

A human IgG1 mAb called MOR103 is directed against GM-CSF, or granulocyte-macrophage colony-stimulating factor. The mAb inhibits the connection between GM-CSF and its receptor, which stops further signal transduction. GM-CSF primarily functions as a pro-inflammatory cytokine by activating, maturing, and differentiating macrophages[48]. Dendritic cells, which are necessary for the start and development of immune responses mediated by cells. A powerful adjuvant for eliciting immunological responses to foreign proteins and peptides derived from self-antigens is soluble GM-CSF. Peripheral myeloid cell migration into the central nervous system requires GM-CSF. The safety, tolerability, and indications of efficacy of MOR103 in RA patients were assessed in a recent Phase I/II dose escalation trial60. Nasopharyngitis was the most frequent adverse event, with no significant treatment-emergent adverse events observed. The results encouraged more research on the mAb to GM-CSF in individuals with RA and possibly other immune-mediated inflammatory conditions. According to a recent investigation, a subset of B cells that co-express high levels of TNFα and IL-6 and create GM-CSF are involved in the pathogenesis of MS. Furthermore, in MS22 patients, this subpopulation of cells increased abnormally. The evidence suggested that multiple sclerosis (MS) is associated with a pro-inflammatory B cell/myeloid cell axis and supported the targeted targeting of certain B cell populations (such those that generate GM-CSF) in MS[49]. A recent clinical trial examined the safety and pharmacokinetics of MOR103 in MS61 patients in a randomized, double-blind, placebo-controlled phase Ib study. Finding out if MOR103 is safe and tolerable in patients with RRMS or SPMS was the main goal. MS patients responded favorably to three separate doses of MOR103 given every two weeks[50].

5.5 GNbAC1

An envelope protein (Env) that is encoded by the Multiple Sclerosis-Associated Retrovirus (MSRV) gene is targeted by the humanized monoclonal antibody GNbAC1. Complementarity-determining regions (CDRs) of a parent murine antibody and human framework sections are present in this recombinant DNA-derived humanized monoclonal antibody (mAb) of the IgG4/κ isotype. With great affinity, GNbAC1 binds specifically to the

extracellular domain of MSRV-Env. Since the viral particles were first discovered in the brain tissue of MS patients, the protein was given the moniker MSRV[51]. Roughly 8% of the human genome is made up of genes related to the human endogenous retrovirus (HERV). MSRV-Env interacts with Toll-like receptor 4 to initiate an autoimmune and pro-inflammatory cascade. The pro-inflammatory characteristics and inhibitory effects on OPC development of the MSRV-Env protein are important for understanding the pathophysiology of multiple sclerosis. The presence of MSRV in the CSF of early MS patients was found to be significantly associated with a larger likelihood of secondary progression of the illness and relapse-unrelated unremitting impairment in a 10-year blind observational study[51]. Additionally, it was discovered that MS patients' brains and peripheral blood mononuclear cells hyperexpress the endogenous retroviruses MSRV/HERV-W, with the MSRV envelope protein being localized to MS plaques. Since the MSRV-Env target protein is extensively expressed in MS patients, particularly in brain demyelinating lesions, and is unknown in normal human physiology, it presents a unique therapeutic opportunity. Preclinical and early clinical research studies evaluated the effectiveness of GNbAC1 in MSRV-Env caused EAEbased on these principles. According to the study, there is no safety risk[52]. Further in vitro tests revealed minimal cross-reactivity with human tissues and no complement or antibody-dependent cytotoxicity. The first-in-man clinical trial including 33 healthy participants and the long-term clinical investigation involving 10 MS patients shown that GNbAC1 elicits a pharmacodynamic response on MSRV biomarkers and is well tolerated in humans without inducing immunogenicity. The pharmacokinetic data validate a dose-linear 6 pharmacokinetics that is consistent with monthly IV infusions and has an elimination half-life of 15–17 days[53]. These findings suggest that GNbAC1, an MSRV-Env mAb antagonist, may offer a novel strategy for treating MS without compromising the immune system.

5.6 Ustekinumab (CNTO-1275)

Human IgG1 mAbutekinumab is produced by immunizing transgenic mice with human Ig (hu-Ig) using recombinant human IL-1270. By binding to the p40 subunit shared by IL-12 and IL-23, the mAb stops these two interfering substances from interacting with the β1 subunit of the IL-12 and IL-23 receptor complexes[54]. Th1 cell differentiation is driven by IL-12, but IL-23 stimulates the Th17 CD4+ cells that produce IL-1772. Ustekinumab has shown promise in treating Crohn's disease , psoriatic arthritis , and moderate-to-severe plaque psoriasis . The following studies provide the rationale for the use of uzekinumab in MS patients: Dysregulation of the Th1/Th17 pathways has been strongly linked to MS in animal models and human disease samples. injection of IL-12 aggravated rodent EAE, which was blocked by injection of anti-IL-12 antibodies[55]. Common marmosets also showed comparable results. the finding that people with secondary chronic progressive course MS have higher serum levels of IL-12. Active MS plaques80 include higher levels of IFNη and IL-17, which are differentiated by IL-12 and IL-23, respectively, and cause tissue inflammation. A study was made in 1981 regarding a 1,000-fold segregated release of the p40 component of IL-12, which was linked to CSF levels of myelin basic protein (MBP), a marker of myelin breakdown. Ustekinumab inhibited inflammation of pre-existing brain lesions, delayed white-matter demyelination, and avoided T2 lesion formation in marmosets with preexisting EAE, according to a different study that employed serial MRI. Lastly, single subcutaneous doses of ustekinumab were demonstrated to be well tolerated in RRMS patients in a phase I clinical study, hence supporting the drug's examination in larger clinical trials[56]. A thorough dose-ranging proof-of-concept research was conducted in a later clinical trial to evaluate the pharmacokinetics, safety, and effectiveness of repeated subcutaneous injections of Ustekinumab in individuals with RRMS. The outcomes demonstrated that stekinumab does not worsen inflammatory demyelination and is generally well tolerated. The medication did not, however, demonstrate any effectiveness in lowering the total amount of MS patients' gadolinium-enhancing T1-weighted lesions. The fact that individuals with advanced disease were included in the study may have contributed to one of the possible failures of this treatment to demonstrate any effect. It is improbable, according to the authors, that Ustekinumab regularly crossed the BBB in this investigation. Therefore, immune cells already present in the central nervous system might not have been impacted, even though peripheral IL-12 and IL-23 may have been neutralized. Currently, this medication is not being used to treat MS[57].

6. Unapproved monoclonal antibodies by the FDA to treat multiple sclerosis: mAbs that react with CNS antigens

6.1 Anti-LINGO-1 antibody (Li81) (BIIB033)

Clinical trials are currently being conducted on the anti-LINGO-1 antibody (BIIB033) as a potential treatment for patients with MS and ON. A functional part (co-receptor) of the Nogo receptor-signaling complex, LINGO-1 (leucine-rich repeat and Ig domain containing NOGO receptor interacting protein-1) interacts with the ligand-binding Nogo-66 receptor (NogoR).In both the embryonic and postnatal stages, 1 is nearly exclusively expressed in CNS neurons and oligodendrocytes. In the EAE model, anti-LINGO-1 antibody was shown to promote spinal cord remyelination. As a stand-in antibody for the human monoclonal antibody Li81 (BIIB033), the murine monoclonal antibody mAb3B5 targets mouse LINGO-1. mAb3B5 restores axon function in animals that have had their spinal cords experimentally demyelinated. Li81, an anti-LINGO-1 antibody, binds to LINGO-1 contact sites that are necessary for protein oligomerization. Two copies of LINGO-1 and two copies of the antibody's Fab region, which is responsible for antigen binding, combine to create a stable complex upon binding to LINGO-1. Epitopes in the LINGO-1 IgG domain important in oligodendrocyte development are blocked by the resultant complex. Immunotherapy against LINGO-1 aims to promote the myelin sheath's regeneration, as it is destroyed in MS CNS lesions. The serum pharmacokinetics of BIIB033 were assessed in MS cohorts and control groups, yielding comparable results in each group. The serum half-life of the antibodies is 15–24 days following intravenous injection. Based on remyelination investigations in rats, serum concentrations associated with intravenous dosages >3 mg per kg in humans are expected to exhibit pharmacological effect. The pharmacokinetics of cerebrospinal fluid (CSF) produced inconsistent results in the examined subjects. Human brain and spinal cord to plasma concentration ratios are probably between 0.1% and 0.4%, while in rats they are between 0.1 and 0.4%[58].

6.1.1 Renew Clinical Trial

The Phase II clinical study RENEW (Biogen) results were published in April of 2015. The study examined the anti-LINGO-1's safety and effectiveness in treating acute optic neuritis (AON). AON harms the optic nerve, potentially leading to visual function loss by axonal injury and loss of the myelin sheath. MS is the most frequent cause of AON. RENEW (NCT01721161) examined the potential of anti-LINGO-1 to facilitate axonal remyelination in the healing of an optic nerve injury in patients with a first unilateral acute optic neuritis episode. The trial was randomized, double-blind, placebo-controlled, and parallel-group. RENEW is a component of the Phase 2 clinical development program for anti-LINGO-1, which also includes the MS SYNERGY trial (see below). For a total of 20 weeks, participants who had experienced their first episode of AON were given either a placebo or six doses of anti-LINGO-1 once every seven days. Using full field visual evoked potential (FF-VEP) to measure the latency of nerve transmission between the retina and the visual cortex in the brain, the RENEW experiment examined the impact on remyelination[59]. In comparison to the unaffected eye at baseline, the primary endpoint assessed the FF-VEP latency for the afflicted eye at week 24. In the protocol population, the results showed a 34% improvement in optic nerve delay recovery when compared to placebo; however, the differences were not statistically significant (p=0.0504), possibly because the study sample was small. Furthermore, changes in the thickness of the retinal layers (optic nerve neurons and axons) and visual function, as determined by low contrast letter acuity and spectral domain optical coherence tomography, respectively, were not affected by the top-line data. Analysis of the retinal ganglion cell layer revealed that significant weakening occurred prior to therapy. Consequently, it's possible that anti-LINGO-1 was unable to demonstrate neuroprotection in this investigation. In light of the excellent primary endpoint results, the authors concluded that this insight provides important information on the rate of axonal damage after an AON attack and will guide future research. Patients in both arms who did not finish the study were included in the analysis of the intent-to-treat (ITT) population, which revealed a favorable trend but did not reach statistical significance. Two patients experienced hypersensitivity reactions around the time of infusion, and one patient experienced an asymptomatic rise in liver transaminases that resolved upon stopping the medication. These were the treatment-related anti-LINGO-1 serious adverse events (SAEs). During the trial, there were no fatalities. Immunogenicity wasn't seen at all[60].

6.1.2 SYNERGY Clinical Trial

The effectiveness and safety of anti-LINGO-1 in individuals with RRMS or secondary progressive multiple sclerosis (SPMS) were examined in the clinical trial SYNERGY (Biogen). The trial is scheduled to conclude in early 2016; it commenced in April 2013. 416 individuals get 3 mg, 10 mg, 30 mg, or 100 mg of anti-LINGO-1 every week in addition to β-interferon 1a and a placebo[61]. kilogramme of mass. For 72 weeks, anti-LINGO-1 is administered once a month. This clinical trial's primary goal is to find evidence of improved cognitive abilities.

6.2. Natural antibodies reactive to the immune system and CNS myelin for MS treatment: Non-FDA-approved monoclonal antibodies

In MS92, an early benign course was linked to high levels of CSF-IgM binding to MBP. Immunosuppressive effect was shown when a monoclonal antibody (mAb) to MBP105-120 that recognized the 222-228 epitope of the extracellular domain of high affinity immunoglobulin gamma Fc-receptor I (CD64) was extracted from EBV+ B cell clones of patients with long-term stable RRMS[62]. Activated monocytes to produce and release large amounts of IL-10 and low levels of IL-12, which in turn stimulated MS-derived T cell lines. It is amazing that monoclonal IgM to MBP with immunosuppressive action can be induced by B cell clones derived from patients with long-term stable MS. The identification of an immunosuppressive IgM mAb as a component of the natural human antibody repertoire and its primary correlation with stable multiple sclerosis (MS) implies that it could potentially contribute to the mechanism of steady course in MS. The discovery that all MS patients receiving mAbs to CD64 had significantly elevated levels of circulating IgM to the CD64 epitope in their serum—but not IgG—provides additional evidence in favor of this theory[63]. Similar in vitro immunosuppressive characteristics were demonstrated by these IgM antibodies and the anti-CD64 222–228 mAb that was extracted from B cell clones. It appears that these circulating IgM attach to CD64 in vivo, which could account for their immunosuppressive action, as they do so in the natural configuration that is expressed on the surface of the transfected cell. These IgM antibodies' in vitro characteristics demonstrate that naturally occurring antibodies (NAbs) primarily serve as protective factors, offering a potential novel treatment option for multiple sclerosis (MS) and other immune-mediated inflammatory central nervous system illnesses[64].

6.3. Natural antibodies reactive to CNS cells for CNS lesion repair: Non-FDA-approved monoclonal antibodies for MS therapy

Despite early doubts about the presence of NAbs, groundbreaking research by Avrameas (94–96) and Notkins (97–98) provided strong proof that NAbs are a component of the human innate immunoglobulin repertoire[65].Newborns possess germline-encoded genes that are resistant to foreign antigens, self- and modified self-structures, and are not stimulated by foreign antigens. Conventional antibodies, on the other hand, need outside stimuli to be produced. Because high affinity binding of a single antigen requires varied light and heavy chain mutations, which are rare or nonexistent in NAbs, they are by definition polyreactive. Both vertebrates and invertebrates have NAbs of the IgM isotype. In vertebrates101, high concentrations of IgG NAbs and, to a lesser degree, IgM and IgA isotypes have been identified[66]. NAbs generally bind their antigen with high avidity but low affinity, which characterizes the total of interactions between the antigen and antibody as opposed to the combined synergistic power of many contacts. Conventional antibodies, on the other hand, usually belong to the IgG isotype and go through affinity maturation along with somatic mutations to guarantee high-affinity antigen binding, which is generally associated with the monospecificity of the antibody. NAbs are classified as natural systemic surveillance molecules based on accumulating data. They target invading pathogens and damaged cells for immune system destruction via opsonization or antibody-dependent cellular cytotoxicity. Certain NAbs have the ability to actively signal in 8 brain cells and tumors. Tumor surveillance may benefit greatly from recognized NAbs' capacity to recognize and occasionally cause apoptosis in tumor cells. Another class of NAbs known as remyelination-promoting antibodies actively encourages healing in demyelinated spinal cord regions in both humans and animals[67].

6.3.1 HIgM22

The Mayo Clinic in Rochester, Minnesota, USA, made the discovery of the human monoclonal IgM antibody 22 (HIgM22). The antibody known as sHIgM22 was identified from a patient suffering from Waldenström macroglobulinemia who did not exhibit any neurological symptoms. The antibody variable region of sHIgM22 was cloned to create rHIgM22, a recombinant version of the antibody[68]. The heavy and light chain framework108 is provided by inserting a DNA sequence into an expression vector. Gram amounts of GMP-grade rHIgM22 antibody were purified in preparation for official toxicological research. In the TMEV-model of demyelinating illness, both the serum and subsequently the recombinant version of the antibody were able to promote spinal cord remyelination[69]. Mice that received rHIgM22 showed more remyelination (59.7% [rHIgM22] vs. 15.8% [control]) and fewer lesions (34.3% [rHIgM22] vs. 41.8% [control]) than those who received control treatment. Similar increases in remyelination were observed in MRI studies conducted on the same experimental animal model. Furthermore, the research showed that the human IgM antibody could cross the blood-brain barrier and enter the central nervous system. According to other studies, immunomodulation is linked to decreased caspase-3 activation and caspase gene expression, anti-apoptotic signaling in pre-myelinating oligodendrocytes, and little to no involvement in the rHIgM22-mediated remyelination effect. The integrity of functioning axons was safeguarded and spinal cord axons were preserved by rHIgM22-promoted remyelination[70].

According to recent findings, a signaling complex in OPCs is in charge of rHIgM22-mediated processes that include the Src family kinases (SFK), integrin αvβ3, and platelet-derived growth factor (PDGF)αR. Lyn113 proposed a role for the astroglial growth factor PDGF in the effects of rHIgM22 in OPCs. Crucially, isolated OPCs do not react; only mixed glial preparations made up of astrocytes, OPCs, and microglial cells show detectable rHIgM22-mediated OPC proliferation[71]. This implies that either direct contact or astrocytic or microglial co-factors supply the required milieu or co-stimulate the proliferative response. A function for secreted astracytic factors in IgM-stimulated OPC proliferation and remyelination is further supported by the observation that astrocytes produce the majority of the PDGF released by glial cells[72]. The safety, tolerability, pharmacokinetics, and immunogenicity of a single intravenous dosage of rHIgM22 in MS patients were assessed in a recently completed phase I clinical trial (NCT01803867). This multicenter, double-blind, randomized, placebo-controlled trial assessed the immunogenicity, pharmacokinetics, safety, and acceptability of a single dose of rHIgM22 in individuals with MS of any kind who had achieved at least three months of clinical stability. Every single one of the seventy-two individuals continued receiving their MS treatments, which included disease-modifying medications. Following a single dosage of rHIgM22, participants in the experiment may be monitored for up to six months. No dose-limiting toxicities were discovered at any of the five dose levels examined. Moreover, all 14 rHIgM22-treated patients had two dose levels of rHIgM22 found in their cerebral spinal fluid (CSF) two days following intravenous injection (i.e., $\geqslant$0.05 ng/ml). Five out of twelve patients had detectable levels of rHIgM22 in their CSF even 29 days after starting treatment116. This human data shows that IgM antibodies can pass the blood-brain barrier and remain in the CSF for approximately a month following therapy (>40% of patients). In October 2015, a phase Ib study (NCT02398461) began recruiting patients with at least one new, active lesion (damaged area) on MRI scans and a history of clinical acute relapse (new or worsening neurological symptoms attributable to MS preceded by a stable or improving neurological state of at least 30 days). The safety and tolerability of a single dosage of rHIgM22 in relapse MS participants will be the main outcome of the experiment. This investigation is expected to be finished in November 2016[73].

6.3.2 HIgM12

The identification of monoclonal IgMs targeting neuronal cells was made possible by the advantageous effects of mAbs targeting myelin/oligodendrocytes in models of demyelinating diseases. Unlike remyelination-promoting antibodies, these antibodies did not affect the amount of glial cell Ca2+ influx in vitro or the degree of remyelination in vivo.Neurite extension was promoted by antibodies (sHIgM12, sHIgM42), and rHIgM12, a recombinant version of sHIgM12, was produced. Neurite outgrowth was enhanced and membrane rearrangement resulted from HIgM12 binding to the neuronal surface. In chronically demyelinated mice, peripheral delivery of rHIgM12 as a single bolus enhanced motor function[74]. In a model of progressive MS121, a single dosage of rHIgM12 increased brainstem NAA concentrations, a biomarker for spinal cord axon density. The antigens for rHIgM12 were found to be gangliosidesand polysialic acid (PSA) bound to the neural cell adhesion molecule (NCAM). NCAM is the predominant polysialylated molecule (>95%) in the central nervous system, containing long, negatively charged α2'-8'-linked sialic acid homopolymers (n>10 sialic acid residues). The developing brain contains large amounts of PSA, and the early production of this protein is closely associated with important developmental processes such as the migration of neural precursors (neuroblasts), axonal sprouting, and the proliferation of oligodendrocyte progenitor cells. Acting as a negative regulator of myelination, PSA-NCAM is expressed at the axonal surface and likely works by impeding the attachment of myelin-forming cells to the axon. In the plaques, PSA-NCAM, which is typically missing from the adult brain, is reexpressed on 9 demyelinated axons. Remyelinated axons in shadow plaques do not exhibit PSA-NCAM. The antibody is presently being developed as an MS treatment agent[75].

7. Professional Views

The prognosis for MS sufferers keeps becoming better as more secure and efficient treatments become accessible. Furthermore, it's possible that the long-term results for MS patients will be positively impacted by the availability of drugs with efficacies greater than those of first-line agents. A schematic overview of the suggested mechanisms of action of mAbs for MS. The immune system is the focus of the majority of authorized antibody treatments. Consequently, immune cells, cytokines, chemokines, or their receptors are the targets of monoclonal antibody therapy, which are beneficial in the management of multiple sclerosis (MS), but they do not prevent or reverse long-term impairments. Finding novel treatment approaches for nearly all neurologic conditions, including MS and neurodegenerative illnesses, is urgently needed. The goal of treatment for demyelinating illnesses such as multiple sclerosis should be to actively stimulate remyelination and repair brain lesions. The outlook for remyelination treatments is positive. Early-stage human clinical trials have commenced, and preclinical research has discovered many targets affecting remyelination in experimental animal models of

demyelinating illness. Combinatorial treatment strategies may involve immune system-targeting drugs to prevent harmful immune system-mediated injury as well as rHIgM22 or anti-LINGO antibodies to promote remyelination. In fact, human monoclonal IgMs directed against the central nervous system may improve the conditions favorable for the regeneration of missing myelin[76]. In animal models of MS, reparative human monoclonal antibodies have the capacity to actively heal central nervous system lesions, making them a promising new class of treatments for MS patients. In the context of therapeutic methods, the disruption of the blood-brain barrier (BBB) is significant. The interface between the vascular and neurological systems is known as the neurovascular unit (NVU), and there are a number of recognized anatomical characteristics between the two systems[77].

Endothelial cells, astrocytes, neurons, and pericytes make up the NVU. Endothelial cells create the blood-brain barrier (BBB), which plays a vital role in separating the central nervous system from the bloodstream. This interaction affects almost every facet of CNS function. The word "barrier" conjures up images of an impenetrable wall separating the neurological and circulatory systems. Nevertheless, the barrier is actually a zone of dynamic molecular transport that keeps the microenvironment's homeostasis stable by continuously controlling the flow of necessary substances, such amino acids, across endothelial walls[78]. After a CNS injury, the blood-brain barrier becomes damaged, which encourages the build-up of cell lytic products and pro-inflammatory cytokines. The ensuing inflammation may lessen the BBB's efflux activity while simultaneously improving the permeability to allow the entry of adaptive immune cells. In certain circumstances, the BBB's collapse might even be advantageous because it will boost the inflow of natural autoantibodies or medications with reparative qualities that target and shield the CNS's intrinsic cells. Nevertheless, the development of novel compounds or methods that would provide more secure and straightforward BBB crossing while lowering the possibility of adverse CNS effects is highly significant and would be crucial for MS treatment. It is hopeful that mice require a relatively small quantity of the human antibody rHIgM22 to stimulate remyelination, and that the blood-brain barrier remains open during the acute stages of human illness. For MS patients, antibody-mediated CNS repair techniques with no- or minimal-toxicity provide promise, in contrast to currently available immunomodulatory medications[79].

8. Conclusion

In conclusion, the evolution of monoclonal antibodies (mAbs) for treating multiple sclerosis (MS) represents a remarkable journey from theoretical promise to clinical reality. Beginning with the pioneering work of Köhler and Milstein in 1975, the development of mAbs has revolutionized the field, offering targeted therapies that selectively address the underlying immunopathogenic mechanisms of MS without compromising overall immune function. From early treatments like muromonab-CD3 to advanced humanized mAbs such as ocrelizumab and rituximab, each generation has brought improved efficacy and safety profiles, marking significant milestones in MS management.Today, the landscape of MS treatment is characterized by a diverse array of mAbs targeting various aspects of the immune response, from B-cell depletion with rituximab to novel strategies like anti-LINGO-1 antibodies aimed at promoting remyelination. These therapies not only aim to mitigate disease activity but also hold promise for restoring neurological function and improving patient outcomes. As research continues to uncover new targets and refine existing treatments, the future of MS therapy with monoclonal antibodies appears poised to realize Ehrlich's vision of targeted, effective, and personalized medicine for all individuals affected by this challenging neurological disorder.

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