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A SYSTEMATIC REVIEW OF MONOCLONAL ANTIBODY BASED THERAPIES FOR MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune, neurodegenerative and disabling disease affecting the central nervous system (CNS). The disease comprises a transition between different stages: the relapsing-remitting form (RRMS) and the progressive forms, which include primary progressive MS (PPMS) and secondary progressive MS (SPMS). MS affects 2.8 million of people worldwide and there is no cure for such disease. Current treatments include disease modifying therapies which aim at palliating the symptoms. Among them, monoclonal antibody based-therapies show advantages when treating MS. The main objective of this systematic review is to evaluate and document the available literature assessing MS therapies based on monoclonal antibodies in the last five years.

The methodology complied with the recommendations offered by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Overall, twenty-eight original publications were selected and reviewed. Most of the chosen literature correspond to phase III trials and focused on RRMS. In general, monoclonal antibody-based therapies were well tolerated. The most efficient drugs target immunological cell depletion or cell migration blockage. New findings regarding the association of Epstein-Barr virus (EBV) infections with MS open the door for the development of future therapeutic strategies and prevention programs.

Keywords: *Multiple sclerosis, disease modifying therapies, monoclonal antibody, targeted therapy, Epstein-Barr virus.*

RESUMEN

La esclerosis múltiple es una enfermedad autoinmune del sistema nervioso central que causa neurodegeneración y pérdida de mielina en las neuronas. La enfermedad se considera una transición entre diferentes estados: el remitente-recurrente y la forma progresiva, la cual incluye los subtipos primario progresivo y secundario progresivo. La esclerosis múltiple afecta a 2,8 millones de personas mundialmente y no existe cura para dicha enfermedad. Los tratamientos actuales se basan en terapias modificadoras de la enfermedad, las cuales buscan aminorar los síntomas. Algunas de estas terapias están basadas en anticuerpos monoclonales debido a que han resultado ser exitosas en el tratamiento de la esclerosis múltiple. El objetico principal de esta revisión sistemática es evaluar el estado, durante los últimos cinco años, de la literatura basada en anticuerpos monoclonales para la esclerosis múltiple.

La metodología empleada ha seguido las directrices de *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA).

En total, veintiocho publicaciones fueron seleccionadas y evaluadas. La mayoría de la literatura escogida corresponde a ensayos clínicos en fase III y evalúan terapias para la forma remitente-recurrente. En términos generales, puede concluirse que las terapias basadas en anticuerpos monoclonales son seguras. Además, los fármacos más eficaces son aquellas con efecto inmunosupresor, o las que impiden el paso de los linfocitos a través de la barrera hematoencefálica.

Palabras clave: *esclerosis múltiple, terapias modificadoras de la enfermedad, anticuerpos monoclonales, terapias dirigidas, virus de Epstein-Barr.*

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1. INTRODUCTION

1.1 Pathology

Multiple sclerosis (MS) is an autoimmune disabling disease which affects the central nervous system (CNS) (Dobson & Giovannoni, 2019; Hauser & Cree, 2020; Jamebozorgi et al., 2021). The main features of the disease are inflammation, demyelination and neurodegeneration. Traditionally, MS has been classified into different stages or forms of the disease. These include 1) the relapsing-remitting form (RRMS), affecting more women, and 2) the progressive form, which includes primary progressive MS (PPMS) and secondary progressive MS (SPMS) (Hauser & Cree, 2020; Mathur et al., 2021). Affecting 90% of MS patients, RRMS undergoes isolated events of CNS inflammation. Over time, episodes of neurological dysfunction (relapses) are alternated with remitting periods. Patients diagnosed with RRMS may either remain stable over long periods (not progressing), or evolve to a secondary progressive form (SPMS). Generally, progressive forms are more disabling as they involve neurodegeneration, whereas RRMS exhibits increased inflammation. A third type of MS, classified as primary progressive (PPMS), affects less than 10% of the MS patients (Hauser & Cree, 2020). Unlike SPMS, PPMS exhibits neurodegeneration from the beginning of the illness. Despite the differences, all forms of MS appear to be manifestations of the same underlying cause.

MS pathology involves CNS damage due to demyelination and to the loss of oligodendrocytes (main components of the myelin sheath) (Jamebozorgi et al., 2021). The process starts when activated T lymphocytes identify myelin, and other CNS antigens, as “foreign”. Subsequently, T lymphocytes become reactive, attacking CNS protein components. B lymphocytes also contribute in a large proportion to this autoimmune response. In a process mediated by other signalling molecules, T cells can cross the blood-brain barrier (BBB). Once in the CNS, T lymphocytes are reactivated by local antigens presented on the surface of dendritic cells, macrophages or B lymphocytes; leading to an inflammatory cascade. The release of cytokines serves as a signal to recruit more T cells, monocytes and B cells; which eventually damage the myelin sheath. In addition, local inflammation and axonal injury may also concomitantly occur (Yamout & Alroughani, 2018).

1.2 Clinical features

MS is not a stationary disease, but a transition between asymptomatic phases and relapses. The clinical symptoms of MS involve vision damage, loss of cognitive function, and of motor capabilities or even urinary incontinence (Yamout & Alroughani, 2018). Patients can also experience electric-shock sensations downwards the spine (Lhermitte's sign) or the Uhthoff's phenomenon. The latter is described as the loss of visual acuity during exercise (Pearce, 2010). At the initial stages of the disease, patients are firstly diagnosed with Clinically Isolated Syndrome (CIS), which often includes optic neuritis, brainstem and spinal cord syndromes (Dobson & Giovannoni, 2019). Afterwards, 50% of CIS patients may evolve to MS. Relapses develop over hours or days and may last for weeks. When the relapse is over, the symptoms fade away. However, in many cases the patient does not completely recover, presenting some persistent damage. For instance, after an optic neuritis episode, colour vision or contrast sensitivity might not be recovered. Over time, it gets more difficult to completely recover after relapses, mainly due to neuronal loss. This leaves behind sustained disability (Dobson & Giovannoni, 2019). Profound lymphatic inflammation lesions predominate in relapsing-remitting forms. However, many lesions are not easily evidenced because size-wise are microscopic.

After 10-15 years RRMS patients might develop SPMS. The latter exhibits higher levels of demyelination and reduction of axonal cord. The proportion of B lymphocytes and plasma cells is greater in SPMS lesions than RRMS. On the other hand, the composition of the inflammatory infiltrate and the histological characteristics are the same (Tallantyre et al., 2009). In fact, the difference between MS forms resides in the proportion of areas affected, with the characteristics above mentioned. It is important to note that there is no clear change between phases, but the progression follows a subtle-changing pattern (Dobson & Giovannoni, 2019).

Only 5-10% of patients develop PPMS. This form shows great neuronal system disability with the following main symptoms: spastic paraparesis, sensory ataxia, cerebellar ataxia, cognitive and progressive visual failure (Dobson & Giovannoni, 2019).

The use of magnetic resonance imaging (MRI) has enabled to point out white matter lesions in asymptomatic patients (Moore, 2009). This led to the definition of the radiologically isolated syndrome (RIS). The term RIS refers to the group of asymptomatic individuals which show demyelinating MRI lesions. RIS is not considered an MS subtype, but a possible indicator of the disease. Indeed, one study stated that, out of a 451 RIS

patients, 34% developed CIS in a period of 5 years (Okuda et al., 2014). To sum up, figure 1 illustrates the course of the disease.

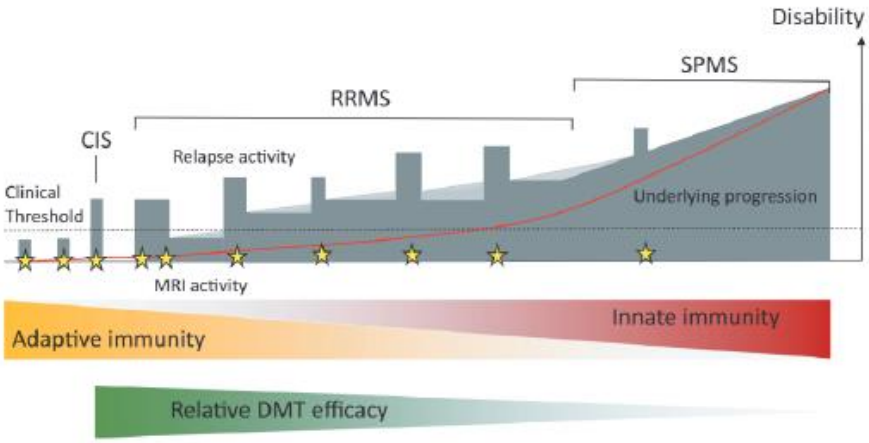

Figure 1. Most patients start with relapsing-remitting MS (RRMS). after the first Clinically isolated syndrome (CIS). Before the first clinical symptoms, disease activity can be identified by MRI (yellow stars). After some years patients might develop a progressive disability (light grey) until they reach the secondary progressive MS stage (SPMS). As the disease progresses, the degree of disability increases and the adaptative immunity response shifts to innate immunity (Piehl, 2021).

1.3 Diagnosis

Although there exist some immunological and radiological markers, MS diagnosis remains clinical (Dobson & Giovannoni, 2019). The first requirement for MS diagnosis is the presence of inflammation and injury in the CNS. Additionally, symptoms must last more than twenty-four hours and arise within at least one month (Hauser & Cree, 2020). The most extended tests to back up the diagnosis are CNS MRI and cerebrospinal fluid (CSF) analysis. MRI reveals lesions during the early stages of MS, when the integrity of the BBB is compromised. Overall, the lesions observed by MRI provide evidence of acute inflammation (Hauser & Cree, 2020). Two of the common MRI measures in MS diagnosis are T1 lesions and T2 lesions. T1 lesions, also termed as “black holes” are good indicators of axonal loss, while T2 lesions suggest the presence of edema or demyelination (Kocsis et al., 2021) . Lesions within the spinal cord and white matter (juxtacortical or infratentorial) are good indicators of MS. Besides, the presence of

lesions in the subcortical white matter is not distinctive of MS. However, if the case is uncertain or there is suspicion of PPMS, a CSF analysis would be more decisive. High levels of mononuclear cells or Immunoglobulin G in the CSF are common in MS patients. However, the elevated antibody production in the CNS is not exclusive of MS, since it can occur with other infections as well. Hence, it must be considered that polymorphonuclear leukocytes, eosinophils, high protein levels or more than 50 cells/mm3 is unusual in MS (Hauser & Cree, 2020).

The 2010 revised McDonald diagnostic criteria are widely accepted for MS. On the one hand, they state the key points for MS diagnosis: a) dissemination in time (two typical clinical attacks), and b) dissemination in space (two different brain lesions). The dissemination in space occurs when demyelinating is found in at least two of the following areas of CNS: periventricular, juxtacortical, infratentorial, or spinal. On the other hand, criteria for PPMS diagnosis are: one year of disease plus a) dissemination in space and b) the presence of inflammatory markers in the CSF, as well as c) elevated immunoglobulin G (Polman et al., 2011). The most recent revision of McDonald criteria, which attempted to facilitate early diagnosis, was done in 2017. Nowadays, to diagnose the disease dissemination in space (at least two lesions in the MRI) is a required event, as well as dissemination in time (at least two hospital visits). Although for the 2017 McDonald Criteria, dissemination in time could be replaced with more than two oligoclonal bands in the CSF (more than two different antibodies helping the immune system to attack CNS autoantigens). (Hartung et al., 2019).

There are some diseases, such as Neuromyelitis Optica spectrum disorder, that can be misdiagnosed as MS. For that reason, it is very important to abide the distinctive symptoms and signs. Neuromyelitis Optica spectrum disorder produces optic neuritis due to an inflammatory demyelination process. Although it is a rare disease, the clinical diagnosis criteria are well defined (Wingerchuk et al., 2006).

1.4 Epidemiology

MS affects mainly people in their early adulthood (twenty to forty years old) (Jamebozorgi et al., 2021). According to the latest atlas published by the MS International Federation (MSIF), there are 2.8 million people living with MS worldwide (MSIF, 2020). This means that 1 out of 300 people has been diagnosed with the disease. Additionally, there has been an increase of 30% of annual cases since 2013. Therefore, it was estimated that, in 2020, the number of affected people would rise up to 3 million. MS prevalence

worldwide is 36 per 100.000 individuals. However, it varies across different regions of the globe (figure 2). For instance, in Europe, Germany (303 per 100.000) and Denmark (282 per 100.00) are the countries with the greatest MS burden (MSIF, 2020).

Figure 2. Number of people with MS in a prevalence of 100000 people (MSIF, 2020).

Figure 2 illustrates differences in MS cases worldwide. The highest levels of prevalence are observed in North America, Europe and Australia, whereas south America, Africa and the southern part of Asia seem less affected. In addition, when comparing the data to 2013 numbers, we find that MS prevalence has doubled the registered number of cses in the past 7 years in the following countries: Argentina, China, Egypt, Germany, Iraq, Israel, Libya, the Palestinian Authority, Serbia, Sri-Lanka, Thailand and the United States. The MSIF argued that this increase might be due to the improvement on diagnosis and counting methods (MSIF, 2020).

It has been reported that MS closely associates with latitude, being the countries around the equator those exhibiting a lower risk (Simpson et al., 2019) . Thus, the higher you move in latitude, the greatest the amount of people affected by MS. This fact has been linked with deficit of vitamin D, in those countries that do not receive enough sunlight (MSIF, 2020). The latitude effect is observed also within countries. For example, the southern part of Australia exhibits a prevalence of 239 per 100,000, whereas in the northern state the prevalence is 75 per 100,000 (MSIF, 2020).

It is also important to mention the gender-bias of the disease with more females affected than males. Approximately 69% of people affected by MS are women, while only 31%

are men. Around the globe, women are more affected in the western Pacific and South-East Asia. In particular, the percentage of women with MS in Europe is 69%, and 66% of them are found in the Eastern Mediterranean (MSIF, 2020). Regarding the age at disease onset, the average age for diagnosis is 32 years, although it can occur at any age. Diagnosis of MS in children is more complicated, however it is estimated that around 1.5% of people with MS are children and teenagers (MSIF, 2020).

Lastly, the average incidence rate is 2.1 per 100,000 people per year (MSIF, 2020). Besides, this number cannot be applied worldwide due to the lack of MS epidemiologic data in certain countries. Only 75 countries reported data to the MSIF, thus, leaving gaps in the estimation of incidence.

1.5 Genetic and environmental factors

The cause of MS remained unknown for many years. Historically, it had been addressed that an environmental antigen, such as a virus, could trigger the autoimmune response of T lymphocytes (Bjornevik et al., 2022; Yamout & Alroughani, 2018). In addition, environmental factors (e.g.: vitamin D deficiency, smoking habits, gut microbiota dysbalance, stress…) and genetics may play important roles (Jamebozorgi et al., 2021; Yamout & Alroughani, 2018).

Although the inheritance of MS is not well defined (Yamout & Alroughani, 2018), there are many genes playing important roles in MS development. Some examples are: *CXCR5, IL2RA, IL7R, IL7, IL12RB1, IL22RA2, IL12A, IL12B, IRF8, TNFRSF1A, TNFRSF14, TNFSF14, HLADRB1, CBLB, GPR65, MALT1, RGS1, STAT3, TAGAP, TYK2, CYP27B1* and *CYP24A1* (Baranzini & Nickles, 2012). Among them, the gene *HLADRB1* coding for the beta chain of the cell surface receptor of the major histocompatibility complex class II, is strongly linked with risk for MS development. In addition, epigenetics can strongly influence MS (Küçükali et al., 2015). Epigenetic mechanisms do not alter the DNA sequence, but they influence gene expression by activating or silencing genes. Specifically, it has been suggested that DNA methylation, histone modification and microRNA (miRNA)-associated post-transcriptional gene silencing impact the risk of MS pathogenesis (Jamebozorgi et al., 2021).

Regarding environmental factors, Epstein-Barr virus (EBV), Human Herpesvirus-6 (HHV-6), Human Endogenous Retrovirus (HERVs), deficit of vitamin D or smoking have been suspected factors in promoting MS for many years (Jakhmola et al., 2021; Simpson

et al., 2019; Zhang et al., 2016). EBV is known to cause mononucleosis and it is associated with several health disorders (Jakhmola et al., 2021). Many studies have associated the presence of EBV with MS (Hassani et al., 2018; Moreno et al., 2018; Serafini et al., 2007). However, the results were inconclusive until 2022, when Bjornevik et al. investigated 801 patients with MS. The results of this investigation showed that most MS cases strongly associate with EBV. This is an important advance to efficiently improve MS treatments, as for example, with directional therapies against EBV (Bjornevik et al., 2022). In addition to EBV, other pathogens have been linked with the increased risk of MS. Strong association between HHV-6 and MS have also been stablished, suggesting that HHV-6 influences CIS and relapses in RRMS patients (Chapenko et al., 2003). By contrast, some studies indicate that, although HHV-6 might favour MS development in some cases, it is not a main trigger for MS (Jakhmola et al., 2021). Regarding HERVs, it has been hypothesized that MSRV, a human retrovirus discovered in 1989, has strong implications in MS aetiology. Apparently, the envelope protein (env) genes of HERV-W family drives oligodendrocyte damage and neuroinflammation, being thereby associated with MS (van Dyk et al., 2018). A recent study elucidated the mechanism on how HERV-W-env initiates inflammation and neurodegeneration in MS (Giménez-Orenga & Oltra, 2021). They stated that HERV-W-env acts like a “superantigen”, releasing proinflammatory cytokines and activating T lymphocytes and vascular endothelial cells. Furthermore, it sems to favour the demyelination process by inhibiting the differentiation of oligodendrocytes (Giménez-Orenga & Oltra, 2021).

As mentioned before, the prevalence of MS is higher in those areas that do not receive enough sunlight. Thereby, it has been proposed that vitamin D could be a crucial factor for developing MS (Bjornevik et al., 2022). In addition, patients with high levels of vitamin D showed a decreased relapse ratio, according to some studies (Simpson et al., 2010; Smolders et al., 2008). It has also been stated that the incidence of the disease is higher in smokers than in non-smokers. Indeed, smoking increases 1.5 times the likelihood to developing MS (Zhang et al., 2016). Passive smoking is also a gateway for pathogenesis. Further personal features, like altered gut microbiota, contributes to neurodegeneration and neuroinflammation (Mou et al., 2022)

1.6 Immunology

Immune cells are important target for the treatment of MS. Therefore, understanding how the adaptative immune system works in MS requires special attention. Many drugs targeting immune cells have reported to be successful for MS treatment, providing evidence about the importance and impact of the immune system in the course of the disease. Together, B lymphocytes, T lymphocytes, Natural killers (NKs) and microglial cells strongly impact the course of the disease. The comparison between the behaviour of the above mentioned cell types in healthy people and in MS patients, might lead to a better understanding of disease pathogenesis (Baecher-Allan et al., 2018).

The immunological mechanisms underlying MS were firstly described in 1980s. Patients with MS showed evidence of increased CD4 and CD8 T cells within inflammatory lesions. Particularly, CD4 T lymphocytes are located in deep lesions of the CNS and within the CSF. These, after being reactivated by specific antigens, recruit additional T cells and macrophages; both contributing to the inflammatory response. With respect to CD8 T cells, they seem to be present at the edges of the lesions (Traugott et al., 1983). The triggering components seem to be Interferon gamma (IFNγ) and interleukin-17 (IL-17). Although the mechanism is not well described, these two cytokines are responsible for initiating the MS pathogenic response. As mentioned earlier, CD4 T cells require to be reactivated by local antigens presented on the surface of dendritic cells and macrophages. The role of IFNγ is to boost the antigen-presenting step, whereas IL-17 is supposed to bring reactive oxygen species to the BBB, thus creating a leak (Huppert et al., 2010). In addition to CD4 T cells, CD8 T cells are also responsible of inducing neuronal injury (Baecher-Allan et al., 2018). Myelin-sensitive CD8 T cells release cytotoxic compounds (granzyme A and B) towards adjacent axons, causing oligodendrocyte death. They are also believed to secrete IFNγ and IL-17 once inside the CNS. The idea was supported by the presence of high levels of granzyme A and granzyme B within the CNS of MS patients (Malmeström et al., 2008). Moreover, neuronal damage was found in lesion areas caused by CD8 T cells (Melzer et al., 2009).

NKs and B cells were also demonstrated to contribute to the course of the disease (Baecher-Allan et al., 2018). The fact that some therapies target these two cell types, support the evidence that NK and B cells play an important role in MS. A deep knowledge regarding the underlying immune mechanisms, can help setting up efficient treatment strategies. Daclizumab is an example of an approved FDA (Food and Drug Administration) drug which aims at increasing the NK population to minimize relapse

ratios (Baecher-Allan et al., 2018). On the other hand, it has been hypothesised that B cells contribute to the disease my mediating the antigen-presenting process (Molnarfi et al., 2013).

1.7 Therapy and treatment

Currently, there is no cure for MS. The aim of the available therapies is to minimize the disability condition and to reduce relapse ratios (Montalban et al., 2018). In particular, the current goal for MS treatments is what was termed NEDA or "no evident disease activity" (Dobson & Giovannoni, 2019). Since the approval of the first drug by the FDA (1993) the outlook greatly changed. Currently, more than a dozen of drugs exist for the treatment of RRMS, whereas just one drug is approved for PPMS (Tackenberg et al., 2019).

Disease modifying therapies began in 1993. These include immunosuppressant and immunomodulatory therapies, both focused on ameliorating MS symptoms (Hauser & Cree, 2020). As the name indicates, they modify the progress of the pathology by suppressing the auto-reactive immune system. Nowadays, a broad variety of disease modifying therapies exits. Beta-interferon (IFN-β) therapies are the most widely employed means of coping with MS since 1993 (Bourque & Hawiger, 2021.). IFN- β minimizes the response of CD4 and CD8 T cells, kills pathogenic B cells and modulates dendritic cells. Approved IFN-β commercially exist under the following names: betaferon, avonex, rebif and plegridy. An additional extended and commonly used treatment is glatiramer acetate (GA). This latter molecule blocks the action of antigen presenting cells, as it is formed by natural constituents of the myelin protein (Tackenberg et al., 2019). Dimethyl fumarate (DMF) and diroximel fumarate directly affect CD4 T cells, B cells and NK cells function (Bourque & Hawiger, 2021.).

The blockade of lymphocyte migration is also an important approach for some disease modifying therapies. For example, by disturbing the sphingosine 1-phosphate (S1P) receptors, the treatment prevents T lymphocytes from crossing the BBB (Bourque & Hawiger, 2021). The interruption can be non-selective or selective. The only non-selective S1P modulator is fingolimod (gilenya), which is a derivative from a fungal compound. Selective inhibitors include: ozanimod (zeposia) and siponimod (mayzent) (Piehl, 2021). Other approved treatments include cladribine (mavenclad) and mitoxantrone (novantrone). cladribine was approved in 2019, whereas mitoxantrone is a DNA-intercalant employed in the treatment of cancer (Piehl, 2021).

IFN- β, GA or S1P modulators are employed as first line MS therapy options. They are considered low to moderate efficacy disease modifying therapies. However, if the course of the disease requires it, the therapy is likely to be changed to a highly effective medicine (monoclonal antibodies) (Goldschmidt & McGinley, 2021). Monoclonal antibodies exhibit potential advantages for the targeted treatment of autoimmune diseases, and some are currently approved by FDA to treat MS. Monoclonal antibodies show benefits for patients to whom other disease modifying therapies failed (Rose et al., 2008). Monoclonal antibody-based therapies constitute the focus of this review. Therefore, a deeper insight on the background of this topic is provided as follows.

1.7.1 Approved monoclonal antibody-based drugs

Natalizumab was approved in 2004, showing high efficacy against relapses. This monoclonal antibody attaches to the α4-integrin, thus stopping cell migration through the BBB. The mechanism of action is similar to S1P modulators. Besides its success in treating MS, it was retrieved from the market and reintroduced again, in 2006, due to the risk of developing progressive multifocal leukoencephalopathy (Goldschmidt & McGinley, 2021; Tackenberg et al., 2019).

Alentuzumab (lemtrada) is an anti-CD52 monoclonal antibody that kills B and T lymphocytes which express CD52 antigen on their surface (Tackenberg et al., 2019). It is a highly efficient drug; however, a suitable monitoring plan must be stablished due to the risk of developing additional immune diseases. As a result of major immunosuppression caused by alentuzumab, it is common for MS patients to develop Graves' disease (Rose et al., 2009).

Ocrelizumab is the first and only disease modifying therapy approved for PPMS. It is an anti-CD20 monoclonal antibody targeting B lymphocytes. It has been reported to be highly effective in blocking B lymphocytes, showing benefits in MS lesions (Hauser & Cree, 2020). Rituximab was the first antibody proven to be successful against CD20, however it was never approved for MS (Tackenberg et al., 2019). Nowadays, there is a novel anti-CD20 antibody accepted for MS therapy (ofatumumab); and others are under evaluation in current clinical trials (ublituximab and inebilizumab) (Bourque & Hawiger, 2021). It is worth emphasizing that all the approved drugs discussed above are employed for treating RRMS, except Ocrelizumab, which is the only treatment available for PPMS. Table 1 summarises the currently approved monoclonal antibody-based drugs for the treatment of MS.

Table 1. Approved MS monoclonal antibodies- based therapies (Adapted from Piehl, 2021).

Substance	Brand name	Mechanism	Approved (EU)	Indications EU	Reference
Natalizumab	Tysabri	Cell migration modulator	2006	RRMS second line	(Polman et al., 2006)
Alemtuzumab	Lemtrada	Cell depletion	2013	RRMS second line	(Factor, 2010)
Ocrelizumab	Ocrevus	Cell depletion	2018	RRMS, PRMS	(Hauser et al., 2017)
Ofatumumab	Kesimpta	Cell depletion	2020	RRMS	(Hauser et al., 2020)

1.8 Justification

MS affects around 2.8 million people worldwide (MSIF, 2020). There is no cure for such disease, which strikingly affects daily life of patients. Apart from the neurodegenerative and disabling condition, suicide is also frequent among patients experiencing MS (Piehl, 2021). Thereby, there is an urgent need to developing effective strategies for MS management. Progress on protein markers has been made and the number of potential therapies has increased in the past years. In fact, there are currently more than 10 FDA approved disease modifying drugs for RRMS, although only one for PPMS. Among all available treatments, four are based on monoclonal antibody technology. Treatment approaches and decisions are made based on the patient's profile (Goldschmidt & McGinley, 2021).

Monoclonal antibodies exhibit certain advantages when treating MS (Rose et al., 2009). Usually, they are employed as a second line treatment for patients to whom other diseases modifying drugs fail. However, an alternative approach points out the use of

highly effective therapy (including monoclonal antibodies) starting at the time of MS diagnosis (Goldschmidt & McGinley, 2021). Regarding progressive forms, the only drug available is based on monoclonal antibodies. A systematic review of the evidence on the effects of monoclonal antibody-based therapies should lay grounds to understand and document current directional therapies for MS treatment based on monoclonal antibodies, helping researchers, clinicians and educated patients update on these encouraging therapeutic options.

2. OBJECTIVES

The present study focused on reviewing the available original publications evaluating the use of monoclonal antibodies as MS treatments since 2017 using a systematic handling of literature approach. It also reviewed current clinical trials interrogating the use of directional antibody-based therapeutic options.

Therefore, the main objective of this study is to evaluate and document the available literature assessing MS therapies based on monoclonal antibodies in the last five years, with the intention of providing an update of current therapeutic options of this type. Secondary objectives include:

- To provide a bibliometric analysis of the literature available assessing MS therapies based on monoclonal antibodies in the last five years.

- To evaluate the current state of MS treatment in terms of trial's phase, MS subtypes, different drug approaches and main interests.

- To review all the available information regarding efficacy, tolerability and safety of monoclonal antibody-based therapies for MS.

- To understand the mechanisms of action of monoclonal antibody-based treatments.

- To detect possible shortcomings and room for improvement.

3. MATERIALS AND METHODS

3.1 Documentary analysis

To gather initial documentary information for the topic to be examined in this study and its "state of art", the following databases were employed: WOS, PubMed, MEDLINE and ProQuest.

- Web of sciences (WOS): As part of Clarivate Analytics, this database collects bibliographic sources and references since 1900. Its collection covers topics regarding sciences, social sciences, arts and humanities. Additionally, it offers evaluation and analysis tools as the Journal Citation Report or Essential Science Indicators.

- PubMed: containing more than 33 million citations, this free resource is focused on biomedical and life sciences fields. It may include links to the full text from other sources such as PubMed Central (PMC).

- MEDLINE: it provides with citations over 5,600 biomedical journals, in the fields of medicine, pharmacology, neurology, molecular biology, etc. It also contains full text of the most used medical journals.

- ProQuest: This database is a collection of full text journals, newspapers, magazines, reports, etc across the areas of business, health, medicine, social sciences, arts or technology.

In addition, "Multiple sclerosis", "treatment", "therapies", "immunotherapies", "disease modifying therapies", "drugs", and "immunology" where the key words used in the systematic searches performed. As for inclusion criteria, review articles where preferred. The reason behind this selection was to initially estimate the already available reviews and therefore the novelty and needs of the raised aims in this study. Articles where chosen based on the content, the date of publication (most recent), the number of citations and on the journal in which they were published.

Several research attempts were performed by randomly combining the key words mentioned above. This enabled acquiring general information about the topic, in general,

as a broad scope approximation. The number of hits on different therapies was assessed, and the requirement for additional specific terms to be documented as general aspect of the disease allocated. The key words here were: “Relapsing remitting MS”, “progressive MS”, “Ocrelizumab”, “Interferon beta therapies”, “monoclonal antibody therapies”. Finally, based on the results obtained, the term monoclonal antibody-based therapies was chosen as the specific issue to be studied in depth.

3.2 Bibliometric analysis

The methodology applied to this bibliometric analysis complied with the recommendations offered by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009). For this systematic review of the literature, the main database assessed was PubMed, whereas WOS accounts for an additional source of material; both discussed above. The main key words employed were “Multiple sclerosis”, “treatment” and “monoclonal antibodies”. The synonyms and how these were combined are shown below.

- **multiple sclerosis**: "multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]

- **treatment:** "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment's"[All Fields]

- **monoclonal antibody**: "antibody, monoclonal"[MeSH Terms] OR ("antibody "[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibody"[All Fields] OR ("monoclonal"[All Fields] AND "antibody"[All Fields])

To perform the screening process, the terms shown above were combined employing “AND” as connector. All the terms were included in the “topic” section. As mentioned in the objectives section, this focused systematic review includes the results of the last five years. Thus, the screening period of the present analysis comprises from the year 2017 until 2022, both included.

3.2.1 Inclusive and exclusive criteria

The scientific resources and materials of relevance for this systematic review were filtered according to the following inclusive criteria:

- The scientific studies must be published in academical journals.
- They must be related with the matter to be discussed.
- They must be original publications (clinical trials and other experimental primary sources).
- They must be published between 2017 and 2022.
- Articles were required to be written in English as full-text articles.

Thereby, all the articles exhibiting the following characteristics must be excluded:

- Unpublished or data published on unindexed journals.
- Articles not discussing the issue of interest.
- Review articles.
- Articles published before 2016.
- Studies not available in English as full-text articles.

With all of this being said, the final searching equation is showed below;

((("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) AND ("antibody, monoclonal"[MeSH Terms] OR ("antibody"[All Fields] AND "monoclonal"[All Fields]) OR "monoclonal antibody"[All Fields] OR ("monoclonal"[All Fields] AND "antibody"[All Fields]))) AND ((clinicaltrial[Filter]) AND (English[Filter]) AND (2017:2022[pdat])).

After the equation was applied, the final selection of the articles to be reviewed in detail and discussed was done by reading the abstracts. Articles that did not fulfil the inclusive criteria were excluded. Thereby, the selection was done by manual curation according to the information shown in the abstracts. The eligibility process was applied in both, PubMed and WOS-based searches; being PubMed the main reference database used.

In addition, ClinicalTrials.gov was also queried with the aim of completing the lack of information allocated in some papers. The search was performed on February 2022. The figures were elaboratedeither with Excel or BioRender.

4. RESULTS AND DISCUSSION

The results and discussion of this systematic analysis are presented as follows. First, the results of the PRISMA based process are presented, following a bibliometric analysis of the literature. Afterwards, the selected studies are classified according to the phase trial, to the type of patients, to the type of drug and to the objective of the study. Lastly, the outcomes of the selected literature are reviewed, meeting the objectives of this systematic review.

4.1 Results of the PRISMA based process for the selection of literature

PubMed was the main source of information for this systematic review, while WOS account as an additional resource to gather information. Figure 3 summarizes the screening process performed on both databases, as well as the number or articles rendered by the applied search equation and the set eligibility criteria. A total of twenty-eight articles were chosen to perform the systematic review. Twenty-six of them were obtained from PubMed, while the remaining two were acquired in WOS. As seen in figure 3, PubMed holds a larger number or articles than WOS for the selected topic. This fact makes sense, as PubMed is specific for biomedical disciplines. The total number of articles published since 1980s till present were 3550 in PubMed and 3235 in WOS. From them, 309 were clinical trials in PubMed and 240 In WOS. When the results were narrowed down to the last 5 years, 97 were found in PubMed and 38 in WOS. After this screening process, some results still did not meet the eligibility criteria and were dismissed. Specifically, additional 71 publications were dismissed from PubMed, based on their abstracts' information. This was done after removing the duplicates from the merged WOS search. In total, 28 articles were elected for the issue to be discussed. All of the chosen articles are related to the matter to be reviewed and they meet the inclusive criteria.

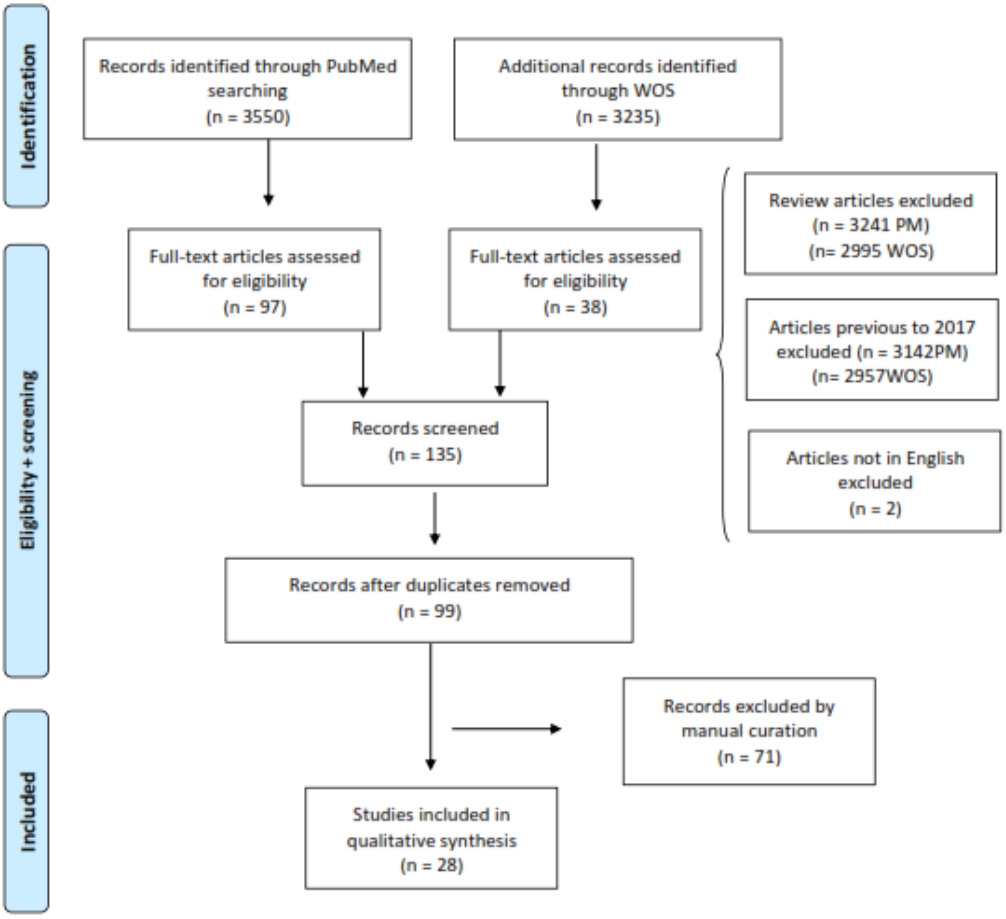

Figure 3. PRISMA diagram flow chart

Figure 4 shows the proportion of articles selected from each database, after removing the duplicates.

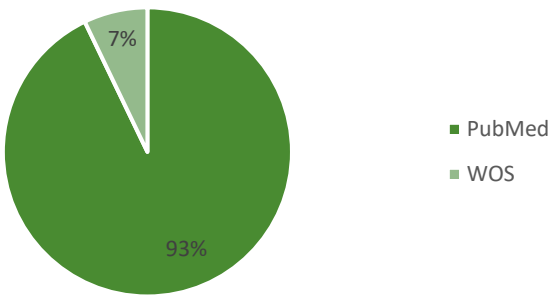

Figure 4. proportion of results obtained according to data base searched after removing the duplicates.

Twenty-six articles (93%) were chosen from PubMed. This does not mean that these articles were not available in WOS, but that the first search was performed in PubMed. After removing the duplicates, two additional articles (7%) were found in WOS, which were not available in PubMed. The systematic searching process is the most accurate, but it encompasses some shortcomings. The use of a second database source enabled to recruit additional literature, therefore obtaining more articles than if only one database was employed.

4.2 Bibliometric analysis of the selected literature

The bibliometric analysis of the results includes the study of the productivity per years (during the last five years) and analysis of the journal of publication by category

4.2.1 Productivity per years

The interest on monoclonal antibody-based therapies for MS has increased over the last five years. The greatest number of articles were published in 202 (8 studies), followed by 2021 with seven published studies. On another side, 2017 accounts for the year with the least number of publications on the topic, with only three articles (figure 5).

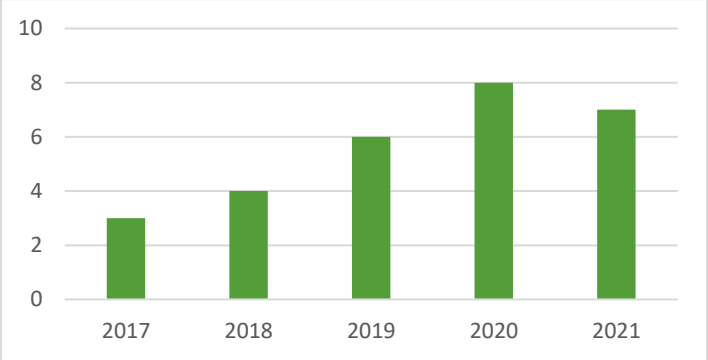

Figure 5. Number of published articles per year

According to figure 5, it can be stated that the interest on this subject has gradually increased since 2017, reaching its maximum point in 2020.

4.2.2 Journal of publication by category

Based on the Journal Citation Reports (JCR) records; 71% of the articles were published in a journal in the field of neurology. Three articles (10%) account for a medical journal, same number as for the publications in journals related to pharmacology. Only one article was published in a journal of psychiatry, while two studies (6%) were published in journals indexed under the immunology category (figure 6). The information is also summarized below, in table 2.

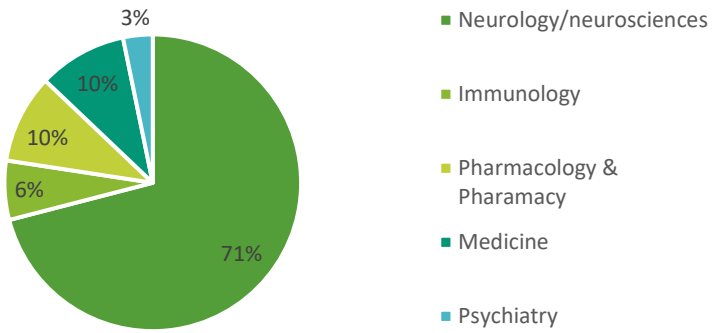

Figure 6. scientific field of journals publishing the selected articles according to JCR.

4.3 General classification of the selected literature documenting clinical trials of antibody-based MS therapies

The final results from the screening process are shown on table 2. Articles are ordered according to the clinical trial which they refer; from phase IV trials to phase I trials, meaning from the most advanced to the earliest phase trials. Because some of the chosen articles report results from more than one clinical trial, table 2 shows the articles that appear more than once. The reason behind is that some trials are extensions of previous ones; or because one investigation holds more than one approach. In addition, table 2 displays the details cohorts studied, the therapeutic target of the studied antibody(ies), the article(s) summarizing the trial, the publishing journal, the objectives and the trial registration number. The results of the studies summarized on table 2 are detailed below.

Table 2. Summary of published clinical trials assessing monoclonal antibody-based therapeutics of MS from 2017 to nowadays.

Registered clinical trial	Phase trial	Cohorts			Therapeutic target	Study and journal of publication	Objective
		Number of participants	Age	Health conditions			
NCT02342704	IV	111	18 to 60 years old.	On therapy for at least 6 months.	α4-integrin.	(Butzkueven et al., 2020) BMJ open.	Natalizumab vs fingolimod.
NCT02255656	IV	1062	Adult	Participants completed at least 48 months in NCT00930553.	CD52 in T and B cells.	(Ziemssen et al., 2020) CNS drugs.	Efficacy and safety of Alemtuzumab after 9 years.
NCT01247324	III	821	18 to 55 years old.	Diagnosed with MS according to revised McDonald criteria.	CD20 in B cells.	(Cree et al., 2021) Multiple sclerosis and related disorders.	Ocrelizumab vs interferon beta-1a in African descendants.
						(Gibiansky et al., 2021) British Journal of Clinical Pharmacology.	Pharmacokinetics and pharmacodynamics of ocrelizumab.
						(Kappos et al., 2020) JAMA neurology.	Disability accumulation in patients.
						(Turner et al., 2019) Journal of neurology.	Efficacy and safety of ocrelizumab by subgroups.
						(Mayer et al., 2019) Multiple sclerosis and related disorders.	Efficacy and safety of ocrelizumab.
						(Hauser et al., 2017)	

NCT01412333	III	835	18 to 55 years old.	Diagnosed with MS according to revised McDonald criteria.	CD20 in B cells.	The New England Journal of medicine.	Ocrelizumab vs IFbeta.
NCT01416181	III	889	18 to 58 years old.	SPM.	α4-integrin.	(Kapoor et al., 2018) The Lancet Neurology.	Natalizumab for SPMS.
NCT00530348	III	581	18 to 50 years old.	Onset of MS symptoms within 5 years.	CD52 in T and B cells.	(Baker et al., 2017) JAMA neurology.	Dynamic of immunological cells.
						(Arnold et al., 2017) Neurology.	Efficacy and safety of Alemtuzumab after 5 years.
						(Ziemssen et al., 2020) CNS drugs.	Efficacy and safety of Alemtuzumab after 9 years.
NCT00548405	III	840	18 to 50 years old.	Diagnosed MS.	Anti CD52 in T and B cells.	(Baker et al., 2017) JAMA Neurology.	Dynamic of immunological cells.
						(Ziemssen et al., 2020) CNS drugs.	Efficacy and safety of Alemtuzumab after 9 years.
						(Gilmore et al., 2020) Journal of Neuroinflammation.	Dynamic of immunological cells.
NCT01194570	III	732	18 to 55 years old.	Diagnosed MS.	Anti CD20 in B cells.	(Gibiansky et al., 2021) British Journal of Clinical Pharmacology.	Pharmacokinetics and pharmacodynamics of ocrelizumab.
						(Mayer et al., 2019) Multiple sclerosis and related disorders.	Safety of ocrelizumab infusions.

						(E. J. Fox et al., 2018) Multiple sclerosis journal.	Ocrelizumab for PPMS.
NCT02792218	III	930	18 to 55 years old.	RRMS	Anti CD20 in B cells.	(Hauser et al., 2020) The New England Journal of medicine.	Ofatumumab vs Teriflunomide.
NCT02792231	III	955	18 to 55 years old	RRMS or SPMS.	Anti CD20 in B cells.		
NCT03085810	III	1225	18 to 55 years old.	RRMS	Anti CD20 in B cells.	(Hartung et al., 2020) Multiple Sclerosis and Related Disorders.	Shorter infusions of Ocrelizumab.
NCT00930553	III	1314	Child, adult, older adult.	Completed a 2 years study period receiving either alemtuzumab or Rebif, and had not subsequently received alternative disease modifying treatments	Anti CD52 in T and B cells.	(Ziemssen et al., 2020) CNS drugs	Efficacy and safety of Alemtuzumab after 9 years.
						(Gilmore et al., 2020) Journal of Neuroinflammation.	Dynamic of immunological cells.
NCT01307332	III	27	18 to 50 years old.	MS onset for 15 years.	Anti CD52 in T and B cells.	(Gilmore et al., 2020) Journal of Neuroinflammation.	Dynamic of immunological cells.
NCT00050778	II	334	18 to 50 years old.	MS onset for 3 years.	Anti CD52 in T and B cells.	(Arroyo et al., 2020) Multiple sclerosis journal.	Safety and efficacy of alemtuzumab after 6 years.
NCT01051349	II	410	10 to 60 years old.	Completed 52 weeks in study NCT00870740.	Anti CD52 in T and B cells.	(Gold et al., 2020) Journal of neurology	Efficacy and safety of daclizumab.
NCT01569451	II	53	18 to 50 years old.	RRMS.	Anti CD20 in B cells.	(Honce et al., 2019) Neurology.	Efficacy and safety of Rituximab plus glatiramer acetate.
NCT01405820	II	290	18 to 55 years old.	RRMS. Treatment with natalizumab for a minimum of 12 months.	α4-integrin.	(Trojano et al., 2021) Multiple sclerosis journal.	Natalizumab efficacy and safety.

NCT02738775	II	49	18 to 50 years old.	Diagnosed MS and active disease.	Anti CD20 in B cells.	(E. Fox et al., 2021) Multiple sclerosis journal.	Efficacy and safety of Ublituximab.
NCT03222973	II	263	18 to 58 years old.	RRMS who had been on an anti-inflammatory DMT or natalizumab treatment for at least 24 weeks.	LINGO-1 protein.	(Cadavid et al., 2019) The Lancet Neurology.	Efficacy and safety of Opicinumab.
NCT01457924	II	232	18 to 55 years old.	RRMS.	Anti CD20 in B cells	(Bar-Or et al., 2018) Neurology.	Efficacy and safety of ofatumumab.
NCT03574428	I	24	18 to 55 years old	Healthy male volunteers	Human endogenous retroviral envelope protein.	(Porchet et al., 2019) Clinical Therapeutics.	Efficacy and safety of Temelimab.
NCT01485003	Case-only	231	18 to 65 years old.	Under disease modifying therapy for less than 36 months.	α4-integrin.	(Perumal et al., 2019) BMC Neurology.	Efficacy and safety of natalizumab.
NA	Pilot study	NA.	Adults.	MS patients with six prior natalizumab infusions.	α4-integrin.	(Schultz et al., 2021) Annals of clinical and translational neurology.	Home therapy.
EudraCT; 2008-002626-11 and 2012-000721-53	NA	23	Adults.	Progressive MS.	Anti CD20 in B cells.	(Bergman et al., 2021) Journal of neurology	Efficacy and safety of rituximab.
NA	Real-world study	35	NA	RRM patients with 10,4 years of disease, with previous disease modifying therapy.	Anti CD52 in T and B cells.	(Zmira et al., 2021) Acta Neurologica Belgica.	Efficacy and safety of Alemtuzumab.

In the following section, the information shown in table 2 will be systematically discussed.

4.3.1 Classification of the selected studies according to the trial's phase

According to table 2, there is only one pilot study (Schultz et al., 2021), while the remaining fit in the category of full clinical trials. Most of the clinical trials reviewed belong to an advanced clinical trial stage: 52% (eleven articles) were classified as phase III trials, 10% (two articles) as phase IV trials and 33% (seven articles) as phase II trials (figure 7). Only one study is under phase I trial (Porchet et al., 2019). As a result, most of the assays include medium to large cohorts, with few exceptions. Most of the studies encompass more than two hundred participants, and five studies possess even more than nine hundred members. Further information can be found in table 2.

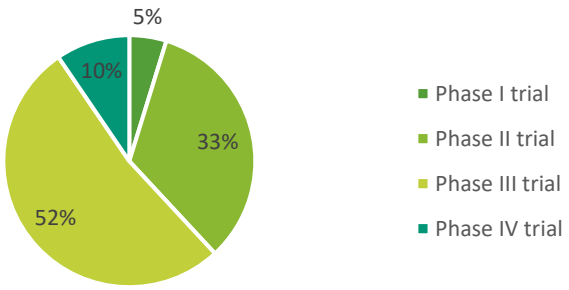

Figure 7. Phase trial of the selected articles

4.3.2 Classification of the selected studies according to the type of patients evaluated

Regarding the clinical trial participant, most of them focussed on RRMS. Particularly, twenty-one studies (75%) included RRMS patients, while. only three (11%) recruited patients with progressive forms of MS (either PPMS or SPMS), and four (14%) included patients of both groups: RRMS and progressive MS (figure 8). Figure 8 clearly shows that the interest concerning RRMS is greater when compared with progressive forms. This might be due to the fact that RRMS is the most common form of MS, thus affecting more people and, therefore, facilitating patient recruitment. However, progressive forms are more disabling and more efforts should be made in this area. Further information can be found in table 2.

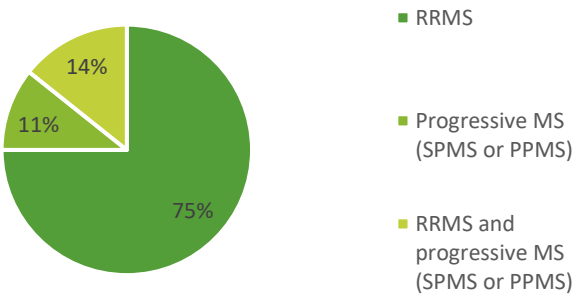

Figure 8. subtype of MS discussed in the articles of interest.

4.3.3 Classification of the selected studies according to the type of drug evaluated

The most studied drug is ocrelizumab, with eight publications (29%); followed by Alemtuzumab (seven trials/ 25%) and Natalizumab (five trials/ 18%). All the three of them are currently approved, which explains the special interest on them during these past years. Ofatumumab is another approved therapy which only counts with two published articles. This novel drug was recently approved in 2020. The rest of the selected articles examine non-approved treatments as; rituximab (two articles), temelimab (one article), opicinumab (one article), daclizumab (one article) and ublituximab (one article). These findings are summarized in figure 9. It can be said that Ocrelizumab is the most studied monoclonal antibody-based drug in the past 5 years according to the published records. Although it was recently approved (2018), it is the most reported therapy. This attention is probably due to its application to PPMS. Further information can be found in table 2.

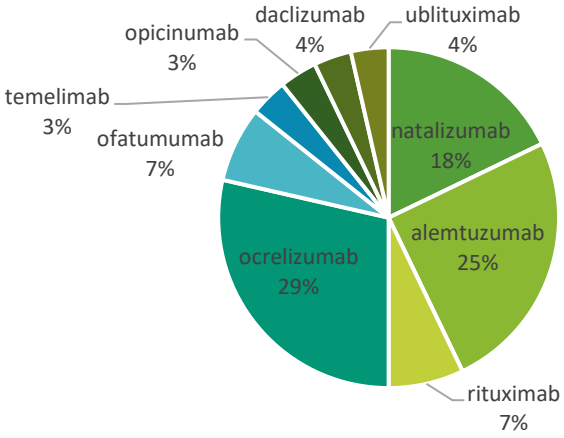

Figure 9. Monoclonal antibodies-based therapies for MS studied in the selected articles

4.3.4 Classification of the selected studies according to the objective of the trial

Figure 10 displays the ratios of the selected literature a per the main aim of the study, by percentage. The main concerns evaluated were the efficacy and safety of a selected drug (63%). Seventeen articles study the effects, concerning efficacy and safety, of each treatment shown in figure 5. Another focus of interest seems to be the comparison between two different therapies, also in terms of efficacy and safety (six articles/22%). One study (7%) evaluated the pharmacokinetic and pharmacodynamic features of a certain drug within the human body (Gibiansky et al., 2021) . Two studies aimed to evaluate the dynamics of immune cells after treatment (Baker et al., 2017; Gilmore et al., 2020). Lastly, one publication examines the possibility of home therapy; again, as a matter of efficacy and safety (Schultz et al., 2021). Further information can be found in table 2.

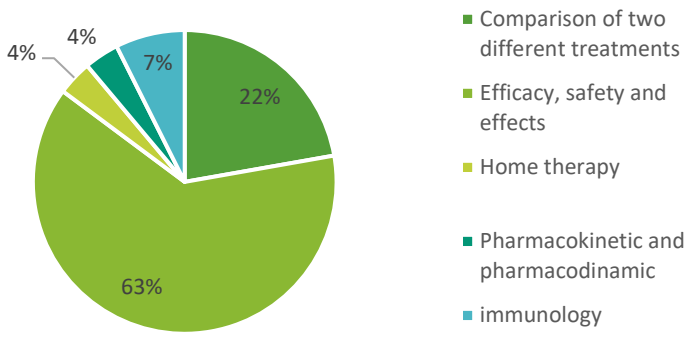

Figure 9. matter of interest among the selected publications

4.4 Review of the outcomes of the selected literature documenting clinical trials of antibody-based MS therapies

The following section reviews the outcomes of the selected literature according to the main aim of the study, including tolerability, safety and efficacy. The analysis will end with illustrations of the mechanism of action for the treatments exhibiting the best outcomes.

4.4.1 Tolerability and safety

Infusion related reactions, side effects and infections related to different treatments have been reported among the studies. Table 3 collects the most common side effects (affecting more than 10% of the patients) across all the studies. For each drug, the outcomes are ordered by the side effect exhibiting the highest percentage of people affected (more common), to the lowest (less common). The total number of participants is shown in brackets in the third column, to illustrate the level of evidence as per cohort size. The percentage of people affected by any severe adverse events is reported as well.

Table 3. side effects with an incidence >10%, severe side effects and number of deaths per drug.

Drug	Side effect	Affected participants in %, (cohort size)	Reference
Alemtuzumab	Infections	90%-84% (581)	(Ziemssen et al., 2020)
		56%-40% (581)	(Arnold et al., 2017)
	Skin disorders	41%-20% (581)	(Arnold et al., 2017)
	Headache	35.4%-18.2% (581)	(Arnold et al., 2017)
	Respiratory infection	20% (35)	(Zmira et al., 2021)
	Autoimmune disorders	19%-13% (581)	(Ziemssen et al., 2020)
		16%-2.9% (581)	(Arnold et al., 2017)
	Nausea	12%-5.7% (581)	(Arnold et al., 2017)
	Severe adverse events	<12% (581)	(Ziemssen et al., 2020)
Daclizumab	Skin disorders	38% (410)	(Gold et al., 2020)
	Gastroenteritis	24% (410)	
	Nasopharyngitis	17% (410)	
	Respiratory infection	15% (410)	
	Severe adverse events	13% (410)	
	Headache	11% (410)	
	Urinary tract infection	11% (410)	
	Urinary tract infection	23% (889)	
	Nasopharyngitis	22% (889)	

Natalizumab	Severe adverse events	20% (889)	(Kapoor et al., 2018)
	Headache	15% (889)	
	Respiratory infection	11% (889)	
Ocrelizumab	Infections	60% (835)	(Hauser et al., 2017)
	Respiratory infection	37%-24% (1225)	(Hartung et al., 2020)
	Nervous system disorders	32%-21% (1225)	(Hartung et al., 2020)
	Fatigue	24%-18% (1225)	(Hartung et al., 2020)
	Skin disorders	10.3%-8.2% (732)	(Mayer et al., 2019)
		10% (1225)	(Hartung et al., 2020)
	Gastroenteritis	10% (1225)	(Hartung et al., 2020)
	Severe adverse events	7% (835)	(Hauser et al., 2017)
		2.4%-1.2% (821)	(Mayer et al., 2019)
Ofatumumab	Infusion related reactions	66%-41% (232)	(Bar-Or et al., 2018)
	Headache	10% (930)	(Hauser et al., 2020)
	Nasopharyngitis		
	Respiratory infection		
	Urinary tract infection		
	Severe adverse events	9% (930)	(Hauser et al., 2020)
		3% (232)	(Bar-Or et al., 2018)
Opicinumab	Influenza-like illness	43% (263)	(Cadavid et al., 2019)
	Headache	25% (263)	
	Respiratory infection	14% (263)	
	Urinary tract infection	14% (263)	
	Fatigue	9% (263)	
	Severe adverse events	6% (263)	
Rituximab	Influenza-like illness	64% (53)	(Honce et al., 2019)
	Respiratory infection	46% (53)	(Honce et al., 2019)
		26% (23)	(Bergman et al., 2021)
	Urinary tract infection	43% (23)	(Bergman et al., 2021)
		25% (53)	(Honce et al., 2019)
	Nervous system disorders	32% (23)	(Bergman et al., 2021)
		9% (53)	(Honce et al., 2019)

	Gastroenteritis	32% (53)	(Honce et al., 2019)
		9% (23)	(Bergman et al., 2021)
	Depression	11% (53)	(Honce et al., 2019)
		4% (23)	(Bergman et al., 2021)
	Paraesthesia	13% (23)	(Bergman et al., 2021)
	Meningitis	9% (23)	(Bergman et al., 2021)
	Nausea	9% (23)	(Bergman et al., 2021)
	Severe adverse events	0.09% (23)	(Bergman et al., 2021)
Temelimab	Headache	30%-25% (24)	(Porchet et al., 2019)
	Nervous system disorders	30%-25% (24)	
	Blood disorders	25% (24)	
	Respiratory infection	25% (24)	
Ublituximab	Infusion related infections	58% (49)	(E. Fox et al., 2021)
	Nausea	15% (49)	(E. Fox et al., 2021)
	Respiratory infection	15% (732)	(E. J. Fox et al., 2018)
	Influenza-like illness	13% (49)	(E. Fox et al., 2021)
	Fatigue	10% (49)	
	Gastroenteritis	10% (49)	
	Headache	10% (49)	

There is evidence showing that alemtuzumab treated patients experience less adverse events after three years of treatment. Most adverse events (99.2%) were mild to moderate and infection rate did not intensify within the treatment (Arnold et al., 2017). Common adverse events include: nasopharyngitis, urinary tract infection, upper respiratory tract infection, and additional infections (predominantly herpetic infections) (table 3). Although the incidence of serious infection was lower than 10% (Ziemssen et al., 2020) , it is worth mentioning that two deaths occurred (Arnold et al., 2017). Autoimmune disorders, mainly thyroid disfunction, was reported with high incidence by several studies (Arnold et al., 2017; Ziemssen et al., 2020; Zmira et al., 2021).

Overall, 87% of participants experienced at least an adverse effect when subjected to daclizumab treatment. Among them, 13% were ranked as severe. Side effects affecting to at least 10% of participants or more were skin diseases (38%), nasopharyngitis (17%), upper respiratory tract infection (15%), headache (11%) and urinary tract infection (11%) (table 3). The overall safety outline observed in this study coincide with previous trials, and no new safety concerns were experienced. Moreover, incidence of infections was consistent over time. The total proportion of patients withdrawing treatment was higher with daclizumab 150 mg dosage (Gold et al., 2020).

Natalizumab was generally well tolerated (Kapoor et al., 2018). The side effects showing greater incidence values were urinary tract infection (23%), nasopharyngitis (22%) headache (15%) and respiratory infection (11%) (table 3). These events remained consistent among patients after several dosage. Furthermore, the profile experience by secondary progressive patients was similar to what has been observed in RRMS. The proportion of patients experiencing serious events was parallel for natalizumab treatment (20%) compared to placebo (22%) (Kapoor et al., 2018). A novel study showed that natalizumab home infusions are as safe as receiving treatment on a clinic. The most common infection at home was urinary infection (Schultz et al., 2021).

Throughout studies, the proportion of infusion related reactions were highest after first dose of ocrelizumab but decreased over successive dosing exposure. Also, the use of appropriate prophylactic treatment contributed to lower down the severity of infusion related reactions (Mayer et al., 2019) . In particular, more than 99% of patients experienced a reduction of reactions thanks to the use of corticosteroids and antihistamines. It is also important to note that African descendants experience a different disease evolution than Europeans. According to Cree et al (2021), adverse events are more frequent among African descendants. In the latest trial, 97.4% of African individuals experienced adverse effects after ocrelizumab treatment, compared to 92% of European patients. Most of the adverse events were mild to moderate with ocrelizumab. The proportion of acute adverse effects was 2.4% (Mayer et al., 2019) and 7% (Hauser et al., 2017). One was life threatening (bronchospasm). Additionally, one death occurred because of suicide (Hauser et al., 2017). The most common infections were respiratory and urinary infections, skin disorders and gastroenteritis (Hauser et al., 2017; Mayer et al., 2019) (table 3).

No patient died when treated with ofatumumab and reported adverse events where low to moderate. Moreover, the proportion of serious events remained between 1% and 2%, with no cases of opportunistic infections (Bar-Or et al., 2018). Shared side effects were

injection-related reactions, nasopharyngitis, headache, upper respiratory tract infection, and urinary tract infection (table 3). Bronchitis occurred in 2.5% and pneumonia in 0.3%. (Hauser et al., 2020).

Patients treated with opicinumab experienced influenza-like illness (43%) and headache (16%) as common side effects (table 3). The proportion of serious events was 6% and included suicide and bipolar disorders. The proportion of people discontinuing the treatment was higher with increased dosage of opicinumab (100mg/kg and 30 mg/kg). (Cadavid et al., 2019).

Rituximab was, in general, well tolerated (Bergman et al., 2021). Urinary tract infection, respiratory infection, depression, gastroenteritis and nervous system disorders are common adverse effects reported by two studies; Bergman et al (2021) and Honce et al. (2019) (table 3). In both studies the number of participants was less than sixty people. However, one assesses the effects of rituximab for RRMS, whereas the other one focuses on progressive forms. This might explain the difference between the incidence values informed by both surveys (43% vs 25%). In addition, influenza-like illness was reported by Honce et al. (2019) and not by Bergman et al (2021). Besides 4 hospitalizations occurred, the incidence of severe adverse events was not very high (Honce et al., 2019). Also, two cases of meningitis were recorded by Bergman et al (2021).

In a phase I trial, temelimab was tested among 24 healthy volunteers. Adverse events with higher incidence rates were respiratory and nervous system disorders. Interestingly, no serious adverse events were reported (Porchet et al., 2019). These findings cannot be compared to other trials since the cohort is constituted by healthy volunteers. On another hand, it opens the door to future studies.

Ublituximab was well tolerated and no patients stopped the treatment. Adverse effects were predominant after first infusion but weakened after subsequent doses. 58% of the patients experienced infusion related reactions. Additional side effects were respiratory infection (15%), nausea (15%), influenza (13%), headache (10%), gastroenteritis (10%) and fatigue (10%) (table 3). The main shortcoming of this trial was the small sample size. Additional research is required regarding this drug (E. Fox et al., 2021).

As the number and conditions of the participants differ across different studies, it is not very accurate to compare the proportion of people affected by any adverse event However, based on the results, it can be stated that all monoclonal antibody-based drugs were safe and well tolerated. The incidence of serious adverse events was not greater than 14% for most cases, except for natalizumab described by Kapoor et al. (2018).

Moreover, the number of deaths remained low among trials, and some of them were not even related to the drug´s effect (Ex.: suicide). The therapy with a lower proportion of severe adverse side events was rituximab (0.09%) (Bergman et al., 2021), as it only contains 23 participants. Based on table 3, the most common adverse effect among all studied treatments were urinary tract infection, respiratory infection, headache and gastroenteritis; all of them in a low to moderate point. Besides, several serious adverse effects were reported by patients, such as autoimmune and mental health disorders that must be taken into consideration.

4.4.2 Efficacy

To assess the efficacy of a drug for MS treatment, the studies were mostly evaluating MS relapses, number of new T1 and T2 lesions, achievement of NEDA and progression of disability as outcome variables. Table 4 shows the most important outcomes and the efficacy proportions across studies. For each drug, outcomes are shown in alphabetic order. If there is more than one reference per outcome, then they are ordered from the highest percentage of people affected to the lowest. The total number of participants is shown in brackets, in the third column. It is important to mention that a high percentage value of MS relapses and new MRI lesions implies a lower effectivity of the drug. On the contrary, elevated values of NEDA are desired, as it indicates a high efficiency of the therapy.

Table 4. Outcomes per drug, study and its incidence

Drug	Outcome	Affected participants in %, (cohort size)	Reference
Alemtuzumab	MS relapses	53%-49% (581)	(Ziemssen et al., 2020)
		29% (35)	(Zmira et al., 2021)
	NEDA	63%-53% (581)	(Ziemssen et al., 2020)
		39% (581)	(Arnold et al., 2017)
		33% (35)	(Zmira et al., 2021)
Daclizumab	MS relapses	29% (410)	(Gold et al., 2020)
	Number of patients with new T1 lesions	46% (410)	
	Number of patients with new T2 lesions	30% (410)	

Natalizumab	Disability worsening	14% (231)	(Perumal et al., 2019)
		5.9%-4.8% (290)	(Trojano et al., 2021)
	MS relapses	15.9% (231)	(Perumal et al., 2019)
		14% (290)	(Trojano et al., 2021)
		5%-2% (889)	(Kapoor et al., 2018)
		1.9% (111)	(Butzkueven et al., 2020)
	NEDA	44.4% (231)	(Perumal et al., 2019)
	Number of patients with new T1 lesions	34% (111)	(Butzkueven et al., 2020)
		26-20% (889)	(Kapoor et al., 2018)
		14% (290)	(Trojano et al., 2021)
	Number of patients with new T2 lesions	40% (111)	(Butzkueven et al., 2020)
		8.3% (290)	(Trojano et al., 2021)
Ocrelizumab	NEDA	47.9% (732)	(E. J. Fox et al., 2018)
	MS relapses	16% (835)	(Hauser et al., 2017)
Ofatumumab	Disability worsening	10.9%-8% (930)	(Hauser et al., 2020)
	Number of patients with new T1 lesions	10% (232)	(Bar-Or et al., 2018)
Opicinumab	Number of patients with new T1 lesions	47%-41% (263)	(Cadavid et al., 2019)
Rituximab	MS relapses	22% (53)	(Honce et al., 2019)
	Number of patients with new T1 lesions	11.1% (23)	(Bergman et al., 2021)
	Number of patients with new T2 lesions	25.93% (23)	
Ublituximab	NEDA	74% (49)	(E. Fox et al., 2021)
	Number of patients with new T1 lesions	0% (49)	
	Number of patients with new T2 lesions	15% (49)	

*NEDA refers to maintenance of both; clinical NEDA and MRI NEDA

Alemtuzumab is currently approved for RRMS treatment. Thereby its outcomes are well studied and, some of them, summarized in table 4. However, a comparison between the available publications is not possible because the characteristics of the cohort are not the same. In patients with active RRMS, more than 53% of them remained relapse-free during 3-9 years of alemtuzumab treatment; and 60% showed improvement in MRI lesions. Moreover, the efficacy was maintained during the whole study (Ziemssen et al., 2020). Similarly, it was reported that 39,5% of patients following this therapy attained NEDA after 5 years (Arnold et al., 2017), and the outcomes remained stable over time. A real-world study of RRMS patients who went through previous disease modifying

therapies stated that 33% of patients achieved NEDA, plus, relapses and brain lesions were significantly reduced (Zmira et al., 2021).

Daclizumab is another drug under clinical trials. Table 4 shows that 29% of participants experienced MS relapses, 46% new T1 lesions and 30% new T2 lesions. The efficacy was maintained over eight years. Besides the low incidence of relapses and MRI outcomes, the study lacks control group. Thereby, conclusions regarding its efficacy are inaccurate (Gold et al., 2020).

Natalizumab is an approved drug to treating RRMS. Findings of Perumal et al. (2019) support the idea that patients treated with natalizumab achieve NEDA when the disease is not in an advanced state. 44% of patient achieved overall NEDA in the first year. This means, that there was no evidence of relapses nor new MRI outcomes. After the trial, only 15.9% of patients experienced MS relapses, and 14% disability worsening (table 4). Furthermore, 49.4% of patients improved their cognitive functions. The results by Trojano et al. (2021) were slightly better, with less proportion of disability worsening. Moreover, they concluded that infusing subcutaneous or intravenous Natalizumab was as safe and efficient than doing it every 6 weeks. On the other hand, infusing natalizumab every 12 weeks turned out with MRI worsening and greater number of relapses; demonstrating that natalizumab's effects are reversible after 8-12 weeks. According to table 4, the number of patients with new T1 lesions was 34% (Butzkueven et al., 2020) vs 14% (Trojano et al., 2021). Percentage of patients with new T2 lesions was 40% (Butzkueven et al., 2020) vs 8,3% (Trojano et al., 2021). An explanation to this could be that the first trial took place for 6 months, whereas the second lasted 12 months, supporting the idea that natalizumab maintains long-term efficacy. A novel pilot study pointed out that home therapy was as efficient as clinical therapy (Schultz et al., 2021). Alternatively, when studying the effects of natalizumab in SPMS, efficacy was also observed regarding MRI measures. In addition, 44% of patients improved their upper limb disability, however, it did not reduce disability progression as expected (Kapoor et al., 2018). As effects of natalizumab treatment differ between RRMS and SPMS, it is suggested that the underlaying mechanisms between these MS subtypes are also unlike.

Ocrelizumab, the only approved drug to cope with progressive forms of MS, has demonstrated to lower relapse rates, to improve disability and to substantially reduce T1 and T2 lesions when compared with IFN-β therapy (Hauser et al., 2017; Kappos et al., 2020; Turner et al., 2019). These findings showed that relapse rates where 46%-47% lower under ocrelizumab therapy (when compared to IFN-β), and 47% of patients

reached NEDA. Furthermore, the drug also demonstrated to reduce the deterioration of upper extremity in patients with progressive forms of MS (E. J. Fox et al., 2018).

Ofatumumab trials for RRMS reduced new brain lesions in more than 90%. The most effective subcutaneous administration of ofatumumab happened to be 60mg over 12 weeks (Bar-Or et al., 2018). Similar findings were reported by Hauser et al. (2020), who stated that ofatumumab is more efficient than teriflunomide in reducing MRI lesions. The drug was also associated with lower relapse rates but did not improve disability condition.

Opicinumab was tested for RRMS and SPMS therapy. However, there were no significant effects when comparing opicinumab group *versus* placebo. The highest score of disability improvements occurred with opicinumab 10 mg/kg (65%), whereas the lowest rates were with opicinumab 100 mg/kg (40%). In contrast, 49% of participants assigned to placebo confirmed disability improvement. Overall, findings did not support the linear dose-response plus no major enhancements were recorded (Cadavid et al., 2019).

Two clinical trials assessed the efficacy and safety of rituximab for MS therapy. The major limitation for both trials is the small sample size, plus the lack of control group in Bergman et al (2021). In an attempt to cope with PPMS, rituximab treated patients showed an important worsening in walking ability. On the other hand, it seemed to enhance hand function (Bergman et al., 2021). In regard to RRMS, Honce et al, (2019) suggested that rituximab therapy followed by GA might be more beneficial than GA monotherapy. After the assay, 44,44% of participants achieved NEDA with rituximab-GA compared to 19,23% with GA monotherapy. No differences were observed in T1 lesions while T2 lesions were reduced with the combinatory treatment.

The outcomes of a phase II clinical trial for ublituximab treatment appear to be promising. After the treatment, 95% of relapse rate was reduced and 93% of patients remained relapse-free. Moreover, 74% of the patients achieved overall NEDA. No patient showed new T1 plus only 15% exhibited T2 lesions. Although the sample size of this study is small, the favourable outcomes have brought this drug to phase III clinical trial (E. Fox et al., 2021).

Based on table 4, the best outcomes regarding MS relapses and new T1 and T2 lesions were reported by ublituximab treatment (E. Fox et al., 2021). However, the sample size of this study is very small (49 participants). On the other hand, the worst outcomes were reported with alemtuzumab for MS relapses (Ziemssen et al., 2020); opicinumab for new T1 lesions (Cadavid et al., 2019); and natalizumab for new T2 lesions (Butzkueven et al., 2020). In terms of NEDA achievement, the most successful therapy was ublituximab.

The efficacy of natalizumab, ocrelizumab, alemtuzumab and ofatumumab are well studied as they are approved MS drugs. Natalizumab and alemtuzumab are currently approved as second-line treatments for RRMS. However, findings from Perumal et al. (2019) demonstrated that greater benefits can be achieved, in terms of NEDA, if employed as first line therapy. Regarding the therapies that are currently under trial, outcomes from ublituximab and daclizumab seem to be promising. Besides, these trials account with some shortcomings such as small sample size or the lack of control group (E. Fox et al., 2021; Gold et al., 2020). Rituximab therapy followed by GA has also shown to be more effective than GA monotherapy (Honce et al., 2019). The only drug that showed no beneficial outcomes was opicinumab (Cadavid et al., 2019). Moreover, no other drug than ocrelizumab has demonstrated to be effective for PPMS. Overall, it can be stated that monoclonal antibody based-therapies reduce relapse rates and improve both, brain lesions and disability. The outcomes seem to be more beneficial than interferon beta treatments, although the latest is still the first-line therapy option.

4.4.3 Mechanisms of action

The therapeutic target of each drug is shown on table 2. Most of the treatments studied are focused on cell depletion to minimize patient's immunoglobulin autoreactivity. Alemtuzumab and daclizumab target T and B lymphocytes, while ocrelizumab, ofatumumab, rituximab and ublituximab neutralize B lymphocytes only. The first two bind to the CD52 antigen expressed in both, T and B lymphocytes. On another hand, ocrelizumab, ofatumumab, rituximab and ublituximab attach to antigen CD20, which is only present in B cells lymphocytes. The precise mechanism of action is not fully clarified. It is understood that, somehow, the binding of the drugs to immunological cells enhances cellular cytolysis, cellular phagocytosis, cellular apoptosis and cellular lysis (Gibiansky et al., 2021) (figure 10). Targeting T lymphocytes logical, as MS has classically been considered a T-cell mediated autoimmune disorder. However, findings show that B cells play an important role in the course of the disease (Baker et al., 2017; Gibiansky et al., 2021). Thereby, many treatments successfully target B-cells. However, B-cell depletion has been linked to the development of secondary autoimmune diseases as side effects (Baker et al., 2017).

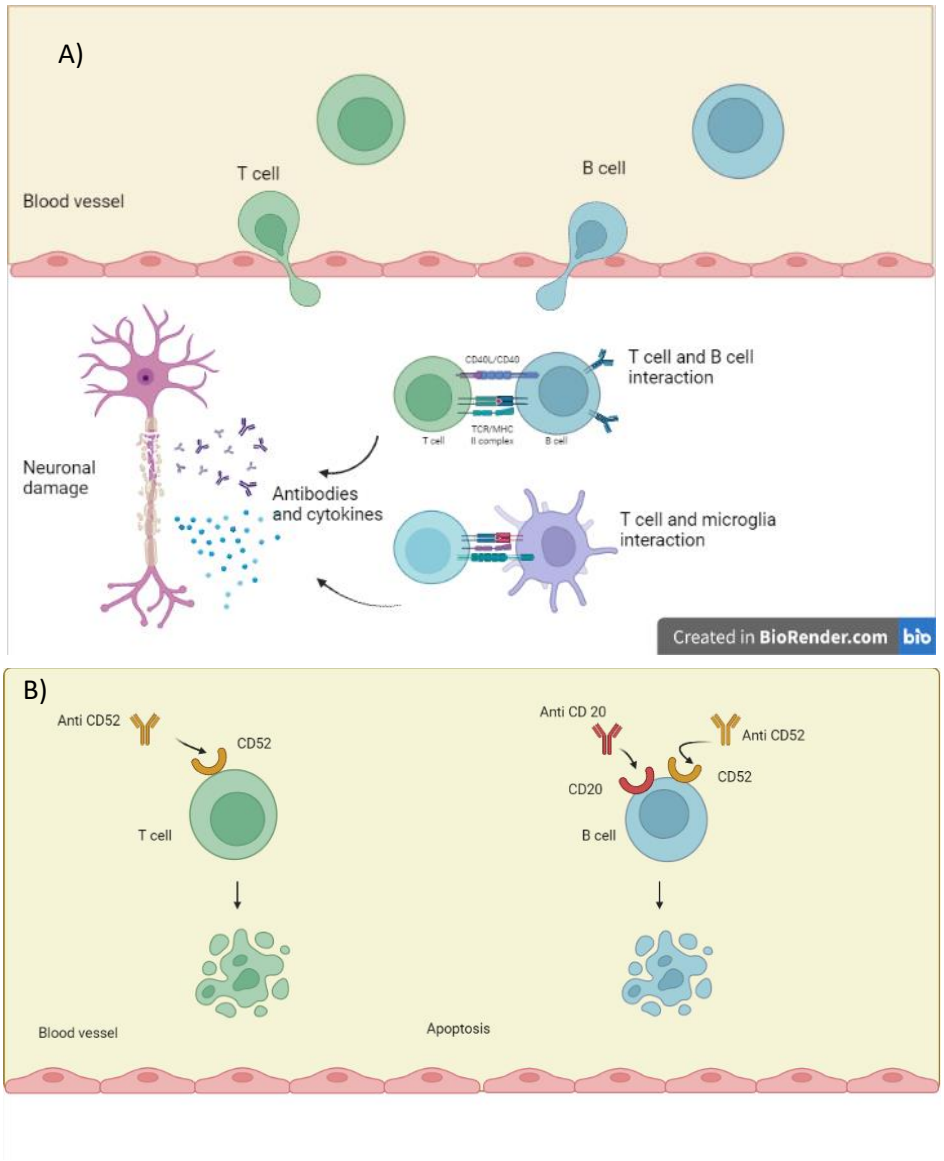

Figure 10. A) MS pathogenesis. Immune cells can cross the BBB. Once in the CNS, T cells are reactivated by local antigens presented on the surface of dendritic cells, macrophages or B-cells. The release of cytokines recruits more immune cells, leading to axonal damage. B) Two therapy approaches are the use monoclonal antibodies against CD52 (yellow) or against CD20 (red), causing apoptosis of immune cells. Created with Biorender.com (accessed on 5 June 2022).

It was stated that alemtuzumab is among the most powerful therapies approach for MS (Baker et al., 2017). The drug brings about a marked great depletion of B and T lymphocytes, which is linked with the inhibition of RRMS. Indeed, the involvement of some regulatory B cells and NK cells have been linked with the risk of T1 lesions. On the contrary, T2 lesions were associated with T cells (Gilmore et al., 2020). Several studies demonstrated the long-term inhibition of both cell types, with B lymphocytes recovering faster (within 6 months) than T lymphocytes. The setback is that repopulation of B

lymphocytes in an environment lacking T lymphocytes enhances the risk of infection or secondary autoimmune diseases development, which must be taken into consideration (Baker et al., 2017; Gilmore et al., 2020). Furthermore, the implementation of additional B-cell targeting therapies after alemtuzumab may lead to worst and fatal outcomes (Baker et al., 2017).

Several drugs deplete only B cells (ocrelizumab, ofatumumab, rituximab and ublituximab), which demonstrated to be a potential treatment approach (Bergman et al., 2021; Hauser et al., 2020; Honce et al., 2019). The studied B-cell-depleting monoclonal antibodies attach to a transmembrane antigen (CD20), each of them to a specific epitope, on the surface of pre-B cells. This induces cell death and phagocytosis through NK and macrophages. After therapy, B lymphocytes are can repopulate since CD20 is not expressed on stem cells (E. Fox et al., 2021). Although B-cell targeting had been assumed to be inefficient for SPMS (Bergman et al., 2021), it has proved to be effective for RRMS as for PPMS (E. J. Fox et al., 2018). In fact, ocrelizumab is the only drug approved for PPMS. Gibiansky et al. (2021) demonstrated a high degree of B-cell depletion after ocrelizumab therapy in both, RRMS and PPMS. Most of the patients (90%) experienced a repopulation of immunological cells after 2,5 years of the last infusion.

Natalizumab exhibits a different mechanism of action. It acts by blocking the migration of cells through the BBB. The antibody binds to α-integrin, an extracellular protein of the lymphocytes that interacts with VCAM1 receptors expressed over the BBB. The interaction of α-integrin and VCAM1 modulates the passage of lymphocytes to the brain (figure 11). Natalizumab shows high effectiveness in RRMS. In addition to preventing cell migration through the BBB, it supresses chronic inflammation and disrupts cell recruitment (Kapoor et al., 2018).

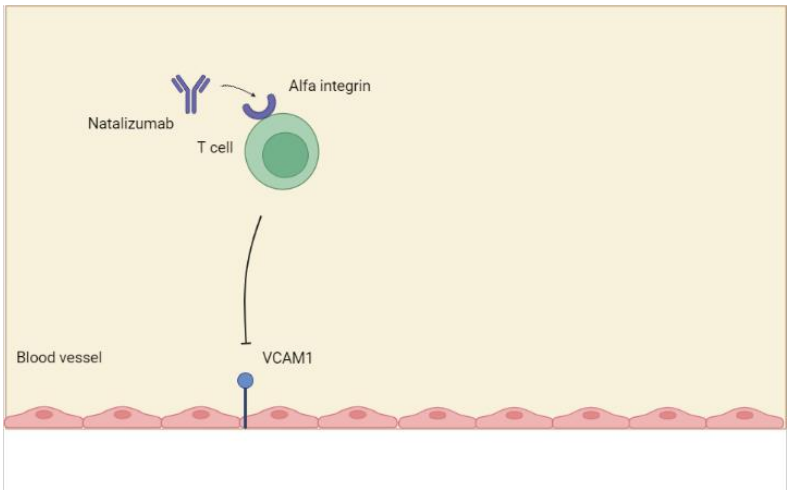

Figure 11. Natalizumab is an anti-alfa integrin, which acts preventing cell migration through BBB. Created with Biorender.com (accessed on 5 June 2022)

Opicinumab is a monoclonal antibody against LINGO-1 glycoprotein. When this protein is expressed on the surface of CNS neurons and oligodendrocytes, it promotes demyelination coupled with oligodendrocyte, neuronal and axonal damage (Cadavid et al., 2019). Although there is no evidence that opicinumab interferes with T-cells and cytokine production, it appears to facilitate remyelination *in vitro* (Mi et al., 2009). However, findings from Cadavid et al., (2019) were not promising and did not meet the primary hypothesis. Overall, findings did not support the linear dose-response plus no major enhancements were recorded.

The last therapy approach reviewed in this study is the one offered by temelimab. This monoclonal antibody targets an envelope protein of HERVs, which it has been linked with the risk of developing MS. The approach seems to be reasonable, as human endogenous retrovirus induces myelin degeneration by generating reactive oxygen and nitrogen species, as well as cytokines. The study by Porchet et al., (2019) was a phase I trial, aimed at assessing high doses of temelimab in healthy male volunteers. Thus, more efforts should be made regarding this therapy option.

It is evident that the majority of the monoclonal antibody-based therapies target immunological cell depletion. This approach, together with cell migration blockage have shown the best outcomes for treating MS and ameliorating the symptoms so far.

5. CONCLUSIONS

Based on the objectives and from the results obtained it is concluded:

a) The interest on monoclonal antibody-based MS therapies has gradually increased since 2017, reaching its maximum point in 2020. In addition, most of studies are published in journals categorized in the field of neurology.

b) Most of the literature assessing monoclonal antibody-based therapies for MS in the last five years are in phase III trials and focus on RRMS. The most studied drug over the last five years is ocrelizumab. The main interests when evaluating a therapy option are safety, tolerability and efficacy.

c) All monoclonal antibody-based drugs are safe and well tolerated. The incidence of serious adverse events is not greater than 14% for most cases. The most common adverse effects among all monoclonal antibody treatments are urinary tract infection, respiratory infection, headache and gastroenteritis.

   In terms of efficacy, natalizumab, ocrelizumab, alemtuzumab and ofatumumab are well studied. Natalizumab and alemtuzumab are currently approved as second-line treatments for RRMS. However, findings demonstrate that greater benefits can be achieved, in terms of NEDA, if employed as first line therapy. Regarding the therapies that are currently under clinical trials, outcomes from ublituximab and daclizumab seem to be promising. Also, Rituximab therapy followed by GA has also shown to be more effective than GA monotherapy.

d) Most of the monoclonal antibody based-therapies target immunological cell depletion. This approach, together with cell migration blockage have been reported the best therapies for treating MS and ameliorating the symptoms. However, several serious adverse effects have been reported by patients, such as infections linked to the immunomodulatory effect of these drugs.

e) Among the reviewed drugs that still remain under clinical trial (not approved), ublituximab and daclizumab seem to be the most promising ones. Therefore, further investigations must continue. Additional efforts should be invested for PPMS and SPMS.

6. CURRENT DEVELOPMENTS AND FUTURE DIRECTIONS

EBV has long been suspected to be, somehow, related to MS pathogenesis. Studies supporting this idea demonstrated the presence of EBV in MS lesions (Serafini et al., 2007), however the results remained inconclusive. Additionally, the fact that anti-CD20 monoclonal antibodies (targeting B cells) are among of the most effective treatments for MS, strongly backed up this hypothesis, as EBV remains in latent phase as host of memory B cells (Hauser et al., 2017). The decisive connection between EBV and MS was made in 2022 by Bjornevik et al. The study assessed 801 MS cases, reporting only one EBV-negative individual among them. Furthermore, at baseline the patients that were EBV-negative had no signs of neurodegeneration. However, after being infected with EBV, all but one turned EBV-positive and exhibited neurodegeneration plus MS onset. The study also determined that the presence of cytomegalovirus lowers the risks associated with EBV, underlying the interconnection between environmental factors that affect disease development. These findings strongly suggest that EBV is a causing agent of MS pathogenesis. Although the gene *HLADRB1* is also a known strong risk factor for MS, most MS patients happen to be EBV positive. Thereby, a suitable EBV vaccine could have greater benefits for MS prevention when compared with B-cell depleting therapies (Bjornevik et al., 2022). Further studies in this field demonstrated the presence of a molecular mimicry between EBNA1 and GlialCAM, which triggers MS pathogenesis (Lanz et al., 2022) (figure 12). EBNA1 is a nuclear antigen of EBV, essential for the latent infection of the virus (Frappier, 2015), while GialCAM is a protein expressed by glial cells in the CNS (Favre-Kontula et al., 2008). The similarity between these two molecules is the main cause leading the autoimmune process, fact which is further supported by the occurrence of cross reactivity between EBNA1 and GlialCAM (Lanz et al., 2022). Lanz et al (2022) reported that antibodies for *IGHV3-7* gene-encoded heavy chains bound EBNA1 and GlialCAM, thus creating a direct link between both, EBV and *IGHV3-7* with MS pathogenesis. In addition to GlialCAM, other two molecules present in glial cells were previously reported to exhibit molecular mimicry with EBV surface protein, EBNA1, these are; Myelin Basic Protein (MBP) (Jog et al., 2020) and Anoctamin 2 (Tengvall et al., 2019) (figure 12).

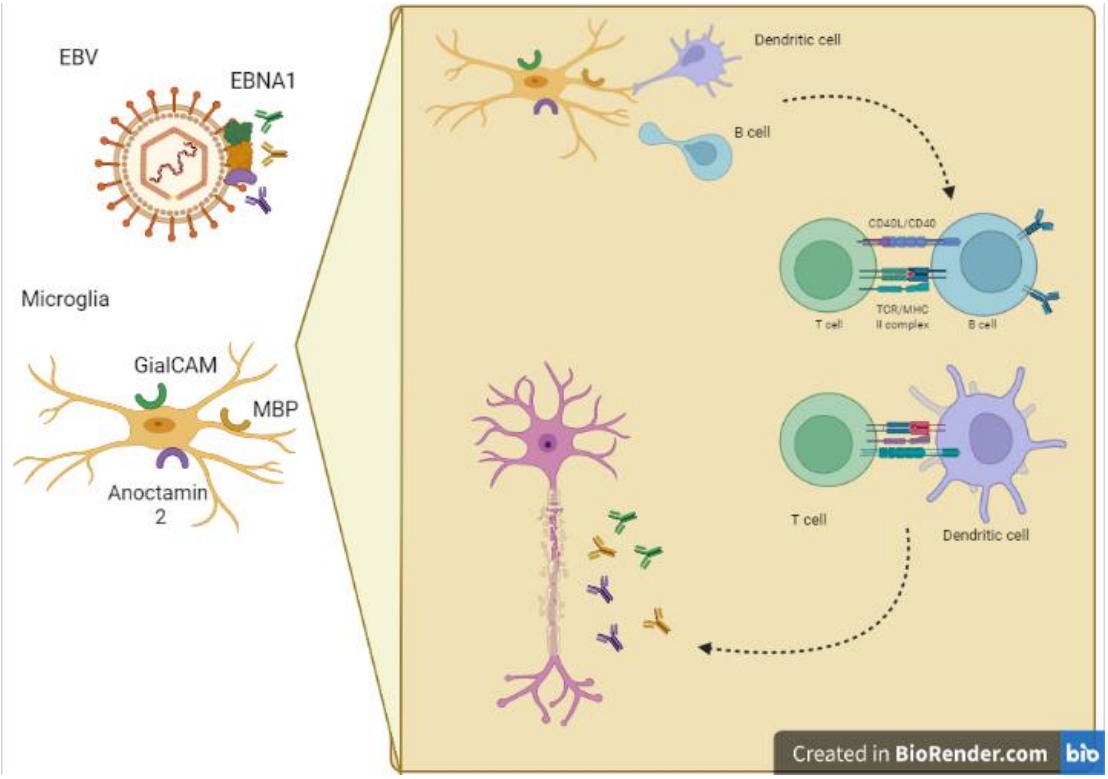

Figure 12. MS pathogenesis as a consequence of molecular mimicry of GlialCAM, MBP or Anoctamin 2 with EBNA1. Created with Biorender.com (accessed on 5 June 2022).

This paradigm raised interest in EBV based therapies for MS treatment. Currently, an mRNA vaccine against EBV is being assessed under phase I clinical trial (NCT05164094). Although the main purpose of the latest trial is to avoid mononucleosis and EBV infection, it may facilitate and encourage MS prevention as well. Moreover, vaccination may also benefit already infected cases of EBV, specially in those who hold a persistent-latent infection (more than 90% of the adult population) (Dobson et al., 2022). Future research lines regarding anti-EBV therapies may include anti-virals, monoclonal antibodies against EBV or targeted immunotherapies against EBV infected cells. Understanding the association between EBV and MS might show potential pathways for prevention. However, it cannot be forgotten than environmental and genetic factors play an important role for the course of the disease. Thus, alternative therapies should not be dismissed. In reference to monoclonal antibody-based therapies, efforts must be continued for some promising drugs such as ublituximab and daclizumab. Lastly, more attempts are needed for the treatment of PPMS and SPMS. As seen in the current systematic review, RRMS is, by far, the most studied MS subtype in terms of therapy. There is no drug approved for SPMS, and only one for PPMS. The number of approved RRMS drugs is greater because RRMS affects more people and because it is

more difficult to treat the disease when it is more advanced, since the neuronal damage is extended. However, progressive forms are more disabling and new approaches should be evaluated.

Overall, I hope that this work will help to comprehend the course of MS monoclonal antibody-based therapies and contribute to their further refinement and implementation.

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