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Placing CD20-targeted B cell depletion in multiple sclerosis therapeutic scenario: Present and future perspectives

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ABSTRACT

Multiple sclerosis (MS) is an acquired demyelinating disease of the central nervous system (CNS) that traditionally has been considered to be mediated primarily by T cells. Increasing evidence, however, suggests the fundamental role of B cells in the pathogenesis and development of the disease. Recently, anti-CD20 B cell-based therapies have demonstrated impressive and somewhat surprising results in MS, showing profound anti-inflammatory effects with a favorable risk–benefit ratio. Moreover, for the first time in the MS therapeutic scenario, the anti-CD20 monoclonal antibody ocrelizumab has been granted for the treatment of the primary progressive form of the disease. In this review, we provide a brief overview about anti-CD20 B cell-based therapies in MS, in the perspective of their influence on the future management of the disease, and of their possible positioning in a new wider therapeutic scenario.

1. Introduction

Multiple sclerosis (MS) is the most frequent chronic inflammatory disease of the central nervous system (CNS) affecting > 2 million people worldwide [1]. About its etiopathogenesis, a genetic susceptibility is heavily influenced by environmental factors, including: a) geographical/latitude effects (mostly related to sunlight exposure); b) life style habits (including diet and smoking) [2–5]; and c) infections (primarily, Epstein-Barr virus-related). MS pathologic features are characterized by inflammation, demyelination, and axonal loss, which underlie an extreme inter- and intra-individual variability of neurological signs and symptoms, typically disseminated in time and space, and, ultimately, of prognosis of the disease [1,6,7]. As for the clinical evolution, about 80% of people with MS experienced a relapsing-remitting course (RRMS), that is characterized by attacks of neurologic symptoms (also called relapses or exacerbations) which are followed by periods of partial or complete recovery (remissions) [8]. Most people with RRMS may transit to a secondary progressive course (SPMS), in which there is a progressive accumulation of disability over time. Approximately 10% of patients suffer from primary progressive MS (PPMS), which is characterized by accumulation of disability since the beginning of the disease, with or without superimposed relapses [1].

Following the diagnosis of MS, the current international guidelines recommend starting treatment as soon as possible with a disease modifying therapy (DMT). The therapeutic choice is influenced by a) disease activity, b) disability status, c) risk-benefit assessment, and d) not less important, the patient's preference. The current licensed DMTs for MS are divided in two lines of treatment: first-line DMTs and second-line DMTs, which are mainly prescribed in cases of first-line DMT inefficacy. As a whole, one-third of patients respond to first-line DMTs, with a reduction in the relapse rate and stability of the lesion burden on the brain magnetic resonance imaging (MRI). These drugs, however, have little or no impact on long-term disability accrual, whereas initial data seem to support favorable effects on this important aspect of the disease by second-line DMTs [9–11].

On the other hand, first-line DMTs are usually safer and better tolerated than second-line DMTs, which, in turn, are characterized by the best efficacy profiles, in parallel with moderate-to-severe and

Abbreviations: ADAs, Anti-drug antibodies; AEs, adverse events; APCs, antigen-presenting cells; BBB, blood-brain barrier; BAFF, B cell-activating factor; CNS, central nervous system; DHAP, dexamethasone high-dose cytarabine cisplatin; DMT, disease modifying therapy; FDA, food and drugs administration; EAE, experimental autoimmune encephalomyelitis; mAbs, monoclonal antibodies; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorders; OCBs, oligoclonal IgG bands; OCR, ocrelizumab; OFA, ofatumumab; PML, progressive multifocal leukoencephalopathy; BRegs, regulatory B cells; RRMS, relapsing-remitting multiple sclerosis; RTX, rituximab; SPMS, secondary progressive multiple sclerosis; JCV, JC virus.

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potentially limiting adverse effects [12,13].

In the last years, we have witnessed impressive changes in MS therapeutic armamentarium and the therapeutic options are becoming more and more numerous and complex. In clinical practice, after initiating a first-line DMT, patients are monitored for disease activity, safety, tolerability, and adherence. When the onset of the disease is particularly severe from the clinical and radiological points of view, second-line DMTs can be started without using first-line DMTs. Patients continue the same DMT until the evidence of sub-optimal response, or if major adverse events (AEs), or adherence issues arise. The two main reasons for discontinuing DMTs are the lack of efficacy, and occurrence of AEs. When the response to a DMT is sub-optimal, patients should be switched to another DMT characterized by higher efficacy, in order to minimize the risk of accumulation of neurological deficits and long-term irreversible disease progression. Some patients are destined to get worsen, despite highly effective agents because of the inability of these drugs to fully curb the inflammation. These patients could be candidate for a hematopoietic stem cell transplantation that produces a new immune system that switch off inflammation [14,15]. The occurrence of mild-to-moderate up to severe AEs, or even a high risk of potentially occurring AEs, such as the JC virus serostatus-related risk of progressive multifocal leukoencephalopathy in patients on natalizumab, can induce a DMT shift [16]. Adherence to a DMT is also essential in a chronic condition, such as MS, and it is influenced by many factors, including the route of drug administration (*e.g.*, injection *vs* oral administration) and tolerability issues (*e.g.*, flushing and gastrointestinal upset by dimethyl fumarate).

Historically, MS has been described as a T cell-mediated autoimmune disorder, especially after the formal demonstration that both the MS-like pathology and relapsing clinical course were replicated in experimental autoimmune encephalomyelitis (EAE),the MS model obtained in marmoset [17]. However, the attempts at inducing EAE by the administration of encephalitogenic T cells showed that only by the co-administration of these cells with pathogenic autoantibodies (MOG antibodies in the MOG-induced EAE) could yield the MS-like demyelinating features [18]. The encephalitogenic T cells and the ongoing inflammatory response are necessary to open the blood-brain barrier (BBB), thus allowing the autoantibodies to enter the CNS and attack myelin. Meanwhile, the discovery that, within the MS brain lesions, infiltrates of B cells and plasma cells/blasts were responsible for the production of immunoglobulins with restricted heterogeneity, which were first described in the CSF (cerebrospinal fluid) as oligoclonal IgG bands (OCBs) on electrophoretic separation [19], favored the hypothesis that these antibodies could be pathogenic, similarly to what demonstrated for MOG antibodies in EAE. However, pathology studies showed that the antibodies bound to myelin sheaths had broad specificities, different from those found in EAE [20].

But, beyond the possible and still pending pathogenic role of the oligoclonal IgG, B cells could exert (co)-pathogenic roles in MS, acting as antigen-presenting cells (APCs) and as producers of both pro-inflammatory and anti-inflammatory cytokines. Moreover, tertiary ectopic follicles, which contain B and T cells, plasma cells/blasts and dendritic cells, were found in parenchymal plaques, in leptomeninges, and as perivenular expansions. These follicles characterize more frequently the secondary progressive form of MS (SPMS), which usually follows RRMS after a variable number of years from onset, and associate with more severe disease courses [21].

Finally, the impressive and renewed enthusiasm on B cells and MS received a fundamental boost with the advent of very promising B cell-depleting therapies; the targeted depletion of CD20 + B cells has proven to be an extremely effective method of suppressing inflammatory activity in MS, after the first demonstration of efficacy that dates back to 2008 [22]. Thereafter, the following anti-CD20 monoclonal antibodies (mAbs) have been used for MS treatment: rituximab (RTX), ocrelizumab (OCR), and ofatumumab (OFA), and others are in development.

The aim of our review is to provide a critical point of view about the CD20-targeted B cell depleting therapies in MS, with particular attention on how they could influence the management of patients in the future, and on their possible positioning within the expanding MS-related therapeutic armamentarium.

2. B cells in MS pathogenesis

The CNS has long been considered as an immune-privileged site, but accumulating data indicate that it is rather an immune-specialized site, as, among other features, blood peripheral cells of the immune system physiologically enter the parenchyma to permit effective immune surveillance(patrolling activity) [23–25]. Other features that contribute to the immune-specialization include the presence of barriers able to restrict the passage of large molecules and limit broader cell infiltration, such as the BBB, the blood–meningeal barrier, and the blood-CSF barrier [24].Within this complex scenario, very few B cells infiltrate the healthy CNS, whereas their number dramatically increases during inflammation. Increasing evidence suggests that, during inflammation, B cells settling the CNS mature outside, in secondary lymphoid organs, particularly at the deep cervical lymph node stations [26,27]. In line with this hypothesis, high-throughput sequencing studies on the antibody repertoire showed that clonally expanded B cells that encountered CNS antigens and experienced antigen-driven affinity maturation were present in both the CNS and peripheral blood compartments, and that the founding members of clones were more often detectable in the deep cervical lymph nodes [26]. Interestingly, interruptions of these 'reverberating' CNS-lymph node-CNS circuits involving both T and B cells can underlie at least part of efficacy of the drugs that prevent these cells from entering the CNS (natalizumab), or that deplete B cells (RTX and biosimilars). Moreover, it is well-established that both trafficking and residence of B cells into the CNS are sensitive to fluctuations of pro- and anti-inflammatory cytokines, which can promote the compartmentalization of the B cell response [28], and the persistence of memory B cells, plasmablasts, and plasma cells within the inflamed CNS [29]. As a result, mature B cell and plasma blast counts in the CSF correlate with the number of MS lesions on the brain MRI, and MS disease progression seems to be slower in patients without CSF OCBs [30].Finally, early demyelinating lesions exhibit significantly more B cells and plasma cells than lesions in later stages [31,32]. The role of the above-mentioned tertiary ectopic follicles, which contain plasma cells/blasts producing oligoclonal immunoglobulins, in MS progression and in the formation of cortical lesions has been recently hypothesized in earlier stages of the disease too [30,33].

Overall, many questions about the role of B cells in MS pathogenesis remain still unanswered. What factors drive B cells into the CNS, through which pathways do they travel, and is this cell traffic persistent or transient? When during disease do B cells populate the CNS, and are there other CNS niches in which B cells thrive? How do immune cell aggregates in the tertiary ectopic follicles contribute to MS pathology? However, notwithstanding all these open questions there is convincing evidence that an abnormal B-cell activation within and, possibly, outside the CNS can contribute to the pathogenesis and tissue damage in MS [26].

3. CD20 + Bcell-depleting therapies in multiple sclerosis

As reported in the introduction of this review, MS has been regarded as a mainly T cell-mediated disease. The possibility that B cell-targeting therapies could work in this disease was therefore viewed with skepticism for long time. Moreover, it has been a dominant belief, and it is also considered likely at present that OCBs can be an epiphenomenon of an abnormal immune system activation in the MS brain (8). As an indirect clue to support this view, the removal of antibodies with plasma exchange failed to obtain meaningful therapeutic results in this disease [34]. On the other hand, when Hauser and colleagues first proposed a trial with the anti-CD20 B cell-targeting monoclonal antibody RTX in

MS [35], they legitimately thought that it would take enough time before the drug lowered the whole humoral immune response and could be efficacious [35–37]. Decreasing autoantibody production by long-lived plasma cells was indeed a rational goal of the trial. But, being non-ethical to leave the placebo group without therapy for one year, food and drugs administration (FDA) established that the primary endpoint should have been measured at six months. It seemed clear that this timing would have been too short and have caused the failure of the trial. Unexpectedly, however, a rapid-onset efficacy of RTX in strikingly reducing both clinical and MRI activity was demonstrated [35]. The leading hypothesis of the trial was therefore wrong, and a novel view on B cell functions opened. The B cell roles as selective APCs that present previously encountered antigens to T cells directly, or *via* 'antigen shuttling' through macrophages, and as pro-inflammatory cytokine producers resulted emphasized to explain RTX efficacy [35].

CD20 is a four-transmembrane protein expressed on the surface of a part of B-lineage cells, from pre-B cells to memory B cells, but not on antibody-producing plasma cells or plasmablasts, although the results of a study in autoimmune mice suggests that anti-CD20 treatment may reduce the level of circulating autoantibodies possibly targeting CD20+ short-lived plasmablasts [36].Moreover, a subpopulation of T cells expressing CD20 has been described and demonstrated to be depleted from the blood by the anti-CD20 antibody-based therapies [38–40]. Such evidence can also suggest that the depletion of CD20 + T cells may contribute to the effects of anti-CD20 targeting drugs [41]. More recently, *in vitro* studies suggested that the RTX-mediated B cell depletion strongly reduces a particular characteristic of T cells, called 'autoproliferation', together with pro-inflammatory cytokine responses, and IFN-γ production [42].Additional, very preliminary data indicate that these autoproliferating T cell subtypes might possibly contribute to MS pathogenesis and progression [42]. Moreover, Jelcic and colleagues showed that the counts of blood T cells, among which the activated effector memory CD4+ T cells, were significantly reduced in RTX-treated patients *in vivo*, and that a drop of T cell autoproliferation followed the selective abrogation of B cell autoproliferation induced by ibrutinib, a Bruton tyrosine kinase inhibitor, thus suggesting the therapeutic possibility of selectively depleting only the potentially harmful autoproliferating B and T cells, instead of all the CD20 + B cells [42].Interestingly, the main genetic factor of MS, HLA-DR15, plays a central role in autoproliferation [42].Ibrutinib and biosimilars, which inhibit an enzyme fundamental for B-cell development, are in development for several autoimmune diseases including MS.

To date, three CD20-targeted B cell depleting therapies have been studied in MS: RTX (chimeric human/mouse IgG1), OCR (humanized IgG1), and OFA (fully human IgG1), all recognizing different epitopes of the CD20 protein, and showing different safety profiles (see Table 1 and Fig. 1).

Given the purpose of this review, we will not deeply go through these drugs, but will mainly focus on their possible placement in the MS therapeutic scenario.

3.1. Rituximab

RTX (MabThera®, Roche, Basel, Switzerland) was the first approved anti-CD20 drug for non-Hodgkin's lymphoma in 1998, and later for chronic lymphocytic leukemia, certain forms of vasculitis, and rheumatoid arthritis. RTX was tested in the above-mentioned phase II placebo-controlled trial in RRMS [35], and in a phase II/III trial in PPMS [43]. Thereafter, further clinical development was interrupted by the manufacturer,due to the patent expiration in the USA, scheduled between 2015 and 2018 [44]. However, during the following, and especially last years we have witnessed an impressive increase of off-label use of RTX for treating MS in clinical practice [45–48], up to reaching an approximate 40% share of all the prescribed DMTs in Sweden [49]. A recent study compared RTX to fingolimod in RRMS patients switching from natalizumab and demonstrated that RTX had a greater power in controlling disease activity and a better safety profile [50]. The topic of discontinuation of natalizumab is of great importance in the MS management, because it has been associated with rebounds of disease activity, and at present there are no established guidelines regarding the therapeutic management of post-natalizumab treatment. In another study, RTX was compared to other DMTs in a population-based sample of treatment naive RRMS, showing superiority over all other DMTs, including a lower relapse rate *vs* natalizumab [49].Moreover, a propensity matched study of 461 patients with RRMS treated with RTX, and either interferon beta or glatiramer acetate, showed a compelling 87% advantage of RTX in reducing relapse rates [51].

3.2. Ocrelizumab

OCR (Ocrevus®, Roche, Basel, Switzerland) has been recently approved by FDA and by the European Medical Agency for the treatment of RRMS and PPMS. The license has been granted after the positive results of a phase II study in RRMS, followed by two other phase III studies always in RRMS, evaluating 600 mg of OCR every 6 months against interferon beta-1a 44 μg three times weekly (Rebif®44). Moreover, in a placebo-controlled phase III trial,732 patients with PPMS were randomly assigned in a 2:1 ratio to receive OCR (600 mg), or placebo every 6 months) [52]. OCR was associated with lower rates of clinical and MRI progression than placebo. In detail, the percentage of patients with confirmed disability progression at 12 weeks was 32.9% in the OCR group *vs*39.3% in the placebo group ($p = .03$). Significant differences between the two groups were found for a) the worsening of performance on the timed 25-ft walk (38.9% *vs* 55.1%;$p = .04$);b) the total volume of brain lesions on T_2-weighted MRI sequences(decrease by 3.4% *vs* increase by 7.4%;$p < .001$); and c) the percentage of brain volume loss on MRI(0.90% *vs* 1.09%;$p = .02$). The infusion-related reactions, upper respiratory tract infections, and oral herpes simplex infections were more frequent with OCR and neoplasms occurred in 2.3% of the patients who received OCR *vs* 0.8% of patients who received placebo. Overall, with the exception of an increased risk of tumors, there was no clinically significant between-group difference in the rates of AEs and serious infections.

3.3. Ofatumumab

OFA (Arzerra®, Novartis, Basel, Switzerland)is a human IgG1 monoclonal antibody that binds a membrane-proximal CD20 epitope different than those recognized by both RTX and OCR [53]. Such binding to a particular epitope should entails a more efficient complement-dependent cytotoxicity [53]. In a phase II, double-blind, placebo-controlled, manufacturer-sponsored study, 38 RRMS patients were randomized to intravenous OFA at doses of 100 mg, 300 mg, or 700 mg, or placebo 2 weeks apart. A 99% reduction of new brain MRI lesions in the first 24 weeks after OFA treatment was found. The most common AE was an infusion reaction during the first dose. There was no reduction in serum IgG concentrations. A second phase II manufacturer-sponsored study of 4 doses of subcutaneous OFA *vs* placebo in 238 patients with RRMS showed a 65% reduction of new gadolinium-enhancing brain MRI lesions for each OFA dose, with > 90% reductions in weeks 4 to 12. In addition, no new or unexpected safety shortcoming occurred up to 48 weeks after starting the treatment. Injection-related reactions of mild to moderate severity in 97% of the cases, were the most common AE (52% in the OFA group *vs* 15% in the placebo group) [54]. Two identical, manufacturer sponsored, head-to-head, double-blind, phase III trials testing subcutaneous OFA (20 mg) *vs* teriflunomide are enrolling [55].

As for the differences, among the CD20-targeting B cell-depleting drugs, over the relative impact of complement-dependent cytotoxicity on their efficacy in human pathologies, some debate exists. *In vivo* studies in transgenic mice suggest that effector-mediated mechanisms are the most important [56]. Available evidence from direct head-to-

Table 1
Features of clinical trials of anti-CD20 B cell-based therapiesin multiple sclerosis.

DRUG, disease form, trial design, N. of patients, duration (Authors, year)	Type of intervention	Outcomes (Efficacy/Safety)
RTX, RRMS, phase I, open-label, multicentre, *N* = 26, 72 weeks *(Bar-Or A,* et al*., 2008)*	1000 mg iv. at 1 and 15 days at weeks 0 and 24 N. of cycles: 2	Neuroradiological activity: GdE lesions and mean number of new T2 lesions decreased. Clinical activity/disease progression: relapse free patients: 80.8%. AEs: AEsDR: 65.4% (mild 19.2%, moderates 46.2%)
RTX, RRMS, phase II, randomized, double-blind, multicentre placebo controlled, *N* = 104, 48 weeks HERMES *(Hauser SL,* et al*., 2008)*	1000 mg iv. at 1 and 15 days N. of cycles: 1	Neuroradiological activity: reduction (volume and number) of GdE lesions and volume of T2 lesions (24 and 48 weeks). Clinical activity/disease progression: reduction of ARR at 24 weeks. AEs: AEsDR: mild to moderate 92%
RTX, PPMS, phase II randomized, double-blind, multicentre placebo-controlled *N* = 439, 96 weeks OLYMPUS *(Hawker K,* et al*., 2009)*	1000 mg iv. at 1 and 15 days at weeks 0, 24, 48 and 72 N. of cycles: 4	Neuroradiological activity: less increase in T2 lesion volume ($P < .001$). AEs: comparable frequency between groups. SAEs: higher frequency in the RTX group
RTX, RRMS, phase II, open label, add-on therapy. *N* = 30, 52 weeks *(Naismith RT,* et al*., 2010)*	375 mg/m2 iv. weekly (4 doses)	Neuroradiological activity: reduction of mean number of GdE lesions ($P < .0001$). Clinical activity/disease progression: EDSS stability: 70% ARR decreased from 1.27 to 0.23 AEs: comparable frequency
OCR, RRMS,phase II, multicentre, randomized, parallel, double-blind. *N* = 220, 24 weeks *(Kappos L,* et al*., 2011)*	600 or 2000 mg iv, at 1 and 15 days (one cycle). IFN -β1a im: 30 μg once a week.	Neuroradiological activity: reduction of total number of GdE lesions: ($p < .0001$). Clinical activity/disease progression: reduction of ARR ($p = .0005$ and $p = .0014$ for 600 mgand 2000 mg respectively). AES: comparable between groups. One patient died (relationship with drug not confirmed).
OCR, RRMS,phase III. Multicentre, randomized, double-blind. *N* = 800 (OPERA I) and N = 800 (OPERA II) 96 weeks *(Hauser SL,*et al*., 2016)*	600 mg iv. 24-weeks cycles First cycle: twice 300 mg iv at 1 and 15 days, then single dose 600 mg iv. IFN -β1a sc: 44 μg three times weekly. IFN-β1a sc	Neuroradiological activity: reduction of total number of GdE lesions: 94% (OPERA I) and 97% (OPERA II). Reduction of new or enlarging T2-lesions: 77% (OPERA I) and 83% (OPERA II). Clinical activity/disease progression: reduction of ARR: 46% (OPERA I) and 47% (OPERA II). Reduction of confirmed progressive disability: 40%(OPERA I and II). AES: comparable between groups.
OCR, PPMS, phase III. Multicentre, randomized, placebo-controlled, double blind, *N* = 732, 120 weeks ORATORIO *(Montalban X,* et al*., 2017)*	300 mg iv.at 1 and 15 days at weeks 0, 24, 48, 72 and 96 N. of cycles: 5	Neuroradiological activity:Reduction of T2 lesion volume. Clinical activity/disease progression: risk reduction of progression of clinical disability: 24%and 25% (12–24 weeks). AEs: frequency comparable between groups. Frequency of malignancies higher inthe ocrelizumab group *vs* placebo.
OFA, RRMS Phase I/ II. Randomized, double-blind, placebo-controlled *N* = 38. 24 weeks *(Sorensen PS,* et al*., 2014)*	Two infusions of 100,300 and 700 mg IV at week 0 and 2	Neuroradiological activity:reduction of total number of GdE lesions. AEs: frequency comparable between groups.Infusion-related AEs more frequent in the ofatumumab group.
OFA, RRMS Phase II. Randomized, double-blind, placebo-controlled, parallel group *N* = 221. 24 weeks *(Bar Or,* et al*., 2018)*	3, 30 or 60 mg sc. every 12 weeks or 60 mg sc. every 4 weeks	Neuroradiological activity: reduction in the number of new and cumulative GdE lesions *vs* placebo. AEs:Infusion-related AEs more frequent inthe ofatumumab group.
OFA, RRMS, Phase III, randomized, double-blind/ double-dummy, active-controlled, multicentre. *N* = 1884 patients enrolled across 385 centres in 37 countries (ASCLEPIOS *I* = 928 and ASCLEPIOS II = 956). Flexible trial duration. *(HauserSL, et al, 2017)*	Patients randomized (1:1) to receive either ofatumumab 20 mg s.c. injections every 4 weeks (following an initial loading regimen of three 20 mg s.c. doses per week in the first 14 days) or teriflunomide 14 mg orally once daily	End of Study will be declared based on a pre-planned analysis of blinded data. When each study is powered to 90% for the primary and to ≥80% for all key-secondary endpoints.

AEs: Adverse events, AEsDR: Adverse events drug-related, ARR: annualized relapse rate, DMTs: disease modifying therapies, EDSS: expanded disability status scale, GdE: Gadolinium-enhancing, IFN-β1a: interferon beta 1a, MRI: magnetic resonance imaging, MS: multiple sclerosis, OFA: ofatumumab, OCR: ocrelizumab, PPMS: primary progressive MS, RRMS: relapsing-remitting MS, RTX: rituximab,SAEs: severe adverse events.

head comparison, in oncological field, indicates that the advantages of OFA *vs* RTX do not appear to translate into clinical superiority [56]. The ORCHARRD trial enrolled patients with relapsed or refractory diffuse large B-cell lymphoma who were treated with the protocol DHAP (dexamethasone, high-dose cytarabine, cisplatin), and then randomized to a combination with OFA or RTX; no clinical advantage was seen between the two groups [57]. Obviously, such evidence cannot be directly translated into the MS reality. Analogous head-to-head studies are needed in the wider field of the acquired demyelinating syndromes, which include neuromyelitis optica spectrum disorders (NMOSD), mainly affecting adults, and acute disseminated encephalomyelitis, mainly affecting children.

3.4. Open questions about the choice of anti-CD20 drugs

Many questions are raising about the reasons which tend to lead the

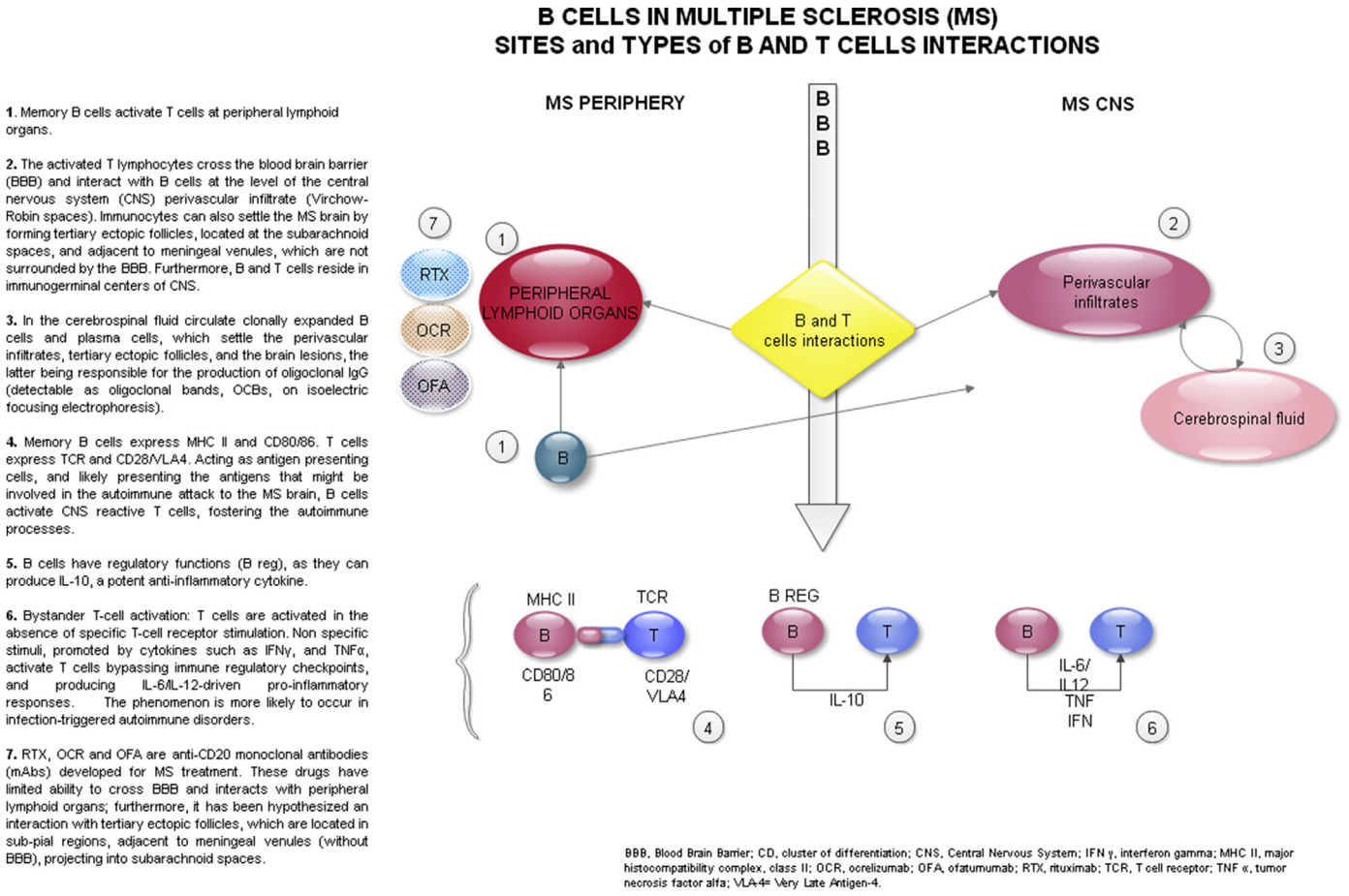

Fig. 1. B cells in Multiple Sclerosis: sites and types of B and T cells interactions.

MS specialists to the use of RTX when another anti-CD20 drug, namely OCR, is licensed for MS treatment. The major open questions on the preferential use of RTX regard: a)strictly medical concern, leaving cost issues aside, as the costs of RTX and its biosimilars are substantially lower than those of OCR; b) safety and effectiveness, which have long been assessed in real life in large numbers of patients in autoimmune conditions for RTX (although most of the data come from those with rheumatoid arthritis); c) slight differences in the mechanisms for depleting B cells, namely OCR has a higher capacity for antibody-dependent cellular cytotoxicity, and weaker complement-dependent cytotoxicity in comparison with RTX. Nevertheless, the data on the reduction of clinical relapses and of new lesions on the brain MRI are robust in recent MS trials for both RTX and OCR [22,58,59].

Moreover, both RTX and OCR have been tested in PPMS. In the Olympus study, RTX led to a reduction in the proportion of patients with 12 week-confirmed disability progression (8.3 percentage points), while the same figure for OCR in the Oratorio study was 6.4 percentage points ($p = .03$) [22,43,60]. About *immunogenicity,* the production of anti-drug antibodies (ADAs) may impact negatively the efficacy and tolerability of a therapy with monoclonal antibodies. In three trials of RTX in MS, ADAs were found in 25% and 29% of RRMS patients, and in 7% of PPMS patients. However, although a higher production of ADAs associated with the degree of B cell depletion, no clear correlations with clinical outcomes were described [61,62]. About OCR, ADAs were found in 0.4% and 1.9% of RRMS and PPMS patients, respectively [63].Such findings clearly suggest that RTX is more immunogenic than OCR, but, in addition to the current uncertain clinical meaning of the ADAs, caution is warranted since the methods of ADA detection differed between the studies. Lastly, regarding *safety,* infusion reactions and upper respiratory infections are the most common AEs overall for both RTX and OCR. The risk of progressive multifocal leukoencephalopathy (PML), a rare and devastating demyelinating disease of the CNS caused by the JC virus (JCV) usually occurring in immune-compromised patients, is low [64]. Long term data on safety is available from studies in patients with rheumatoid arthritis exposed to RTX [65]. The prevalence of PML is estimated to be 1/25,000 [66]. The *caveat* that what observed in rheumatoid arthritis cannot be simply translated into MS, again, should be considered. Another safety issue for these drugs regards cancer risk. The detected malignancies were doubled in the OCR groups *vs* the placebo group along the registrative process but designing a profile risk is difficult when the observation time is restricted to a few years only [38]. In contrast, RTX has been used for long time in other diseases (for almost two decades), and no serious concerns for increased risks of cancer have emerged. Obviously, extrapolation to MS reality should be done with caution due to the huge demographic and clinical differences in patient populations and administration regimens.

Finally, another open issue in anti-CD20 B cell-based therapies in MS and, more in general, in acquired demyelinating syndromes, concerns the duration of treatment and especially the timing of the re-infusion using RTX. In NMOSD, the efficacy of RTX is strictly dependent on the maintenance of B-cell depletion, and not on the amount of drug given. B-cell repopulation timing, however, is extremely variable and can span form a few months to several years [67]. For this reason, personalized therapeutic regimens based on the monitoring of circulating CD19+ B cells have been proposed, and retreatments are given only when repopulation emerges, thus allowing the reduction of the drug dosage without affecting efficacy [68]. However, the cut-offs set for repopulation (in most cases CD19+ B cells < 1% of peripheral blood mononuclear cells, or < 0.1% of total lymphocytes) are arbitrary and often dependent on single center experiences [69]. In

addition, it has been suggested that the monitoring of the CD19 + CD27 + B cells, namely the memory B-cell population, with a cut-off of 0.05% of total lymphocytes for the first two years of treatment could be the most reliable indicator for retreatment [69]. It must be considered, though, that all these data have been collected in patients with NMOSD, and no consensus is currently available for the timing of retreatment in patients with MS. As above mentioned, for this disease, OCR is the only licensed B-cell depleting drug, which is given every six months indefinitely. The adverse effects of the resulting long-lasting depletion of memory B cells are barely predictable at present.

In conclusion, we dramatically need effectiveness and safety studies, with stringent prospective follow-ups, which should compare the two drugs to find definite answers to the above-mentioned open questions. Investigators at the University of Colorado have launched such a study [70].

4. Future perspectives

T cells are still considered the master orchestrators in MS pathogenesis, but the advances in the B cell-oriented basic and clinical research have established the key role for B cells too. The impressive results of CD20-targeting drugs in modulating the inflammatory aspects of MS paved the way through a new therapeutic approach for patients, providing the opportunity to target directly some key components of the immune system, such as the CD20 antigen, without significantly compromising the function of the whole immune system. The ideal treatment should be based on a personalized approach determined by an individual patient's profile based on severity and prognosis of the disease, and on balanced treatment risks. The development of biomarkers in MS that can predict relapse rate and disability progression at onset, monitor ongoing disease activity, and assess treatment response has so far been limited since the potential candidates have lacked specificity, reproducibility, and accessibility in the clinical practice [71]. Despite considerable efforts, the only robust markers commonly utilised remain MRI and CSF OCBs, but both provide very limited prognostic information. Several additional potential biomarkers have been proposed, such as chitinase-3 like 1, neurofilament light chains, IgM OCBs and serum B cell-activating factor (BAFF), that is a cytokine that acts as potent B cell activator (see below). However, all of these biomarkers have so far failed to be applied in clinical practice [71].

The very recent evidence that the frequency of CD20 + T cells is significantly increased in the blood of RRMS patients, and that such subpopulations produce high level of pro-inflammatory cytokines (IFNγ, TNFα, and GM-CSF) opens new mechanistic interpretations of the CD20-targeting therapies, so far attributed to the depletion of B cells only, and to the reduced activity of T cells ascribed to the decrease of stimuli from the depleted B cells. A similar mutual depletion following RTX therapy has been proposed for the so-called autoproliferating B and T cells [29], which should exert pivotal roles in fostering MS pathology.

However, following the impressive results of CD20-targeting agents in controlling MS [22,59,72], alternative methods of depleting B cells have been investigated. One approach has been the use of CD19-targeting antibodies (MEDI-551), which target a broader range of B cells [73]. CD19 antigen is a type I transmembrane glycoprotein that is expressed on early pro-B cells, late pro-B cells, memory B cells, plasmablasts, and some plasma cells, the latter being the main cellular source of protective, highly target-specific antibodies, but also of autoantigen-specific antibodies. A differential expression of CD19 or CD20 antigens on plasmablasts and plasma cells suggested potential differences in the outcome of their therapeutic targeting [74]. MEDI-551 (an afucosylated humanized IgG1 kappa anti-CD19 monoclonal antibody) effectively blocked the formation of new MRI lesions in a phase II trial (NCT01585766) in MS [75]. Treatment-related AEs observed up to week 24 were single events. The most frequently seen AEs included nasopharyngitis (24%), upper respiratory tract infection (19%), urinary tract infection (14%), urinary tract inflammation (14%), pyrexia (14%), and increased blood pressure (14%). Overall, in this phase 1 study (n = 28), MEDI-551 appeared to have an acceptable safety and tolerability profile during the period tested [75].

Another attempt at targeting the humoral immune response has involved the down-regulation of growth and differentiation factors for B cells, which are described as altered in MS patients, particularly during relapses [76]. To this regard, atacicept, a recombinant fusion protein, composed of the transmembrane activator and calcium modulator and cyclophilin ligand interactor protein (TACI) and the constant region of humanIgG1, was tested in a placebo-controlled, double-blind, phase 2 trial. Atacicept is able to neutralize a proliferation-inducing ligand (APRIL) and the B lymphocyte stimulator (BLyS)/BAFF, that stimulate B cell growth and activation [77]. The drug, however, not only reduces circulating B cells, but also acts on plasma cells, decreasing serum antibody titers [78]. Unexpectedly, RRMS patients treated with atacicept suffered from dose-dependent disease exacerbations [79], and, in another trial, a higher proportion of optic neuritis patients converted to clinically definite MS *vs* placebo-treated patients [80]. As a result, the two trials were terminated early. From a speculative point of view, these findings are not easily interpretable based on current knowledge, underline the difficulties in successfully translating experimental insights from bench to bedside, and suggest that drugs targeting plasma cell can be detrimental in MS.

MS therapeutic landscape is impressively changing, and it is logical to speculate that, in such a complex disease, new emerging therapies should be focused to target the many components and functions of the autoimmune response, as soon as the knowledge about these aspects growths and new breakthroughs emerge. Moreover, interrupting the chain of pathological events when they have been already started could be not enough. The selective prevention of the pathogenic immune cells from entering the CNS through the BBB, and the developing of new drugs for neuro-protection and remyelination are unmet needs that should be pursued in the future. Such strategies could protect axons and myelin sheath from initial and further damage, and, hopefully, restore neurological functions in MS patients.

Another hot topic regards the strategies of switching from other DMTs (first line, or even second line treatments) to the CD20-targeting therapies, in the cases of therapeutic failure, or safety alerts. So far, there is scarce evidence in the literature on such topic, as the most studied switch is from natalizumab to RTX [33]. Moreover, pre-marketing trials include naïve-therapy MS patients, and therefore, over the medium-long term period, possible safety issues in patients whose immune system has been challenged by other previously taken DMTs are barely predictable. These concerns are particularly troubling when switching from medications, such as dimethyl fumarate, fingolimod, or other cytotoxic drugs that can produce lymphopenia, which, in turn, could be prolonged for variable time even after stopping the therapy. Due to the absence of guidelines on this topic, we feel to recommend institution of CD20-targeting therapies when any safety alerts are resolved, and the patient's lymphocyte counts return to the pre-therapy values.

Another important open question is: can RTX and OCR be used as a first-line therapy, in a sort of induction protocol, once definitely assessed are reasonably good level of safety? And if yes, for how long should be the period of induction? Induction protocols have been successfully conducted using RTX in various neurological and non-neurological autoimmune diseases and monitoring the re-emergence of CD19 + or CD27 + B cells, whereas the 6-month dosing schedule of OCR seems not to permit such strategies. On the other hand, a critical point regards the plasma cells and other CNS-resident B cells that escape CD20-targeting therapies, as only limited amounts of therapeutic monoclonal antibodies cross the BBB, and that likely contribute to the still understudied processes underlying neurodegeneration in the absence of active neuroinflammation in MS.

But, induction therapy schemes apart, current worrisome

uncertainties refer to the duration of the treatment regimen, and which criteria should be used for interruption. Is it possible to hypothesize a time-schedule induction therapy followed by active surveillance with strict clinical and brain MRI follow-ups, or the introduction of less efficacious, but safer DMTs? As a matter of fact, today we have no accurate and reliable biomarkers that could allow an effective real monitoring of the disease activity and of neurodegeneration. Moving towards this direction, the possible future development of B cell therapies against specific subpopulations, for instance the B-cell clones responsible for OCB production, could preserve the non-detrimental, protective B cells, such as those with regulatory functions (BRegs), which are also depleted by CD20-targeting therapies, and which could contribute to neural repair [81]. Another promising option is represented by the above mentioned Bruton tyrosine kinase inhibitors (*e.g.*, Imbruvica), which could selectively deplete only the autoproliferating B and T cells that are more involved in the immunological processes fostering MS pathogenesis and progression.

In conclusion, we could affirm that B cell therapies are still in their infancy stage and we need more knowledge of the specific B cell-orchestrated autoimmune mechanisms in MS, so to aspire to a selective immunomodulation and/or immunosuppression in this disease. We also need therapies that combine very high efficacy and excellent safety profiles, today available only for the well-known and established first-line DMTs.

At present, there is a compelling need of extension studies performed in real life to shed light on the long-term period safety of CD20-targeting therapies, and on the best criteria for the stratification of MS patients that, at onset of the disease, should be assigned to a given treatment, among the expanding therapeutic MS armamentarium.

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