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Balancing Long-Term Efficacy and Immunological Safety: Serious Infection Risk during Extended Ocrelizumab Therapy in Multiple Sclerosis.

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Abstract

Highly efficient treatments for Multiple sclerosis (MS) have changed the treatment strategy in a way that relapse rates are minimized and clinical disease activity is prevented. The use of the Ocrelizumab over a longer period, however, raises the issue of immunological safety and infection risks. This review looked at all the information about infections that people got when they used Ocrelizumab for a long time. Additionally, we reviewed the effectiveness of ocrelizumab therapy within the term and the types of infections suffered by individuals. In addition, we considered a disease known as hypogammaglobulinemia and the ways it is presently screened. In this paper we used PubMed and Google Scholar as our databases to identify relevant data between (2016-2026). Twenty articles concerning the topic of adult sclerosis have been identified. These adults have been diagnosed with sclerosis based on the McDonald criteria. Ocrelizumab is a drug that is an anti-CD20 monoclonal antibody. It works well for people with relapsing and progressive MS. It reduces the number of relapses and stops the disease from getting worse plus, it decreases the number of lesions on the MRI. However, within long-term taking of this medication, depletion of B cells happened, and it could lead to the gradual suppression of humoral immunity due to IgM and then IgG depletion. Decreased IgG is associated with the high risk of infections; however, the suggested guidelines for monitoring (IgG < 4 g/L and change in therapy if IgG drops to 3-3.5 g/L) lack evidence. Common infections include respiratory and soft tissue infections, UTIs, and herpes zoster. Rare opportunistic infections include hepatitis B infection reactivation and progressive multifocal leukoencephalopathy, which is more often caused by prior disease-modifying treatments. Monitoring should consist of baseline evaluation of tuberculosis, hepatitis B, and HIV infection; regular complete blood counts and immunoglobulin levels; immunization prior to therapy; and the possibility of extending dosing intervals, immunoglobulin replacement, or switching therapy for recurrent infections or severe reduction in IgG levels. In general, prolonged ocrelizumab is an effective treatment of MS, although the risk of infection is significant, cumulative, and requires personalized immune monitoring.

Keywords: Multiple sclerosis, Ocrelizumab, B cells, CD20, relapsing-remitting.

Background

The development of high-efficacy disease-modifying therapies (DMTs) has changed the management of multiple sclerosis, leading to a substantial reduction in relapse rate and improved control of disease activity. However, the significant use of these therapies raises concerns regarding their long-term Immunological safety [1]. People who take ocrelizumab are more likely to get tract infections, respiratory tract infections and nasopharyngitis. There is also a risk of getting Hepatitis B even if the patient did not have it at the start of treatment. This can happen for as long as six weeks later. Ocrelizumab is an example of a -CD20 drug and the problems people have with these drugs show how important immune cells are in multiple sclerosis and in keeping us healthy. Multiple sclerosis is a long-term disease that affects the nervous system [1]. It usually happens to adults. Multiple sclerosis

is characterized by the loss of a covering on nerve cells, which can lead to damage to the nerves and loss of nerve function. This can cause a lot of problems for people, with sclerosis. Although MS was a T cell-mediated disease, pathologic specimens of demyelinating lesions showed infiltration by macrophages, reactive astrocytes, CD3+ T cells, and few plasma cells [2]. With a predominance of CD8+ T cells over CD4+ T cells in active lesions [2]. Accumulating evidence over the past few decades demonstrates the role of B cells in the pathogenesis of the disease; B cells are identified in perivascular areas and around large veins within the central nervous system. Aggregation of B cells resembles lymphoid follicle-like structures observed within meninges. This suggests that the B cell can get activated locally within the brain and contribute towards chronic inflammation [1,2]. In addition, the function of B cells to produce antibodies and secrete inflammatory cytokines leads to the reactivation of self-reactive CD4+ T cells. These understandings contributed towards new therapeutic approaches involving B cell depletion and the development of anti-CD-20 therapies like ocrelizumab, which is humanized glycosylated anti-CD20 monoclonal antibody that depletes CD20 positive B cells through different mechanisms such as apoptosis, complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC)[3].

The studies on ocrelizumab have shown that it works well and is safe for people with sclerosis, specifically the kinds known as RRMS and PPMS. When people with RRMS got ocrelizumab in the phase of the study they had fewer MS flare up each year and fewer problems showed up on their brain scans than the people who got ineffective treatment. The next phase of the study, which included the OPERA I and OPERA II trials confirmed that ocrelizumab is better at treating sclerosis than Interferon beta-1a. Ocrelizumab really made a difference for people with sclerosis in these studies. Importantly ocrelizumab became the first anti-CD20 approved for PPMS in phase III ORATORIO with reduced disability, progression, and lower new MRI lesions. Evidence from multiple cohorts suggests a relative reduction in disability progression following ocrelizumab initiation compared with baseline disease activity [3,4]. Although all anti-CD20 therapies lead to profound depletion of B cells, their long-term immunological impact can differ according to route of administration, dosing interval, and reconstitution window. Complete peripheral B cell depletion occurs within 2 weeks of first infusion while reconstitution of B cells to baseline level is achieved within 2.5 years after last infusion. One of the limitations of measurement of CD20 using peripheral blood samples is that it does not reflect the depletion of CD20 within CNS or lymphoid tissue [3,4].

Infusion-related reactions (IRRs) are recognized with ocrelizumab administration, although they are managed with premedication; serious infections or bronchospasm have been reported, leading to withdrawal from the ORATORIO trial [5]. Repeated treatment cycles may contribute to a cumulative immunologic burden, leading to suppressed immune function over time. Consequently, B-cell depletion leads to secondary hypogammaglobulinemia, a reduction in immunoglobulin serum level, which is a well-known complication of prolonged anti-CD20 therapies and is associated with high risk of infection. Although plasma cells are spared during ocrelizumab therapy due to lack of CD20 expression, secondary hypogammaglobulinemia still develops through several mechanisms. Long-lived plasma cells may still require continuous retrieval from progenitor B cells; depletion of memory B cells

leads to limited generation of short-lived plasma cells [5]. IgM levels typically decrease before IgG, while reduced IgG levels are more clinically significant in prediction of risk of infection due to their important role in protective immunity which is consistent with elevated risk of infection in long-term therapy of anti-CD-20 [5].

Despite the established efficacy of ocrelizumab, balancing the therapeutic benefits of sustained elimination of B cells and the immunologic cost of prolonged ocrelizumab treatment in MS is challenging, and leaves important questions unsolved, including, first, at which level immunoglobulin levels become clinically unacceptable, and whether this threshold is affected by patient profile, which patients are at higher risk of adverse events, and who need dose adjustment. Although monitoring immunoglobulin levels is highly effective in determining the data of SRIs in real life, its impact on improving patient health outcomes remains uncertain [6]. Furthermore, peripheral B cell depletion used to monitor treatment does not reflect the immune activity within the CNS and lymphoid tissue. Accordingly, this narrative review aims to provide a comprehensive understanding of serious infection risks associated with extended ocrelizumab therapy in MS, focusing on long-term efficacy and infectious outcomes. Specifically, the clinical significance of secondary hypogammaglobulinemia and its relationship to infection risk and assessing the adequacy of current immunological monitoring approaches [6].

Methodology

This is a narrative review that studies the effects of ocrelizumab and its association with infections in Multiple Sclerosis patients where a comprehensive search was conducted on PubMed and Google Scholar to include: peer-reviewed literature and articles that evaluate the real-world consequences and clinical profile of Ocrelizumab in patients with MS. The search was conducted for literature published within the past ten years (2016-2026).

Search strategies

Included use of key words which described the Population (MS patients) Intervention (“Ocrelizumab” OR “Ocrevus”) Comparison (Anti-CD20 antibodies like Ocrelizumab, Ofatumumab, Rituximab) Outcome (“Ocrelizumab” AND “Infection risk”) and Time (over a period of ten years) and MeSH (Medical subject headings) like “Multiple Sclerosis” “Relapsing-Remitting” “Chronic Progressive”. The search was restricted to English language. Twenty such articles were selected and analysed on which this narrative review is based.

Inclusion criteria

Eligible literature was restricted to cohort studies, national registries like DMSR (Danish multiple sclerosis registry) along with single or multicenter observational studies. Studies must evaluate patients aged more than or equal to eighteen years or older with a formal diagnosis of MS according to McDonald’s criteria. Trials or observations including patients >65years to map real-world clinical

practice. Selected literature provides qualitative and quantitative data on occurrence, treatment dose, type of infection, and severity. Studies also look at the system data, such as: Blood lymphocyte levels, Neutrophil levels, Serum IgG concentration.

Exclusion criteria:

Studies that mention the use of drugs that suppress the immune system apart, from MS disease-modifying treatments are not included. Observational windows which were short-term or had small sample sizes which could not provide long-term safe outcomes. Articles published before 2016. This study has limitations like those by design, ethnographic, and observational factors. First, variable observation windows and small sample sizes limit the-term evaluation of custom interventions like drug holidays or extended dosing intervals, while a follow-up under two years in some cohorts lacks the power to capture long-term correlations between serious infections and time-dependent immunoglobulin declines. Second, geographic and registry homogeneity. The literature evaluated is heavily relying on Caucasian-dominated datasets and introduces echogenicity limitations that mask diverse genetic variations in immune and metabolic baselines.

Discussion

Multiple sclerosis is a disease that affects the central nervous system for a time. It usually happens to adults when they are between 20 and 40 years old [1]. At first people thought it was because of T cells. Then they found out that B cells also play a big role in making the disease worse. There are some medicines called monoclonal antibodies that target the bad B cells. These medicines are Rituximab, Ocrelizumab, Ofatumumab and Ultuximab [6]. We will talk about Ocrelizumab in detail. Ocrelizumab is a kind of medicine that targets the B cells that have CD20 on them. The good thing about Ocrelizumab in Multiple Sclerosis is that it works for a time. People use Ocrelizumab to control the inflammation in Multiple Sclerosis for a time. When you take this medicine, it helps to stop the disease from getting worse. It also helps to keep the disease from coming and it makes sure that the MRI scans stay stable [6]. The best part is that it helps to slow down the progression of the disability in people, with Multiple Sclerosis.

Long term efficacy stability of Ocrelizumab in Multiple Sclerosis Ocrelizumab therapy is used in MS for the sustained long-term control of the inflammatory activity of the disease [7]. Prolonged activity of anti-CD20 antibodies has been shown to maintain suppression of relapsing disease, sustained MRI stability and slow disability progression. These long-term efficacy profiles have contributed to the widespread adoption of Ocrelizumab. Studies have shown that consistent B cell depletion provides prolonged control of the inflammatory activity which ultimately results in the marked suppression of the new or enlarged T2 lesions. B cells play a central role in antibody formation, antigen presentation, cytokine production, and ectopic lymphoid follicle formation [7]. Ocrelizumab targets the CD20 surface antigen present on pre-B cells, mature B cells and memory B cells. CD20 surface antigen is absent from hematopoietic stem cells and differentiated plasma cells, these cells are preserved.

This specific targeting helps preserve some baseline immunoglobulin production during the early stages of the treatment while at the same time suppressing the pathogenic immune activity. Some studies have shown that long-term therapy in patients with a progressive form of MS benefits in reducing confirmed disability progression and preserving neurological function for a longer duration [8]. This is important because progressive disability remains a difficult challenge in the treatment of MS. Ocrelizumab has been widely adopted due to its sustained efficacy and acceptable tolerability, however, there has been emerging evidence that continuous immune depletion may alter immune competence over time. Immune system consequences during prolonged Ocrelizumab therapy Extended treatment duration causes long-term B cell depletion which although it provides substantial therapeutic efficacy also causes chronic humoral immune suppression which produces cumulative immune consequences that may predispose patients to increased risk of infections and reduced vaccine responsiveness [9].

Ocrelizumab is linked directly to the depletion of CD20+ B cells, CD20- Plasma cells are preserved initially but due to lack of replenishment later there is depletion of plasma and memory B cells; this may result in secondary hypogammaglobulinemia which is characterized by declining serum immunoglobulin concentrations of IgM initially and IgG follows. IgM producing short-lived plasma cells are more dependent on ongoing B cell replenishment and therefore are reduced first in the serum immunoglobulin concentration. Similarly, patterns of IgM decline have been reported in patients receiving Rituximab, Ofatumumab and Ublituximab [8,9]. IgG-producing plasma cells have a comparatively longer lifespan and relative persistence of pre-existing humoral immunity during early therapy, resulting in IgG decline that develops later and tends to usually occur after prolonged or repeated treatment cycles.

Prolonged immune depletion over many years, maintenance of adequate baseline immunity initially but persistent inability to regenerate the B cell population results in narrowing of the humoral immune diversity. This also contributes to the increased infection susceptibility therefore some studies propose individualized dosing strategies, extended interval dosing or immune monitoring approaches to balance efficacy with long term immune preservation. Neutropenia is presented as another immune complication but is less common. Some studies have shown Late-onset Neutropenia associated with long- term anti CD20 therapy which further contributes to increased immune susceptibility. The proposed explanation for neutropenia is altered bone marrow regulation, immune-mediated destruction or cytokine dysregulation; the precise mechanism is not entirely understood [8,9].

To summarize, Ocrelizumab has immunological effects that extend beyond B-cell depletion and evolve progressively. Therefore, long-term therapy requires continuous reassessment and immunological monitoring to check the balance between durable disease control and preservation of adequate immune function. Serious infections during extended Ocrelizumab therapy Serious infections represent the principal safety concerns associated with long-term Ocrelizumab therapy. Some studies suggest that along with prolonged therapy risk factors such as advancing age, disability progression, gender, hypogammaglobulinemia and severe immune dysfunction also play a role in increased susceptibility to serious infections, some studies have shown evidence that there is no association of these factors with

the increased susceptibility. Respiratory tract infections are reported as the most common infectious complication associated with Ocrelizumab therapy [10].

Infections may involve the Upper or Lower respiratory tracts and may range from mild viral illness to severe pneumonia that requires hospitalization. They are identified as the predominant infection category in long-term cohort studies. Impaired humoral defenses against respiratory pathogens secondary to B-cell depletion as well as declining immunoglobulin levels increase susceptibility to these infections [11]. Particularly vulnerable population includes- Elderly patients, smokers and patients with significant disability and impaired pulmonary function. Urinary tract infections are observed during therapy specifically among patients with advanced neurological disability. In progressive MS- Neurogenic bladder dysfunction, Urinary retention, catheterization, and impaired mobility are common, significant baseline UTI risks independent of therapy. Immune suppression associated with anti-CD20 increases the frequency and severity of these infections. Recurrent UTIs have become clinically significant in patients with higher Expanded Disability Status scale (EDSS) scores and prolonged disease duration. Skin and soft tissue infections- Cellulitis, abscesses, and Wound infections have also been reported in patients with long-term anti-CD20 therapy although these are less common. These are particularly seen in patients with other comorbidities- Impaired mobility, diabetes, obesity, and chronic skin breakdowns. Bacterial clearance is impaired due to reduced capacity to generate effective humoral immunity [10,11].

Opportunistic infections are relatively uncommon. Rare cases of Herpes reactivation, Fungal infections, Hepatitis B reactivation and Progressive Multifocal Leukoencephalopathy (PML) have been reported.PML is extremely rare in Ocrelizumab therapy as compared with Natalizumab but vigilance is necessary in patients with prior immunosuppressive exposure. Opportunistic infections emerge only in profound severe immune dysfunction, prolonged hypogammaglobulinemia and advanced age [11].

Age as a risk factor:

One of the most consistently identified risk factors for serious infection in Multiple sclerosis with the use of Ocrelizumab is immunosenescence [12]. According to a study from a large Swedish real-world registry. It is highlighted that older patients with MS are not well represented in clinical trials, even though they might have infection risk. Because immunosenescence weakens the immune system, a lot of older patients have disability from multiple sclerosis, and sometimes they have other comorbidities. The study also pointed out that the researchers still do not fully know if the treatment for MS affects different age groups in different ways when it comes to infection risk.

Other studies also support these findings. Infection complications are more frequent in older patients, and patients who were hospitalized because of infection were usually older than those who were not hospitalized. Immunosenescence may make the effect of ocrelizumab stronger, since the drug already lowers B cells. So, this can make older patients with MS more vulnerable to serious infection [12].

Disability level (EDSS)

The degree of disability (EDSS) emerged as a pivotal variable in the included studies (long-term ocrelizumab safety registry, n>6,000) found that patients who are wheelchair-dependent or have any walking difficulties are at significantly higher risk of infection (the Danish anti-CD20 registry) identified higher EDSS at a baseline as an independent predictor of both hospitalized serious infection and herpes zoster reactivation. Reinforced these findings, reporting 23.5% in PPMS versus 8% overall [12].

Prior infection history

Although prior infection history was not uniformly defined as an independent classifying variable. It implicitly indicated that patients with a cumulative history of infections had significantly higher infection rates noted that recurrent urinary tract infections in PPMS patients significantly increased the infection rate in that group, highlighting the importance of recording and documenting prior infections, in addition to particularly recurrent bladder infection, as part of any risk stratification framework. IgG levels and Low Immunoglobulin [13]. When IgG levels go down it can mean that B cells have been suppressed for a time. This decrease in IgG levels is important to note because it helps figure out how likely someone is to get an infection (n=266, longest reported follow-up cohort) reported that 32% of the patients developed IgM hypogammaglobulinemia, 3.5% IgA, and 4.2% IgG further explains the partial mechanism by which anti-CD20 treatment eliminates B-cells, and over time, Immunoglobulin-producing plasma cell populations become progressively depleted. Lower levels of IgM and IgG increase the risk of getting herpes zoster [13].

Having Other Health Issues:

Things like diabetes COPD and bladder problems can make it harder for the body to fight off infections when B cells are suppressed. These health issues make it more likely for someone to get sick. indicated that heart disease, other systemic diseases, and depression increased infection rates confirmed through multivariable Cox regression that comorbidity burden was a major independent predictor of serious infection and hospitalization. Neurogenic bladder dysfunction, common in multiple sclerosis, creates a structural predisposition to recurrent urinary tract infection. Other diseases, such as chronic obstructive pulmonary disease and diabetes, compromise respiratory and systemic host defenses, thereby increasing vulnerability to infections during ocrelizumab therapy [14].

Treatment duration and cumulative dose

Longer treatment with -CD20 medicine has been linked to a higher risk of low antibody levels. This is supported by research showing that the anti-CD20 medicine a patient takes as much as their antibody levels decline. A study of over 500 patients found that higher doses of -CD20 medicine substantially increase the risk of low antibody levels. When people take this medicine that targets CD20 for a time

it gets rid of the B cells in their body. B cells are important because they help make antibodies. Without these B cells the body has time fighting off infections. The risk of getting an infection from CD20 medicine does not stay the same all the time. It gets higher the longer people take the medicine and the more treatment they get [15]. To manage this risk patients on -CD20 therapy needs regular monitoring of their antibody levels and B cell counts. This monitoring helps doctors identify patients who're at higher risk of getting infections. Doctors can help these patients by keeping an eye on them. This way doctors can do things to prevent infections from happening in the place. People who get -CD20 treatment need to be taken care of, so they do not get infections. Doctors should check on them. Changing their treatment if they need to this can help make the risk of infection smaller. The goal is to provide the possible care for patients taking anti-CD20 medicine. Regular check-ups and monitoring are crucial for patients on term anti-CD20 therapy. This approach helps to prevent infections and ensure the outcomes, for patients [15].

Monitoring and mitigation strategies:

Immunoglobulin monitoring

The regular IgG, IgM, and IgA measurement are considered as a cornerstone of safety management. The mean annual decline of IgG is 0.33 g/L /year [10], IgG<4 g/L clinically warrants heightened vigilance, and IgG<3 g/L prompted consideration of Immunoglobulin replacement or treatment modification [16].

Infection screening:

For Latent TB, Hepatitis B, and HIV are essential to do pre-treatment screening, during therapy for opportunistic infection is critical, alongside the routine of CBC, as low lymphocytes count is the strongest independent predictor of herpes zoster reactivation [16].

Vaccination timing:

The live attenuated vaccine and all other vaccines should be completed before starting ocrelizumab, the inactivated vaccines are allowed during therapy but produce suboptimal responses. Vaccines should be timed 3-6 months after last infusion for patients who are already on treatment [16].

Extended interval dosing (EID)

There are some centers are using EID (>6 months interval) for stable patients to allow the recovery of partial B-cell and Ig while maintaining efficacy suggests using a lower dose of Ofatumumab it may cause less profound neutropenia in high-risk patients, there is no formal approval yet, but observational data its support vigilant use in selected patients [16].

Treatment interruption

Treatment interruption or modification is warranted when serum IgG levels fall below the critical threshold of 3.5–4 g/L, or upon the occurrence of serious or recurrent infectious complications [17]. In situations like these doctors may try treatments such as: Increasing the time between treatments or they could start giving immunoglobulin therapy through a vein or under the skin, they may switch to another treatment for the disease that has a safety record, these treatments help lower the risk of infections, they also try to balance the effects of keeping B cells. When anti-CD20 therapy stops the body's immune system starts to recover. It can take around 12 to 24 months for immunoglobulin levels in the blood to return to normal. However, B-cell reconstitution and restoration of normal immune function do not always occur at the same time [17]. Some patients may have immunoglobulin levels for a long time, and this is more likely for those who had term or high-dose treatment. During this recovery time patients still need to take precautions and be closely monitored to prevent infections. Furthermore, emerging evidence suggests that relying solely on IgG thresholds as the criterion for treatment interruption may be insufficient. The monitoring of B cell subsets, particularly memory B cells, transitional B cells, and plasma blasts, could give a more accurate method to predict the suitability of discontinuation in therapy as these B cell subsets are early markers of immunological impairment before any decrease in immunoglobulins can be detected. The classification of patients into such categories will help prevent the development of severe hypogammaglobulinemia and subsequent infections [17].

Knowledge gaps and future directions

No standardized IgG cut-offs: Currently the IgG levels below which we should be careful and consider stopping treatment are based on expert opinions not on evidence from studies. These levels are set at 4 g/L for caution. 3 G/L for stopping treatment. These levels do not work the same for everyone [18]. Some people with IgG levels below 3 g/L do not have problems while others with high IgG levels above 4 g/L get infections. This shows that we need a personalized approach to assess the risks. We need to study people with multiple sclerosis to find IgG levels that are safe and work for each person. These studies should consider IgG levels, other health issues and treatment pervious history to make guidelines [18]. We need studies that follow people over time to make sure we have good evidence for IgG thresholds. This way we can make sure that people with sclerosis get the best possible care. More research is needed to get evidence-based IgG thresholds. The goal is to have a way to decide when to be cautious or stop treatment.

Moreover, it depends on IgG levels and their medical history. So, IgG levels are important. We need to look at them carefully. The current IgG thresholds are not validated in MS trials. They are based on what experts think, not on evidence. Therefore, large studies are urgently needed for evidence-based IgG thresholds. The studies should consider IgG levels and other factors. This will help to make an approach for people, with multiple sclerosis.

Unclear immune reconstitution timeline

The recovery of the system after stopping anti-CD20 therapy is not well understood. This is a gap in what we currently know. Available data from people treated with rituximab shows that their serum IgG levels partially recover over 12 to 24 months after stopping treatment. However, similar data for ocrelizumab is. Varies in how it was collected. This makes it hard to draw conclusions about how quickly the immune system recovers after ocrelizumab treatment [18]. The difference in recovery may be due to how each drug works and how much it depletes B-cells. How often it is dosage. Some early evidence suggests that ofatumumabs lower dosing regimen may allow for B-cell recovery. This is because it doesn't deplete B-cells much or for as long as other treatments. We need more research in large clinical trials to confirm this before it can be used to guide treatment decisions [18].

Need for predictive biomarkers

The current risk stratification models for infectious complications during anti-CD20 therapy are largely based on simple clinical parameters and general immunological markers and are not sufficiently sensitive or specific to accurately predict individualized risks. The use of B-cell subset profiling - based on memory B-cells, transitional B-cells and plasma blasts - is suggested as a good potential panel of predictive markers that can offer finer-grained immunological cues than standard IgG monitoring. In addition, absolute lymphocyte count was found to be the most powerful independent adjusted risk factor for herpes zoster reactivation in anti-CD20 treated patients, highlighting the importance of cellular immune parameters in a detailed risk assessment [19]. Other candidate biomarkers such as $CD4^+$ lymphopenia, natural killer (NK) cell cytotoxic activity and vaccine-specific antibody titers have been shown to have a theoretical and preliminary clinical relevance as markers of impaired humoral and cell-mediated immunity. These biomarkers have not yet been validated in sufficiently sized cohorts of individuals with MS in a prospective manner. The design and validation of a multi-parametric biomarker panel combining humoral and cellular immuno-parameters is the next major challenge for future research and could revolutionize the management of the disease from a reactive to a proactive and precise approach [19].

Individualized dosing:

Future clinical studies need to give emphasis on the study of the ‘treat to target’s approach, where treatment is decided based on specific immunological parameters rather than on predetermined dosing regimens [20]. This method needs to include real-time monitoring of the kinetics of B-cell reconstitution, immunoglobulin levels in serum, and history of infections to tailor treatment dose and inter-dosing periods on a per-patient basis. Moreover, there is a lack of prospective randomized head-to-head studies comparing the three anti-CD20 therapies, ocrelizumab, rituximab, and ofatumumab regarding their infectious risks, immunoglobulin profile, and timeline of immune reconstitution [20].

Immune aging in MS patients

The influence of immunological ageing or immune senescence on the safety and tolerability of chronic anti-CD20 therapy is an extremely under-researched area. The pattern of infectious risk, vaccine response, and the ability of reconstituting the immune system after cessation of the therapy in older

patients can be quite different and qualitatively distinct from those in younger people due to thymic atrophy, decreased output of naive lymphocytes, and B-cell receptor diversity in older patients. However, there is an evident tendency of underrepresentation of older patients in the key clinical trials of multiple sclerosis. Consequently, there is a considerable lack of information regarding how the currently existing schemes of risk stratification work in older patients. Age-stratified immunological surveillance protocols and separate studies involving patients above 60 years who receive chronic anti-CD20 therapy are extremely needed [20].

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