DERLEME REVIEW

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Infusion-Related Reactions with Anti-CD20 Monoclonal Antibody Treatments in Multiple Sclerosis: Traditional Review

Anti-CD20 Monoklonal Antikor Tedavileri ile Görülen İnfüzyon İlişkili Reaksiyonlar: Geleneksel Derleme

Cansu GÖNCÜOĞLU[a], Kübra Nur ÖKSÜZOĞLU[b], Aygin BAYRAKTAR EKİNCİOĞLU[b]

[a]Department of Clinical Pharmacy, Selçuk University Faculty of Pharmacy, Konya, Türkiye
[b]Department of Clinical Pharmacy, Hacettepe University Faculty of Pharmacy, Ankara, Türkiye

ABSTRACT Multiple sclerosis (MS) is a chronic disease that affects the central nervous system. The objective of the treatment of MS is to prevent relapses, to delay disability and loss of brain volume. It has been shown that B cells play an important role in the progression of the disease. B cells carry the CD20 surface marker and anti-CD20 monoclonal antibodies bind to CD20 marker. Therefore, anti-CD20 monoclonal antibodies cause depletion of B cells. Due to their different chemical structures and binding sites, the cell killing mechanisms and cell surface binding rates of monoclonal antibodies also differ. Monoclonal antibody treatments are known as highly effective and well tolerated options in the treatment of MS. Rituximab and ublituximab are chimeric, ocrelizumab is humanized, and ofatumumab is a fully human antibody. The most common and outstanding adverse effect is known as infusion-related reactions, which are most commonly seen with rituximab. Infusion-related reactions observed in about 40-70% of patients receiving rituximab, 20-30% with ocrelizumab, 20-50% with ofatumumab and 40-50% with ublituximab. The grades of infusion-related reactions varies. Although it is possible to prevent certain infusion-related reactions with premedication, it is sometimes necessary to interrupt the infusion or to implement symptomatic treatment. Therefore, patients and healthcare professionals should be aware of the possibility of an infusion-related reaction. This review aims to increase the visibility of infusion-related reactions occurring with monoclonal antibody treatments and to facilitate to prevention.

Keywords: Multiple sclerosis; infusions; monoclonal antibody

ÖZET Multipl skleroz (MS), santral sinir sistemini etkileyen kronik bir hastalıktır. MS tedavisinin amacı; atakları önlemek, özürlülüğü ve beyin hacmi kaybını geciktirmektir. B hücrelerinin hastalığın ilerlemesinde önemli bir rol oynadığı gösterilmiştir. B hücreleri, CD20 yüzey proteinini taşımakta ve anti-CD20 monoklonal antikorları da CD20 proteinine bağlanmaktadır. Böylece anti-CD20 monoklonal antikorları B hücrelerinin tükenmesine neden olmaktadır. Farklı kimyasal yapıları ve bağlanma yerleri nedeniyle monoklonal antikorların hücre öldürme mekanizmaları ve hücre yüzeyine bağlanma oranları da farklılık göstermektedir. Monoklonal antikor tedavileri, MS tedavisinde oldukça etkin, sık tercih edilen tedavi seçenekleridir ve tolere edilebilir oldukları bilinmektedir. Rituksimab ve ublituksimab şimerik molekülken; okrelizumab insanlaştırılmış, ofatumumab ise tamamen insan antikorudur. En yaygın görülen advers etki, infüzyon ilişkili reaksiyonlardır. İnfüzyon ilişkili reaksiyonların anti-CD20 monoklonal antikorlarından en sık rituksimab ile görüldüğü bilinmektedir. Rituksimab alan hastaların %40-70'inde, okrelizumab alanların %20-30'unda, ofatumumab alanların %20-50'sinde ve ublituksimab alanların %40-50'sinde infüzyon ilişkili reaksiyonlar bildirilmiştir. Bu antikorların ortaya çıkardığı infüzyon ilişkili reaksiyonların dereceleri ise değişmektedir. Premedikasyon ile infüzyon ilişkili reaksiyonları kısmen önlemek mümkün olsa da bazı durumlarda infüzyona ara vermek veya semptomatik tedavi uygulamak gerekebilmektedir. Bu nedenle hastalar ve sağlık çalışanlarının, infüzyon ilişkili reaksiyonların farkında olması önerilmektedir. Bu derleme, monoklonal antikor tedavileri ile oluşan infüzyon ilişkili reaksiyonların görünürlüğünü artırmayı ve bu reaksiyonların önlenmesini kolaylaştırmayı amaçlamaktadır.

Anahtar Kelimeler: Multipl skleroz; infüzyonlar; monoklonal antikor

Multiple sclerosis (MS) is chronic and autoimmune disease that is characterized by central nervous system damage. It is estimated that 2.8 million people have MS in the world and its incidence was found to be 2.1 per 100,000 people per year in a study involving 75 countries.[1] Although MS is a common dis-

Correspondence: Cansu GÖNCÜOĞLU
Department of Clinical Pharmacy, Selçuk University Faculty of Pharmacy, Konya, Türkiye
E-mail: cansugoncuoglu@gmail.com

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ease, the etiology of the disease has not yet been fully elucidated. However, some genetic and environmental factors are thought to trigger the onset of the disease. It is known that it is not an inherited disease, genetic factors are thought to have an influence on the etiology of MS. The possible risk of MS in first-degree relatives of patients is expressed as 10-50 times higher than in the relatives compared to the general population. Potential risk factors for development of MS are established as female gender, genetics, infection of Epstein-Barr virus, smoking and low vitamin D level.[2]

The aim of the treatment is to prevent relapses, to delay disability and loss of brain volume.[3] In the progression of MS, B cells play an important role, as studies have shown.[4] Most B cells carry the CD20 surface marker. Anti-CD20 monoclonal antibodies bind to CD20 marker and cause depletion of B cells. In the treatment of MS, monoclonal antibody treatments are highly effective and well tolerated options. Due to their different structures and binding sites, cell killing mechanisms and cell surface binding rates are different.[5] Although the role of CD20 is not yet known precisely, it is thought to play an crucial role in the flow of calcium across membranes, enabling the activation of B cells.[6]

The first explored anti-CD20 monoclonal antibody is rituximab, which is a human-mouse chimeric antibody. Ublituximab is also a human-mouse chimeric antibody, whereas ocrelizumab is a humanized anti-CD20 monoclonal antibody. Recently available ofatumumab, is a fully human anti-CD20 monoclonal antibody; unlike rituximab, ublituximab and ocrelizumab, it is administered subcutaneously.[7] The most common adverse effects seen with anti-CD20 monoclonal antibodies are infusion-related reactions and are most commonly seen with rituximab. Generally, grade 1 or 2 reactions are observed, but in rare cases, reactions can lead to life-threatening situations.[8-10] Therefore, it is important to monitor patients during the infusion. In studies evaluated rapid infusion, which aimed to reduce the use of hospital resources, it was observed that rapid infusion regimen did not change the safety profile of drugs in patients who could tolerate the first dose without infusion-related reactions.[11,12] Considering the benefit-risk ratio for the patient, anti-CD20 monoclonal antibodies are appropriate treatment options for patients with MS. The aim of this review is to evaluate infusion-related reactions observed with anti-CD20 monoclonal antibodies in the treatment of MS.

TREATMENT IN MS

In the management of MS, interferon-beta (IFN-β), glatiramer acetate, dimethyl fumarate and teriflunomide are considered first-line treatments, whereas fingolimod and cladribine are the second line treatment options.[7] In patients who do not respond to the first or second line treatments or that are in advanced stages of the disease, immunosuppressives (cyclophosphamide, methotrexate, azathioprine, mitoxantrone, mycophenolate mofetil) or monoclonal antibody treatments can be considered.[13]

Monoclonal antibodies are relatively new treatment strategy that is highly effective and well tolerated in variety of disease types.[5] Natalizumab is the first monoclonal antibody used in the treatment of MS. Natalizumab is targeted to α4 integrins and reduces transmission of proinflammatory cytokines to brain tissue in the central nervous system.[14] As another monoclonal antibody, alemtuzumab is targeted to CD52, which is associated with activation and migration of T lymphocytes. It binds to the CD52 surface marker, which is found in excess on the surface of lymphocytes, causing the destruction of these cells and thus selectively destroys T and B cells.[15] Other monoclonal antibody treatments are rituximab, ocrelizumab, ofatumumab, and ublituximab and they are targeted to CD20 marker.

ANTI-CD20 MONOCLONAL ANTIBODY TREATMENTS

MS is thought to be T cell-mediated demyelinating disease of the central nervous system previously, but it has been shown that B cells also act a remarkable part in the progression of the disease in recent studies.[4,16] It is demonstrated that B cells carry the CD20 surface marker, but its function is not fully understood yet. On the other hand, monoclonal antibodies cause cell destruction by binding to the CD20 marker (Figure 1).[5]

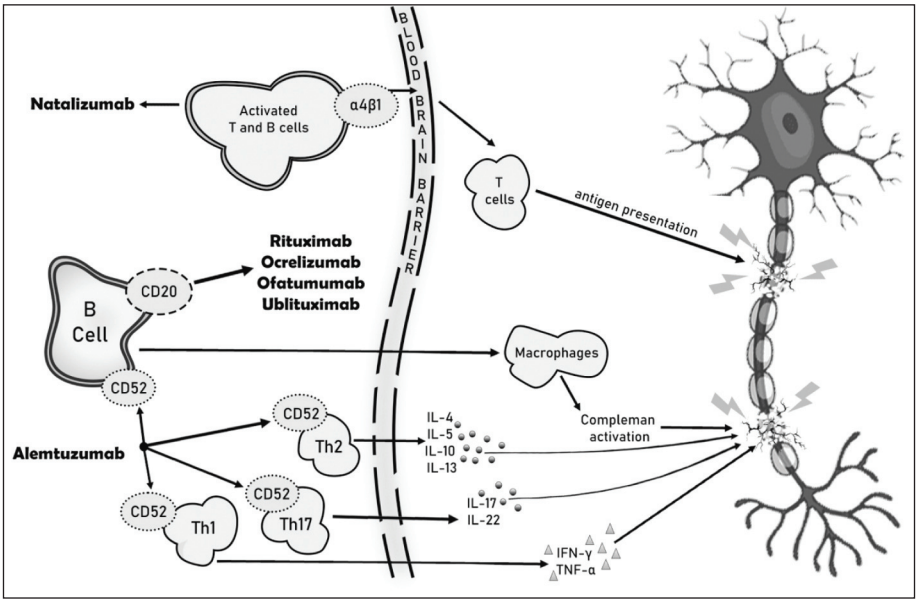

FIGURE 1: Mechanism of action of monoclonal antibodies in the treatment of multiple sclerosis.
IL: Interleukin; IFN-γ: Interferon gamma; TNF- α: Tumor necrosis factor alpha.

INFUSION-RELATED REACTIONS

Infusion-related reactions are defined as "Symptoms experienced by patients during the infusion of pharmacological agents or any event occurring on the first day of drug administration."[17] Symptoms include itching, skin rash, fever, chills, throat irritation, nausea, headache, cough, fatigue, dizziness, hypotension, bronchospasm, angioedema, ventricular fibrillation, shock, and anaphylaxis.[18,19] The National Cancer Institute has classified hypersensitivity reactions according to their severity to standardize the reporting of adverse effects (Table 1).[20] Infusion-related reactions occur commonly with monoclonal antibody therapies.[8] These infusion-related reactions are thought to be caused by the release of cytokines as a result of antibody-antigen interactions between monoclonal antibody on lymphocytes and CD20.[21] Most of the infusion-related reactions associated with monoclonal antibody treatments are mild, and severe reactions are generally unlikely.[22] It was observed that infusion-related reactions were more common in the first dose and diminished in subsequent doses.[23-25]

Although monoclonal antibody treatments may be the reason for occurrence of different hypersensitivity reactions, the incidence of cytokine-mediated reactions is higher. The symptoms of all immune-me-

TABLE 1: Grading of infusion related reactions adapted from Criteria of National Cancer Institute v5.0.[20]

Grade 1	Mild-temporary reactions including flushing and rash. Interruption of infusion or intervention is not required.
Grade 2	Flushing, rash, dyspnea, urticaria can be observed. Symptomatic treatment or interruption of infusion is indicated, and the patient responds promptly to symptomatic treatment. Prophylactic treatment is indicated for less than 24 hours.
Grade 3	Bronchospasm, edema, hypotension occur with or without urticaria. Prolonged symptoms or recurrence of symptoms following initial improvement. Hospitalization is indicated for clinical sequelae.
Grade 4	These are life-threatening conditions. Urgent intervention is required.
Grade 5	Death.

diated infusion reactions are similar, which makes difficult to determine the cause of the reaction. Anaphylactic reactions occur within the first few minutes of the infusion, infusion-related reactions may last up to 24 hours after the first administration of monoclonal antibody treatments, but are often resolve after the infusion.[26] In other hypersensitivity reactions, complement activation acts by activating mast cells, basophils, and endothelial cells, while cytokine-mediated reactions cause immune activation of monocytes, macrophages, T and B cells and rapid release of proinflammatory cytokines [interleukin (IL-6), IL-10 and IFN-γ].[27]

Identification of the symptoms of hypersensitivity reactions facilitates distinguishing the type of reactions. For example, urticaria, angioedema, and hypothermia are observed in anaphylactoid reactions, while fatigue, headache, itching, dyspnea, and flushing may be observed in cytokine-mediated reactions. Unlike anaphylactoid reactions, cytokine mediated reactions become milder by repeated administration.[27]

RITUXIMAB

Rituximab is a human-mouse chimeric monoclonal antibody, which binds to the CD20 antigen and depletes B cells mainly with complement-dependent cytotoxicity and to a lesser extent, antibody-dependent cellular cytotoxicity.[6,7] In the HERMES and OLYMPUS studies, rituximab is found to be effective in MS, but there is no consensus regarding its doses and frequency of administration.[28,29] However, the most common administration procedure is known as 1 g intravenous (IV) on days 1 and 15 and 1 g every 6 months for maintenance.[7] Infusion-related reactions are the most common adverse effect of rituximab treatment, followed by infections and lymphopenia.[19]

Infusion-related reactions occurred with the use of rituximab have been reported at higher rate than with other monoclonal antibodies. Although hypotension has been reported to occur generally within 30 minutes to 2 hours after initiation of the rituximab infusion, severe hypotension has also been reported within 5 minutes of the first rituximab administration. In every case, blood pressure of patients returned to normal range after cessation of the infusion.[30]

The risk of infusion-related reactions is higher with the first dose of rituximab in the treatment of MS. These reactions are usually mild to moderate, however, in some cases, patients may need to be hospitalized or, rarely, reactions may become life-threatening.[9] In a study conducted among 140 patients with Non-Hodgkin lymphoma, 39% of patients experienced varying degrees of infusion-related reactions during rituximab treatment, particularly at the first administration (84% of patients). This rate was decreased to 9% at the 2nd, 2% at the 4th, 2% at the 5th, and 4% of patients at the seventh administration of rituximab treatment. It was indicated that 42% of patients experienced grade 1 and 58% of patients experienced grade 2 infusion-related reactions (Table 2).[9]

It has been known that rituximab can be given by a 90 minutes rapid infusion (in the first 30 minutes 20% of total dose, over the next 60 minutes remaining 80%) and well tolerated in patients who can tolerate the first dose without experiencing infusion-related reactions. It was suggested that 60 (during the first 15 minutes, rituximab is infused at 100 mg/h and the remaining dose is infused for at least 45 minutes) minutes rapid infusion of rituximab is feasible and safe in the subsequent infusions, which has concluded in a significant reduction in the use of hospital resources.[11,12] In a study evaluating a 90 minutes rapid infusion regimen of rituximab in patients with several autoimmune diseases, it was found that 82% of patients had not experienced with infusion related reactions.[31] Ten (19%) patients experienced at least 1 reaction (regardless of severity) and 9% of the patients had an infusion-related reaction in the first infusion but not in the second. Common symptoms in patients were rhinitis (11%), pharyngeal symptoms (7%) and dyspnea, cough and allergic reactions (9%). Grade 2 reactions have occurred only in one patient at the first and second infusions. The initial infusion related reaction was treated by 20 minutes interruption of the infusion and administration of oral antihistamine, therefore initial infusion was fulfilled without any difficulties. On the second infusion, the same procedure was implemented. Two (4%) of the patients had grade 3 reactions at the first and second infusions, patients recovered after needing an infu-

TABLE 2: Summary of infusion-related reactions seen with anti-CD20 monoclonal antibodies.

Drug	n	Patient population	Grade of infusion-related reactions at first infusion	Overall incidence of infusion-related reactions
Rituximab	140	Patients with lymphoma	Grade 1: 42% of patients Grade 2: 58% of patients	Infusion-related reactions occurred in 39% of patients[9]
	292	Patients with PPMS	Grade 1-2: 58.6% of patients Grade 3-4: 8.6% of patients	Infusion-related reactions occurred in 67.1% of patients[29]
Ocrelizumab	486	Patients with PPMS	Grade 1: 26.5% of patients Grade 2: 12.1% of patients Grade 3: 1.2% of patients	Infusion-related reactions occurred in 39.9% of patients[34]
	745	Patients with RRMS	Grade 1: 62.6% of patients Grade 2: 34.6% of patients Grade 3: 2.8% of patients	Infusion-related reactions occurred in 26.5% of patients in the conventional group (28.8% in shorter infusion group)[23]
	129	Patients with RRMS	Grade 1: 7.8% of patients Grade 2: 4.8% of patients	Infusion-related reactions occurred in 12.4% of patients[24]
	825	Patients with MS	Grade 1: 21.9% of patients Grade 2: 8.5% of patients Grade 3: 1.7% of patients Grade 4: 0.1% of patients	Infusion-related reactions occurred in 34.3% of patients[33]
Ofatumumab	946	Patients with RRMS	Grade 1: 10% of patients Grade 2: 4% of patients	Infusion-related reactions occurred in 20.2% of patients[40]
	121	Patients with RRMS	Grade 1-2: %52 of patients	Infusion-related reactions occurred in 52% of patients[53]
	13	Patients with lymphoma	Grade 1: 46.2% of patients Grade 2: 7.7% of patients	Infusion-related reactions occurred in 20.5% of patients[43]
	34	Patients with leukemia	Grade 1: 62% of patients with short infusion Grade 2: 9% of patients with short infusion	Infusion-related reactions occurred in 62% of patients[45]
Ublituximab	48	Patients with RRMS	Grade 1-2: 50% of the patients	Infusion-related reactions occurred in 50% of the patients[25]
	14	Patients with lymphoma or leukemia	Grade 1-2: 40% of the patients	Infusion-related reactions occurred in 40% of patients[46]

MS: Multiple sclerosis; PPMS: Primary-progressive MS; RRMS: Relapsing-remitting MS.

sion interruption of more than 20 minutes and administration of IV antihistamine, thus managed to complete rituximab treatment. Patients presented the same symptoms on the subsequent infusion and the same procedure was implemented. Grade 4 and 5 reactions were not observed at all.[31]

OCRELIZUMAB

A humanized anti-CD20 monoclonal antibody, ocrelizumab, selectively depletes B cells through a variety of pathways including apoptosis, cytotoxicity and phagocytosis. Ocrelizumab therapy preserves B-cell remodeling and pre-existing humoral immunity by lymphoid stem cells.[32] Studies demonstrated the effectiveness of ocrelizumab in MS by decreases in the numbers of annual relapse rate, new magnetic resonance imaging lesions, progression of disability, and brain atrophy.[33,34]

Ocrelizumab is the first treatment approved for primer-progressive MS.[35] It can be used in relapsing-remitting or secondary-progressive MS if patients do not respond to INF-β, teriflunomide, dimethyl fumarate or glatiramer acetate treatment for at least one year. Initially, 300 mg is administered on the 1st and 15th days, and 600 mg IV ocrelizumab is administered at 6 months intervals in the maintenance therapy. In order to prevent infusion-related reactions that may occur during the administration, the use of filters during infusion is recommended.[7]

The most frequently reported adverse event among patients treated with ocrelizumab is infusion-related reactions, which are generally not life-threat-

ening.[34] In the ORATORIO study, infusion-related reactions were more common with ocrelizumab than with placebo and 2 (0.4%) patients discontinued ocrelizumab treatment because of infusion-related reactions.[34] Patients in the ocrelizumab group experienced more adverse events (9.7%) leading to modifications in infusion rate or infusion discontinuation than in the placebo group (5.0%).[34] In the OPERA-I study, 30.9% of patients in the ocrelizumab group and 7.3% of patients in the IFN-β 1a group had infusion-related reactions, whereas in the OPERA II study, these rates were 37.6% and 12%, respectively. In the OPERA-I study, one patient who received ocrelizumab developed severe bronchospasm during the first infusion, but the patient had improved with symptomatic intervention.[33]

The most common infusion-related reactions with ocrelizumab are itching, rash, flushing, and throat irritation. It has been determined that female gender, young age, and high body mass index are related with the risk of infusion-related reactions in ocrelizumab treatment.[33] In another study female gender, ethnicity and history of co-occurring tremor emerged as risk factors of having an infusion related reactions with the odds ranging from 2.60-3.98.[36]

The frequency and severity of infusion-related reactions were similar in conventional and short duration of infusions with ocrelizumab. A shorter infusion reduced the overall stay for infusion and reduced overall hospital burden.[37] In the ENSEMBLE PLUS study, 27% of patients in the conventional group and 29% of patients in the 2 hours rapid infusion group experienced an infusion-related reaction at the first dose. None of the infusion-related reactions that were observed in patients were found to be critical or fatal. Adverse effects in the short infusion were not different from the proven safety profile of ocrelizumab. The severities of infusion-related reactions were similar in both groups. Limiting the infusion process to 2 hours, reduced overall hospital stays from 6 hours to 4 hours and reduced the workload of hospital staff.[23] In the CHORDS study investigating safety profile of shorter infusions with ocrelizumab, no serious or life-threatening infusion-related reactions were observed during the infusion. Grade 1 or 2 infusion-related reactions have been reported in 12% of patients. Among the patients who experienced reactions, 7% required interruption of the infusion or reduction in infusion rate. All patients completed therapy without serious reactions or discontinuation of therapy. Overall, the findings suggest that safety profile of ocrelizumab has not changed significantly by administration of short-term infusion.[24]

OFATUMUMAB

Ofatumumab is a fully human anti-CD20 monoclonal antibody. Although the exact mechanism of action is unknown, ofatumumab is thought to selectively bind and inhibit CD20 on B lymphocytes.[38] In a study, 99% reduction was reported in new brain lesion activity after ofatumumab treatment compared to placebo.[39] In the ASCLEPIOS I and ASCLEPIOS II studies, effectiveness of ofatumumab and teriflunomide in relapsing-remitting MS (RRMS) patients were investigated, and results were in favor of ofatumumab in the reduction of annual relapse rates.[40] Ofatumumab is the first B-cell targeted monoclonal antibody treatment to be used by self-administration in MS. The recommended dose is 20 mg by subcutaneous injection on the 1st, 7th and 14th days, followed by 20 mg once a month.[38] Prophylaxis with analgesics, antihistamines, or steroids has not been shown to diminish importantly the rate of adverse effects experienced with ofatumumab.[40]

Infusion-related reactions, headache, injection site reactions (mild or moderate erythema, pain, itching, and swelling), nasopharyngitis, upper respiratory and urinary tract infections are the most common adverse reactions seen with ofatumumab.[38,40] Infusion-related reactions with a range between mild to moderate were reported in the MIRROR study, which occurred particularly within 1 day after the first dose of ofatumumab.[41]

Infusion-related reactions consist approximately 60% of all adverse events occurred with ofatumumab. Almost 40% of all infusion-related reactions occur in patients receiving ofatumumab for the first time (Table 2). Most infusion-related reactions are grade 1 or 2 that do not preclude administration of subsequent doses of ofatumumab. Patients who could not toler-

ate rituximab due to severe infusion-related reactions were able to tolerate ofatumumab therapy. Most ofatumumab infusions in these patients did not cause any infusion-related reactions.[42,43] In a study conducted among patients who received IV ofatumumab for rheumatoid arthritis, infusion-related reactions were observed as the most common adverse event and the incidence of reactions was found to be higher on the first day of the infusion. Infusion-related reactions were generally mild to moderate and significantly reduced during the 2nd infusion. The most common symptoms were rash, urticaria, throat irritation, cough and itching.[44] Ofatumumab was well tolerated and no unexpected adverse effects were observed with ofatumumab in RRMS patients.[39]

In the phase II study evaluating the safety of rapid infusion with ofatumumab, it was found that most of the infusion-related reactions occurred during the first and 2nd infusions. Thirty-four patients participated in the study and 87% completed the 3rd infusion in 2 hours and 15 minutes instead of 4 hours, and only one patient had an infusion-related reaction. Therefore, a rapid infusion of ofatumumab is considered to be safe and well tolerated.[45]

UBLITUXIMAB

Ublituximab has not yet been approved for the treatment of MS. Also there are limited data available regarding the efficacy of ublituximab in MS. In a study of ublituximab in RRMS patients, no new or enlarging lesions were detected at weeks of 24 and 48. In addition, 93% of patients were free of relapse during 48-weeks. The most common adverse effects were infusion-related reactions that are seen in 50% of patients, particularly seen on the first day of infusion. The frequencies of infusion-related reactions did not appear to increase by administration of higher doses or rapid infusion.[25]

In the phase II study, ublituximab was generally well tolerated and no patient had to discontinue the treatment due to adverse events. The most common adverse event associated with ublituximab was infusion-related grade 1 or 2 reactions, no grade 3 or 4 reactions have been reported.[25] Infusion-related reactions with ublituximab occurred in 40% of cancer patients who were exposed to rituximab previously. All infusion-related reactions were treated with discontinuation of the infusion and situation resolved without any clinical sequelae.[46]

MANAGEMENT OF INFUSION-RELATED REACTIONS

The infusion-related reactions are generally managed by premedication. Thirty minutes prior to infusion, premedication with an antihistamine (pheniramine or diphenhydramine) and paracetamol should be administered to minimize the occurrence of cytokine-mediated reactions.[7] In addition, 100 mg IV prednisolone should be administered shortly prior to the infusion to diminish the severity of the reactions. In case of mild or moderate infusion-related reaction, the infusion rate can be reduced and then can be increased if symptoms subside.

Premedication reduces the occurrence of infusion-related reactions. In a study with ocrelizumab, 10 mg cetirizine and 75 mg ranitidine were given the night before and on the morning of the infusion, as premedication.

Given the fact that efficacy of histamine-2 receptor antagonists in premedication therapy is still controversial, the necessity of its use should always be questioned.[47] Along with this procedure, the patients were administered 50 mg IV diphenhydramine, 125 mg IV methylprednisolone (or equivalent steroid), and 650 mg oral paracetamol just before the infusion. As a result, 60% reduction in infusion-related reactions was observed.[48]

Considering patients co-medications, antihypertensive drugs should be discontinued 12 hours before the infusion due to the risk of hypotension.[49] Once hypotension is observed, 1,000 mL of 0.9% normal saline can be administered. If patient's blood pressure is increased, administration of 25 mg captopril or 10-20 mg nifedipine can be considered. In the case of bradycardia, 1 mg IV bolus atropine; in case of tachycardia along with hypertension, 20 mg IV labetalol can be given, otherwise oral propranolol can be preferred. In the literature, it has been suggested that beta-blockers mask the symptoms of cardiac anaphylaxis and cause severe bronchoconstriction by

causing alpha-adrenergic activity whereas angiotensin converting enzyme (ACE) inhibitors increase the degree of anaphylactoid reaction, albeit minimally.[50] In a study demonstrated that aeroallergen immunotherapy is considered relatively safe in patients who routinely take ACE inhibitors compared to those using beta blockers.[51] In a retrospective study including patients who had subcutaneous immunotherapy, it was reported that the degree of anaphylactoid reaction has increased by the use of ACE inhibitors/angiotensin receptor blockers and diuretics, but no significant increase was observed by the use of calcium channel blockers. In the view of these findings, it should be remembered that calcium channel blockers may have advantages in patients who receive immunotherapy, however, more studies conducted with larger sample size are needed to have robust conclusions.[52]

If patients experience with rash and redness on skin, corticosteroid (20 mg methylprednisolone or equivalents) and antihistamine can be administered. Epinephrine, corticosteroids and oxygen support should be given if there are signs of respiratory distress, furthermore bronchodilators can be considered for bronchospasm.[22,26]

CONCLUSION

In recent years, the value of anti-CD20 monoclonal antibody therapies has increased, and they have become frequently preferred options in the treatment of MS. The effectiveness of rituximab, ocrelizumab, ofatumumab, and ublituximab on MS have been investigated in various studies, and it has been reported that especially ocrelizumab and ofatumumab have favorable effects on the treatment of MS. Despite previous studies, there is still a need for comprehensive and real-life data on the efficacy and safety of those treatments. It is known that the most common adverse effect of anti-CD20 monoclonal antibody treatments is infusion-related reactions. Among aforementioned drugs, the infusion-related reaction was most commonly seen in rituximab treatment. These reactions may usually be prevented by appropriate premedication, discontinuation of drug or symptomatic treatment. Patients and healthcare professionals should be aware of the possibility of an infusion-related reaction. Appropriate precautions should be taken to reduce morbidity, including appropriate education, reporting, and premedication. Therefore, it is recommended that clinicians should reconsider the risks and benefits of a particular treatment for a patient, then closely monitor the patients during the infusion of monoclonal antibody therapy.

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Authorship Contributions

Idea/Concept: *Cansu Göncüoğlu, Aygin Bayraktar Ekincioğlu;* ***Design:*** *Cansu Göncüoğlu, Aygin Bayraktar Ekincioğlu;* ***Control/Supervision:*** *Cansu Göncüoğlu, Aygin Bayraktar Ekincioğlu;* ***Data Collection and/or Processing:*** *Kübra Nur Öksüzoğlu;* ***Analysis and/or Interpretation:*** *Kübra Nur Öksüzoğlu, Cansu Göncüoğlu;* ***Literature Review:*** *Kübra Nur Öksüzoğlu, Cansu Göncüoğlu;****Writing the Article:*** *Kübra Nur Öksüzoğlu;* ***Critical Review:*** *Cansu Göncüoğlu, Aygin Bayraktar Ekincioğlu.*

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