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The Egyptian Rheumatologist 43 (2021) 253–256

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

journal homepage: www.elsevier.com/locate/ejr

Six month assessment of low dose rituximab in the treatment of rheumatoid arthritis during coronavirus disease 2019 (COVID-19) pandemic

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ARTICLE INFO

Article history:
Received 1 May 2021
Accepted 3 May 2021
Available online 6 May 2021

Keywords:
Covid-19
Immunoglobulin levels
Rheumatoid arthritis
Rituximab

ABSTRACT

Aim of the work: To evaluate the 6-month treatment responses to low dose rituximab (LDR) compared to standard dose rituximab (SDR) in rheumatoid arthritis (RA) patients whose treatments were disrupted due to the pandemic with increased disease activity and to examine the effect of LDR treatment on serum immunoglobulin (Ig) levels.
Patients and methods: Records were retrospectively analysed for 80 patients on SDR not admitted to the hospital due to fear of infection during pandemic, with increased disease activity and were resumed on LDR (500 mg intravenous RTX-infusion twice with 15 days intervals, and repeated for the second time in all patients after 6 months). Disease activity score (DAS-28) values were obtained. The Ig levels of the patients before and after rituximab treatment were calculated.
Results: The mean age of patients was 55.1 ± 13.1 years. They were 46 (57.5%) female and 34 (42.5%) male (F:M 1.4:1) with median disease duration of 13 (0.5–50) years. After the second dose of LDR, there was a significant decrease in the disease activity DAS28 (6.5 ± 1.01 to 3.2 ± 1.2, $p < 0.0001$) and acute phase reactants with a tendency to decrease in Ig levels. After LDR, 6 (7.5%) patients developed COVID-19 infection that did not require hospitalization. There was no difference between the Ig levels of patients with and without COVID-19 infection.
Conclusions: LDR is an effective treatment option in the treatment of RA. In our study, none of our patients developed severe COVID-19 infection requiring hospitalization, and LDR may be preferred during the COVID-19 pandemic period.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by persistent synovitis, systemic inflammation, and autoantibodies. The etiology of RA is not yet known. Etiological roles of genetics, immunological disorders, sex, hormonal causes, infections, trauma and stress are investigated [1]. Rituximab (RTX) used in RA treatment is a high affinity chimeric CD20-specific monoclonal autoantibody. CD20 is a non-glycosylated phosphoprotein found on the surface of naive B cells that have passed through the bone marrow into the blood. It is not found in plasma cells and stem cells that have returned to bone marrow. Located in mature cells but not in stem cells makes CD20 a suitable target [2].

Rituximab's action is thought to kill CD20 positive B cells after binding to the cell surface receptor by a combination of antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, phagocytosis and apoptosis by the reticuloendothelial system and destroy them from the peripheral circulation. In this way, B cells are displaced for 6 to 12 months or longer [3]. RTX has been shown to be effective and safe in RA. However, there is no consensus regarding the optimal dose. In 2006, the FDA approved the use of standard dose RTX (SDR:1000 mg intravenous on the 1st and 15th days repeated every 6 months) combined with methotrexate in the treatment of RA [4]. However, no significant difference was observed in terms of efficacy and safety comparing low dose RTX (LDR: 2x500 mg) with SDR [5]. It is reported that decreases in immunoglobulin M (IgM) levels after RTX treatment

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
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https://doi.org/10.1016/j.ejr.2021.05.001
1110-1164/

may be associated with infection [6]. However, such effect has not been fully elucidated.

During the coronavirus disease 2019 (COVID-19) pandemic, patients with RA faced remarkable difficulty to obtain their medications with subsequent change in their disease status. Challenges of the pandemic have hastened changes in the way we deliver health care [7] and reshaped the treatment strategies [8]. In COVID-19, the innate immune system is activated producing and releasing proinflammatory cytokines such as interleukins (IL-6, IL-1β and IL-8) and tumor necrosis factor-α and when severe may eventually lead to an excessive inflammatory response and to the *cytokine storm* syndrome [9]. In cases such as the COVID-19 pandemic, where the risk of transmission is high and may cause death, it is inevitable that this jeopardy is higher in immunosuppressed patients. In studies comparing SDR and LDR, while there was no significant difference in terms of efficiency and safety, it was found that the frequency of serious infections in LDR treatment was lower than SDR [5,10–12].

The purpose of the current study was to evaluate the 6-month treatment responses to LDR treatment compared to SDR, in RA patients on SDR whose treatments were disrupted due to the pandemic and with increased disease activity. Also, the aim of this work was extended to examine the effect of LDR treatment on serum Ig levels.

2. Patients and method

The records of 80 RA patients fulfilling 2010 American College of Rheumatology/ European League Against Rheumatism (ACR / EULAR) classification criteria [13] were retrospectively studied. The patients had an increased activity and were not admitted to hospital due to fear of infection during pandemic. Treatment was resumed with LDR (500 mg intravenous RTX-infusion twice with 15 days intervals, and repeated in all patients in the 6th month). Patients with missing file records, pregnant patients, patients under 18 years of age, patients with acute infection, selective IgA deficiency, primary or secondary immunodeficiency were excluded. The study protocol was approved by the medical faculty ethics committee (No. E-77192459–050.99–8298). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Sociodemographic data such as age, gender, disease duration, alcohol use, smoking and comorbidities were recorded. Disease modifying antirheumatic drugs (DMARDs) used were noted. The erythrocyte sedimentation rate (ESR, mm/hr), C-reactive protein (CRP, mg/L), rheumatoid factor (RF, IU/ml), anti-cyclic citrulled peptide (anti-CCP, U/ml) values and disease activity score (DAS28) were obtained [14].

The Ig levels of the patients before and after RTX treatment were calculated. The Ig levels (IgG: 7.67–15.9 g/L; IgM: 0.37–2.86 g/L and IgA: 0.61–3.56 g/L) were accepted as normal values (measured by immunonephelometry, kits info: BNII™ System, Siemens Healthcare Diagnostics, Marburg, Germany).

Statistical analysis: The statistical package for the social sciences (SPSS) version 26 was used (Chicago, IL, USA). Normality of distribution was assessed by *Kolmogorov-Simirnov* test. Data were presented as mean and standard deviation or median and range. Student *t* test was used for comparison of normally distributed data, and Mann Whitney *U* test was used for non-normally distributed data. Pearson Chi-square test and Fisher's exact test were used for categorical data. Paired Samples Test and Wilcoxon signed-rank test was used to evaluate Ig levels or DAS28 before and after treatment. $P < 0.05$ significance level was accepted.

3. Results

The mean age of 80 patients was 55.1 ± 13.1 years. They were 46 (57.5%) female and 34 (42.5%) male (F:M 1.4:1). The median disease duration was 13 (0.5–50) years. 4 (5%) patients drink alcohol and 22 (27.5%) smoke. At least one comorbidity was present in 43 (53.8%) patients; hypertension in 17, chronic pulmonary disease in 13, diabetes mellitus in 12, hypercholesterolemia in 9 and obesity in 8. 1 patient had amyloidosis. 62 (77.5%) patients were receiving corticosteroids (mean dose 6.1 ± 4.7; 0–17.5 mg/day), 69 (86.3%) were on methotrexate (MTX) (9.5 ± 4.7; 0–17.5 mg/week), 33 (41.3%) leflunomide (6.5 ± 8.4; 0–20 mg/day), 51 (63.7%) hydroxychloroquine (HCQ) (187.5 ± 163.3; 0–400 mg/day) and 16 (20%) sulfasalazine (318.8 ± 671.5; 0–2000 mg/day).

Table 1 shows the laboratory investigations and disease activity before and after 6 months of LDR therapy during the pandemic. Before LDR, low IgG level was present in 18 (22.5%), low IgM level in 3 (3.8%), with low IgA level in 1 (1.3%), while after 6 months became present in 10 (12.5%), 4 (5%) and 1 (1.3%), respectively. While no patients developed COVID-19 infection in the *first* 6 months after LDR treatment, 6 (7.5%) developed non-severe COVID-19 infection that did not require hospitalization in the *second* 6 months. Patients were diagnosed with clinical findings that may be compatible with COVID-19 infection (fever, cough, dyspnea, headache, sore throat, muscle and joint pain, extreme weakness, new taste and smell loss, diarrhea) and positive polymerase chain reaction (PCR) tests studied on throat and nasopharyngeal swab samples. None of those patients with COVID-19 had pulmonary involvement and computerized tomography (CT) chest were normal. The time for the patients to be diagnosed with COVID-19 was, respectively 13th, 20th, 21st, 26th, 37th, 41st days after the 2nd treatment cycle. In accordance with the current treatment guideline in Turkey, all patients with COVID-19 were treated by favipiravir 2 × 1600 mg loading dose, 2 × 600 mg maintenance (4 days) dose. PCR tests performed in the 1st month after favipiravir treatment were negative in all 6 patients, and there were no clinical symptoms compatible with COVID-19. Serum Ig levels in all patients with infection were within normal limits. 2 infected patients had low disease activity (3.2 > DAS28 > 2.6) and 4 were in remission (DAS28 ≤ 2.6). In patients who developed COVID-19, steroids were discontinued gradually, while DMARDs except HCQ were discontinued.

Comparison of patients characteristics with and without COVID-19 infection is presented in Table 2.

Table 1
Laboratory investigations and disease activity before and after 6 months of low dose rituximab (LDR) therapy in rheumatoid arthritis patients (RA) during the pandemic.

Parameter median (range)/ mean ± SD	RA patients on LDR (n = 80)		p
	before	*after*	
ESR (mm/1st hr)	46 (2.20–110)	25 (2.0–98)	**<0.0001**
CRP level (mg/L)	20.5 (0.36–196)	6 (0.20–54)	**<0.0001**
RF level (IU/ml)	53 (0–442)	56.5 (0–355)	0.16
Anti-CCP (U/ml)	78 (0–300)	72.5 (0–310)	0.72
IgG level (g/L)	10.09 ± 2.92	10.02 ± 2.54	0.63
IgM level (g/L)	0.79 (0.3–2.34)	0.75 (0.25–2.9)	0.1
IgA level (g/L)	2.05 (0.56–3.8)	2.1 (0.38–3.87)	0.09
DAS28	6.5 ± 1.01	3.2 ± 1.2	**<0.0001**

RA: rheumatoid arthritis, LDR: low dose rituximab, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, Ig: Immunoglobulin, DAS28: disease activity score. Bold values are significant at $p < 0.05$

Table 2
Comparison of the patients characterisitcs with and without coronavirus disease-2019 (COVID-19) infection.

Parameter median (range),mean ± SD or n (%)	RA patients with and without COVID-19 infection (n = 80)		p
	No (n = 74)	Yes (n = 6)	
Gender F:M	42:32 (1.3:1)	4:2 (2:1)	1
Smoking	20 (27)	2 (33.3)	0.67
Alcohol use	3 (4.1)	1 (16.7)	0.27
Comorbidities	39 (52.7)	4 (66.7)	0.68
Age (years)	56.2 ± 12.9	41.7 ± 4.4	**0.008**
Disease duration (years)	13.5 (0.5–50)	3 (1–38)	0.08
ESR (mm/1st h) (*before* LDR)	46 (2.20–110)	45.5 (6–86)	0.86
(*after* LDR)	25 (6–65)	47 (2–98)	0.18
CRP (mg/L) (*before* LDR)	22.1 (0.36–196)	12 (3.76–87)	0.8
(*after* LDR)	5.2 (0.20–54)	39.1 (2.20–49)	**0.009**
RF (IU/ml) (*before* LDR)	58.5 (0–442)	40 (0–148)	0.31
(*after* LDR)	57.5 (1–355)	36.5 (0–198)	0.23
Anti-CCP (U/ml) (*before* LDR)	78 (0–300)	112 (0–300)	0.83
(*after* LDR)	72.5 (0–310)	112 (0–300)	0.86
IgG level (g/L) (*before* LDR)	10.1 ± 2.97	9.67 ± 2.52	0.72
(*after* LDR)	10.04 ± 2.58	9.6 ± 2.08	0.69
IgM level (g/L) (*before* LDR)	0.78 (0.3–2.34)	0.98 (0.58–1.01)	0.66
(*after* LDR)	0.76 (0.25–2.9)	0.66 (0.3–0.9)	0.41
IgA level (g/L) (*before* LDR)	1.96 (0.56–3.8)	2.61 (0.7–3.35)	0.44
(*after* LDR)	1.95 ± 0.71	1.83 ± 1.05	0.79
DAS28 (*before* LDR)	6.5 ± 1.01	6 ± 0.44	0.16
(*after* LDR)	3.2 ± 1.2	3.6 ± 1	0.41
Steroids dose (mg/day)	5 (0–10)	7.5 (0–15)	**0.036**
MTX dose (mg/week)	10 (0–17.5)	8.75 (0–15)	0.45
LFN dose (mg/day)	0 (0–20)	0 (0–10)	0.43
HCQ (mg/day)	200 (0–400)	200 (0–200)	0.43
SAZ (mg/day)	0 (0–2000)	500 (0–2000)	0.05

RA: rheumatoid arthritis, COVID-19: coronavirus-2019, DAS28: disease activity score, LDR: low dose rituximab, ESR: erythrocyte sediemntation rate, CRP: C-reactive protein, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, Ig: Immunoglobulin, DAS28: disease activity score. Bold values are significant at $p < 0.05$.

4. Discussion

The impact of the COVID-19 pandemic is negative on the quality of life of RA patients with many contributing factos [15]. Patients on DMARDs remain concerned about potential risks of severe COVID-19 outcomes; Meanwhile, several have been proposed as COVID-19 therapies [16]. In fact, it has been suggested that the course of COVID-19 might be less favourable in patients with inflammatory rheumatic and musculoskeletal diseases receiving rituximab compared with those not [17]. From the start of the pandemic, patients treated with RTX approached their rheumatology team in large numbers to ask their opinion on the risk of COVID-19, and whether they should continue with RTX treatment or not [18].

In the present study, disease activity significantly improved after LDR treatment. Although the recommended dose was 1000 mg intravenously every 6 months and on the 1st and 15th days, there was no significant difference in terms of efficacy and safety comparing LDR with SDR [5]. In the MIRROR (Methotrexate Inadequate Responders Randomized Study of Rituximab) study, LDR and SDR were compared with no significant difference in the primary endpoints ACR20, 50 and 70 responses while the EULAR response was better in the SDR group [19]. The results of the present study are compatible, yet the small number of patients and short follow-up period are limitations to this work. Interestingly, in a case with clinical relapse of acquired immune-mediated thrombotic thrombocytopenic purpura, it was successfully treated with LDR plus corticosteroids without the use of plasma exchange, which was unavailable during the COVID-19 pandemic [20]. A LDR regimen achieved reasonably good clinical outcomes in RA patients at the end of 6 months, at a significantly lower cost [21].

In this work there was basal hypogammaglobulinemia with a tendency to lower IgG levels after LDR. In 119 patients with RA; *De la torre et al.* [22] investigated serum Ig levels after the initiation of RTX, and IgM and IgG were found to be low before treatment in 2.5% and 3.4% respectively. After the first RTX course, IgM and IgG levels were found low in 9.2% and 11.8% of patients, respectively. After five cycles, these rates reached 38.8% and 22.2%. As a result, it was underlined that patients with lower baseline serum Ig levels tend to develop persistent IgM and IgG hypogammaglobulinemia due to the accumulating decreases after repetitive cycles suggesting that naive and/or pre-switch memory B cells (follicular B cells) were failing to differentiate into plasma cells. As a consequence, marginal zone B cells (IgM + CD27 +) may not be able to rapidly regenerate after depletion, contributing to incremental decreases in IgM production [22].

Infections in RA patients receiving RTX treatment are often minor and mostly involve upper respiratory and urinary tract infections. In the REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab in RA) study, there was only a slight increase in serious infections compared to placebo (5.2% vs. 3.7%/100 patient years). There is no data on an increase in opportunistic infections including tuberculosis [23]. Although low IgG levels are inherently associated with an increased risk of infection [24], the role of immune and native IgM in protecting against numerous infections has been highlightened [25].

While the patients did not experience any infection in the first 6 months after LDR treatment, 6 developed COVID-19 infection that did not require hospitalization in the second 6 months. These infections regressed with antiviral treatments. Disease duration, pre- and post-LDR treatment ESR, RF, anti-CCP, serum IgG, IgM, IgA levels and pre-treatment CRP levels were similar in patients with and without infection. Patients who developed infections were younger than those who did not, and the mean CRP values were significantly higher during the second cycle of LDR.

In this study, Ig levels tended to decrease after LDR treatment and did not seem to be associated with infection development. Similarly, *Dass et al.* found no difference between the decrease in IgM level after SDR treatment and the incidence of infection [2]. Moreover, in a registry study examining 1303 RA patients treated with SDR, it was shown that low IgM before starting treatment

with RTX was not associated with an increase in infection risk [26]. *Marco et al.* [27] studied 191 patients with different autoimmune diseases and found that 37% with normal IgM and 43% with low IgM levels developed infection, but this was comparable. In a study of 30 patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) treated with RTX, *Shah et al.* no association between IgM hypogammaglobulinemia and general infections was found [28]. Conversely, *Besada et al.* [29], in a study of 30 patients with granulomatosis with polyangiitis (GPA), argued that large decreases in serum IgM levels after the first RTX course may be useful in predicting the development of severe infections. The main difference that distinguishes the current work from all other studies is that LDR was used instead of SDR.

In the present study, the mean steroid dose was significantly higher in patients who developed infection after LDR compared to those without. High doses of steroids used in RA treatment may facilitate the development of detected infections. It has been argued that concomitant corticosteroid administration may contribute to a decrease in IgG levels in patients treated with RTX [30]. The results of scientific studies on Ig levels after RTX treatment differ. The reason for this difference may be the underlying disease, different follow-up periods, previous immunosuppressive drug use, the doses and durations of the drugs used, and possibly the genetic makeup of an individual.

In conclusion, LDR treatment was effective in active RA patients who could not receive SDR treatment during the COVID-19 pandemic. None of the patients on LDR developed severe COVID-19 infection requiring hospitalization, and LDR may be considered a promising therapeutic option during the COVID-19 pandemic.

Funding

The authors received no financial support for the research and/or authorship of this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Firestein GS. Etiology and pathogenesis of rheumatoid arthritis. In: Ruddy S, Harris ED, Sledge CB, (eds). Kelley's Textbook of Rheumatology. Sixth ed, Philadelphia. WB Saunders. 2001;921-66.
[2] Dass S, Vital EM., Emery P. Rituximab. In: Rheumatoid Arthritis, Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME. Weisman MH (eds). Mosby.2009;362-366.
[3] Salvarani C, Brown Jr RD, Muratore F, Christianson TJH, Galli E, Pipitone N, et al. Rituximab therapy for primary central nervous system vasculitis: A 6 patient experience and review of the literature. Autoimmun Rev 2019;18(4):399–405.
[4] Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dörner T, et al. Dörner T et al.: Rituximab Consensus Expert Committee. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70(6):909–20.
[5] Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequater Esponders (SERENE)). Ann Rheum Dis. 2010;69(9):1629–35.
[6] Kridin K, Ahmed AR. Post-rituximab immunoglobulin M (IgM) hypogammaglobulinemia. Autoimmun Rev 2020;19(3):102466. doi: https://doi.org/10.1016/j.autrev.2020.102466.
[7] Abualfadl E, Ismail F, Shereef RRE, Hassan E, Tharwat S, Mohamed EF, et al. ECR COVID19-Study Group. Impact of COVID-19 pandemic on rheumatoid arthritis from a Multi-Centre patient-reported questionnaire survey: influence of gender, rural-urban gap and north-south gradient. Rheumatol Int 2021;41(2):345–53.
[8] Gheita TA, Salem MN, Eesa NN, Khalil NM, Gamal NM, Noor RA, et al. ECR COVID19-Study Group. Rheumatologists' practice during the Coronavirus disease 2019 (COVID-19) pandemic: a survey in Egypt. Rheumatol Int. 2020;40(10):1599–611.
[9] Gheita TA, Fathi HM, ElAdle SS, Eesa NN, Hammam NH. Coronavirus disease 2019 (COVID-19) an emerging trigger for primary fibromyalgia syndrome: A tale of three cases post-COVID-19. Int J Clin Rheumatol 2021;16(4):129–35.
[10] Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U, et al. Rheumatic Diseases Portuguese Register. Effectiveness of two different doses of rituximab for the treatment of rheumatoid arthritis in an international cohort: data from the CERERRA collaboration. Arthritis Res Ther 2016;18(1). doi: https://doi.org/10.1186/s13075-016-0951-z.
[11] Barmettler S, Ong M-S, Farmer JR, Choi H, Walter J. Association of Immunoglobulin Levels, Infectious Risk, and Mortality With Rituximab and Hypogammaglobulinemia. JAMA Netw Open 2018;1(7):e184169. doi: https://doi.org/10.1001/jamanetworkopen.2018.4169.
[12] Henry J, Gottenberg JE, Rouanet S, Pavy S, Sellam J, Tubach F et.al. Auto-Immunity and Rituximab investigators. Doses of rituximab for retreatment in rheumatoid arthritis: influence on maintenance and risk of serious infection. Rheumatology (Oxford). 2018;57(3):538-47.
[13] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2569–81.
[14] Prevoo MLL, Van'T Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LBA, Van Riel PLCM. Van De Putte LBA, Van Riel P. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38(1):44–8.
[15] Zomalheto Z, Assogba C, Dossou-yovo H. Impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection and disease-2019 (COVID-19) on the quality of life of rheumatoid arthritis patients in Benin. Egyptian Rheumatologist 2021;43(1):23–7.
[16] D'Silva KM, Wallace ZS. COVID-19 and Disease-Modifying Anti-rheumatic Drugs. Curr Rheumatol Rep 2021;23(5):28.
[17] Avouac J, Drumez E, Hachulla E, Seror R, Georgin-Lavialle S, El Mahou S, et al. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. Lancet Rheumatol 2021. doi: https://doi.org/10.1016/S2665-9913(21)00059-X.
[18] Dougados M. Managing patients with rheumatic diseases treated with rituximab during the COVID-19 pandemic. Lancet Rheumatol. 2021;epub ahead of print.
[19] Rubbert-Roth A, Tak PP, Zerbini C, Tremblay JL, Carreño L, Armstrong G et al; MIRROR Trial Investigators. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR). Rheumatology (Oxford).2010;49(9):1683-93.
[20] Galindo-Calvillo CD, Rodríguez-Roque CS, Gómez-De León A, Tarín-Arzaga L, Gómez-Almaguer D. Treating thrombotic thrombocytopenic purpura without plasma exchange during the COVID-19 pandemic. A case report and a brief literature review. Transfus Apher Sci. 2021:103107. doi: https://doi.org/10.1016/j.transci.2021.103107.
[21] Chandramohan P, Jain A, Antony G, Krishnan N, Shenoy P. Low-dose rituximab protocol in rheumatoid arthritis-outcome and economic impact. Rheumatol Adv Pract. 2021;5(1):rkaa077. Chandramohan P, Jain A, Antony G, Krishnan N, Shenoy P. Low-dose rituximab protocol in rheumatoid arthritis-outcome and economic impact. Rheumatol Adv Pract. 2021;5(1):rkaa077.
[22] De La Torre I, Leandro MJ, Valor L, Becerra E, Edwards JC, Cambridge G. Total serum immunoglobulin levels in patients with RA after multiple B-cell depletion cycles based on rituximab: relationship with B-cell kinetics. Rheumatology (Oxford) 2012;51(5):833–40.
[23] Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793–806.
[24] Lee ML, Gale RP, Yap PL. Use of intravenous immunoglobulin to prevent or treat infections in persons with immune deficiency. Annu Rev Med. 1997;48:93-102.
[25] Ehrenstein MR, Notley CA. The importance of natural IgM: scavenger, protector and regulator. Nat Rev Immunol. 2010;10(11):778–86.
[26] Gottenberg J-E, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010;62(9):2625–32.
[27] Marco H, Smith RM, Jones RB, Guerry M-J, Catapano F, Burns S, et al. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. BMC Musculoskelet Disord. 2014;15(1). doi: https://doi.org/10.1186/1471-2474-15-178.
[28] Shah S, Jaggi K, Greenberg K, Geetha D. Immunoglobulin levels and infection risk with rituximab induction for anti-neutrophil cytoplasmic antibody-associated vasculitis. Clin Kidney J. 2017;10(4):470–4.
[29] Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. Rheumatology (Oxford) 2013;52(11):2041–7.
[30] Payandeh Z, Bahrami AA, Hoseinpoor R, Mortazavi Y, Rajabibazl M, Rahimpour A, et al. The applications of anti-CD20 antibodies to treat various B cells disorders. Biomed Pharmacother. 2019;109:2415–26.