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Retrospective Study

Outcomes of a 12-month course of early and late rituximab BCD020 biosimilar administration in juvenile systemic lupus erythematosus: A retrospective study

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Abstract

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BACKGROUND

Juvenile systemic lupus erythematosus (SLE) is a severe life-threatening disease. The place of rituximab in juvenile SLE management is still undefined. Early biological intervention might improve disease outcomes.

AIM

To assess the differences in the outcomes of different type of rituximab administration (early and late).

METHODS

In the retrospective cohort study the information about 36 children with SLE with early (less than six months from onset) rituximab administration (ERA), and late (more than one year) rituximab administration (LRA). We compared initial disease characteristics at onset, on the baseline - the start of rituximab and end of the study - (EOS) - 12 months, outcomes, and treatment characteristics.

RESULTS

The main differences at baseline were: Higher daily median dose of corticosteroids , MAS frequency and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) in the ERA group. No differences in the main SLE outcomes between groups at the EOS were observed. The part of lupus-nephritis patients who achieved remission changed from 44% to 31% in ERA and 32% to 11% in the LRA group. Patients with ERA had a shorter time to achieve low daily corticosteroid dose (≤ 0.2 mg/kg)-1.2 (0.9; 1.4) years compared to 2.8 (2.3; 4.0) years ($P = 0.000001$) and higher probability to achieve this low dose [HR = 57.8 (95%CI: 7.2; 463.2), $P = 0.00001$] and achieve of the remission (SLEDAI = 0); HR = 37.6 (95%CI: 4.45; 333.3), $P = 0.00001$]. No differences in adverse events, including severe adverse events were observed during the study.

CONCLUSION

ERA demonstrated a better steroid-sparing effect and a possibility of earlier remission or low disease activity, except for lupus nephritis. Further investigations are required.

INTRODUCTION

Juvenile systemic lupus erythematosus (SLE) is the most common form of pediatric connective tissue disease with multi-system involvement and a poor prognosis[1]. The severity of this condition in adolescents and young adults is associated with an increased risk of kidney, blood vessel, and central nervous system complications, as well as more severe damage and activity. This necessitates the use of higher doses of systemic corticosteroids and immunosuppressive agents[2]. Corticosteroids continue to be the mainstay of treatment for juvenile SLE with lupus nephritis (LN)[3]. However, the potential toxicity of these drugs and the need for long-term therapy has led to the development of steroid-sparing strategies[4].

There are no current standardized recommendations for corticosteroid tapering and withdrawal in juvenile SLE, despite the European Alliance of Associations for Rheumatology recommendations to minimize corticosteroid use[5]. The current

standard of care treatment (SOCT) includes combinations of corticosteroids, cytotoxic agents, and antimalarials, and the place of biological treatments has not yet been established. Treatment with cytotoxic agents can lead to adverse events involving blood, liver, kidney, and increased risk of fertility problems and cancer in adults[2,5]. Biological treatments have disease-modifying effects that are similar to or better than SOCT, with fewer adverse events, and may enhance or replace SOCT in some cases.

Several biologics have been developed for the treatment of SLE: Belimumab, which is approved for both adults and children, anifrolumab, which is only approved for adults, and rituximab, which has not yet been approved despite its known clinical efficacy[6-9]. Belimumab is approved for pediatric and adult patients with mild to moderate SLE[6,7]. It acts as a steroid-sparing agent for patients with corticosteroid dependence, especially those who have previously achieved remission. It is unlikely to be effective in patients with highly active SLE[6,7].

Anifrolumab, an anti-interferon drug, may control lupus similar to non-biological disease-modifying anti-rheumatic drugs, but it has only been approved for adults at this time. Rituximab is typically used for severe, life-threatening forms of lupus, but it has not been officially approved for either adults or children with lupus. Rituximab is included in all current recommendations for lupus treatment in adults and children, but it is usually reserved as a last resort when other treatments have failed[2,4]. Rituximab can be considered in cases of severe lupus with damage to the kidneys, central nervous system, and blood if standard treatments have not been effective[2,4].

The question of whether rituximab can be used as a first-line treatment, with or without SOCT, is still open and requires further research[2,4]. Several retrospective studies have failed to show the benefits of rituximab over traditional non-biologic DMARDs, and there have been no prospective, placebo-controlled trials comparing rituximab with SOCT in children with SLE[10,11].

The study aimed to compare the outcomes of early *vs* late administration of rituximab.

MATERIALS AND METHODS

Study design

In the retrospective cohort study, the available information about 35 SLE (8 boys and 27 girls) patients from our cohort ($n = 165$, 21.2%), during whom rituximab was initiated was included in 2012-2022. All patients failed conventional non-biologic treatment, had high disease activity, or realized corticosteroid dependence/toxicity. Diagnosis of SLE was made using Systemic Lupus International Collaborating Clinics classification criteria[12]. The Damage Index was assessed with the Pediatric Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index[13]. Lupus nephritis was diagnosed according to the criteria of the International Society of Nephrology/Renal Pathology Society[14,15].

Rituximab BCD020 biosimilar was prescribed in a dosage of 375 mg/m² every week (2-4 infusions) with repeated courses every 6-12 months (2-4 infusions) according to disease activity, B-cell depletion, and IgG levels.

All patients were divided into two groups: Early start of rituximab administration - ERA (less the six months from onset) and late rituximab administration - LRA (more than one year). The study's flow chart is in Figure 1.

Assessment and outcomes

In each patient we evaluated the dynamics of the following parameters of SLE and treatment at three time points: (1) Disease onset; (2) On the baseline - the start of rituximab; and (3) At the end of the study - 12 months: Demography: Gender, onset age; Disease activity: The levels of antinuclear antibodies, antibodies to double-stained deoxyribonucleic acid (ds-DNA), C3, C4, hemoglobin, platelets, complete blood count, erythrocyte sedimentation rate, C-reactive protein, urea, creatinine, serum protein and albumin, proteinuria, presence of leucocyturia and hematuria, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[12], Damage Index[13] and LN activity stage[14,15], B-cell level, and IgG, the part of patients achieved the SLE remission; The

concomitant treatment: The part of patients being treated with corticosteroids (including median dose), with non-biologic DMARD; Adverse events.

Statistical analysis

The sample size was not calculated initially. The statistical analysis was performed with the software STATISTICA, version 10.0 (StatSoft Inc., United States). All continuous variables were checked by the Kolmogorov-Smirnov test: No normal distribution was identified. Continuous variables are presented as median and percentiles (25%; 75%). Categorical variables are presented as proportions. Missing data were not imputed or included in the analysis. Pearson's χ^2 test or Fisher's exact test in the expected frequencies < 5 was used to compare the independent categorical variables and the Mann-Whitney test for continuous variables. A comparison of two dependent quantitative variables was carried out using Wilcoxon's matched paired test and the Mac-Nemar test was applied for dependent categorical variables. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Patients' characteristics at the disease onset

The studied population consisted of 8 boys (23%) and 27 girls (77%). There were no significant differences between the group with ERA and LRA, except the higher level of SLEDAI in ERA group 23 (16; 26) compared to LRA - 14 (11; 19) points (*P* = 0.012), and prevalence of the patients with high disease activity (SLEDAI grade IV) - 63% *vs* 21% (*P* = 0.043). Patients from the ERA group had a higher frequency of pleurisy 44% *vs* 16% (*P* = 0.068), pericarditis 38% *vs* 11%, (*P* = 0.058), ascites 25% *vs* 5% (*P* = 0.07) and macrophage activation syndrome 25% *vs* 5% (*P* = 0.096) with a borderline level of significance.

Baseline patients' characteristics

The time before rituximab from SLE onset was different between groups: 3 (2; 6) months in ERA and 22 (14; 36) months ($P = 0.00001$) for LRA. Patients with ERA continued to have higher levels of SLEDAI [22 (15; 26) vs 10 (6; 16), $P = 0.003$] and had higher daily median doses of corticosteroids [1.0 (0.6; 1.0) vs 0.3 (0.2; 0.8) mg/kg, $P = 0.027$] and WBC levels [$8.4 (5.7; 13.5) \times 10^9/L$ vs $5.1 (3.7; 8.3) \times 10^9/L$, $P = 0.035$]. Also, patients from the ERA group had higher ANA-positivity - 94% vs 68%, $P = 0.075$ and ANA titer [1280 (1000; 2560) vs 320 (0; 5120), $P = 0.077$] lower C3 [0.57 (0.4; 0.8) g/L vs 0.85 (0.7; 1.1) g/L, $P = 0.059$], and C4 fractions of complements [0.10 (0.06; 0.14) g/L vs 0.19 (0.10; 0.24) g/L, $P = 0.075$] with borderline significance. There were no differences in the proportion of LN patients and non-biologic DMARD treatment. The baseline characteristics in both groups are in Table 1.

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The characteristics of patients at the end of the study

There were significant differences in the main outcomes in both groups 12 months of the treatment, except for the higher level of platelets in the group with early rituximab administration (Figure 2). A higher frequency of patients with active LN in the ERA group (31% vs 11%) was observed, but the data were non-significant ($P = 0.150$). The part of patients with LN remission decreased from 44% to 31% in ERA and from 32% to 11% in LRA groups. Patients with early rituximab administration had a shorter time to achieve low daily corticosteroid dose (≤ 0.2 mg/kg) 1.2 (0.9; 1.4) years compared to 2.8 (2.3; 4.0) years ($P = 0.000001$) and higher probability to achieve this low dose [LogRank test $P = 0.00015$; HR = 57.8 (95%CI: 7.2; 463.2), $P = 0.00001$], and higher probability to achieve the remission [SLEDAI = 0; LogRank test $P = 0.021$; HR = 37.6 (95%CI: 4.45; 333.3), $P = 0.00001$]. The data are in Table 2 and Figure 3.

Safety of rituximab treatment

During the 12-month rituximab course, no differences in severe adverse events were observed. Nearly half of the patients of both groups received co-trimoxazol profilaxis. The IgG level was similar in both groups, but patients with ERA frequently had low IgG

levels (< 4.5 g/L) and a higher proportion of ERA patients had B-cell depletion. The number of patients who received replacement IVIG treatment was equal in both groups.

DISCUSSION

In this small study, some differences in the outcomes between early and late administration of rituximab for the treatment of juvenile SLE were observed. Patients who received early rituximab had the potential for faster tapering of systemic corticosteroids and a quicker achievement of SLE remission, with the exception of patients with lupus nephritis.

The role of rituximab in SLE has not yet been fully established, despite its known efficacy. It is typically used as a treatment for resistant disease or as a new treatment for severe, life-threatening courses of the disease[15]. Rituximab's effectiveness was demonstrated in a large meta-analysis of 35 uncontrolled studies and case reports, in which 91% of the 188 patients showed significant improvement in at least one systemic SLE manifestation[15]. Many uncontrolled trials and case reports have shown the effectiveness of rituximab compared to randomized controlled trials, such as EXPLORER and LUNAR, which did not reach the primary endpoints[16,17]. Both trials showed effectiveness compared to placebo[16,17]. Rituximab is recommended to reduce disease activity, serum levels, proteinuria, and the need for corticosteroids[18]. According to these studies, rituximab works better as an adjuvant therapy to control severe manifestations of SLE rather than as an induction therapy[19]. Rituximab has not yet been approved by the Food and Drug Administration for use in the treatment of SLE in the United States.

The steroid-sparing effect of rituximab has been demonstrated in the majority of pediatric and adult studies of SLE, similar to our findings, with a greater potential to reduce corticosteroid use when rituximab is administered early[1,11,19,20].

Corticosteroids, being the basis of SLE treatment have severe damage, related to their toxicity (osteoporosis, avascular necrosis, cataract, steroid diabetes, striae, hypertension, etc.)[21]. Adults with childhood SLE onset had significantly higher corticosteroid-

induced damage, compared to patients with disease onset after 18 years (OR: 1.7, 95%CI 1.1-2.8)[22]. Pediatric SLE patients with short stature (23%) had higher cumulative corticosteroid dosage[23]. Delayed puberty, caused by corticosteroids, had at least 15% of females and 24% of males[24]. The transition from oral to intravenous use of corticosteroids might decrease the corticosteroid-associated side effects; decrease the cumulative dose of oral corticosteroids with equal efficacy. Repeated IV usage of corticosteroids improved outcomes in LN and helped to reduce the dose of oral corticosteroids[25] Low dose intravenous corticosteroid therapy was effective as high dose in patients with LN with less number of corticosteroid-associated side effects[26]. The possibility of faster achievement of remission with lower corticosteroid burden may improve the disease outcomes with less damage and higher quality of life. The contemporary guidelines for pediatric and adult SLE recommend reducing corticosteroids as much as possible[4,27]. Early administration of rituximab seems a good tool to an end. Long term rituximab therapy showed higher relapse-free survival rate in adult SLE patients compared to standard conventional treatment[28].

Lower IgG levels and higher proportion of patients with B-cells was observed in the ERA group, compared to LRA. It could be explained that patients with ERA received more treatment agent in the same time and this effect might be related to cumulative effect of combined therapy with different targets. Fortunately this low IgG level did not lead to increased frequency or severity of infections which was demonstrated earlier[29,30].

In the recent study from India authors suggested the rituximab was effective (decreased SLEDI, corticosteroids and proteinuria and no flares in 82% of children during 24 months) and safe treatment for pediatric SLE in a country with a very high burden of infectious diseases[31].

The early onset of SLE is significant, as juvenile SLE is characterized by higher disease activity, a greater medication burden, and an increased risk of internal organ damage compared to adult-onset SLE[32-34]. In a multivariate model adjusted for age, disease duration, and other clinical characteristics, juvenile SLE ⁷ was independently

associated with an increased risk of death (hazard ratio 3.1, 95%CI 1.3-7.3)[35]. Survival rates in children with juvenile SLE (mean age 11.6 ± 2.6 years) are 88% at 2 years, 76% at 5 years, and 64% at 10 years after diagnosis[36]. Irreversible organ damage develops in 44.2% of children with juvenile SLE, occurring only 3.8 years after diagnosis, which suggests a high risk of comorbidity accumulation at a young age in these patients in adults[37].

In general, the same immunosuppressive drugs are used to treat both juvenile and adult SLE. Hydroxychloroquine is prescribed to all patients with adult and juvenile SLE who have no contraindications to its use[4]. Along with hydroxychloroquine, GCs are the mainstay of treatment for adult SLE patients because of their anti-inflammatory and immunosuppressive effects[38]. However, prolonged use of glucocorticoids leads to numerous side effects, including increased risk of infections, metabolic disorders, cardiovascular disease and irreversible organ damage[38]. Non-biologic disease-modifying drugs are prescribed less frequently in adult SLE patients than in children[35]. Mycophenolate mofetil, cyclophosphamide and azathioprine are the main drugs used to treat lupus nephritis in both adults and children with SLE[4].

Regarding biologic agents, belimumab or anifrolumab is recommended for patients who do not respond to hydroxychloroquine monotherapy or in combination with glucocorticoids and/or other immunosuppressive drugs, or for patients who cannot reduce the dose of glucocorticoids below acceptable doses for continuous use. The use of rituximab may be considered in severe, organ-threatening, refractory disease[4].

Due to the severity of SLE in children, they often receive more corticosteroids and cyclophosphamide. This can lead to over-treatment, as physicians are often concerned about the disease and its potential complications. As a result, pediatric SLE patients may suffer more from treatment-related damage than disease-related damage. The early use of biologics in the treatment of juvenile SLE could help to improve this situation and reduce the need for corticosteroids and cyclophosphamide with better outcomes.

CONCLUSION

The study showed that ERA had a better steroid-sparing effect and the possibility of earlier remission or lower disease activity, except in patients with lupus nephritis. No significant differences were found in severe adverse events between the ERA and LRA groups, and further research is needed.

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