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Case Control Study

The comparison of treatment outcomes with BCD020 rituximab bioanalog compared to standard of care treatment in juvenile systemic lupus erythematosus: the data of 12 months case-control study

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Abstract**BACKGROUND**

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Systemic lupus erythematosus (SLE) is the most frequent and serious systemic connective tissue disease. Nowadays there is no clear guidance on its treatment in childhood. There are a lot of negative effects of standard-of-care treatment (SOCT), including steroid toxicity. Rituximab (RTX) is the biological B-lymphocyte-depleting agent suggested as a basic therapy in pediatric SLE.

AIM

To compare the benefits of rituximab above SOCT.

METHODS

The data from case histories of 79 children from the Saint-Petersburg State Pediatric Medical University from 2012 to 2022 **years**, were analyzed. The diagnosis of SLE was

established with SLICC criteria. We compared the outcomes of treatment of SLE in children treated with and without RTX. Laboratory data, doses of glucocorticosteroids (GCS), disease activity measured with SELENA-SLEDAI, and organ damage were assessed at the time of initiation of therapy and one year later.

RESULTS

Patients, treated with rituximab initially had a higher degree of disease activity with prevalence of central nervous system and kidney involvement, compared to patients with SOCT. One year later the disease characteristics became similar between groups with a more marked reduction of disease activity (SELENA-SLEDAI activity index) in the children who received rituximab (-19 points (17; 23) since baseline) compared to children with SOCT (-10 (5; 15.5) points since baseline, $P = 0.001$), the number of patients with active lupus nephritis, and daily proteinuria.

During rituximab therapy, infectious diseases had three patients; one patient developed a bi-cytopenia.

CONCLUSION

Rituximab can be considered as the option in the treatment of severe forms of SLE, due to its ability to arrest disease activity compared to SOCT.

INTRODUCTION

Systemic lupus erythematosus (SLE) is one of the most frequent systemic connective tissue diseases, which is characterized by an unpredictable course, affecting different organs and systems, often simultaneously^[1,2]. Juvenile SLE has a more aggressive and severe course in children compared to adults, due to a higher frequency of kidney, central nervous system, and blood involvement^[2-5]. Macrophage activation syndrome (MAS) is a difficult-to-recognize life-threatening complication of SLE, belonging to the family of hemophagocytic lymphohistiocytosis influencing the disease course and outcomes^[6]. The disease severity and outcomes related to lupus nephritis (LN) occur in

about 40% of patients, most often during the first 5 years from the onset of the disease^[7-9]. Reduced damage to organs and systems, flare prevention, and improved quality of life of the patients are the main treatment goals of SLE^[1,2]. Standard of care treatment (SOCT) for SLE includes glucocorticosteroids, hydroxychloroquine, and cytostatic drugs such as cyclophosphamide, cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil (MMF) and usually associated with toxic side effects^[2,4,5,10]. Despite the toxicity of glucocorticosteroids and the recommendations of the European Alliance of Associations for Rheumatology (EULAR) to minimize doses, there are no uniform schemes and rates of reduction of glucocorticosteroids, except for lupus nephritis^[4,11]. The optimization of SLE treatment in children is necessary. The use of biological drugs makes it possible to achieve faster remission and reduce the toxic side effects of SOCT^[12].

Rituximab is one of the biologics used for the treatment of SLE. Rituximab is a chimeric mouse antibody directed against the CD20 antigen of B-lymphocytes. Depleting the pool of B-lymphocytes, rituximab acts only on mature B-lymphocytes, without affecting stem and plasma cells^[3]. Rituximab is proposed in some studies as an alternative or additional therapeutic approach for SLE^[13-15]. In North America (USA, Mexico), Europe, and Australia, rituximab is still used as an induction therapy for lupus nephritis off-label, despite the first successful reports in LN were published about 20 years ago^[12,16]. The data about rituximab efficacy in SLE are contradictory. Rituximab is still considered an off-label drug only if first-line therapy with cyclophosphamide or MMF fails, according to the EULAR2019 recommendations^[17]. However, the position of using rituximab as a starting therapy in combination with corticosteroids and non-biological disease-modifying antirheumatic drugs (DMARDs) remains open and requires more evidence of efficacy and safety^[2,8,10,18-19].

Our study aimed to compare the safety and efficacy of rituximab therapy in comparison with SOCT in children with systemic lupus erythematosus.

MATERIALS AND METHODS

Study design

A single-center retrospective cohort study included the data from the medical histories of 79 SLE children from 2012 to 2022.

Inclusion criteria

i) the diagnosis of systemic lupus erythematosus in patients under 18 years of age was established according to the criteria of Systemic Lupus International Collaborating Clinic (SLICC) 2012^[20].

ii) patients were selected from the database if the data about at least 12 months of observation were available.

Exclusion criteria

Absence or incomplete information about the first 12-month course of the treatment

Population and treatment arms

Nineteen children from the study group received rituximab therapy in the first six months from the onset of the disease and were observed at least twelve months from the initiation of the rituximab therapy. Sixty children received SOCT, which included glucocorticosteroid, hydroxychloroquine, non-biologic DMARDs, such as mycophenolate mofetil, cyclosporine, cyclophosphamide, and also were observed at least one year after the start of therapy.

Indications for the rituximab were:

- a highly active course of systemic lupus erythematosus with kidney and central nervous system involvement, including resistance to previous therapy;
- a presence of a recurrent course of autoimmune hemolytic anemia or thrombocytopenia, requiring repeated doses of corticosteroids, replacement therapy (blood and platelet transfusion);
- a presence of signs of corticosteroid toxicity if it is impossible to reduce the dose of corticosteroids to 10 mg/day or 0.2 mg/kg/day, whichever is less.

Rituximab treatment protocol

Rituximab was prescribed at a dose of 375 mg/m² weekly, no more than 500 mg per infusion (2-4 infusions) with repeated courses every 6-12 months, depending on the degree of disease activity, the severity of B-cell depletion, the level of IgG. The decision about the treatment protocol was made by the group of the most experienced pediatric rheumatologists.

Assessments and outcomes

The assessment of the main characteristics of patients was carried out at the time of the initiation of RTX or SOCT, then after 12±3 months from the start of therapy. At each time point, laboratory parameters were evaluated: complete blood cell, immunological tests - antinuclear antibodies (ANA), antibody against double-stained DNA (anti-dsDNA), complement level, assessment of urine protein excretion, presence of active lupus nephritis), the daily dose of GCS, the calculation of disease activity on the SELENA-SLEDAI scale, which allows to distinguish four degrees of disease activity: 0 points - no activity, 1-5 points - minimal activity, 6-10 points - moderate activity, 11-19 points - high activity, and >20 points - very high activity^[21]. MAS was diagnosed according to the previously published criteria by Parodi *et al*^[22].

Methods of statistical data analysis

The analysis of the obtained data was carried out ⁷ using the statistical software package Statistica v. 10.0 (StatSoft Inc., USA). Quantitative variables were assessed for compliance with normal distribution using the Kolmogorov-Smirnov test allows to use of nonparametric methods of analysis due to the absence of the normal distribution. The description of quantitative variables was expressed in the ² median and quartiles Me (Q1; Q3). The categorical variables were expressed in absolute numbers and parts (%). Comparison of two independent ³ groups of quantitative variables was carried out using the Mann-Whitney test, categorical variables - using the Chi-square test, or Fisher's ⁵ exact test, if the expected frequency was less than 5. Differences or relationships were considered statistically significant if $p < 0.05$.

RESULTS

The characteristics of the patients in the SLE onset

Patients, treated with rituximab were older at the initial point of the study (baseline-start of the therapy), compared to patients from the SCOT group. They had frequently central nervous system (CNS) involvement, hepatomegaly, lymphadenopathy, palmar erythema, proteinuria, decreased glomerular filtration rate (GFR), and higher SLEDAI (more patients with high activity, grade four) and higher frequency of using high-dose IV glucocorticosteroids. They also tended to more frequent development of pleurisy, and lupus nephritis. The incidence of MAS was also higher in the group of children treated with rituximab. All cases of MAS developed during the disease onset. Early treatment with rituximab allowed the use of fewer non-biologic DMARDs. The baseline characteristics of children from two groups are presented in Table 1.

The characteristics of the patients (outcomes) at the end of the study

At the end of the study, after twelve months, the disease characteristics between studied groups became equal, except for a tendency to higher levels of hemoglobin and lower part of patients having anti-dsDNA antibodies and low complement. Detailed characteristics of children at the end of the study are presented in Table 2.

During the 12-month study period the more impressive reduction of the SLEDAI, the number of patients with active LN, and daily proteinuria were observed. Data are in Table 3.

DISCUSSION

In our study, some benefits of rituximab treatment for pediatric SLE were found. During the 12-month observation period, a more impressive reduction in disease activity and improvement in lupus nephritis was observed.

Rituximab has not received official approval either in adult or pediatric practice despite many years of experience in the treatment of systemic lupus erythematosus, [8,10,17]. Numerous series of retrospective studies and published clinical cases have shown the effectiveness of rituximab in patients with varying degrees of activity systemic lupus erythematosus, including forms with a catastrophic course, which, together with expert opinion, allowed to include rituximab into the treatment algorithms for the of systemic lupus erythematosus both for children and adults [3,9,23].

Biological drugs, including rituximab, are recommended for the treatment of SLE, but the study results are contradictory [24,25]. Some randomized controlled trials (RCTs) showed improvement in blood tests (anti-dsDNA, normalization of complement levels of C3 and C4), without changes in the outcomes of the disease one year after the start of treatment [24]. In the largest randomized controlled trial the Lupus Nephritis Assessment with Rituximab study (LUNAR), there was no significant difference in achieving a complete response between patients receiving rituximab and SOCT at the control time points, although the proportion of patients with a partial response was greater in patients, treated with rituximab [24]. There was a significant improvement in serological markers of disease activity, such as a decrease in antibodies to DNA, an increase in complement levels, and a decrease in the degree of proteinuria in patients who received rituximab, which was also noted in the non-randomized studies [3,10,25,26].

The results of the above-mentioned studies corresponded with our results: improvement of certain laboratory parameters has been achieved, but there is no statistically significant difference between the outcomes of the disease a year after the start of therapy. The analysis of various non-randomized studies from different countries of the world showed a positive effect of rituximab in systemic lupus erythematosus in adults and children [3,5,10]. Reduction of the activity of the disease, increased hemoglobin level, decreasing ESR and levels of ANA and anti-dsDNA antibodies, and the part of children having cytopenia demonstrated in several studies [3,5,10,27]. Rituximab is effective for the treatment of lupus nephritis in children,

whom increased C3 and C4 Levels, GFR, and serum albumin and decreased urine albumin/creatinine ratio and proteinuria and GCS dose detected [3,5,10,17,26-28]. Additionally, some studies reported a decrease in creatinine, but the data were statistically non-significant[17]. There is also conflicting data that the use of biological therapy for lupus nephritis did not lead to a decrease in the albumin-creatinine ratio[29]. A recent study on 14 pediatric LN showed the additional rituximab therapy to conventional therapy improved proteinuria, eGFR, and serological markers. Three patients who required acute kidney replacement therapy became dialysis-free after rituximab[30]. We found decreased activity and proteinuria in our study similar to previous. The absence of a significant effect in some randomized studies suggests to use of rituximab not as a means of inducing remission, but as an auxiliary therapy in patients with SLE[31].

However, 27 studies demonstrated the positive effect of rituximab in patients refractory to standard therapy, including cyclophosphamide and MMF[17]. The inclusion of patients with primary LN without preceding experience of cyclophosphamide or MMF in a large randomized LUNAR study did not show the superiority of rituximab over non-biological DMARDs[24]. On the one hand, rituximab has shown its effectiveness in patients who have not previously received any treatment, which does not allow us to evaluate the benefits of rituximab in comparison with standard non-biological therapy. On the other hand, rituximab was able to induce remission in cases where standard therapy with non-biological DMARDs failed and disease duration and treatment exposure were longer[17,32-33].

In our study, rituximab was prescribed to children in the first year of the disease who had had a higher disease activity at the time of initiation of therapy. There was no statistically significant difference in the activity of SLE between the two groups at the end of the study, but at the same time, there was a more significant decrease in the activity of the disease in the RTX group. It allows us to conclude that RTX shows its effectiveness in a more severe course of the disease.

Limitations: Our study has limitations, related to retrospective study designs, initial differences between studied groups, missing data, and absence of a unique treatment protocol with administration and tapering of the drugs. Personal opinion about prescribing the rituximab and all the abovementioned limitations may make the study results inaccurate and other-estimated.

CONCLUSION

Rituximab can be considered as the option in the treatment of severe forms of SLE, due to its ability to rapidly arrest the disease activity compared to SOCT. Faster and intensive reduction of the disease activity and better nephritis outcomes are the main benefits of rituximab above the SOCT. Further pediatric randomized controlled trials are required to evaluate its efficacy and safety in comparison with standard therapy, with further consideration of the possible use of rituximab as an induction therapy in children with high-moderate disease activity.

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