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Brief communication

Rituximab use in young adults diagnosed with juvenile idiopathic arthritis unresponsive to conventional treatment: report of 6 cases

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. Without an effective therapy, patients may progress quickly to functional disability. Recently, depletion of B cells emerged as a new approach for the treatment of autoimmune diseases, including JIA.

We describe six cases of JIA patients followed at a referral center for Rheumatology and Pediatric Rheumatology, submitted to treatment with rituximab (RTX) after refractoriness to three anti-TNF agents.

Patients received RTX cycles with two infusions every six months. Response to treatment was assessed by DAS28, HAQ/CHAQ, and an overall assessment by the doctor and the patient.

Of our six patients, four were girls (mean age at onset of disease: 6.1 years; mean disease evolution time: 15.1 years; mean age upon receiving RTX: 21.6 years). Four patients belonged to polyarticular subtype (1 rheumatoid factor [RF]-negative, 3 FR-positive), a patient with systemic JIA subtype with a polyarticular course and arthritis related to enthesitis. Of our six patients, five responded to treatment; and during the course of 12 months, the clinical response was maintained, although not sustained. However, discontinuation by infusion reactions caused the withdrawal of RTX in two patients.

The use of RTX in JIA is restricted to cases refractory to other biological agents and, even considering that this study was held in a small number of advanced patients, RTX proved to be an effective therapeutic option.

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Uso de rituximabe em adultos jovens com diagnóstico de artrite idiopática juvenil refratária ao tratamento convencional: relato de 6 casos

Palavras-chave:
Artrite idiopática juvenil
Crianças
Rituximabe
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RESUMO

A artrite idiopática juvenil (AIJ) é a doença reumática mais frequente na infância. Sem terapia efetiva, os pacientes podem evoluir rapidamente para incapacidade funcional. Recentemente, a depleção dos linfócitos B surgiu como nova abordagem para o tratamento de doenças autoimunes, incluindo a AIJ.

Descrevemos seis casos de pacientes com AIJ, acompanhados em um centro de referência em Reumatologia e Reumatologia Pediátrica, submetidos ao tratamento com rituximabe (RTX) após refratariedade a três anti-TNF.

Os pacientes receberam ciclos de RTX com duas infusões a cada seis meses. A resposta ao tratamento foi avaliada pelo DAS28, HAQ/CHAQ, avaliação global do médico e do paciente.

Dos seis pacientes, quatro eram meninas (média de idade de início da doença: 6,1 anos; média de tempo de evolução de doença: 15,1 anos; média de idade ao receber RTX: 21,6 anos). Quatro pacientes pertenciam ao subtipo poliarticular (1 fator reumatoide (FR) negativo, 3 FR positivo), um paciente com AIJ subtipo sistêmico com evolução poliarticular e um com artrite relacionada à entesite. Dos seis pacientes, cinco responderam ao tratamento e durante a evolução de 12 meses, a resposta clínica foi mantida, embora não sustentada. No entanto, a descontinuação por reações infusionais motivaram a suspensão do RTX em dois pacientes.

O uso do RTX em AIJ é restrito aos casos refratários a outros biológicos e, mesmo tendo sido realizada em um número pequeno de pacientes e de forma tardia, mostrou ser uma opção terapêutica eficaz.

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and without appropriate treatment it can quickly result in functional disability.[1]

Recently, B lymphocyte depletion emerged as a new therapeutic approach for JIA and SLE.[2–7] Rituximab (RTX) is a chimeric monoclonal antibody directed against the CD20 pre-B cells and mature B cells with efficacy and safety in adult patients with rheumatoid arthritis (RA) with an inadequate response to disease-modifying drugs (DMARDs) and anti-TNF-alpha inhibitors.[8–12]

The objective of this study was to describe six patients with JIA followed in a Pediatric Rheumatology Unit between 1993 and 2014 who underwent treatment with RTX.

Methods

Six patients diagnosed with JIA according to the ILAR (International League of Associations of Rheumatology) criteria[13] received RTX cycles with two intravenous infusions of 1 g each on days 1 and 15, every six months.

The clinical response was measured by DAS28 (Disease Activity Score in 28 joints),[14] erythrocyte sedimentation rate (ESR), Health Assessment Questionnaire (HAQ)[15] or the Child Health Assessment Questionnaire (CHAQ)[16] and evaluation of visual analog scale (VAS) of the patient and the physician.

The assessments were performed before and every six months of treatment. According to EULAR (European League Against Rheumatism) criteria, the patients were classified as good responders if improvement in DAS28 was greater than 1.2, moderate responders if between 0.6 and 1.2, and non-responders if less than 0.6, in two consecutive measurements. Clinical remission was defined as a DAS28 less than 2.6.[17]

Primary failure was defined as a reduction lower than 0.6 of DAS28 after 12 weeks and secondary failure, such as loss of efficacy over 24 weeks in patients who had responded in the first 12 weeks.[17] Adverse events were recorded.

Case report

The mean onset age of the disease was 6.1 years and mean disease duration was 15.1 years. The mean age at start of RTX was 21.6 years (18–26 years) (Table 1). Uveitis was not observed in any patient.

Table 1 – Clinical data of 6 patients treated with rituximab.

	Age at diagnosis	Age at rituximab	JIA subtype
DAB	5	19	Polyarticular RF +
DC	5	24	Systemic
DSS	7	21	Enthesitis-related arthritis
FAGS	7	26	Polyarticular RF−
MILP	4	20	Polyarticular RF+
ELS	9	18	Polyarticular RF+

Case 1

DAB, 19 years old, female, erosive polyarticular JIA diagnosed since the age of five, positive rheumatoid factor (RF), being followed since the age of 11.

The patient has taken glucocorticoids (GCs), methotrexate (up to 1 mg/kg/week) for five years, cyclosporine (5 mg/kg/day) for five months and cyclophosphamide (up to 1 g/m^2) for three months with partial response to all treatments. She initiated treatment with infliximab (5 mg/kg every six weeks) for two years, followed by etanercept (0.8 mg/kg/week) for four months and adalimumab (24 mg/m^2) for four years.

Due to refractoriness and intense disease activity, RTX was introduced at 19 years of age, combined with leflunomide (20 mg/day) and prednisone at an initial dose of 20 mg, with progressive tapering up to withdrawal.

After 6 months of the first intravenous infusion, the patient presented clinical improvement. Currently, the patient is clinically stable, with no arthritis and no morning stiffness. She remains on leflunomide, and is currently receiving the fourth cycle of RTX.

Case 2

DC, 25 years, male, systemic onset JIA and polyarticular course, negative RF, diagnosed since the age of five, started follow-up at this clinic two years later.

Initially, the patient was on indomethacin (2 mg/kg/day) and methotrexate (1 mg/kg/week) associated with GCs (up to 1 mg/kg/day). When he was 14, he presented macrophage activation syndrome, with pulse therapy being performed with intravenous methylprednisolone, and cyclosporine being started (5 mg/kg/day). After two years thalidomide (2.5 mg/kg/day) was initiated, with partial response. When he was 19, he started infliximab (5 mg/kg every 6 weeks), developing anaphylaxis in the 9th dose. He switched to adalimumab (24 mg/m^2) and etanercept (0.8 mg/kg/week), with secondary failure after 9 and 10 months, respectively.

RTX was started at 24 years old, presenting sustained response, although with infusion reactions controlled with the use of intravenous GC, antihistamines and a decrease in infusion rate. He was concomitantly on cyclosporine (150 mg/day) and prednisone (20 mg/day). However, after the fourth cycle of RTX, the patient developed serum sickness, and discontinued the treatment.

After stopping RTX, the disease became more active, requiring other medications and he had primary failure to tocilizumab (8 mg/kg/dose) and abatacept (10 mg/kg/dose) and was referred to autologous bone marrow transplantation (ABMT).

Case 3

DSS, 26, male, diagnosed with enthesitis-related arthritis (ERA) JIA since the age of seven. He began follow-up when he was 13 years old. The evolution was polyarticular erosive, associated with severe intestinal involvement, with Crohn's disease being diagnosed.

He took methotrexate (up to 1 mg/kg/week) for 10 years, sulfasalazine (40 mg/kg/day) for five years, plus methylprednisolone and cyclophosphamide intravenous pulse therapy (up to 1 g/m^2) for one year, and multiple joint injections with GCs. He started infliximab (5 mg/kg/dose every 6 weeks) with good initial response and failure after two years of treatment. He used cyclosporine (5 mg/kg/day) and methylprednisolone pulse therapy, with no response for one year. Adalimumab (24 mg/m^2) was introduced but there was no response after four months of treatment (primary failure).

When he was 21, he received the 1st cycle of RTX. He showed significant joint improvement after 12 months. However, it had to be discontinued due to recurrence of fistulizing intestinal disease. Although he previously had secondary failure to IFX, this was reintroduced combined with methotrexate (25 mg/week) and prednisone (20 mg/day). However, due to disease activity and refractoriness, ABMT was indicated.

Case 4

FAGS, 32, female, erosive polyarticular JIA diagnosed since seven years of age, negative RF, followed since she was 15 years old.

She presented polyarthritis of small and large joints, with good response to treatment with methotrexate (up to 1 mg/kg/week) and tapered doses of GCs in the first year. She remained asymptomatic until she was 20 years old, when arthritis reappeared.

In the first year of recurrence, the patient was restarted on methotrexate (25 mg/week) and prednisone (20 mg/day). Due to elevated transaminase levels, the dose of methotrexate was reduced (15 mg/week) and sulfasalazine (40 mg/kg/day) and chloroquine (5 mg/kg/day) were associated. At 24 years old, leflunomide (20 mg/day) was started, but there was no response after twelve months. She presented primary failure to the three anti-TNF blockers, and RTX was started at the age of 26. Concomitant to treatment, the patient received methotrexate (25 mg/week) and prednisone (10 mg/day). Six months after the first intravenous infusion there was a significant improvement in pain while synovitis persisted. She maintained disease activity although with satisfactory results, according to the EULAR response. After 12 months of treatment with RTX, cyclosporine (150 mg/day) was introduced with no success.

After the fourth cycle of RTX, the patient presented clinical worsening (secondary failure) and it was replaced by tocilizumab (8 mg/kg/dose) with partial response. At present, she is on abatacept (10 mg/kg/dose), but with poor response and the need for multiple intra-articular injections and high doses of prednisone (20 mg/day). Given the refractoriness of the case, the patient was referred to ABMT.

Case 5

MILP, 20, female, polyarticular JIA since the age of four, positive RF, followed since 12 years old.

She had already received methotrexate, had gastrointestinal intolerance, and it was replaced by azathioprine (2 mg/kg/day). Subcutaneous methotrexate (up to

Table 2 – Clinical and laboratory progress of patients after treatment with rituximab.

Patient	DAB	DC	DSS	FAGS	MILP	ELS
DAS28						
Initial	4.77	5.02	7.21	8.42	5.19	4.28
6 months	3.25	4.32	5.12	6.61	4.31	4.09
12 months	1.66	3.08	4.05	4.28	3.21	2.58
18 months	1.38	3.12	4.78	4.32	4.36	
24 months		3.67	4.95	7.41		
HAQ/CHAQ						
Initial	0.875	1.5	2.25	1.75	2.25	0.5
6 months	0	1.25	2.0	1.25	2.0	0.25
12 months	0	0.5	1.75	0.75	2.11	0
18 months	0	0.5	2.0	1.125	2.25	
24 months		0.5	2.0	1.5		
PtGA						
Initial	8	9	10	8	6	6
6 months	1	5	9	6	6	4
12 months	1	5	7	4	5	0
18 months	1	4	5	4	7	
24 months		4	7	5		
PhGA						
Initial	6	8	10	10	6	4
6 months	1	5	9	9	7	3
12 months	1	5	9	9	5	1
18 months	1	5	9	9	7	
24 months		5	10	10		
ESR (mm/1st.h)						
Initial	26	32	19	23	78	62
6 months	8	28	25	42	64	54
12 months	28	20	15	30	15	40
18 months	7	26	28	17	23	
24 months		25	45	125		
CRP (mg/dL)						
Initial	14	10.2	41	52	1.54	7.1
6 months	3.7	7.1	35.1	26.3	2.36	18.2
12 months	17	5.8	15.8	11.7	0.84	13.6
18 months	<6	4.2	22.5	15.9	1.87	
24 months		4.9	26.4	64.8		
Adverse events/complications						
6 months	–	–	–	–	Pre-medication Infusion reaction	–
12 months	–	Infusion reaction	Infusion reaction	Infusion reaction	Infusion reaction	Infusion reaction
18 months	–	Infusion reaction	Infusion reaction	Infusion reaction	Infusion reaction	Infusion reaction
24 months		Infusion reaction	Infusion reaction	Infusion reaction	Infusion reaction	Infusion reaction
Response to treatment	Yes	Yes	Yes	Yes	Yes	Yes

DAS28, Disease Activity Score in 28 joints; HAQ, Health Assessment Questionnaire; CHAQ, Child Health Assessment Questionnaire; PtGA, patient's global assessment of visual-analogical scale; PhGA, physician's global assessment of visual-analog scale; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

1 mg/kg/week) and intravenous pulse therapy with methylprednisolone were started.

At the age of 12, infliximab (5 mg/kg every 6 weeks) was started in combination with cyclosporine (5 mg/kg/day), with partial response after one year. After two years, a combination of methotrexate and leflunomide was introduced (20 mg/day) with good response for nine months. At the age of 15 etanercept (0.8 mg/kg/dose) was started and bilateral hip arthroplasty was performed, and as she presented clinical and laboratory disease activity, adalimumab (24 mg/m^2) was started at 16 years of age, with good response for one year.

At the age of 20, she had severe clinical and laboratory inflammatory activity and received the 1st cycle of RTX. She remained on methotrexate (1 mg/kg/week) and GCs (up to 0.5 mg/kg/day). She received a second intravenous infusion of RTX and due to infusion reaction, the infusion rate had to be slowed. During disease progress, the patient always maintained clinical and laboratory activity, requiring increased

doses of GCs. Due to refractoriness of the disease, treatment with tocilizumab was indicated.

Case 6

ELS, 20, female, erosive polyarticular JIA positive RF, since she was 9 years old and on treatment since 10 years of age.

She had already received GCs (up to 1 mg/kg/day) orally for five months with significant adverse events. At the first visit, methotrexate (0.4 mg/kg/week) and naproxen were initiated, and GCs tapered. During follow-up, intravenous pulse therapy with methylprednisolone was carried out due to inflammation, anemia and persistence of the joint disease.

When she was 10, cyclosporin (up to 5 mg/kg/day) was associated, and disease activity was maintained. After a year, therapy with infliximab was initiated (5 mg/kg every 6 weeks). At 13 years old, therapy with adalimumab (24 mg/m^2) was initiated, with good response for the first two years. After this period, a treatment was conducted with etanercept (0.8 mg/kg/dose) for 11 months with poor response, and RTX was indicated.

She received the 1st cycle of RTX when she was 18, with clinical improvement for three months. After three months of medication, there was clinical and laboratory worsening and infection. However, in the following months, the patient had significant improvement in pain. The patient is awaiting a fourth dose of RTX in combined use with subcutaneous MTX (40 mg/week).

Discussion

RTX is an alternative therapy for refractory JIA patients.[2,3,5–7] There are no controlled clinical trials with RTX in JIA and evidence is limited to case series reports.[6,7,18,19] The dose and dosing intervals were determined taking into account the experience and clinic logistics.

The clinical improvement observed by patients treated with RTX suggests an important role for B cells in JIA (Table 2).[2,6,19,20] It was observed that in the children joints with JIA there is oligoclonal expansion of B cells and increased IL-12 production, and subsequent activation of T cells. In adults, there is B cell depletion in blood and synovial tissue.[10]

All six patients responded to treatment at six and 12 months, but the clinical response was not maintained in three of them, experiencing disease activity and refractoriness, since half of the patients had indication of ABMT. It is also important to note that RTX was introduced late and after failure to three anti-TNF blockers. Thus, B lymphocyte depletion therapy, even though it was employed in a small number of patients and belatedly, proved to be an effective and safe therapeutic option in half the cases.

Randomized controlled and pivotal trials of RTX showed that efficacy was greater in adult patients with positive RF or anti-citrullinated protein antibodies, highlighting the humoral response in these patients.[21–23] In our study, half of the sample did not have RF and none of the patients had anti-citrullinated protein antibodies. This aspect did not affect the therapeutic response in the short and medium term, although, interestingly, it was these patients who did not claim benefits and have been referred to the ABMT.

Adverse events observed in our patients were similar to those described in the literature. The main one was the infusion reaction that occurred in two patients and led to permanent discontinuation of the medication despite adequate response of the disease.

Some limitations may be listed, such as the small number of patients, lack of data on the CD19 cell count and radiographic information of structural damage in the initial evaluation and follow-up. However, the data are consistent with the population of real life in this age group.

Thus, RTX is a treatment option in active, severe JIA and unresponsive to DMARDs and anti-TNF blockers. The safety and efficacy demonstrated by this study should encourage studies with more patients, in order to determine the possibility of a window of opportunity in patients with JIA.

Conflicts of interest

The authors declare no conflicts of interest.

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