

# A successful treatment of juvenile idiopathic arthritis with rituximab: A report of two cases

Khadija Berrada, Fatima Ezzahra Abourazzak, Imane El Mezouar, Faiza Lazrak, Nacira Aradoini, Latifa Tahiri, Taoufik Harzy

## Abstract

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown cause that starts before 16 years of age and lasts at least 6 weeks. It is the most common chronic inflammatory disease in childhood and often persists through adulthood and can lead to severe disability. Biologics are an important therapeutic option for treating patients with JIA. The efficiency of rituximab has not been proven for this indication. Its use has rarely been reported in the literature.

We report two new cases of severe and refractory polyarticular JIA with positive rheumatoid factor affecting two African females aged 17 and 18 years successfully treated with rituximab. According to our experience, the use of rituximab in the treatment of JIA, especially in severe polyarticular forms with positive rheumatoid factor, might be a good alternative. Larger therapeutic trials should be conducted in this direction in order to prove the effectiveness of this biotherapy for this indication.

**Key words:** Polyarticular JIA, rituximab, biologic agents, B-cell depletion

## Introduction

Juvenile idiopathic arthritis (JIA) is the most common autoimmune-autoinflammatory disease in childhood and affects approximately 1 in 1000 children (1, 2). It is also one of the major causes of acquired disability and impairment of quality of life in childhood. Without appropriate treatment, JIA may result in devastating consequences. This underscores the importance of early and aggressive treatment in patients with JIA to prevent long-term disability (3, 4). Biologics are an important therapeutic option for treating patients with JIA. They have been designed to target key cytokines implicated in JIA, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), and interleukin-6 (IL-6), as well as signaling molecules involved in the regulation of T-cell and B-cell lymphocyte responses. Up to now, the U.S. Food and Drug Administration (FDA) has approved three biologic agents for use in moderate to severe polyarticular JIA: etanercept, adalimumab, and abatacept (5). The anti-CD20 antibody rituximab has not been evaluated in controlled trials for this indication but seems to be an interesting option (6).

## Case Presentations

### Case 1

A 17-year-old African female with a 5-year history of refractory polyarticular JIA with positive rheumatoid factor (RF) was admitted for active disease. During these 5 years, her disease was active and involved multiple joints, such as the shoulders, hips, knees, ankles, wrists, and proximal interphalangeal (PIP) joints, and caused deformities on her fingers. Her physical examination revealed severe growth retardation (weight=25 kg, height=1.26 m) and numerous joint deformities with active synovitis (Figure 1). Her functional condition steadily deteriorated, and she could no longer stand or walk, being incapacitated by severe hip pain and her numerous joint deformities. The functional impact of the disease was assessed using the Child Health Assessment Questionnaire (CHAQ), which was at a high level of disability: CHAQ=2.5.

The patient also had major steroid-induced adverse effects, including growth retardation and osteoporosis, with several vertebral fractures.

Lab results indicated a seropositive, highly active disease assessed by the Disease Activity Score (DAS28-ESR=6.41, C-reactive protein=60 mg/dL, erythrocyte sedimentation rate (ESR)=77 mm/1 h, RF=161 UI/mL) and vitamin D deficit: 6 ng/mL. The radiological assessment showed severe joint destructions of the wrists, PIP joints, hips, knees, and ankles with diffuse bone demineralization and multiple vertebral fractures (Figures 2-4).



Department of Rheumatology, CHU  
Hassan II University Hospital, Fez,  
Morocco

Address for Correspondence:  
Khadija Berrada, Department of  
Rheumatology, CHU Hassan II  
University Hospital, Fez, Morocco

E-mail: khadija\_medica@hotmail.com

Submitted: 11.06.2014

Accepted: 10.07.2014

Copyright 2014 © Medical Research and  
Education Association

**Figure 1.** Joint deformities of the hands**Figure 2.** Severe joint destruction of the hands and wrists

The patient was initially treated with methotrexate and corticosteroids without improvement. Hence, rituximab was introduced at a dose of 375 mg/m<sup>2</sup> of body surface area weekly for 1 month.

Along with rituximab, the patient was treated with concomitant methotrexate 10 mg weekly and bisphosphonate with high-dose vitamin D and calcium.

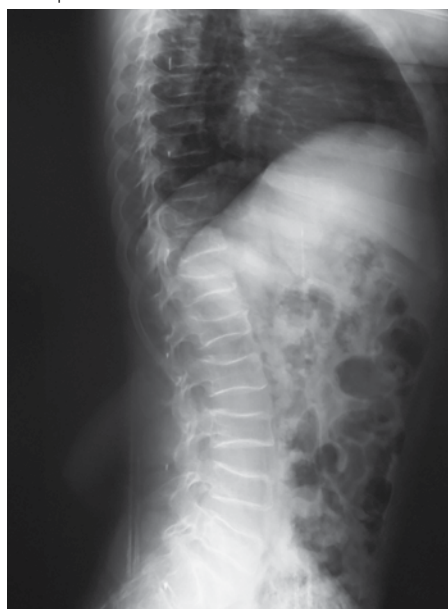
Within several weeks, clinical improvement, with a significant decrease of the intensity of her joint pain and synovitis, was noted and persisted during a 7-month follow-up (DAS28-ESR=3.87).

As the patient is a minor, written informed consent was obtained from the patient's legal guardian for publication of the case.

## Case 2

A 18-year-old African female presented with a 8-year history of refractory polyarticular JIA with positive RF. The clinical examination found a deformity of the left fourth finger, reduced (flexion/extension) range of motion of the left wrist with irreducible flexum of the right elbow at 60°, and reduced flexion of the knees. Her functional condition was also assessed using the CHAQ, showing a high level of disability: CHAQ=1.

Laboratory tests showed moderate inflammatory syndrome (ESR=23, CRP=15) and positive

**Figure 3.** Severe joint destruction of the hips**Figure 4.** Bone demineralization with multiple vertebral fractures

RF (RF=172 UI/mL). The radiological assessment showed joint destruction (hands, feet, wrists, right elbow, and knees) with atlanto-axial dislocation (Figure 5, 6).

The DAS28-ESR was 3.85, indicating a moderate activity of the disease. The patient was treated with methotrexate (interrupted because of digestive intolerance) and steroids for 6 years without improvement. Because of activity and severity of the disease, treatment with rituximab was initiated at a dose of 2 g in two infusions 15 days apart, with good clinical outcome (DAS 28-ESR=2.5).

The patient is currently enjoying sustained remission lasting 6 months, with no evidence of systemic inflammation or active synovitis.

Written informed consent was obtained from the patient for publication of the case report and any accompanying images.

## Discussion

Juvenile idiopathic arthritis is the most common pediatric rheumatic disease, which, with-

**Figure 5.** Destruction and flexum of the right elbow**Figure 6.** Atlanto-axial dislocation

out effective therapy, results in rapid disability of patients (3, 4). In fact, up to 10% of JIA patients are severely disabled or handicapped (7).

According to the International League of Associations for Rheumatology (ILAR) classification, JIA is subclassified into seven distinct categories, mainly based on the number of joints affected, the presence of extra-articular manifestations, the presence or absence of rheumatoid factors and HLA-B27, and finally, the family history (8).

The goals in treating JIA are to eliminate active disease, normalize joint function, preserve normal growth, prevent long-term joint damage, and prevent patient disability (9).

Until now, methotrexate has been one of the most common drugs for the treatment of patients with JIA, with efficacy and safety that satisfy the current criteria of evidence-based medicine. However, conventional immunosuppressants are ineffective in almost 50% of patients, as they fail to provide sufficient control of clinical symptoms of JIA or inhibit the progression of joint destruction, and they frequently induce adverse reactions that limit their use (3, 10). Treatment-resistant courses of JIA result in joint destruction and growth retardation, which lead to major functional limitations. Specifically, patients with polyarticular onset have the poorest prognosis, with a remission rate of only 15% over 10 years (11).

Biologic agents are genetically engineered drugs designed to selectively block the effects of cytokines implicated in JIA, including TNF- $\alpha$ , IL-1, and IL-6, as well as signaling molecules involved in the regulation of B-cell and T-cell lymphocyte responses (4, 12). With the advent of biologic therapeutics over the past 10 years, there has been a rapid increase in the number and types of agents available for the treatment of JIA. Much of the treatment of childhood arthritis builds on experience gained from adult patients and studies (1, 13).

Rituximab is a chimeric mouse-human monoclonal antibody against the CD20 antigen on the surface of B-lymphocytes. It binds to CD20 and causes B-cell death by antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity, and apoptosis. It leads to rapid and sustained depletion of B-cells (9, 5, 14).

Rituximab is a well-established therapeutic option in adult rheumatoid arthritis. It has not been regularly studied in JIA so far. The fact that rituximab was successful in our cases of polyarticular JIA strongly supports the hypothesis that B-cells play a role in the pathogenesis of the disorder. This would seem intuitive, since this subset of JIA shares many features consistent with rheumatoid arthritis (RA). Although studies suggest that the response to rituximab in RA is related to RF positivity, treatment was beneficial in a patient reported by A. Kuek et al. (15), despite the absence of autoantibodies. This would indicate that the loss of B-cell tolerance is not the only B-cell process operating in JIA. It is now known that B-lymphocytes have much broader functions within the immune system, including T-cell activation and cytokine synthesis (5, 2). There have been a few published reports on rituximab for the treatment of JIA. Six case reports of patients with systemic or polyarticular JIA have been published to date, most of which indicated that rituximab is effective and well tolerated (6, 10, 7). El-Hallak et al. (10) reported their experience in 10 children from a single center with various autoimmune conditions treated with rituximab with

the lymphoma protocol of 375 mg/m<sup>2</sup> weekly x 4 weeks, one of whom had polyarticular JIA. His rheumatoid factor status was not reported. This patient did respond well to the therapy (10, 2). While some case reports and series have described beneficial effects in nonresponsive patients, there was only one study with a larger number of patients (3). Through this 2-year study, Alexeeva et al. (3) demonstrated a high level of efficacy of rituximab in children with the most severe forms of JIA refractory to many therapies, including TNF inhibitors. Rituximab successfully induced the remission of arthritis and reduced extra-articular manifestations without the need for oral prednisolone administration and, consequently, without the severe irreversible complications of glucocorticoid therapy (3). They suggested that rituximab might be a promising therapeutic option in severe refractory JIA. Our data fully support the results of the rituximab efficacy and safety study.

Rituximab was approved for the treatment of rheumatoid arthritis in adults, but its usefulness in the treatment of children with severe refractory JIA deserves to be proven.

Specific B cell depletion may represent a true alternative to conventional immunosuppressive therapy in the treatment of refractory polyarticular JIA, and we encourage further investigation in this area.

**Ethics Committee Approval:** N/A.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - K.B., F.A., T.H.; Design - K.B., F.L., I.E.; Supervision - F.A., L.T., T.H.; Resource - K.B., A.N., F.A.; Materials - K.B., T.H., F.A., L.T.; Data Collection&/or Processing - K.B., F.L., N.A., I.E.; Analysis&/or Interpretation - K.B., F.A., L.T., T.H.; Literature Search - K.B., F.A., L.T.; Writing - K.B., F.A.; Critical Reviews - F.A., L.T., T.H.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

1. Hayward K, Wallace CA. Recent developments in anti-rheumatic drugs in pediatrics: treatment of juvenile idiopathic arthritis. *Arthritis Res Ther* 2009; 11: 216. [CrossRef]
2. Stoll ML, Gotte AC. Biological therapies for the treatment of juvenile idiopathic arthritis: Lessons from the adult and pediatric experiences. *Biologics* 2008; 2: 229-52.
3. Alexeeva EI, Valieva SI, Bzarova TM, Semikina EL, Isaeva KB, Lisitsyn AO, et al. Efficacy and safety of repeat courses of rituximab treatment in patients with severe refractory juvenile idiopathic arthritis. *Clin Rheumatol* 2011; 30: 1163-72. [CrossRef]
4. Huang JL. New advances in juvenile idiopathic arthritis. *Chang Gung Med J* 2012; 35: 1-14.
5. Gökçe İ, Demirkaya E. New Treatment Strategies in the Treatment of Juvenile Idiopathic Arthritis. *Turk J Rheumatol* 2011; 26: 71-85. [CrossRef]
6. Quartier P. Current treatments for juvenile idiopathic arthritis. *Joint Bone Spine* 2010; 77: 511-6. [CrossRef]
7. Kasher-Meron M, Uziel Y, Amital H. Successful treatment with B-cell depleting therapy for refractory systemic onset juvenile idiopathic arthritis: a case report. *Rheumatology* 2009; 48: 445-6. [CrossRef]
8. Horneff G. Treatment Options With Biologics for Juvenile Idiopathic Arthritis. *Int J Clin Rheumatol* 2011; 6: 1-19. [CrossRef]
9. Borker A, Choudhary N. Rituximab. *Indian Pediatr* 2011; 48: 627-32. [CrossRef]
10. El-Hallak M, Binstadt BA, Leichtner AM, Bennett CM, Neufeld EJ, Fuhlbrigge RC, et al. Clinical effects and safety of rituximab for treatment of refractory pediatric autoimmune diseases. *J Pediatr* 2007; 150: 376-82. [CrossRef]
11. Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence. *Clin Rheumatol* 2008; 27: 67-76. [CrossRef]
12. Baildam EM, Saladi S. Rituximab in ANA positive polyarticular juvenile idiopathic arthritis (JIA) with uveitis. *Pediatr Rheumatol Online J* 2008; 6: 71. [CrossRef]
13. Reiff AO. Juvenile rheumatoid arthritis: New perspectives in treatment. [http://www.medscape.org/viewarticle/571688].
14. Breda L, Del Torto M, De Sanctis S, Chiarelli F. Biologics in children's autoimmune disorders: efficacy and safety. *Eur J Pediatr* 2011; 170: 157-67. [CrossRef]
15. Kuek A, Hazleman BL, Gaston JH, Ostor AJ. Successful treatment of refractory polyarticular juvenile idiopathic arthritis with rituximab. *Rheumatology* 2006; 45: 1448-9. [CrossRef]