Case Report

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Treatment of early rheumatoid arthritis with certolizumab pegol after failure of disease-modifying antirheumatic drugs: a report of two cases

Rheumatoid arthritis is a severe systemic inflammatory disease, characterized by polyarticular synovitis and subsequent structural changes to the cartilage. Diagnosis and treatment in the early disease stages are extremely important, as disease evolution may cause articular deformities, leading to patient disability, worsened Quality of Life (QoL), and reduced survival. The main treatment objectives include decreasing the inflammatory process, controlling or blocking the evolution of osteoarticular lesions, and improving patient QoL. This article describes the evolution of two patients diagnosed with early rheumatoid arthritis with very aggressive characteristics and who, upon failure of treatment with disease-modifying antirheumatic drugs, successfully underwent therapy with certolizumab pegol.

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Introduction

Rheumatoid arthritis is a constantly evolving, deforming, and disabling inflammatory disease that reduces survival; the early diagnosis and treatment of rheumatoid arthritis aim to restrict the inflammatory reaction and intra-articular lesions, and improve Quality of Life (QoL) [1,2].

Rheumatoid arthritis can present severe joint impairment even in the early disease phase. In the absence of a response to Disease-Modifying Antirheumatic Drugs (DMARDs), the use of medicines able to rapidly change the evolution of the disease should be indicated, such as biologic agents targeted at Tumor Necrosis Factor (TNF)-α (e.g. etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol). These biologic agents have similar high efficacy and safety, and restrict the osteoarticular destruction and systemic manifestations of the inflammatory process [3,4].

The main objective of this manuscript is to present two cases of early rheumatoid arthritis, with therapeutic failure of conventional synthetic DMARDs (csDMARDs), which were treated with certolizumab pegol. Therapeutic efficacy was evaluated by comparing the following indices at baseline and after 24 weeks of treatment with certolizumab pegol: general state (Visual Analog Scale [VAS]), inflammation (Erythrocyte Sedimentation Rate (ESR) within the first hour), and disease activity (Disease Activity Score [DAS28]), and QoL (Health Assessment Questionnaire [HAQII]) [3]. The following laboratory criteria, specific to the use of biologic agents, were assessed: Serology for hepatitis B and C; tuberculosis screening through the Purified Protein Derivative (PPD) skin test, and chest X-ray. Certolizumab pegol was administered subcutaneously, with an induction dose of 400 mg at weeks 0, 2, and 4, and a maintenance dose of 200 mg every 14 days [5].

Clinical case 1: early seronegative rheumatoid arthritis

This case describes a female patient, aged 34 years, with polyarthritis for a period of 6 months which affected the hands, wrists, elbows, knees, and ankles. The patient experienced a decrease in physical activity and QoL.

Complementary exams

ESR: 36 mm; rheumatoid factor (RF): negative; Waaler-Rose reaction: negative; anti-cyclic citrullinated peptide (CCP): 1.2 EliA U/

mL (normal <70 EliA U/mL); liver enzymes, urea, and creatinine: normal; serology for hepatitis B and C: negative. An ultrasound scan of the right wrist demonstrated signs of articular inflammation and the presence of the Doppler signal **(FIGURE 1)**. An X-ray of the hands and wrists showed an increase in soft parts and osteopenia. DAS28: 7.05; HAQII: 2.2; VAS: 7. The diagnosis was seronegative rheumatoid arthritis.

Initial treatment

Hydroxychloroquine 400 mg/day, methotrexate 10 mg/week, folic acid 5 g/week, and naproxen 1 g/day. Without improvement, prednisone 10 mg/day was started after 2 weeks. After 24 weeks, the patient showed a worsened condition with polyarthritis and the following parameters: VAS: 6; DAS28: 6.15; HAQII: 2.6; ESR: 36 mm. Negative test for hepatitis B and C, normal chest X-ray and zero millimeters PPD (non-reactive). The situation demonstrated a lack of csDMARD efficacy, and treatment with certolizumab pegol was prescribed.

Treatment with certolizumab pegol

The patient's condition improved; after 24 weeks, in the absence of treatment-emergent adverse events, the patient had no pain or articular edema. Activity parameters were: VAS: zero; DAS28: 1.34, demonstrating remission of disease activity; HAQII: 0.4, indicating an improvement in QoL and recovery of daily activities. A degree of improvement in the inflammatory process was seen in the wrist ultrasound scan, with a decreased severity of inflammatory manifestations, which was also characterized by the disappearance of the Doppler signal **(FIGURE 1)**.

Clinical case 2: early seropositive rheumatoid arthritis

This case relates to a female patient, aged 46 years, who was an athlete with polyarthritis for a duration of 2 months (VAS: 7; DAS28: 5.95; HAQII: 2.1).

Complementary exams

ESR: 35 mm; C-reactive protein: 0.41 mg/mL (normal <0.3 mg/mL); RF: 463 IU; Waaler-Rose reaction: 1/250; anti-CCP: 158 EliA U/mL; liver enzymes, urea, and creatinine: normal. Serology for hepatitis B and C: negative, PPD: non-reactive, chest X-ray: normal; X-ray of the hands and wrist showed increased soft parts and periarticular osteopenia. The diagnosis was seropositive rheumatoid arthritis.

Initial treatment

Prednisone 10 mg/day, methotrexate 10 mg/week, folic acid 5 mg/week, and celecoxib 200 mg/day. After 12 weeks, an improvement in the patient's overall and articular condition was observed (VAS: 5), with less severe arthritis. ESR: 30 mm, DAS28: 5.81, HAQII: 2.1. The overall picture for the patient consisted of aggressive disease, with decreased inflammation, a guarded prognosis, and major hair loss (methotrexate-related adverse event). Due to the lack of an adequate response to the csDMARD, treatment with biologic agents was prescribed.

Treatment with certolizumab pegol

The use of certolizumab pegol provided a pronounced improvement, as early as the induction period, which was subsequently sustained and intensified. Corticosteroid tapering was started after 15 days, and suspended

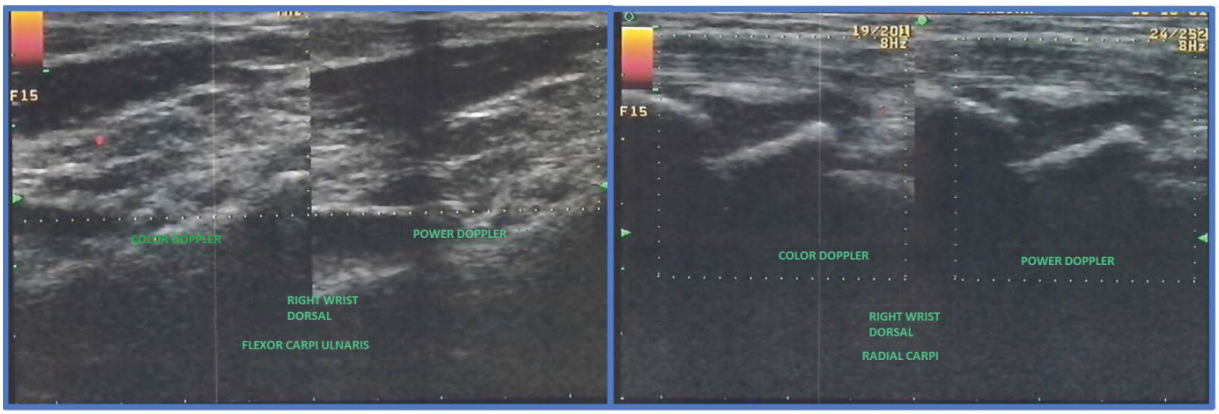

Figure 1. Left panel: ultrasound scan of the right wrist with signs of inflammation and the presence of the Doppler signal, after the use of csDMARDs and before the use of certolizumab pegol. Right panel: ultrasound scan after 24 weeks of treatment with certolizumab pegol showing a decrease in the inflammatory process and disappearance of the Doppler signal.

after 30 days. The patient experienced a recovery of physical activity and QoL, and sports practice was resumed after 45 days of treatment. After 24 weeks of therapy, there was a significant improvement in disease and inflammatory activity parameters–VAS: 0; ESR: 6 mm; DAS28: 1.34 (remission); HAQII: 0.24 **(TABLE 1)**. The patient did not present any new manifestations of articular inflammation, or adverse events. She continued practicing sports and returned to work.

Discussion

The presentation of these two cases highlights the low efficacy of csDMARDs in the treatment of rheumatoid arthritis with diverse characteristics. In case 1, a seronegative rheumatoid arthritis patient was treated with methotrexate, hydroxychloroquine, and corticosteroids with a good initial response. However, after 6 months, she still presented disease activity on the ultrasound scan, with the presence of the Doppler signal and synovitis in the tendons of the hands and wrists **(FIGURE 1)**. In case 2, a patient with a seropositive rheumatoid arthritis diagnosis also showed a good initial response to csDMARD therapy; however, she experienced a major adverse event (hair loss) related to methotrexate.

In both cases, the initial clinical improvement did not reach levels of disease remission, maintaining an active and aggressive inflammatory reaction, with severe arthritis, a decline in general health state, and a loss of QoL. As these data indicate a worse prognosis and a rapid and detrimental evolution, patients classified as non-responders to csDMARD therapy (in addition to experiencing adverse events) are indicated to switch to biologic agents [6].

In both cases, we used certolizumab pegol, a TNF-α inhibitor composed of a humanized Fab fragment combined with polyethylene glycol (PEG); certolizumab pegol has proven efficacy and safety, including among patients with early rheumatoid arthritis [7,8]. Moreover, certolizumab pegol does not have an Fc fragment, which is linked to avoidance of Fc-mediated effects such as complement- or antibody-dependent cytotoxicity [9-11], limited trans-placental transfer in non-human studies [12,13], and longer residency in inflamed tissues [14,15]. PEGylation of the molecule prolongs its half-life and therapeutic effects, and may reduce immunogenicity, renal elimination of the molecule, catabolism, and Fc receptor-mediated clearance [16]. In clinical practice, PEGylated products are used in the treatment of various diseases, such as combined immunodeficiency disease, leukemia, neutropenia, hepatitis C, acromegaly, macular degeneration, and anemia [17]. Clinical studies with certolizumab pegol in rheumatoid arthritis demonstrate a rapid clinical response with sustained and progressive efficacy results, mainly after 6 weeks of continued use and starting within up to 12 weeks [18,19].

Table 1. Disease parameter scores (VAS, ESR, DAS28, and HAQII) at baseline and after 24 weeks of certolizumab pegol treatment in rheumatoid arthritis patients after the failure of DMARDs.
DAS28: Disease Activity Score of 28 joints or Disease Activity Index (<2.6: remission of arthritis; 2.7 to 3.2: low activity; 3.2 to 5.1: moderate activity; >5.1: high disease activity); ESR: erythrocyte sedimentation rate (normal up to 10 mm within the first hour: no inflammation); HAQII: Health Assessment Questionnaire (0: minimal loss of function; 3: completely disabled. A reduction of 0.22 represents a significant clinical improvement); RA: rheumatoid arthritis; VAS: Visual Analog Scale for overall evaluation of the general state of the patient (0: no pain; 10: extreme pain, bedridden).

Case	Parameters Time	VAS	ESR	DAS28	HAQII
Case 1 Seronegative RA	Baseline	6	36	6.15	2.6
	24 weeks	0	3	1.34	0.24
	Absolute change (%)	−6 (100%)	−33 (91.7%)	−4.81 (78.2%)	−2.36 (90.8%)
Case 2 Seropositive RA	Baseline	7	35	5.95	2.1
	24 weeks	0	6	1.21	0.4
	Absolute change (%)	−7 (100%)	−29 (82.9%)	−4.74 (79.7%)	−1.7 (80.9%)

In case 1, the use of certolizumab pegol provided consistent and sustained improvements and, after 24 weeks, the patient was asymptomatic with a 100% reduction in the VAS score, a 91.7% reduction in ESR, and recovery of normal daily activities with a HAQII of 0.24 and DAS28 of 1.34, indicating clinical remission. In case 2, disease evolution was similar, with a major improvement after the use of certolizumab pegol. After 24 weeks, there was a 100% reduction in the VAS score, 80.9% in HAQII, 79.7% in DAS28, and 82.9% in ESR. Remission of the condition allowed the patient to resume her daily work activity.

In both cases, the action of certolizumab pegol was effective and superior to that of csDMARDs, interfering positively with the activity of the disease, with a rapid onset of action and sustained control of disease progression, including a very favorable safety profile.

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