

Rituximab in the refractory Felty's syndrome

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ABSTRACT

The authors report a case of a 29 year old woman who has seropositive rheumatoid arthritis for six months, and developed severe granulocytopenia and important splenomegaly, however she didn't show any joint inflammation. She did not respond either to pulse or oral steroids, or to oral methotrexate and leflunomide. She also developed an adverse reaction to the use of infliximab and did not respond well to adalimumab. Although she has had repeated infections, despite the various forms of antibiotics and long-term use of G-CSF, with high titers of rheumatoid factor, and high levels of ESR and CRP, the classic Rituximab method for treating rheumatoid arthritis was used. There was a good clinical response with an increase in the number of neutrophils following normalization of them, together with the reduction of rheumatoid factor titers, ESR and CRP. At the moment, the patient is in remission, according to both clinical and laboratory criteria and taking 5mg of prednisone per day and 10mg of methotrexate per week.

Keywords: rheumatoid arthritis, Felty's syndrome, treatment, rituximab.

Rituximab in the refractory Felty's Syndrome

INTRODUCTION

Felty's syndrome (FS) is a rare and severe form of seropositive rheumatoid arthritis, generally associated with neutropenia and, in some cases, splenomegaly.¹ For many years, splenectomy was the main therapy, however this modality has been replaced by immunosuppressive and biological agents, and its current indication is restricted to cases refractory to clinical treatment.² The use of rituximab, a monoclonal anti-CD20 antibody, for treating Felty's syndrome has been described in the literature in six patients up to the present moment, and in two of them there was no response.³⁻⁷ The authors report the case of a patient with refractory FS characterized by important neutropenia and recurring infections, who has been treated successfully with rituximab.

CASE REPORT

Female patient, 29 years old with a two years history of rheumatoid arthritis (RA) carrier diagnosed according to the American College of Rheumatology (ACR)⁸ criteria. She first presented with symmetric polyarthritis of the wrists, shoulders, metacarpophalangeal, proximal interphalangeal and temporomandibular joints, accompanied by morning stiffness longer than one hour and rheumatoid factor of 79IU (normal < 20 U).

After six months of treatment with corticosteroids (10 mg/day) and methotrexate (20 mg/week), she presented a satisfactory clinical response (DAS28 < 2.6) and there were no destructive articular alterations.

At the occasion the patient presented agranulocytosis of rapid and severe evolution, with neutrophils levels getting to 96/mm³, splenomegaly (14 cm below the costal arch) and without recurrence of the arthritis. At that moment, the rheumatoid factor titer was of 3,590U, ESR of 98 mm/1h and CRP of 135 mg/dl. Serologies for HCV, HIV, HBV, dengue fever,

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toxoplasmosis, CMV, Parvovirus B19 and Mantoux test were negative.

The myelogram revealed hypercellularity of all lineages, and the bone marrow biopsy didn't reveal any myelodysplasia pattern, lymphoproliferation or large granular lymphocyte syndrome. It was then defined the Felty's syndrome diagnosis. Treatment was begun with a granulocyte colony stimulating factor (G-CSF), methotrexate was kept and the dosage of oral prednisone raised to 40 mg/day, taken for three months, without clinical response. Leflunomid was chosen in replacement to methotrexate, in a dosage of 20 mg/day, and intravenous metilprednisolone, also without clinical response after three months. Due to the persistence of the neutropenia, infliximab was started as per the standart protocol and suspended after the second infusion due to a severe cutaneous allergic reaction. Then, adalimumab was prescribed for three months, also without clinical response.

Since the beginning of the neutropenia, the patient presented recurrent infections episodes, especially in the upper respiratory tract, always accompanied by fever and intense compromising of the general state, needing hospitalization. With the failure of the instituted treatment and the persistence of infectious recurrences, despite the various antibiotic schemes, the use of G-CSF (filgrastine) and prophylaxis with azitromicin, rituximab was started as per the standart RA protocol. Adverse events were not observed prior or post infusion.

After three months of rituximab, the patient presented complete clinical response, with decrease of the febrile episodes in more than 75% and the infection rate in more than 50% (Table 1). In addition it was noticed an increase in the neutophil count with posterior normalization (Figure 1) and a decrease in the rheumatoid factor titer, ESR and CRP (Table 2).

Table 1
Granulocytopenia Response Criteria⁹

COMPLETE RESPONSE	
Increase of granulocytes to 2,000/mm ³ or two of the following:	
•	Reduction of the infection rate by at least 50%
•	Decrease of the incidence of cutaneous ulcers by at least 50%
•	Reduction of the incidence of febrile episodes by at least 75%
PARTIAL RESPONSE	
Increase of the granulocytes between 1.000 and 2.000/mm ³ or two of the following:	
•	Reduction of the infection rate by at least 25%
•	Decrease of the incidence of cutaneous ulcers by at least 25%
•	Reduction of the incidence of febrile episodes by at least 25%

Currently, nine months after rituximab infusions, she is on 5 mg of prednisone daily and 10 mg of methotrexate weekly and her disease activity is well under control.

DISCUSSION

FS is characterized by chronic arthritis, splenomegaly and leukopenia, occurring in less than 1% of RA patients. The predominant age bracket is from the fifth to the seventh decades, RA usually has been present for 10 years or more before granulocytopenia is recognized. Two thirds are female, 95% HLA-DR4 and it is rare in black people. It's generally associated to a severe disease, positive rheumatoid factor in high titers, besides extra-articular exuberant manifestations including vasculitis, which can result in mononeuritis multiplex and necrotizing skin lesions, hepatomegaly, pleuropericarditis, rheumatoid nodules in subcutaneous, lymphadenopathy, thrombocytopenia, fever and episcleritis.¹⁰⁻¹⁴

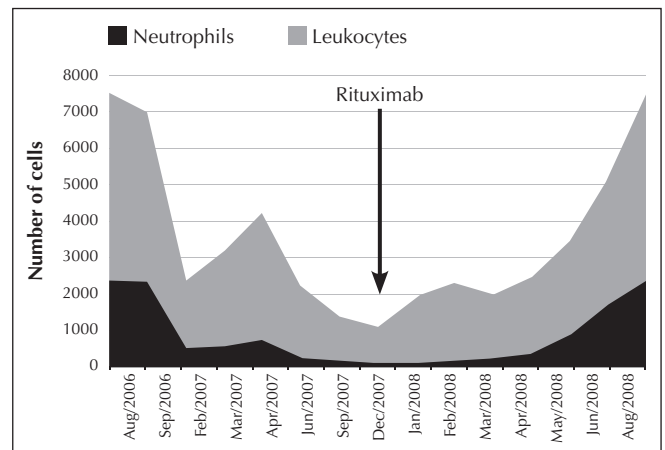


Figure 1. Distribution of leukocyte and neutrophil counts before and after rituximab.

Table 2
Variation of RF, ESR and CRP values before and after rituximab infusion

	Pre-rituximab		Post-rituximab			
			W6	W10	W16	W28
RF	3590	NR	NR	NR	NR	791
ESR	95	28	38	23	23	26
CRP	105	3.3	5.9	4.5	4.5	2.4

NP = not performed; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; CRP = C reactive protein; W=weeks

The articular disease is usually severe in terms of both erosions and deformities. Approximately one third of the patients have inactive synovitis, although almost always showing elevated levels of ESR. Rarely granulocytopenia and splenomegaly appear before or simultaneously with the arthritis.^{10,13,14}

The cause of granulocytopenia in FS is multifactorial, and it is a result of the unbalance between granulocyte production and their removal from the circulatory pool, besides the splenic sequestration, generally not causing symptoms unless bacterial infections occur. Those are usually recurrent and the respiratory tract infection and the skin are the most common, occurring more often when the of granulocyte count is below 1000/mm³, a determinant prognostic factor.^{14,15}

Methotrexate is an effective drug in most FS patients, with improvement generally occurring in the first two months of treatment. Nevertheless, there are no randomized controlled clinical trials, and these results are based on reports with few cases. The average dosage used in these reports was 13 mg/week, orally.^{16,17}

There are reports with limited experience of the use of other drugs, such as sulfasalazine, azathioprine, cyclosporine, cyclophosphamide and leflunomide.¹⁸⁻²¹

Corticosteroids can elevate the granulocyte count in FS by two mechanisms: immunosuppressive action and granulocyte kinetics alteration.²²⁻²⁴ Prednisone, at least 30 mg/day, generally normalizes the number of granulocytes, although its effect is not sustained when the dosage is reduced to less than 10 mg/day, unless other drugs are added.²⁵ Intravenous metilpredni-

solone has been used for granulocytopenia, and infections are the main obstacle for its use.²⁶

The use of etanercept and infliximab in the treatment of FS didn't show benefit in three cases reported in the literature.^{4,27,28} Endovenous gamaglobulin does not seem to be effective for treatment of neutropenia occurring in the FS also.²⁹

Growth stimulating factors are frequently used in the FS, and are effective in reversing granulocytopenia and reducing infectious complications in most patients. However, flaws have been reported and cost is another limiting factor, particularly with prolonged use. Besides that, adverse effects like synovitis and leukocytoclastic vasculitis can occur.³⁰

For many years, splenectomy was the main therapy, however this modality has been replaced by immunosuppressive and biological agents, and its current indication is restricted to cases refractory to clinical treatment.²

Rituximab, a chimeric monoclonal antibody directed against the CD-20 antigen on B-lymphocytes, has been used in the treatment of FS. The mechanism of neutropenia is multifactorial and in that subtype of patients in which there is autoantibodies formation, rituximab can be beneficial. Nevertheless, various factors can concur to the lack of its effectiveness in FS.^{31,32}

Rituximab's inability of to bind to plasma cells, which are CD-20 negatives;

Other B cell-dependant mechanisms (immunoglobulins, antigen presentation, T cell cooperation); and

Table 3

Laboratory and clinical characteristics of patients with Felty's Syndrome treated with rituximab

References	Patients	Dosage	Clinical characteristics and previous treatment	Response and follow-up
Sordet <i>et al.</i> ³	02	375 mg/m ² , 4 weeks	67 years; 53 years male (both); RA active, RF positive; MTX, SSZ, CS	After six months, control of laboratory and clinical activity, however without response for FS in both cases.
Weinreb <i>et al.</i> ⁴	01	650 mg/week, 4 weeks	51 years, Fem.; RA seropositive; MTX, CS, HCQ, INF and G-CSF	Decreased RF and normalization of neutrophils count nine months after the infusion.
Lekharaju; Chattopadhyay ⁵	01	1g, two infusions, 14 days interval	41 years, Fem.; RA active seropositive and neutropenia; CS, MTX, SSZ, G-CSF	Increase of neutrophils count after four weeks with sustained response after 14 months.
Chandra; Margulis; Schiff ⁶	01	660 mg, single infusion	60 years, male; RA seropositive, nodular; CS, Gold, HCQ, DPA and LEF	Decrease and sustained response of the neutrophils; remarkable symptoms remission.
Salama <i>et al.</i> ⁷	01	1g, two infusions, 14 days interval	35 years, Fem.; Dysplasia of all the cellular lineages in the biopsy; FS refractory and hemolysis; CIC, LEF, ADA	Improvement of arthritis and hemolysis, without response to thrombocytopenia and leukopenia.
Fragoso <i>et al.</i> , 2008	01	1g, two infusions, 14 days interval	29 years, Fem.; Neutropenia, RF +; CS orally and IV, MTX, LEF, INF, ADA, G-CSF	Improvement of the neutrophil count after three months; sustained response after nine months.

Fem.: female; RF: rheumatoid factor; MTX: methotrexate; SSZ: sulfasalazine; CS: corticosteroid; HCQ: hydroxychloroquine; DPA: D-Penicillamine; INF: infliximab; LEF: leflunomide; CIC: ciclophosphamide; ADA: adalimumab; G-CSF: granulocyte stimulating factor; IV: intravenous

Subpopulations of T lymphocytes that have anti-granulocytic activity can exist independently of the B cells.

These mechanisms can justify the controversial results found in the existing reports in the literature of the use of rituximab in refractory FS (Table 3).

Although FS occurs more frequently in active and severe RA, a percentage of patients do not present inflammatory articular activity,¹⁴ as occurred with our patient, maintaining DAS28 always lower than 2.6, since the beginning of the neutropenia, even though she presented elevated levels of inflammatory markers (CRP and ESR) and of RF.

Interestingly, our patient age was (29 years old) very inferior to the one in which the appearance of FS is more frequent¹⁴ (between 50 and 70 years old). The average age of patients earlier reported was of 51.2 years (35 to 67 years).³⁻⁷

As well as in the literature reports,³⁻⁷ our patient used various drugs, such as prednisone, metilprednisolone, methotrexate, leflunomide, G-CSF and anti-TNF, without response to neutropenia.

Rituximab is an already well-established therapy for patients with seropositive RA which showed to be promising in some reported cases of FS. The choice of using it was based on the fact that the patient presented elevated titers of rheumatoid factor, myelogram demonstrating hypercellularity and refractoriness to the drugs previously used. Despite the multifactorial pathogeny of FS, rituximab can be an effective and safe therapeutical option, and it can be used before splenectomy, decreasing the morbidity and mortality of these patients.

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