American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2015; 16: 211-214
DOI: 10.12659/AJCR.892541

Received: 2014.09.21
Accepted: 2014.11.28
Published: 2015.04.09

Rituximab-Related Late-Onset Neutropenia in Patients with Rheumatic Diseases: Successful Re-Challenge of the Treatment

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Tatiana Reitblat
B 2 Alexander Wechsler
ACEF 1 Olga Reitblat

1 Department of Rheumatology, Barsilai Medical Center, Ashkelon, Israel
2 Department of Nephrology, Barsilai Medical Center, Ashkelon, Israel

Corresponding Author: Tatiana Reitblat, e-mail: reitblat@barzi.health.gov.il
Conflict of interest: None declared

Case series
Patient: Female, 56 • Male, 64
Final Diagnosis: Neutropenia after Rituximab
Symptoms: Cough • diarrhea • fever • headache
Medication: Rituximab
Clinical Procedure: —
Specialty: Rheumatology

Objective: Unusual or unexpected effect of treatment

Background: We describe here 2 patients who developed late-onset neutropenia after Rituximab treatment. While this phenomenon is well described among patients suffering from hematological malignancies, such adverse effects are rare among patients with rheumatic diseases.

Case Report: Two patients, the first with rheumatoid arthritis and the second with granulomatosis with polyangiitis, were treated by Rituximab after all previous treatments failed. The patients developed late-onset neutropenia after several courses of treatment. The first patient, with symptomatic neutropenia, recovered after a single dose of granulocyte macrophage stimulating factor, and the second patient's neutrophils increased spontaneously. Both patients were retreated by rituximab in their scheduled time without further complications.

Conclusions: Our case series is unique because the same phenomenon appeared in patients with different rheumatic diseases. This case series confirms the possibility of continuing the treatment without further adverse effects.

MeSH Keywords: Arthritis, Rheumatoid • Biological Therapy • Neutropenia • Vasculitis

Abbreviations: LON – late-onset neutropenia

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/892541

1365 — — 14

Background

Rituximab is a chimeric human-mouse monoclonal antibody that reacts specifically with CD20 antigen presented on B-cells. Rituximab has been in use for treatment of B-cell lymphoma since 1997. In 2006 it was approved for the treatment of Rheumatoid arthritis. Since then, many other autoimmune diseases have been treated by Rituximab, including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, vasculitis, pemphigus, pemphigoid, thyroid ophthalmopathy, Sjögren's syndrome, and systemic lupus erythematosus.

The drug is generally well tolerated and has a favorable toxicity profile in patients with both malignant and autoimmune disease [1]. However, with the increasing use of Rituximab, a growing number of rare adverse effects have been recognized. These include various infections, progressive multifocal leukoencephalopathy, reactivation of hepatitis, and late-onset neutropenia (LON) [2]. According to the National Cancer Institute common Toxicity Criteria, LON is defined as grade III–IV neutropenia, in which absolute neutrophil count is less than 1.0×10^3/Liter, occurring 4 weeks after the last Rituximab administration [3]. The reported incidence of LON secondary to Rituximab in the treatment of hematological malignancy is between 3% and 27% [4]. Reports of LON in the treatment of autoimmune disease are rare [5].

Herein, we report 2 cases of LON after Rituximab treatment from a single centre.

Case Report

First case

A 56-year-old patient had been suffering from rheumatoid factor-positive, anti-CCP antibody-positive rheumatoid arthritis since 1998. His permanent treatment since the onset of his illness was methotrexate 20 mg/w and prednisolone 5 mg/d. The patient was treated by infliximab 3 mg/kg for 3 years and after that etanercept 25 mg×2/w for 7 years. In 2010, treatment with Rituximab 1000 mg twice in 6 months (rheumatoid arthritis protocol) was introduced because of Etanercept secondary failure. The patient received 5 courses of the treatment without any adverse events. His illness was in remission.

Two months after his last treatment, the patient was hospitalized due to systemic fever of 39.0°C and general weakness. The patient denied extreme headache, coughing, dysuria, diarrhea, joint pain exacerbation, and new use of drugs.

Physical examination did not reveal any pathological finding. Blood and urine test results were negative for microbial and viral infections. White blood cell count was 350 cells in mm^3, and neutrophils count was 200 cells in mm^3. No anemia or thrombocytopenia were reported. The patient was diagnosed as suffering from neutropenic fever due to Rituximab treatment. Treatment with granulocyte-macrophage colony stimulated factor was introduced. A patient did not receive any other treatment. After 3 days of treatment, his leukocyte count began to increase and returned to normal range. The patient received the next course of Rituximab treatment a year after the described episode, without LON appearance following treatment.

Second case

A 64-year-old male was hospitalized with a clinical picture of acute renal failure, respiratory distress, systemic fever, weight loss, and fatigue.

He became ill 2 weeks before.

His past medical history was remarkable for hyperthyroidism, which was treated with propylthiouracil for 4 years.

The CT examination of chest and head revealed bilateral maxillary sinus mucosal thickening and multiple infiltrates in the lungs.

Maxillary sinus biopsy showed necrotizing inflammation.

Blood test was positive for anti Proteinase-3 antibody. Rheumatoid factor and antinuclear antibody were negative. Complement C3 and C4 were within normal range.

The patient was diagnosed as having Granulomatosis with Polyangiitis. Intravenous pulse Cyclophosphamide and Prednisone treatment were introduced. Unfortunately, the patient developed severe leukopenia, followed by myopathy as complications of his treatment. One month after Cyclophosphade and Prednisolone discontinuation, Rituximab treatment of 1000 mg twice in 2 weeks every 6–12 months was introduced (according to rheumatoid arthritis treatment protocol). Three months after the first treatment, the patient developed leucopenia of $1000/mm^3$, with neutrophiles count of $700/mm^3$ and normal hemoglobin and platelets count. There were no clinical signs of infection. The patient was not hospitalized, and did not receive any additional treatment. White blood cell count returned to normal after 1 month, without any additional treatment. Six months after the first course, the patient received a second course of Rituximab at the same dose. Leukocyte count on the beginning of treatment was $4710/mm^3$, with neutrophils count $2929/mm^3$; 2 months later, leucocyte count was $5170\ /mm^3$ with neutrophils count $3240/\ mm^3$.

The patient is now stable.

Discussion

Several mechanisms for late-onset neutropenia following Rituximab treatment have been suggested, but currently there is no obvious explanation for this phenomenon.

A direct toxic effect of Rituximab on bone marrow was suggested, but was excluded for several reasons: CD20 is not expressed on granulocyte or on stem or progenitor cells and the late onset of neutropenia is not correlated with the drug's pharmacokinetics and pharmacodynamics [6].

Voog et al. suggested the mechanism of immune mediated neutropenia. They demonstrated direct immunofluorescence IgG type antibodies bound to the surface of neutrophils in 2 of their patients. However, these findings were not consistently demonstrated in further studies [7].

Papadaki et al. described a significant infiltration of bone marrow and peripheral blood by T-large granular lymphocytes in their patients with LON. The authors suggested that secretion of Fas/Fas ligand by these cells might lead to apoptosis of mature neutrophils [8].

Dunleavy et al. found changes in the level of stromal-derived factor-1 during the period of B-cell recovery after the Rituximab treatment. They hypothesized that consumption by rapidly expanding B-cells could result in disruption of gradients of the factor in bone marrow, resulting in blockade of neutrophil egress into the circulating blood [4].

Several retrospective studies attempted to identify risk factors for LON. All studies presented patients with different hematological malignancies. Because of the heterogeneity of the patient population, no study was able to pinpoint statistically significant risk factors for the development of LON. Nevertheless, there were several notifications for the possible risk factors, such as number of Rituximab treatments <4 *vs.* >4, and previous chemotherapy [9]. Weng et al. suggested that specific polymorphism in immunoglobulin G Fc receptor FCγRIIIa 158 V/F was correlated with higher rates of LON in patients with non-Hodgkin lymphoma [10]. They showed that each additional V allele was associated with a 3-fold increase in odds ratio for development of neutropenia.

Age, sex, and bone marrow involvement do not correlate with LON appearance [11].

The most important question in the setting of LON appearance is its clinical significance.

Risk of infection or the risk of neutropenia by re-challenge of the medicine may affect treatment strategy and patient outcome.

There is no established consensus about the frequency and severity of infectious complications among rheumatologic patients with LON. While Tesfa et al. described the increased risk of infection in their patients with LON [12], Besada et al. [13] did not find a significantly higher incidence of infectious complications in their group of patients.

The rate of infectious complications in the studies dealing with hematological malignances among patients with LON ranges from 0% to 20% [6]. Theoretically, risk of infection is associated with hypogammaglobulinemia. This phenomenon is a well described sequela of Rituximab treatment, so the variations in incidence of infectious may be explained by the depth of hypogammaglobulinemia in each individual patient.

The dilemma regarding renewed Rituximab treatment after an episode of LON is fundamental, since this drug is given as a last-line treatment in advanced, refractory rheumatological diseases.

The published data is scarce, and is probably biased because of selection of patients for whom the treatment was recommenced. It seems that LON recurrence is not a common phenomenon [12,14], so it may be possible to re-challenge the treatment under special circumstances.

Our case series confirms the possibility of continuing the treatment without reappearance of LON.

Conclusions

We presented our experience treating 2 patients with different rheumatological diseases and different immunologic pathogenetic mechanisms, who developed LON after Rituximab treatment.

The patients have no common features in the pathogenesis of their disease, in their previous treatment, nor in the number of previous Rituximab courses. These differences stress the fact that the appearance of LON may be a universal feature of the medicine itself. Another important aspect in our case series is that the patients continued their treatment after recovery from LON, without subsequent changes in blood count. We cannot explain this phenomenon, but this fact confirmed the possibility of treatment re-challenge.

Statement

There were no competing interests and nothing to disclose.

References:

1. Boye J, Elter T, Engert A: An overveiw of the current clinical use of the anti-CD20 monoclonal antibody rituximab. Ann Oncol, 2003; 14: 520–35
2. Ram R, Ben-Bassat I, Shpilberg O et al: The late adverse events of rituximab therapy – rare but there. Leuk Lymphoma, 2009; 50: 1083–95
3. Cancer Therapy Evaluation Program. Common Toxicity Criteria version 2.0 (CTC). Bethesda (MD): Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1999
4. Dunleavy K, Tay K, Wilson WH: Rituximab-associated neutropenia. Semin Hematol, 2010; 47: 180–86
5. Rios-Fernández R, Gutierrez-Salmerón MT, Callejas-Rubio JL et al: Late-onset neutropenia following rituximab treatment in patients with autoimmune diseases. Br J Dermatol, 2007; 157: 1271–73
6. Wolach O, Bairey O, Lahav M: Late-onset Neutropenia After rituximab Treatment. Medicine, 2010; 89: 308–18
7. Voog E, Morschhauser F, Solal-celigny P: Neutropenia in patients treated with rituximab. N Engl J Med, 2003; 348: 2691–94
8. Papadaki T, Stamatopoulos K, Stavroyianni N et al: Evidence for T-large granular lymphocyte-mediated neutropenia in Rituximab-treated lymphoma patients: report of two cases. Leuk Res, 2002; 26: 597–600
9. Cattaneo C, Spedini P, Casari S, et al. Delayed-onset peripheral blood cytopenia after rituximab: frequency and risk factor assessment in a consecutive series of 77 treatments. Leuk Lymphoma, 2006; 47: 1013–17
10. Weng WK, Negrin RS, Lavori P, Horning SJ: Immunoglobulin G Fc receptor FcgammaRIIIa 158 V/F polymorphism correlates with rituximab-induced neutropenia after autologous transplantation in patients with non-Hodgkin's lymphoma. J Clin Oncol, 2010; 28: 279–84
11. Nitta E, Izutsu K, Sato T et al: A high incidence of late-onset neutropenia following rituximab-containing chemotherapy as a rimary treatment of CD20-positive B-cell lymphoma: a single-institution study. Ann Oncol, 2007; 18: 364–39
12. Tesfa D, Ajeganova S, Hägglund H et al: Late-onset neutropenia following rituximab therapy in rheumatic diseases: association with B lymphocyte depletion and infections. Arthritis Rheum, 2011; 63: 2209–14
13. Besada E, Koldingsnes W, Nossent J: Characteristics of late onset neutropenia in rheumatologic patients treated with rituximab: a case review analysis from a single center. QJM, 2012; 105: 545–50
14. Breuer GS, Ehrenfeld M, Rosner I et al: Late-onset neutropenia following rituximab treatment for rheumatologicconditions. Clin Rheumatol, 2014; 33: 1337–40