Late-onset neutropenia after treatment with rituximab for rheumatoid arthritis and other autoimmune diseases: data from the AutoImmunity and Rituximab registry


To cite this version:
J. Salmon, P. Cacoub, Bernard Combe, J. Sibilia, Béatrice Pallot-Prades, et al.. Late-onset neutropenia after treatment with rituximab for rheumatoid arthritis and other autoimmune diseases: data from the AutoImmunity and Rituximab registry. RMD Open : Rheumatic & Musculoskeletal Diseases, EULAR ; BMJ, 2015, 1 (1), pp.e000034. 10.1136/rmdopen-2014-000034 . hal-01933103

HAL Id: hal-01933103
https://hal.umontpellier.fr/hal-01933103
Submitted on 31 May 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License
Late-onset neutropenia after treatment with rituximab for rheumatoid arthritis and other autoimmune diseases: data from the AutoImmunity and Rituximab registry

J H Salmon,1 P Cacoub,2 B Combe,3 J Sibilia,4 B Pallot-Prades,5 O Fain,6 A Cantagrel,7 M Dougados,8 E Andres,9 O Meyer,10 P Carli,11 E Pertuiset,12 I Pane,13 F Maurier,14 P Ravaud,13 X Mariette,15 J E Gottenberg,16 on behalf of all the investigators of AIR registry, the French Society of Rheumatology and the Club Rhumatismes et Inflammations


▸ Prepublication history and additional material for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2014-000034).

Received 4 December 2014
Revised 23 April 2015
Accepted 28 April 2015

ABSTRACT

Objectives: To evaluate the prevalence of late-onset neutropenia and its complications in patients treated with rituximab (RTX) for rheumatoid arthritis (RA) and other autoimmune diseases (AIDs) in a prospective registry.

Methods: The AutoImmunity and Rituximab registry is an independent 7-year prospective registry promoted by the French Society of Rheumatology. For each episode of neutropenia, data were validated by the clinician in charge of the patient.

Results: Among 2624 patients treated with RTX for refractory AIDs, and at least 1 follow-up visit (a total follow-up of 4179 patient-years in RA and 987 patient-years in AIDs), late-onset neutropenia was observed in 40 patients (25 RA (1.3% of patients with RA, 0.6/100 patient-years), and AIDs in 15 (2.3% of patients with AIDs, 1.5/100 patient-years)). 6 patients (15%) had neutrophils <500/mm³, 8 (20%) had neutrophils between 500 and 1000/mm³, and 26 (65%) had neutrophils between 1000 and 1500/mm³. Neutropenia occurred after a median period of 4.5 (3–6.5) months after the last RTX infusion in patients with RA, and 5 (3–6.5) months in patients with AIDs. 5 patients (12.5%), 4 of them with neutrophils lower than 500/mm³, developed a non-opportunistic serious infection and required antibiotics and granulocyte colony-stimulating factor injections, with a favourable outcome. After resolution of their RTX-related neutropenia, 19 patients (47.5%) were re-treated, and neutropenia reoccurred in 3 of them.

Conclusions: Late-onset neutropenia might occur after RTX and may result in serious infections. Thus, monitoring of white cell count should be performed after RTX. However, in this large registry of patients with AIDs, the frequency of RTX-induced neutropenia was much lower than that previously reported in patients treated for blood malignancies or AIDs.

Key messages

What is already known about this subject?
Late-onset neutropenia rituximab was mainly reported in patients treated for lymphoma but data in patients with rheumatoid arthritis and other AIDs are very limited.

What does this study add?
The incidence of LON is much lower in RA and other AIDs than in blood malignancies. Neutropenia is usually mild and might not be complicated with infections.

How might this impact on clinical practice?
Instead of monitoring whole blood count after each cycle of RTX, a more pragmatic approach could be to have a blood count performed in the event of fever or infection in the months following RTX treatment.

INTRODUCTION

Late-onset neutropenia (LON) after B-cell depletion by rituximab (RTX) was mainly reported in patients treated for lymphoma with an observed prevalence of 8%.1 LON can occur from 1 month up to 1 year after RTX.9 The mechanism of this complication remains poorly understood. Several assumptions exist regarding the pathogenesis of neutropenia after RTX in B-cell lymphoma, including the role of antineutrophil antibodies, large granular lymphocytes, competition for growth factors between lymphopoiesis and granulocyte colony-stimulating factor injections, with a favourable outcome. After resolution of their RTX-related neutropenia, 19 patients (47.5%) were re-treated, and neutropenia reoccurred in 3 of them.

Conclusions: Late-onset neutropenia might occur after RTX and may result in serious infections. Thus, monitoring of white cell count should be performed after RTX. However, in this large registry of patients with AIDs, the frequency of RTX-induced neutropenia was much lower than that previously reported in patients treated for blood malignancies or AIDs.
activating factor of the tumour necrosis factor (TNF) family (BAFF) after B-cell depletion might also play a role by favouring B-cell repopulation to the detriment of granulopoiesis.\textsuperscript{7} The pathogenesis and concomitant treatments are very different between autoimmune diseases (AIDs) and lymphomas, which are usually treated with associated chemotherapy. Data on LON in patients with rheumatoid arthritis (RA) and other AIDs are very limited.\textsuperscript{10–15} One series of patients included 209 patients (162 RA and 47 AIDs, including 15 with systemic lupus erythematosus (SLE), 13 with granulomatosis with polyangiitis (GPA), 6 with juvenile RA and 13 with other AIDs), among whom 11 (5.2%: 5 RA and 6 AIDs) developed neutropenia.\textsuperscript{10} Recently, a retrospective series of 108 patients with RA reported 5 LON, of whom 2 developed infection.\textsuperscript{15} The aim of the present study was to evaluate the prevalence of LON and its complications in a large prospective cohort of patients treated with RTX for AIDs.

**METHODS**

The French Society of Rheumatology and the Club Rhumatisme Inflammations have set up the AutoImmunity and Rituximab (AIR) registry. The AIR registry is a multicentre prospective cohort designed to study the safety and efficacy of RTX in the treatment of RA and other refractory AIDs. Follow-up data are collected every 6 months over 7 years. Serious adverse events, including serious infections (requiring hospitalisation and/or intravenous antibiotics), cancers and deaths, are validated by the two coordinators of the registry using chart copies.

The methodology of the registry was reported previously.\textsuperscript{16,17} This study was approved by the French authorities Comité Consultatif sur le Traitement de l’information en matière de Recherche dans le domaine de la Santé and Commission Nationale de l’Informatique et des Libertés. Written informed consent was obtained from all patients. Neutropenia is defined by an absolute blood neutrophil count less than 1500/mm\textsuperscript{3}. Neutrophil count was requested at inclusion and at each follow-up visit (3 months, 6 months then every 6 months, or at any time in case of treatment change). Late-onset RTX-related neutropenia was defined as an absolute neutrophil count of ≤1.5×10\textsuperscript{9}/L starting from 4 weeks after termination of RTX therapy until 12 months after the last RTX infusion.\textsuperscript{2} Neutropenia prior to RTX and other drug-related neutropenia were excluded. At each visit, the crf includes specific questions regarding the potential complications of neutropenia. For each episode of neutropenia, data were abstracted from the electronic crf, validated and completed if necessary, using a specific questionnaire, by the clinician in charge of the patient.

**Statistical analysis**

Patients contributed person-years of follow-up between the first infusion of the first cycle and death, or the last follow-up visit. For the incidence rate calculation of neutropenia, the time of neutropenia was used as the right censoring rule. Rates of neutropenia are presented as event/100 patient-years. Data are presented as median (IQR) for quantitative values and proportions for qualitative values. All analyses were performed using SAS software V.9.3 (SAS system SAS Institute, Cary, North Carolina, USA). In univariate analysis, a χ\textsuperscript{2} test or Fisher’s exact test was used for qualitative data according to application requirements. A non-parametric Mann-Whitney U test was used for quantitative values. A p value <0.05 was defined as significant.

**RESULTS**

**Characteristics of patients with neutropenia**

At the time of analysis, 2624 patients had at least one follow-up visit, including 1975 patients with RA and 649 patients with other AIDs. The median follow-up of patients with RA was 24.2 months (14.7–35.3) (4179 patient-years) and that of patients with AIDs was 17.4 months (5.6–29.1) (987 patient-years). The median follow-up after the last regimen of RTX was 14.4 months (7.1–27.8) in RA and 18.6 months (8.5–31.8) in AIDs. The median (IQR) number of blood counts was 4 (3–6) for patients with RA. The median (IQR) interval between blood counts was 5.2 (4.1–6.7) months for patients with RA. The median (IQR) interval of blood counts/cycles of RTX was 2 (1.4–3) for patients with RA. Neutropenia was reported in 85 patients (48 RA and 37 AIDs). Forty-five patients were excluded since they actually had neutropenia prior to RTX (n=22, including dysmyelopoiesis (n=3), Felty’s syndrome (n=1), cyclic neutropenia (n=1), autoimmune neutropenia (n=1), no specific diagnosis (n=16)), had other drug-related neutropenia (n=8, including interferon treatment for hepatitis C virus infection (n=7), chemotherapy for lymphoma (n=1) or had normal neutrophil counts within 1 year after RTX infusions and one occurrence of neutropenia more than 1 year after RTX infusions (n=13) (figure 1). For the remaining 40 patients, including 25 RA (1.3% of patients, 0.6/100 patient-years) and 15 AIDs (2.3%, 1.5/100 patient-years), 7 SLE, 7 vasculitis (including 6 cryoglobulinemia-related vasculitis and 1 GPA and 1 myositis), no other cause of neutropenia but RTX was identified by the clinician. The characteristics of these 40 patients (37 women, 3 men) with LON are summarised in table 1.

**Characteristics of late-onset neutropenia**

Six patients (1 RA (0.05% of patients with RA, 0.02/100 patient-years) and 5 AIDs (0.7% of patients with AIDs, 0.5/100 patient-years)) had neutrophils <500/mm\textsuperscript{3}, 8 (7 RA and 1 AIDs) had neutrophils between 500 and 1000/mm\textsuperscript{3} neutrophils, and 26 (17 RA and 9 AIDs) had neutrophils between 1000 and 1500/mm\textsuperscript{3}.

Neutropenia occurred after a median period of 4.5 (3–6.5) months after the last infusion of RTX in patients with RA and 5 (3–6.5) months in patients with AIDs. In patients with RA, neutropenia occurred after the first
cycle in 2 patients, after the second cycle in 4 patients, after the third cycle in 7 patients with RA and after the fourth cycle or later in 12 patients. In patients with AIDs, neutropenia occurred after the first cycle in 9 patients, after the second cycle in 5 patients and after the fourth cycle in 1 patient. Numerous episodes of neutropenia occurred after the second or subsequent cycle of RTX (92% in RA and 44% in AIDs). They were mainly mild neutropenia (blood neutrophil count between 1000 and 1500/mm³ in 17 RA and 2 AIDs; between 500 and 1000/mm³ in 6 RA and 1 AIDs; 3 AIDs had neutrophils <500/mm³).

Five patients (1 RA and 4 AIDs) (12.5% of patients with neutropenia), four of them with neutrophils lower than 500/mm³, developed a non-opportunistic serious infection and required antibiotics and granulocyte colony-stimulating factor (G-CSF) injections, with a favourable outcome. These episodes of neutropenia occurred after the first cycle for 2 patients, after the second cycle for 2 patients and after the fourth cycle for 1 patient. No patient had an opportunistic infection (table 2). In all patients, the outcome was favourable after treatment.

Associated factors with LON in RA
Among the baseline characteristics of patients with RA, including gender, disease duration, RF and anti-cyclic citrullinated peptide activity, the number of previous synthetic disease-modifying antirheumatic drugs (DMARDs), number of previous anti-TNF, disease activities at enrolment, concomitant treatment with DMARD or corticosteroids, serum gammaglobulin and IgG levels, only female gender and age were associated with neutropenia (table 3).

Re-treatment with RTX
Nineteen patients (47.5%) with previous neutropenia after RTX received a new infusion of RTX after resolution of their neutropenia (13 patients with RA with a previous blood neutrophil count between 1000 and 1500/mm³, four patients with RA between 500 and 1000/mm³, and two patients with SLE between 1000 and 1500/mm³). In the patients re-treated with RTX, the median number of

Table 1 Characteristics of the 40 patients who developed rituximab-related neutropenia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RA</th>
<th>AIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Age</td>
<td>54.3±19 years</td>
<td>56.7±13 years</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>RA</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>SLE</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Myositis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Disease duration</td>
<td>9.2±7.5 years</td>
<td>9.3±8 years</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Yes: 27 (67.5%)</td>
<td>No: 13 (32.5%)</td>
</tr>
<tr>
<td>Mean dose of corticosteroids</td>
<td>RA: 6.3±7.2 mg/day</td>
<td>AIDs: 10.8±17.2 mg/day</td>
</tr>
<tr>
<td>Concomitant immunosuppressant</td>
<td>Absent: 23 patients</td>
<td>Present: 7 patients</td>
</tr>
<tr>
<td>other than corticosteroids</td>
<td>Methotrexate: 7</td>
<td>Hydroxychloroquine: 2</td>
</tr>
<tr>
<td></td>
<td>Leflunomide: 4</td>
<td>Cyclophosphamide: 8</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate mofétil: 1</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Azathioprine: 1</td>
<td>+Hydroxychloroquine: 2</td>
</tr>
<tr>
<td>Regimen of rituximab</td>
<td>1 g×2: 32 (80%)</td>
<td>+Mycophenolate mofétil: 1</td>
</tr>
<tr>
<td></td>
<td>375 mg/m²×8 (20%)</td>
<td>+Hydroxychloroquine</td>
</tr>
</tbody>
</table>

AIDs, autoimmune diseases; F, female; M, male; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
cycles was 3 (2–4) in RA and 2 (2–2) in AIDs. The median follow-up of the re-treated patients was 26.1 months (21.8–39.2) in RA and 25.2 months (19.6–30.8) in AIDs. Neutropenia reoccurred in three of them (blood neutrophil count between 1000 and 1500/mm³ in two, and between 500 and 1000/mm³ in one). None of these recurrent episodes of neutropenia required growth factors or was complicated by an infection.

**DISCUSSION**

The occurrence of late-onset neutropenia after RTX was infrequent in a large prospective registry, and the related complications were moderately severe. However, the rate of late-onset neutropenia after RTX in patients with RA and other AIDs has not been clearly determined. The AIR registry was very well adapted to this purpose since the occurrence of neutropenia and the blood neutrophil count were specifically requested in the e-crf at each follow-up visit. In addition, data validation by the clinician allowed us to identify patients with neutropenia unrelated to RTX. However, the main limitations of the study are related to its observational design, and missing data, notably duration of neutropenia that was not requested by the crf.

The first important result of this study is the low rate of late-onset neutropenia after RTX in RA (1.3% of patients, 0.6/100 patient-years) and other AIDs (2.3%, 1.5/100 patient-years) in a large multicentre registry of unselected patients. The rate observed in this study is much lower than in the few previous reports concerning AIDs.10–12 Despite the observational setting of this registry study, patients had regular assessments of neutrophil...
counts approximately every 6 months. However, asymptomatic LON can occur in between blood tests. Thus, it cannot be ruled out that the higher frequency of neutropenia after RTX in patients with haematological malignancies could also be partly related to the more frequent follow-up of blood counts by haematologists than by rheumatologists. Therefore, the actual frequency of LON in this study might be underestimated as reported in lymphomas. In our study, the mean time of onset of neutropenia was approximately 5 months, in accordance with what has been observed in this previous studies in AIDs and in lymphoma (around 6 months), confirming their known late onset. No risk factor of neutropenia could be identified among the baseline characteristics of patients with RA, except age and female gender. Concerning gender, this may be simply due to the significantly higher prevalence of AIDs in women. Of note, lymphoma gender-based differences in RTX clearance were reported in elderly (>70 years) female patients treated with RTX for diffuse large B-cell lymphomas. The large numeric disequilibrium between 25 patients with RA with neutropenia and over 1900 patients without neutropenia inevitably led to a flawed statistical analysis due to type 2 errors.

The second important result was the low number of complications associated with neutropenia after RTX. First, most of the LONs were mild (>300/mm³), and only a minority of the patients who had a very low blood neutrophil count required growth factors and antibiotics. Among the five patients who required growth factors and antibiotics, two had concomitant cyclophosphamide and were not treated with a concomitant immunosuppressant other than RTX. Concordantly, a previous report also showed that complications usually concern patients with a very low blood neutrophil count. However, the overall rate of infections was higher in that previous report than in this study, which might be related to a different distribution of AIDs. No opportunistic infection or death was related to neutropenia. Thus, late-onset neutropenia does not seem to increase the risk for serious infection as much as RTX-related hypogammaglobulinemia. The absence of clinical consequences of most of these neutropenias might explain that more than half of the patients with RA with a history of previous RTX-induced mild neutropenia were subsequently re-treated with RTX. However, data regarding the risk of reoccurrence of neutropenia after re-treatment with RTX are not available in the literature. Interestingly, in this study, a recurrent episode of uncomplicated neutropenia was observed in only 16% of re-treated patients, with only one patient having a blood neutrophil count below 1000/mm³. However, no firm conclusions can be drawn about RTX re-treatment of patients with previous LON, since there was a selection bias in patients who were re-treated, all of whom had previously experienced only mild neutropenia.

**CONCLUSION**

Late-onset neutropenia might occur after RTX in patients with RA and other AIDs, but its incidence is much lower than in patients with blood malignancies. In addition, late-onset neutropenia is usually mild and might not be complicated with infections. Regarding clinical practice, it has been recommended to monitor whole blood count after each cycle of RTX. Since late-onset neutropenia is not frequent, not predictable and of varying onset and duration, and since it rarely results in significant infection, a more pragmatic approach could be to have a blood count performed in the event of fever or infection in the months following RTX treatment.

**Author affiliations**

1Rheumatology Department, CHU Reims, Reims, France
2Department Hospitalo-Universitaire I2B, UPMC Univ Paris 06, CNRS, UMR 7211, INSERM, UMR S 959, Department of Internal Medicine, Groupe Hospitalier Pitié-Salpêtrière (AP-HP), Paris, France
3Rheumatology Department, Lapeyronie University Hospital, Montpellier I, University, UMR535, Montpellier, France
4Rheumatology Department, National Center for Rare Systemic Autoimmune Diseases, Hôpitaux Universitaires de Strasbourg, INSERM UMRs 1109, Université de Strasbourg, Strasbourg, France
5Rheumatology Department, CHU Saint-Etienne, Saint-Etienne, France
6Department of Internal Medicine, Hôpital Jean Verdier, Bondy, France
7Rheumatology Center, Purpan Hospital, Paul Sabatier University, Toulouse, France
8Medicine Faculty, Paris-Descartes University, Paris, UPRES-EA 4058, Cochin Hospital, Rheumatology B, Paris, France
9Department of Internal Medicine, University Hospital of Strasbourg, Strasbourg, France
10Rheumatology Department, GroupeHospitalier Bichat-Claude Bernard (AP-HP), Paris, France
11Department of Internal Medicine, Hôpital D’Instruction des Armées Sainte-Sève 41 Anne, Toulon, France
12Rheumatology Department, CH René Dubos, Pontoise, France
13Centre de Recherche en Épidémologie et Statistiques, INSERM U1153, Centre d’Épidémiologie Clinique, Hôtel Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris (AP-HP), Descartes University, Paris, France
14Department of Internal Medicine, CHR Metz, Metz, France
15Rheumatology Department, Hôpitaux Universitaires Paris-Sud, AP-HP, INSERM U1184, IMVA: Center of Immunology of Viral Infections and Autoimmune Diseases, Paris, France
16Rheumatology Department, National Center for Rare Systemic Autoimmune Diseases, Hôpitaux Universitaires de Strasbourg, CNRS, Institut de Biologie Moléculaire et Cellulaire, Immunopathologie et Chimie Thérapeutique / Laboratory of Excellence Medalis, Université de Strasbourg, Strasbourg, France

**Acknowledgements**

Roche provided an unrestricted educational grant to the French Society of Rheumatology but was not involved in the design, protocol, data collection or statistical analysis of the study. The authors thank all the investigators who have included patients in the AIR registry, the French Society of Rheumatology (SFR), the Club Rhumatismes et Inflammation, the French National Society of Internal Medicine (SNFSI) for their implication in the AIR registry, Rosemary Jourdan (Roche), Jamila Filipceck and Nadine Mackenzie (formerly Roche). They also thank the 14 research study nurses of the AIR registry, Rosemary Jourdan (Roche), Jamila Filipceck and Nadine Mackenzie (formerly Roche).

**Contributors**

All the authors contributed to data collection, interpretation of results and edited the manuscript. IP and PR performed statistical analyses. JHS, JEG and XM initiated the study and wrote the manuscript.
Competing interests None declared.

Patient consent Obtained.

Ethics approval Comité Consultatif sur le Traitement de l’information en matière de Recherche dans le domaine de la Santé.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES