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ORIGINAL RESEARCH

# Risk of severe infection associated with immunoglobulin deficiency under rituximab therapy in immune-mediated inflammatory disease

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## ABSTRACT

**Objectives** We evaluated the risk of severe infection in patients with immune-mediated inflammatory disease (IMID) treated with RTX and with Ig deficiency.

**Methods** This was an observational, retrospective single-centre study of patients undergoing treatment with at least one rituximab (RTX) infusion for an IMID until 31 May 2020. Patients were followed up for at least 12 months after the last infusion or until severe infection or death. Ig deficiency was classified as prevalent (before RTX) or acquired (normal Ig assay results before RTX but Ig deficiency during a follow-up).

**Results** Of 311 patients, 10.6% had prevalent and 19.6% acquired Ig deficiency. Prevalent Ig deficiency was related to concomitant treatment with glucocorticoids (GCs), in particular with a high daily dose at baseline; and acquired Ig deficiency to cumulative dose of RTX, mean Disease Activity Score in 28 joints (DAS28), immunosuppressor or GCs therapy at baseline, diabetes mellitus and obesity. Overall, 14.5% of patients had a severe infection during follow-up, which was numerically but not statistically more frequent in patients with prevalent Ig deficiency than normal Ig level. On multivariate analysis, risk of severe infection was associated with chronic pulmonary disease, GCs dose and mean DAS28-C reactive protein. In a time-dependent analysis, risk of severe infection was not associated with Ig deficiency, either acquired or prevalent (adjusted HR 1.04 (95% CI 0.5 to 2.3), p=0.92).

**Conclusion** Risk of severe infection was not associated with RTX-induced Ig deficiency in patients with an IMID. RTX management should be discussed according to an individual assessment of the infectious risk, especially in patients with GC therapy or chronic lung disease.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Most of the safety data on rituximab (RTX) has been obtained from patients with rheumatoid arthritis (RA) and were reassuring regarding the risk of severe infection related to immunoglobulin deficiency.
⇒ For patients receiving RTX for other immune-mediated inflammatory diseases (IMIDs), data on safety are limited, with most studies including few patients and results being discordant, with still a concern regarding the risk of severe infection linked to hypogammaglobulinaemia in these patients.

### WHAT THIS STUDY ADDS

⇒ Risk of severe infection was not associated with RTX-induced immunoglobulin deficiency in patients undergoing treatment for an IMID, mostly RA.
⇒ Risk of severe infection during RTX treatment was increased in patients with prevalent immunoglobulin deficiency, but was mainly due to confounding factors.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ RTX management should be discussed on a case-by-case basis, according to an individual assessment of the infectious risk, especially in patients with glucocorticoid therapy and chronic lung disease.

## INTRODUCTION

Because of the production of autoantibody and proinflammatory cytokines and their antigen-presenting role for T cells, B cells are relevant therapeutic targets in immune-mediated inflammatory diseases (IMIDs). Rituximab (RTX) is a monoclonal antibody targeting CD20, expressed on the surface of B cells, which leads to their depletion. When RTX binds to CD20, it induces B-cell depletion by multiple mechanisms: direct apoptosis, complement-dependent cellular cytotoxicity, or antibody-dependent cellular cytotoxicity. This drug was first approved in oncohaematology and thereafter in several IMIDs such as rheumatoid arthritis (RA) and Anti Neutrophil Cytoplasmic Antigen (ANCA)-associated vasculitis (AAV: granulomatosis with polyangiitis and microscopic polyangiitis).[1] When conventional therapies

have failed, it is sometimes used off-label in other rheumatological conditions such as systemic lupus erythematosus (SLE), primary Sjogren's syndrome, systemic sclerosis, idiopathic inflammatory myositis and cryoglobulinaemia.[1]

In IMID, targeting B cells leads to reduced autoantibody levels, suppression of autoreactive B cells, and a qualitative and quantitative modification of the B-cell repertoire.[2] However, because B lymphocytes are involved in the adaptative humoral immune system by mediating the production of antigen-specific Ig directed against invasive pathogens, the depletion of peripheral B cells could lead to hypogammaglobulinaemia.[3]

Hypogammaglobulinaemia induced by RTX is inconstant. In RA, registry studies reported reduced IgM level in 20% of patients and reduced IgG level in 5%–10%.[4 5] This situation is even more frequent in other IMIDs, with rates up to 58% and 67% for IgM and IgG, respectively, in AAV.[6] Predictors of hypogammaglobulinaemia linked to RTX in IMID are various and include autoimmune cytopenia, exposure to other immunosuppressive treatments such as mycophenolate mofetil or cyclophosphamide, concomitant treatment with glucocorticoids (GCs) and low IgM level before RTX use.[7] According to the increased risk of severe infection in patients with hypogammaglobulinaemia independent of RTX therapy (eg, in variable common immunodeficiency), concerns were raised about potentially increased risk of severe infection related to hypogammaglobulinaemia induced by RTX in IMID.[8]

Most of the safety data on RTX were obtained from patients with RA. In a randomised controlled trial, the rate of severe infection did not differ between patients with hypogammaglobulinaemia and those with normal IgM level.[4 9 10] Nevertheless, in randomised controlled trials, patients are usually selected, have few comorbidities and do not have concomitant treatment such as GCs. Some real-life evidence showed increased risk of severe infection in RA patients with IgG deficiency before RTX initiation,[4 11] but the risk of severe infection is not clearly established in patients with acquired Ig deficiency under RTX.[11 12] In patients receiving RTX for other IMIDs, safety data are limited, with most studies including a limited number of patients and results being discordant.[13–16]

Because of controversial or sparse evidence, we evaluated the risk of severe infection in patients with IMID treated with RTX who presented Ig deficiency (prevalent or acquired).

## MATERIAL AND METHODS

### Study data

This was an observational, retrospective, single-centre study of all patients receiving at least one infusion of RTX for IMID in the department of rheumatology of Montpellier University Hospital between 1 January 2017 and 31 December 2017. We obtained the list of patients who received intravenous RTX from the pharmacy department and also reviewed the electronic outpatient agenda listing all infusions performed during the year. Subsequently, all patients who received at least one infusion of RTX were systematically screened, and data were collected on their disease course over the total period of treatment with RTX, including previous years. After reviewing medical charts, we included patients who received treatment for an IMID (RA, SLE, AAV, Sjögren syndrome, inflammatory myopathy, systemic scleroderma, mixed connective diseases, cryoglobulinaemia vasculitis, overlap syndrome) with at least one Ig assay performed during follow-up and at least one follow-up visit after the last RTX infusion. Patients were followed up at 12 months after the last RTX infusion or until a severe infection or death occurred within 12 months after an RTX infusion or until the end of the study (ie, 31 May 2020). We used data for all patients who did not express their opposition after receiving an information letter. This study followed the STROBE guidelines for observational studies.

### Data collection

We collected the following data at baseline (defined as the first infusion of RTX):

- Demographic (age, sex).
- Clinical data (comorbidities assessed by the age-adjusted Charlson Comorbidity Index[17]; history of a previous severe infection within 12 months; type and duration of IMID; activity of the IMID, when relevant, assessed by the Disease Activity Score in 28 joints (DAS28)).
- Biological data (immunological status, especially rheumatoid factor and anticitrullinated protein antibodies; lymphopenia defined as leucocyte count <1.5 G/L; erythrocyte sedimentation rate; C reactive protein (CRP); Ig assay results).
- Therapeutic data (previous treatment with intravenous immunoglobulin, previous disease modifying antirheumatic drug (DMARD) exposure, concomitant treatment with convention synthetic DMARDs (csDMARDs; ie, methotrexate (MTX), leflunomide, sulfasalazine and hydroxychloroquine) and/or immunosuppressors (ie, mycophenolate mofetil, cyclophosphamide, azathioprine) and/or GCs (daily dose of GCs)).
- We did not have a standardised protocol for checking immunoglobulins in RTX-treated patients, but we recorded Ig assays results when available.

At each hospitalisation for RTX infusion or at each follow-up visit, we collected data on concomitant treatment with DMARDs and/or GCs, daily dose of GCs, DAS28 and DAS28-CRP, and Ig assays (when performed). We also recorded the number of RTX infusions received and calculated the cumulated doses of RTX during the study.

### Outcomes and definition

A low Ig level was defined as: IgG level <6.5 g/L and/or IgA level <0.7 g/L and/or IgM level <0.3 g/L, and/or

gammaglobulin level <6 g/L. Patients with Ig level lower than laboratory thresholds (IgG<6.9 g/L, IgM<0.34 g/L or gammaglobulin<7.1 g/L) but still over the previous low level definition were considered as subnormal. A very low Ig level was defined as: IgG level <5 g/L and/or IgA level <0.5 g/L and/or IgM level <0.2 g/L, and/or gammaglobulin level <4 g/L. From these data, we defined three groups of patients: patients with Ig deficiency before the first infusion of RTX ('prevalent Ig deficiency' group); patients with normal Ig assay results before the first infusion of RTX and at least one Ig deficiency during follow-up ('acquired Ig deficiency' group); and patients with normal Ig assay results before the first RTX infusion and Ig levels remaining in the normal range during follow-up ('normal Ig level' group). The primary endpoint was the occurrence of a severe infection (defined as an infection leading to hospitalisation and/or requiring parenteral antibiotic therapy and/or leading to death) within 12 months after an RTX infusion. For each severe infection, we collected the type of infection, the time since the last RTX infusion and cotreatment used at the time of the severe infection.

### Statistical analysis

Baseline characteristics and disease evolution are described with mean (SD) or frequency (%) as appropriate. We identified risk factors for acquired Ig deficiency with RTX exposure by comparing characteristics of patients in the acquired Ig deficiency group versus the normal Ig level group with exclusion of the prevalent Ig deficiency group by using univariate analysis ($\chi^2$ test or Fisher's exact test for categorical variables, Mann-Whitney test for quantitative variables). We calculated the incidence rate of severe infection as the number of events over exposure time for all patients and each group. We identified risk factors for severe infection for all patients and each group by using univariate analysis ($\chi^2$ test or Fisher's exact test for categorical variables, Mann-Whitney test for quantitative variables) and in multivariate analyses using Cox models. We compared incidence rates of severe infection between groups using a survival model with Kaplan-Meier curves and a log-rank test after restricting the population to a maximum follow-up of 140 months. This restriction was defined to allow for appropriate statistical applicability of the time-dependent proportional-hazards analysis. Then, we developed multiple Cox proportional-hazards models to control for potential confounders on the restricted population including the type of Ig deficiency (prevalent or acquired), an Ig deficiency at the end of follow-up, a very low Ig deficiency at the end of follow-up and the level of gammaglobulin, or IgG, IgM and IgA at the end of follow-up. Because infection could occur before the occurrence of Ig deficiency, we also performed a time-dependent analysis with Ig level as a time-dependent variable. We used SPSS V.23 for statistical analysis. A p<0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics of patients and follow-up

We identified 357 patients who received RTX for an IMID; 8 patients refused to give consent to participate in the study, and 38 were excluded because of missing data. Finally, 311 patients were included in the study (80.7% female; mean (SD) age 57.9 (12.5) years) (table 1). Most patients had RA (85.9%), SLE (4.2%) and AAV (2.6%). Other IMIDs were systemic sclerosis, mixed connective tissue diseases, inflammatory myositis, Sjögren disease and cryoglobulinaemia vasculitis. Patient characteristics differed across IMIDs (see online supplemental table 1). IMIDs were mostly long-term diseases, with a mean disease duration of 13.4 (10.4) years. About two-thirds of patients concomitantly received a csDMARDs (mostly MTX (39.3%)). More than half of the patients also received GCs at baseline and 16% more than 15 mg/day of prednisone equivalent. Overall, 14% of patients had received at least one immunosuppressor (non-cs- or biological/targeted synthetic DMARDs) before their first RTX infusion, with 4.5% still receiving the immunosuppression with RTX. Of note, only three patients had received intravenous Ig before their first RTX infusion. None of them received intravenous Ig during follow-up. The most common comorbidities were chronic pulmonary disease (28.3%), followed by a history of neoplasia (20.9%), obesity (18.7%), cardiovascular comorbidities (13.5%) and diabetes mellitus (12.9%). Twenty patients (6.5%) had a history of severe infection within 12 months before RTX (table 1). Approximately 40% of patients had lymphopenia (lymphocyte count <1.5 G/L) before the first RTX infusion, but no patient had severe lymphopenia (lymphocyte count <0.5 G/L). IMIDs were moderately active at baseline, with mean DAS28 at 4.5±1.6. Patients were followed up for a mean of 66.6 (84) months, with a total exposure of 1623.7 patient-years (mean cumulative RTX dose of 9.2 (4.9) g), with mean DAS28 at 3.5 (1.3) and daily GC dose 3.2 (4.1) mg/day during follow-up.

### Risk factors for acquiring Ig deficiency under RTX treatment

At the end of follow-up, 103 patients (33.1%) were deficient in gammaglobulin and/or IgG and/or IgM and/or IgA. For nine patients, this deficiency could not be dated. For the other patients, all performed an Ig assay in the year preceding or following the first infusion, including 213 patients (70%) who had been tested within 6 months from the first RTX infusion. A total of 33 (10.6%) patients were in the 'prevalent deficiency' group, mainly with low IgG level (see online supplemental table 2). For six of them, the Ig level continued to decrease after the first RTX infusion. At the end of follow-up, the mean gammaglobulin rate was 5.9±1.4 g/L (median 5.5 (min–max 3.0–11.7)) and the mean IgG rate was 6.2±1.6 g/L (median 5.7 (min–max 3.0–12.3)). Only four patients had IgG<4 g/L at the end of follow-up (see online supplemental file 2). Concomitant GC treatment at baseline was more frequent in patients with prevalent Ig deficiency than normal Ig level at baseline (75% vs 57.6%, p=0.05),

**Table 1** Baseline and follow-up characteristics of patients with immune-mediated inflammatory diseases (IMIDs) receiving rituximab (RTX) in the whole cohort and by Ig level during follow-up

| | All patients (n=311)* | Prevalent Ig deficiency (n=33) | Acquired Ig deficiency (n=61) | Normal Ig level (n=208) | P value† |
|---|---|---|---|---|---|
| Age (years), mean (SD) | 57.9 (12.5) | 61.3 (11.8) | 57.6 (12.3) | 57.5 (12.7) | 0.97 |
| Female, n (%) | 251 (80.7) | 27 (81.8) | 45 (73.8) | 173 (83.2) | 0.09 |
| Duration of follow-up (months), mean (SD) | 66.6 (84.0) | 46.1 (30.8) | 81.1 (37.2) | 64.7 (98.8) | 0.21 |
| IMID | | | | | |
| RA, n (%) | 267 (85.9) | 28 (84.8) | 50 (82.0) | 180 (86.55) | 0.37 |
| SLE, n (%) | 13 (4.2) | 1 (3.0) | 5 (8.2) | 7 (3.4) | 0.15 |
| AAV, n (%) | 8 (2.6) | 1 (3.0) | 3 (4.9) | 4 (1.9) | 0.19 |
| Other IMIDs, n (%) | 23 (7.4) | 3 (9.1) | 3 (4.9) | 17 (8.2) | 0.58 |
| Duration (years), mean (SD) | 13.4 (10.4) | 13.8 (9.6) | 12.4 (10.3) | 13.7 (10.5) | 0.40 |
| Comorbidities | | | | | |
| Charlson Comorbidity Index, mean (SD) | 3.6 (1.9) | 4.3 (2.4) | 3.8 (2.1) | 3.4 (1.8) | 0.13 |
| Cardiovascular disease, n (%) | 42 (13.5) | 9 (27.3) | 7 (11.5) | 25 (12.0) | 0.91 |
| Chronic pulmonary disease, n (%) | 88 (28.3) | 13 (39.4) | 14 (23.0) | 59 (28.4) | 0.40 |
| History of neoplasia, n (%) | 65 (20.9) | 9 (27.3) | 13 (21.3) | 43 (20.7) | 0.91 |
| Obesity (BMI>30 kg/m²), n (%) | 57 (18.7) | 4 (12.1) | 16 (27.6) | 34 (16.6) | **0.06** |
| Diabetes mellitus, n (%) | 40 (12.9) | 6 (18.2) | 12 (19.7) | 22 (10.6) | **0.06** |
| Tobacco exposure, n (%) | 122 (63.9) | 15 (75.0) | 25 (65.8) | 78 (61.4) | 0.62 |
| Previous severe infection within 12 months, n (%) | 20 (6.5) | 6 (18.2) | 1 (1.7) | 13 (6.3) | 0.20 |
| Treatment | | | | | |
| No of prior b/tsDMARDs, mean (SD) | 1.5 (1.5) | 1.5 (1.7) | 1.6 (1.4) | 1.5 (1.5) | 0.54 |
| Combination with csDMARDs, n (%) | 196 (63.6) | 25 (75.8) | 35 (58.3) | 129 (62.6) | 0.55 |
| Combination with immunosuppressor, n (%) | 14 (4.5) | 2 (6.1) | 5 (8.3) | 7 (3.4) | **0.15** |
| Concomitant treatment with GCs, n (%) | 182 (60.1) | 24 (75.0) | 39 (65.0) | 113 (55.4) | **0.18** |
| Daily dose of GCs at baseline (mg/day), mean (SD) | 7.2 (10.4) | 9.2 (9.5) | 6.6 (7.4) | 7.0 (11.1) | 0.81 |
| Daily dose of GCs during follow-up (mg/day), mean (SD) | 3.2 (4.1) | 5.1 (4.2) | 2.6 (2.6) | 3.1 (4.4) | 0.45 |
| Cumulative dose of RTX (g), mean (SD) | 9.2 (4.9) | 7.0 (4.3) | 12.4 (4.4) | 8.5 (4.6) | **<0.001** |
| Disease activity | | | | | |
| DAS28 at baseline, mean (SD) | 4.5 (1.6) | 3.7 (1.3) | 4.7 (1.3) | 4.6 (1.6) | 0.73 |
| Mean DAS28 during follow-up, mean (SD) | 3.5 (1.3) | 3.3 (1.6) | 3.3 (1.0) | 3.6 (1.3) | **0.05** |

Bold values correspond to values associated with a significant difference (or with a trend) between patients with acquired ig deficiency and patients with normal Ig level at baseline and at the end of follow up
*Nine patients had undatable Ig deficiency.
†Comparing acquired Ig deficiency versus normal Ig level.
AAV, Anti Neutrophil Cytoplasmic Antigen (ANCA)-associated vasculitis; BMI, body mass index; b/tsDMARDs, biologic/targeted synthetic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic DMARDs; DAS28, Disease Activity Score in 28 joints; GCs, glucocorticoids; NA, not available; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

with a higher daily dose during follow-up (5.1 vs 3.0 mg/day, p=0.006) (online supplemental table 3). Of note, the proportion of patients with previous immunosuppression treatment was higher for those with than without prevalent Ig deficiency, although not significantly (27.3% vs 24.3%, p=0.69), with no difference regarding previous targeted treatments. History of severe infection in the year before inclusion was higher in patients with prevalent deficiency than patients with normal Ig level at baseline (18.2% vs 5.1%; p=0.01). Patients with prevalent deficiency seemed to be followed for a shorter time (mean 46.1 (30.8) vs 68.4 (88.9) months, p=0.15) and had a lower cumulative RTX dose (mean 7.0 (4.3) vs 9.4 (4.9) g, p=0.007) (see online supplemental table 3).

Overall, 269 patients had normal Ig levels at the time of RTX initiation; 61 (22.7% of those with normal Ig level at baseline) exhibited Ig deficiency after the first RTX infusion, fulfilling the definition of 'acquired deficiency',

Table 2 Incidence of severe infection by Ig category, with low deficiency (gammaglobulin<6.0 g/L and/or IgG<6.5 g/L and/or IgM<0.3 g/L and/or IgA<0.7 g/L)

| | All patients (n=311) | Ig deficiency at the end of follow-up (n=100) | Prevalent Ig deficiency (n=33) | Acquired Ig deficiency (n=61) | Normal Ig level (n=209) |
|---|---|---|---|---|---|
| Severe infection within 12 months after the last RTX infusion, n (%) | 45 (14.5) | 13 (13.0) | 7 (21.1) | 5 (8.2) | 31 (14.8) |
| Exposure, patient-years | 1629.2 | 590.1 | 126.8 | 412.2 | 1023.9 |
| Incidence rate (/100 patient-years) | 2.8 | 2.2 | 5.5 | 1.2 | 3.0 |
| Risk of severe infection compared with patients with normal Ig level during the entire follow-up; crude univariate HR (95% CI)*, p value | NA | 0.6 (0.3 to 1.3), 0.21 | 1.6 (0.7 to 3.5), 0.29 | 0.4 (0.1 to 0.98), 0.02 | Ref. |
| Risk of severe infection compared with patients with normal Ig level during the entire follow-up, adjusted HR (95% CI)*, p value | NA | 0.7 (0.3 to 1.5), 0.34 | 1.0 (0.4 to 2.5), 0.96 | 0.4 (0.1 to 1.3), 0.14 | Ref. |

*Multivariate model, adjusted on the type of IMID, chronic pulmonary disease, diabetes mellitus, previous treatment with immunosuppressor, combination with immunosuppressor at baseline, glucocorticoids at baseline, daily dose of glucocorticoids during follow-up, mean DAS28-CRP during follow-up.
DAS28-CRP, Disease Activity Score in 28 joints-C reactive protein; IMID, immune-mediated inflammatory disease; NA, not available; RTX, rituximab.

mainly IgM level (16.3%, online supplemental table 2). Ig deficiency occurred within 25 months (IQR 14.0–45.0) after the first cycle of RTX, after a median of 3 cycles (2.0–5.0) of RTX, and a median cumulative dose of 5 g (2.4–8.0). At the end of follow-up, the mean gammaglobulin rate was 6.9±1.9 g/L (median 6.4 (min–max 3.3–15.8)) and the mean IgG rate was 7.2±1.8 g/L (median 6.6 (min–max 3.1–15.9)). Only 2 patients had IgG<4 g/L at the end of follow-up (see online supplemental file 2).

On univariate analysis, acquired Ig deficiency was associated increased cumulative dose of RTX (p<0.001) and with a trend for the type of IMID (especially SLE (p=0.15)) and for concomitant treatment with an immunosuppressor (p=0.15) or GCs (p=0.18) at baseline, diabetes mellitus (p=0.06) and obesity (p=0.06) (table 1). Of note, acquired Ig deficiency seemed associated with better response to RTX, with reduced mean DAS28 during follow-up (3.3 (1.0) vs 3.6 (1.3), p=0.05).

## Incidence of severe infection and risk factors associated with severe infection

During follow-up, 45/311 patients had a severe infection within 12 months after a cycle of RTX, representing 14.5% of the whole population and with incidence rate 2.8 per 100 patient-years for a 1629.2 patient-year exposure (table 2). Severe infections occurred after a median of 6 months[3–8] after the last RTX cycle. When severe infection occurred, the median age was 66 (57–72) years. Two-thirds of patients were on combination therapy with a csDMARD (one third on MTX and about 20% on leflunomide). Approximately 42% were on GCs and only 4 patients received a prednisone equivalent ≥15 mg/day. In all, 9% of these patients received RTX along with an immunosuppressive drug. More than 40% of severe infections were pneumonia, followed by urinary tract infections (20.0%), and soft tissue infections (8.9%) (data not shown). There was no death related to severe infection.

On univariate analysis (table 3), risk of severe infection within 12 months after the last RTX infusion was associated with chronic pulmonary disease (p=0.001), previous treatment with an immunosuppressor (p=0.005), concomitant treatment with an immunosuppressor (p=0.04) or GCs (p=0.009) and with a higher daily GC dose during follow-up (p<0.001), increased disease activity (p=0.004) or increased CRP level during follow-up (<0.001) and treatment with an immunosuppressor (p=0.009) or GCs (p<0.001) at the end of follow-up. We found a significant inverse association between the occurrence of severe infection and the number of RTX cycles, cumulative RTX dose and total follow-up duration (log-rank test: p<0.01). Of note, patients with RA presented fewer severe infections than those with other IMIDs (13% for RA vs 25% for other IMIDs; log-rank test: p<0.01 (data not shown).

On multivariate analysis (table 4), the occurrence of severe infection remained associated with the presence of chronic pulmonary disease, increased mean dose of GCs and with a trend with increased mean DAS28-CRP during follow-up (p=0.02, p=0.02 and p=0.09, respectively (model 1)) (table 3). Type of IMID (RA or other IMID) and an immunosuppressive drug at inclusion were not associated with the occurrence of severe infection after adjustment for confounding factors.

Regarding Ig deficiency, in multivariate analysis (table 4), neither the type of Ig deficiency (prevalent vs acquired, model 1), nor an Ig deficiency (model 2) or a very low Ig deficiency (model 3) were associated with the risk of severe infections. Regarding the rate of Ig deficiency, neither gammaglobulin level, nor IgG, IgA or IgM

**Table 3** Risk factors associated with severe infection within 12 months after the last RTX infusion in the whole population (univariate analyses)

| | Severe infection (n=45) | No severe infection (n=266) | P value |
|---|---|---|---|
| Age, mean (SD) | 59.2 (15.2) | 57.7 (12.0) | 0.47 |
| Female, n (%) | 36 (80.0) | 215 (80.8) | 0.90 |
| Duration of follow-up (months), mean (SD) | 41.7 (37.6) | 70.8 (88.9) | **0.03** |
| IMID | | | |
| RA, n (%) | 35 (77.8) | 233 (87.6) | **0.03** |
| SLE, n (%) | 3 (6.7) | 10 (3.8) | 0.41 |
| AAV, n (%) | 1 (2.2) | 7 (2.6) | 1.00 |
| Other IMIDs, n (%) | 6 (13.3) | 17 (6.4) | 0.10 |
| Duration (years), mean (SD) | 13.6 (10.1) | 13.3 (10.5) | 0.87 |
| Comorbidities | | | |
| Charlson Comorbidity Index, mean (SD) | 2.4 (1.1) | 2.1 (1.5) | 0.11 |
| Chronic pulmonary disease, n (%) | 22 (48.9) | 66 (24.8) | **0.001** |
| History of neoplasia, n (%) | 9 (20.0) | 56 (21.1) | 0.87 |
| Obesity (BMI>30 kg/m²), n (%) | 6 (13.6) | 51 (29.5) | 0.35 |
| Diabetes mellitus, n (%) | 7 (15.6) | 33 (12.4) | 0.17 |
| Tobacco exposure, n (%) | 13 (52.0) | 109 (65.7) | 0.185 |
| Previous severe infection within 12 months, n (%) | 3 (6.7) | 17 (6.4) | 1.00 |
| Treatment | | | |
| No of prior b/tsDMARDs, mean (SD) | 1.6 (2.0) | 1.5 (1.4) | 0.67 |
| Previous treatment with immunosuppressor, n (%) | 12 (26.7) | 30 (11.3) | **0.005** |
| Combination with csDMARDs, n (%) | 26 (57.8) | 170 (63.9) | 0.38 |
| Combination with immunosuppressor, n (%) | 5 (11.1) | 9 (3.4) | **0.04** |
| Concomitant treatment with GCs, n (%) | 35 (77.8) | 147 (57.0) | **0.009** |
| Daily dose of GCs at baseline (mg/day), mean (SD) | 9.2 (10.1) | 6.9 (10.4) | 0.17 |
| Daily dose of GCs during follow-up (mg/day), mean (SD) | 5.9 (6.6) | 2.7 (3.3) | **<0.001** |
| Disease activity | | | |
| CRP during follow-up, mean (SD) | 16.3 (27.9) | 8.7 (8.7) | **<0.001** |
| Mean DAS28-CRP during follow-up, mean (SD) | 3.6 (1.5) | 3.1 (0.9) | **0.004** |
| Treatment at the end of follow-up | | | |
| Immunosuppressor, n (%) | 4 (8.9) | 3 (1.1) | **0.009** |
| GCs, n (%) | 19 (42.2) | 49 (18.4) | **<0.001** |
| Daily dose of GCs (mg/day), mean (SD) | 3.9 (6.5) | 1.2 (3.0) | **0.006** |
| csDMARDs, n (%) | 28 (62) | 146 (55) | 0.36 |
| Acquired Ig deficiency, n (%) | 5 (11.6) | 56 (21.6) | 0.13 |
| Prevalent Ig deficiency, n (%) | 7 (16.3) | 26 (10.0) | 0.28 |
| Ig deficiency at the end of follow-up, n (%) | 11 (25.6) | 80 (30.9) | 0.48 |
| Very low Ig deficiency at the end of follow-up (n=100) | 5 (11.9) | 40 (17.0) | 0.41 |
| Gammaglobulin rate at the end of follow-up (g/L), mean (SD); median | 8.7 (4.0) | 8.7 (3.2) | 0.94 |
| IgG rate at the end of follow-up (g/L), mean (SD) | 9.1 (3.7) | 9.0 (3.1) | 0.91 |
| IgM rate at the end of follow-up (g/L), mean (SD) | 0.8 (0.6) | 0.7 (0.8) | 0.40 |
| IgA rate at the end of follow-up (g/L), mean (SD) | 2.5 (1.9) | 2.3 (1.2) | 0.50 |

Bold values correspond to values associated with a significant difference (or with a trend) with severe infections
AAV, Anti Neutrophil Cytoplasmic Antigen (ANCA)-associated vasculitis; BMI, body mass index; b/tsDMARDs, biological or targeted synthetic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic DMARDs; DAS28-CRP, Disease Activity Score in 28 joints-C reactive protein; GCs, glucocorticoids; IMID, immune-mediated inflammatory disease; RA, rheumatoid arthritis; RTX, rituximab; SLE, systemic lupus erythematosus.

**Table 4** Risk factors associated with severe infection within 12 months after the last RTX infusion in the whole population (multivariate analyses)

| | Model 1 aHR (95% CI), p value | Model 2 aHR (95% CI), p value | Model 3 aHR (95% CI), p value | Model 4 aHR (95% CI), p value | Model 5 aHR (95% CI), p value |
|---|---|---|---|---|---|
| IMID | | | | | |
| RA | Ref. | Ref. | Ref. | Ref. | Ref. |
| SLE | 1.2 (0.2 to 7.5), 0.85 | 1.1 (0.2 to 6.7), 0.95 | 1.0 (0.2 to 6.6), 0.96 | 1.1 (0.2 to 7.1), 0.91 | 0.9 (0.1 to 6.3), 0.94 |
| Other IMIDs | 1.1 (0.2 to 4.8), 0.90 | 1.0 (0.3 to 4.5), 0.96 | 1.0 (0.2 to 4.7), 0.96 | 1.2 (0.3 to 5.5), 0.82 | 1.2 (0.3 to 5.7), 0.80 |
| Comorbidities | | | | | |
| Chronic pulmonary disease | **2.5 (1.2 to 5.3), 0.02** | **3.0 (1.4 to 6.4), 0.003** | **2.8 (1.3 to 6.0), 0.01** | **2.6 (1.2 to 5.7), 0.01** | **2.7 (1.2 to 5.9), 0.01** |
| Diabetes mellitus | 1.0 (0.3 to 3.0), 0.98 | 0.9 (0.3 to 2.8), 0.92 | 0.9 (0.3 to 2.7), 0.91 | 0.9 (0.3 to 2.8), 0.95 | 1.0 (0.3 to 3.9), 0.94 |
| Treatment | | | | | |
| Previous treatment with IS | 1.4 (0.6 to 3.3), 0.40 | 1.2 (0.5 to 3.3), 0.58 | 1.7 (0.6 to 3.3), 0.37 | 1.4 (0.6 to 3.3), 0.69 | 1.7 (0.6 to 5), 0.31 |
| Combination with IS | 1.4 (0.1 to 10 0), 0.78 | 1.4 (0.1 to 10), 0.74 | 1.7 (0.1 to 10), 0.70 | 1.4 (0.1 to 10), 0.68 | 1.4 (0.1 to 10), 0.62 |
| Concomitant treatment with GCs | 1.4 (0.5 to 3.9), 0.50 | 1.6 (0.6 to 4.2), 0.38 | 1.1 (0.4 to 3.1), 0.82 | 1.3 (0.5 to 3.5), 0.64 | 1.1 (0.4 to 3.1), 0.86 |
| Daily dose of GCs during follow-up (mg/day) | **1.1 (1.02 to 1.2), 0.02** | **1.1 (1.02 to 1.3), 0.02** | **1.1 (1.03 to 1.3), 0.008** | **1.1 (1.03 to 1.2), 0.01** | **1.1 (1.04 to 1.3), 0.006** |
| Mean DAS28-CRP during follow-up | 1.3 (0.9 to 1.9), 0.09 | 1.3 (0.9 to 1.9), 0.10 | 1.3 (0.9 to 1.9), 0.09 | 1.4 (1.0 to 2.0), 0.07 | 1.3 (0.9 to 1.9), 0.09 |
| Acquired Ig deficiency | 0.6 (0.2 to 2.0), 0.41 | NA | NA | NA | NA |
| Prevalent Ig deficiency | 1.1 (0.3 to 3.3), 0.86 | NA | NA | NA | NA |
| Ig deficiency at the end of follow-up | NA | 0.8 (0.4 to 1.9), 0.71 | NA | NA | NA |
| Very low Ig deficiency at the end of follow-up | NA | NA | 0.7 (0.2 to 2.1), 0.48 | NA | NA |
| Rate at the end of follow-up (g/L) | | | | | |
| Gammaglobulin | NA | NA | NA | 1.0 (0.9 to 1.1), 0.98 | NA |
| IgG | NA | NA | NA | NA | 1.0 (0.9 to 1.1), 0.66 |
| IgM | NA | NA | NA | NA | 1.0 (0.7 to 1.6), 0.94 |
| IgA | NA | NA | NA | NA | 1.2 (0.9 to 1.5), 0.24 |

aHR, in multivariate analysis by Cox model, adjusted on the type of IMID, chronic pulmonary disease, diabetes mellitus, previous treatment with immunosuppressor, combination with immunosuppressor at baseline, GCs at baseline, daily dose of GCs during follow-up, mean-DAS28-CRP during follow-up and: Model 1: The type of Ig deficiency (acquired or prevalent); Model 2: Ig deficiency at the end of follow up; Model 3: Very low Ig deficiency at the end of follow up; Model 4: Gammaglobulin rate at the end of follow-up (g/L); Model 5: IgG, IgM and IgA rate at the end of follow-up (g/L) .
Bold values correspond to values associated with a significant difference (or with a trend) with severe infiection

aHR, adjusted HR; DAS28-CRP, Disease Activity Score in 28 joints-C reactive protein; GCs, glucocorticoids; IMID, immune-mediated inflammatory disease; IS, immunosuppressor; NA, not available; RA, rheumatoid arthritis; RTX, rituximab; SLE, systemic lupus erythematosus.

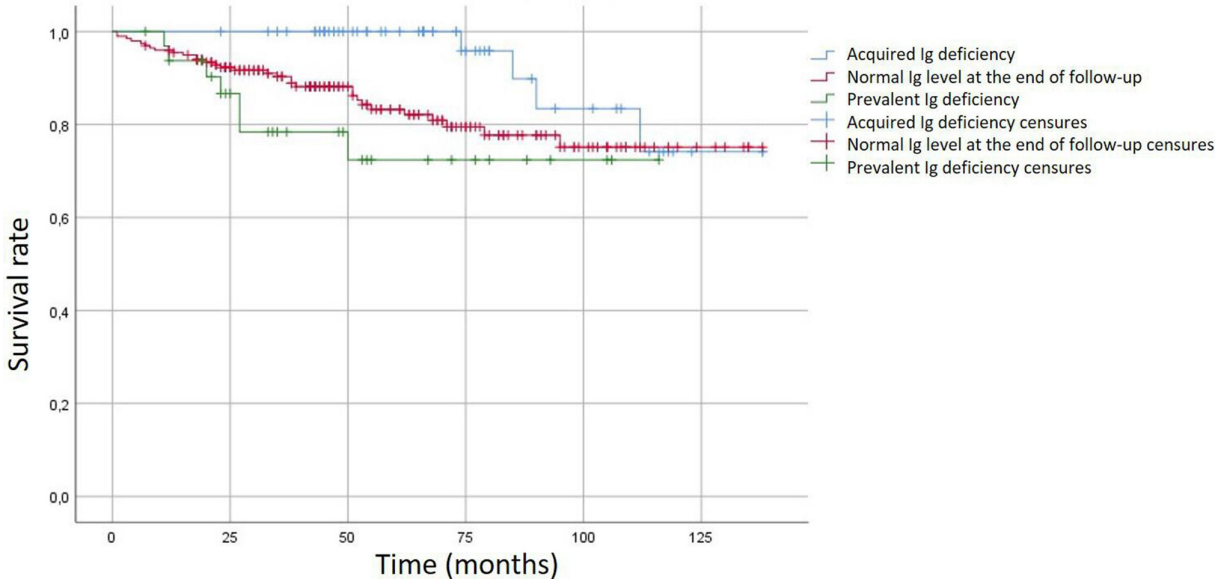


**Figure 1** Occurrence of severe infection according to the presence of prevalent Ig deficiency, acquired Ig deficiency or the absence of Ig deficiency at the end of follow-up (Kaplan-Meier curves, log-rank test, p=0.04).

level were associated with the risk of severe infections (models 4 and 5).

### Incidence of severe infections by Ig category

The crude incidence of infections was 3.0/100 patient-years in the normal Ig group (n=209) and 2.2/) and 2.2/100 patient-years in patients with Ig deficiency at the end of follow-up. Regarding the type of Ig deficiency, the crude incidence of infections was 5.5 and 1.2/100 patient-years in the prevalent Ig deficiency group (n=33), and acquired Ig deficiency group (n=61), respectively (table 2). The incidence rates differed across the three groups (normal, prevalent and acquired deficiency) (figure 1; log-rank test; p=0.04), with a higher infection rate in the prevalent deficiency group than others. Of note, in the acquired Ig deficiency group, considering only the exposure time after the first report of Ig deficiency, the incidence rate of severe infections was 2.9/100 patient-years (similar to that observed in the whole population).

We performed a survival analysis that took into account the date of severe infections and incidence rates of severe infections according to Ig category after restricting the population to a maximum follow-up of 140 months. Thus, we included 294 patients with Ig assay results available in this analysis: 55 patients in the acquired Ig deficiency group, 33 in the prevalent Ig deficiency group and 199 in the normal Ig group. Seven patients were excluded because Ig deficiency was not datable. In the acquired deficiency group, 4 patients (7.2%) experienced a severe infection vs 31 patients (15.6%) in the normal Ig group. In these survival analyses, the incidence of severe infections was significantly higher in the normal Ig level than acquired Ig deficiency group (online supplemental figure 4B), log-rank test; p=0.03). The risk of severe infection was not associated with prevalent Ig deficiency versus normal Ig level before the first infusion of RTX (adjusted HR 1.0 (95% CI 0.4 to 2.5), p=0.96) (table 2). In the crude analysis, risk of severe infection was reduced with acquired Ig deficiency versus normal Ig level during follow-up (crude HR 0.4 (95% CI 0.1 to 0.98), p=0.02) but not after adjustment for confounding factors (adjusted HR 0.4 (95% CI 0.1 to 1.3), p=0.14) (table 2). Similar results were found when we restricted the population to patients with only a very low Ig level at the end of follow-up (online supplemental table 5, figure 6). Nevertheless, the analysis did not take into account the change in Ig level over time. Indeed, infection could occur before the occurrence of Ig deficiency. Therefore, we performed a new analysis, with Ig level status (normal/low) as a time-dependent variable. In this analysis, risk of severe infection was not associated with Ig deficiency, either acquired or prevalent, in patients receiving RTX (adjusted HR 1.04 (95% CI 0.5 to 2.3), p=0.92).

## DISCUSSION

In our study, approximately 15% of patients experienced a severe infection while on RTX. As in other studies, most of these infections were of bronchopulmonary origin. We found a relatively low incidence rate of severe infections (2.6/100 patient-years) despite prolonged follow-up and multiple RTX retreatments. This rate is lower than that found in previous cohort studies such as the AIR-PR registry, even though our population more frequently had pulmonary comorbidities and a history of neoplasia, which both appeared to be risk factors for severe infection in the previous study.[11] However, the proportion of patients on GCs and the mean daily dose at baseline was lower for patients in our study than the previous study. The lower occurrence of severe infections in our study may also be due to an information bias because

data were collected retrospectively with potential omission of information in medical records. Indeed, patients who presented a severe infection may have been cared for outside the Montpellier University Hospital, which may have reduced the rate of severe infections actually recorded.

As observed in previous studies, patients receiving RTX for non-RA IMID had significantly more severe infections than those treated for RA (5.28/100 vs 2.44/100 patient-years, p=0.022). The risk of severe infection with RTX in other IMIDs seemed to be higher with AAV, probably because of the severity of the disease and associated treatments (high-dose GCs and immunosuppression drugs) regardless of RTX. The range of reported incidences of severe infection in AAV was quite large across studies but with a positive association between the cumulative RTX dose and the occurrence of severe infection.[16 18] The occurrence of severe infection with RTX was usually more frequent with other IMIDs (such as SLE and cryoglobulinaemia) than in RA and seemed associated with organ damage, particularly renal lesions, and GCs use.[19 20] This situation may be due to patients with SLE or AAV more often previously receiving a non-DMARD immunosuppressor and a higher dosage of cortisone, especially for vasculitis. In addition, patients with AAV had more pulmonary or renal comorbidities and more history of severe infection.

We then compared the risk of severe infection according to when the deficiency occurred (before and after RTX initiation). Patients with prevalent deficiency had a higher rate of severe infection than those with normal Ig level during follow-up (5.5/100 vs 3.0/100 patient-years) as observed in previous studies.[11 15] Nevertheless, patients with prevalent hypogammaglobulinaemia were more often on GC therapy, with higher doses during follow-up, and were more frequently exposed to an immunosuppressor than patients with normal Ig level. Because these factors were also associated with increased risk of severe infection on multivariate analysis, adjusted specifically on these factors, we did not find an increased risk of severe infection with prevalent Ig deficiency.

Among patients with normal Ig level at the initiation of RTX, one quarter had Ig deficiency after RTX treatment: half with IgM deficiency, one-third with IgG deficiency, and 20% with both. The proportion of patients with acquired IgM deficiency was slightly lower than in other studies of RA patients, despite similar duration of follow-up and mean number of RTX cycles.[7 13] We found an increased risk of acquired Ig deficiency for patients with IMIDs other than RA, especially SLE and AAV, and also with previous non-DMARD immunosuppression drug treatment. Similar results were observed in previous studies.[5 7] Ig deficiency developed under RTX therapy after a mean follow-up of 32 months and a mean cumulative dose of 5.6 g. In contrast to previous studies such as the AIR-PR registry, we did not find an increased risk of severe infection in patients with RTX-acquired Ig deficiency. Moreover, on univariate analysis, acquired Ig deficiency seemed associated with reduced incidence of severe infection. The incidence rate of severe infection in the acquired Ig deficiency group was estimated at 1.5/100 patient-years and was similar between patients with IgG or IgM hypoglobulinaemia. As compared with patients who maintained a normal Ig level, the group with acquired Ig deficiency were followed up significantly longer and received a higher cumulative dose of RTX. This situation could be related to Ig deficiency eventually developing in only patients treated long enough with RTX. On multivariate survival analysis, acquired Ig deficiency was no longer a protective factor for severe infection. Only the presence of pulmonary comorbidities and increased mean dose of GCs remained significantly associated with severe infection.

The strengths of our study are the good representativeness of patients receiving RTX in rheumatology in current practice and a prolonged retrospective follow-up period, allowing to observe the long-term tolerance of RTX. Our study included mainly patients with RA but also a significant proportion receiving treatment for other IMIDs with osteoarticular manifestations. However, subgroup analyses of patients with each type of IMID were not possible because of the small sample sizes in the different autoimmune diseases.

Information bias and missing data are the main limitations of this study because of the retrospective design. However, because severe infections are usually recorded in our centre, even when they occur between two consecutive visits, we believe this bias remains limited. Another limitation is related to the lack of standardised protocol for checking immunoglobulins in RTX-treated patients. Nevertheless, most of them had been tested in the 6 months preceding or following the first RTX. Of note, a cut-off at 4 g/L to consider IgG to be very low/severe would have been more appropriate. Nevertheless, the number of patients who had such low rates were very low (n=6, with four patients in the prevalent group and two patients in the acquired group) which did not allow us to do a statistical analysis with adequate power.

In conclusion, risk of severe infection was not increased in patients with RTX-induced Ig deficiency nor prevalent Ig deficiency before RTX treatment in this cohort of patients with IMIDs, mainly RA. In case of Ig deficiency, RTX management should be discussed on a case-by-case basis, according to an individual assessment of the infectious risk, especially in patients with GC therapy and chronic lung disease. Corticosteroid-sparing must remain an important objective to limit the risk of severe infection.

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