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Hypogammaglobulinemia and Infections in Patients With Multiple Sclerosis Treated With Rituximab

Marine Perriguey, MD, Adil Maarouf, MD, PhD, Jan-Patrick Stellmann, MD, Audrey Rico, MD, PhD, Clemence Boutiere, MD, Sarah Demortiere, MD, Pierre Durozard, MD, Jean Pelletier, MD, PhD, and Bertrand Audoin, MD, PhD

Correspondence
Dr. Audoin
bertrand.audoin@ap-hm.fr

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Abstract

Background and Objectives

To determine the frequency of hypogammaglobulinemia and infections in patients with multiple sclerosis (PwMS) receiving rituximab (RTX).

Methods

This prospective observational study included all consecutive PwMS receiving RTX at the university hospital of Marseille, France, between 2015 and 2020. Patient visits occurred at least every 6 months.

Results

We included 188 patients (151 with relapsing-remitting MS; the mean age was 43.4 years [SD 12.9], median disease duration 10 years [range 0–36], median Expanded Disability Status Scale 5 [range 0–8], median follow-up 3.5 years [range 1–5.8], and median number of RTX infusions 5 [range 1–9]). Overall, 317 symptomatic infections and 13 severe infections occurred in 133 of 188 (70.7%) and 11 of 188 (5.9%) patients, respectively. After 4 years, 24.4% of patients (95% CI 18.0–33.1) were free of any infection and 92.0% (95% CI 87.1–97.1) had not experienced a severe infection. At RTX onset, the immunoglobulin G (IgG) level was abnormal in 32 of 188 (17%) patients. After RTX, IgG level was <7, <6, <4 and <2 g/L for 83 (44%), 44 (23.4%), 8 (4.2%) and 1 (0.53%) patients, respectively. The risk of infection was associated with reduced IgG levels (multivariate Cox proportional hazards hazard ratio [HR] = 0.86, 95% CI 0.75–0.98, p = 0.03). The risk of reduced IgG level <6 g/L increased with age (HR = 1.36, 95% CI 1.05–1.75, p = 0.01).

Discussion

In PwMS receiving RTX, reduced IgG level was frequent and interacted with the risk of infection.

From the Aix Marseille University (M.P., A.M., A.R., C.B., S.D., P.D., J.P., B.A.), APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie; Aix Marseille University (J.-P.S.), APHM, Hôpital de la Timone, Département de Neuroradiologie; Aix Marseille University (A.M., J.-P.S., A.R., C.B., S.D., P.D., J.P., B.A.), CRMBM UMR 7339, CNRS, Marseille, France.

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Glossary

EDSS = Expanded Disability Status Scale; **HR** = hazard ratio; **Ig** = immunoglobulin; **MS** = multiple sclerosis; **PwMS** = patients with multiple sclerosis; **RTX** = rituximab.

B-cell depleting therapy is highly effective against relapsing forms of multiple sclerosis (MS).[1,2] Nonetheless, among disease-modifying therapies for MS, B-cell depleting therapy is associated with the highest risk of infection.[3] Treatment-induced hypogammaglobulinemia contributes to infections in patients with rheumatologic and hematologic diseases and neuromyelitis optica disorders treated with B-cell depleting therapy.[4-6] We do not know whether treatment-induced hypogammaglobulinemia could also be involved and be harmful in patients with MS (PwMS), who are generally younger and with fewer comorbidities than those with other diseases. Pivotal studies[1,7] have demonstrated that hypogammaglobulinemia is infrequent in PwMS during the first years of treatment, but little is known about its potential medium-term incidence in nonselected patients nor about its interaction with the risk of infection.

We report the incidence of hypogammaglobulinemia and infections in PwMS receiving rituximab (RTX) in the MS center of Marseille, France, and followed since their first infusion.

Methods

Study Population

We started to use RTX off-label for PwMS in the MS center of Marseille in 2015. All consecutive patients were prospectively included in an observational study. The induction treatment consisted of 1,000 mg infused twice at 2-week intervals. The maintenance regimen consisted of a single infusion of 1,000 mg administered every 6 months until 2018. After 2018, our department changed the clinical practice concerning the dosing interval used for off-label RTX in relapsing-remitting MS (see reference 8 for more details). We extended the interval between 2 infusions beyond 6 months and up to 24 months, maintaining clinical visits every 6 months and MRI monitoring at least annually.

Medical Visits

Patients visited the center for each RTX infusion, in case of relapse or adverse events, and at least every 6 months. In case of fever, patients had to inform our department at any time. All examinations were performed by the same neurologist of our department (A.R., C.B., A.M., J.P., or B.A.) and included a standardized screening for infection, the most frequent potential adverse event associated with RTX. All infections were graded by using the Common Terminology Criteria for Adverse Events v4.0: grade 1, asymptomatic; grade 2, localized or noninvasive intervention indicated; grade 3, intravenous antibiotic, antifungal, or antiviral drugs indicated, interventional radiology or surgical intervention indicated; grade 4, life-threatening events; and grade 5, death. To be retained as a symptomatic infection (grade ≥ 2), a clinical event must be characterized by physical signs suggestive of infection and fever or positive radiographic or positive laboratory findings.

Serum Levels of Immunoglobulins

Immunoglobulin (Ig) levels were measured before RTX onset and at least every 6 months. Four categories of IgG levels were defined: normal level, ≥7 g/L; reduced IgG level 1, 6–7 g/L; reduced IgG level 2, 4–6 g/L; reduced IgG level 3, 2–4 g/L; and reduced IgG level 4, ≤2 g/L. Corresponding levels for IgM were <0.4 g/L and for IgA <0.7 g/L.

Statistical Analysis

Multivariate Cox proportional hazard models for recurrent events were used to assess the risk of symptomatic infection. Variables tested were age, disease duration, Expanded Disability Status Scale (EDSS) score, sex, and levels of Igs. To account for intraindividual correlation of observations, we included patient ID as a cluster variable. We investigated the occurrence of reduced Ig levels during RTX treatment with similar multivariate models. Hazard ratios (HRs) and 95% CIs were computed for the following variables: age, sex, and disease-modifying therapy with an immunosuppressive action before RTX. We used the Schoenfeld test to check for possible violations of the proportional hazard model. R v4.0.2, including the survival package, was used for statistical analysis, and $p < 0.05$ was considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

The authors obtained ethical approval of the institutional review board of the university hospital of Marseille, France (approval no.: RGPD/Ap-Hm 2021-19), to conduct this study.

Data Availability

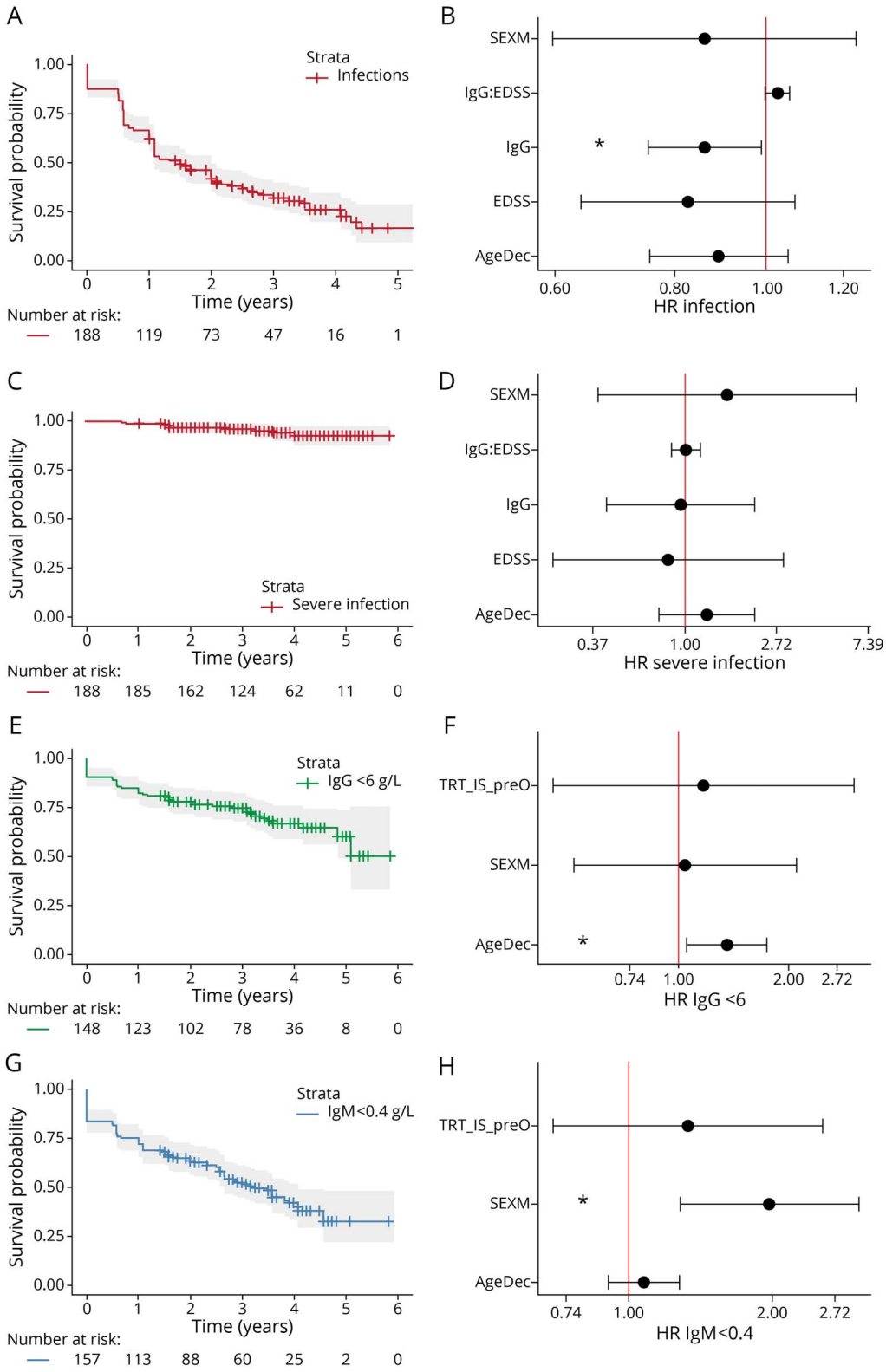
All data analyzed during this study will be shared anonymized by reasonable request of a qualified investigator to the corresponding author.

Results

Study Population

In total, 188 patients received RTX and were followed in our department since 2015; 151 (80.5%) had relapsing-remitting MS, 20 (10.5%) secondary progressive MS, and 17 (9%) primary progressive MS. RTX was used as first-line therapy in 18 patients; 159 (84.6%) patients received at least 1 disease-modifying therapy with an immunosuppressive action before RTX. At RTX onset, the mean age of patients was 43.4 years (SD 12.9), sex ratio 1.7 (F/M; 118/70), median disease duration 10 years (range 0–36), and median EDSS score 5

Figure Time in Years to First Infection or Hypogammaglobulinemia and Predictors



Time in years to first symptomatic infection (Common Terminology Criteria for Adverse Events v4.0, grade ≥2) (A) first severe infection (grade ≥3), (C) first reduced serum immunoglobulin G (IgG) level <6 g/L, (D) and first reduced serum immunoglobulin M (IgM) level <0.4 g/L in patients with multiple sclerosis treated with rituximab (RTX) (G). Predictors of symptomatic infections, (B) severe infections, (D) hypogammaglobulinemia of IgG and IgM after RTX onset, (F) and (H) respectively. Reduced IgA level <0.7 g/L was uncommon at baseline and during the follow-up (figure not reported). A similar model for IgM did not detect any association between the serum level and infections (figure not reported). Data in B, D, F and H are hazard ratios (HRs) (95% CIs). AgeDec = age per decade; EDSS = Expanded Disability Status Scale score; SEXM = sex male; TRT_IS_preO = treatment with an immunosuppressive action before RTX onset.

Table Symptomatic Infections (Common Terminology Criteria for Adverse Events v4.0 grade ≥ 2), Including 13 Severe Infections (grade ≥3), After Rituximab (RTX) Treatment

Type of infection	Episodes
Urinary tract infection	132 (41.5%)
Upper respiratory tract infection	82 (26%)
Lower respiratory tract infection	44 (14%)
Skin infection	24 (7.5%)
Gastrointestinal infection	10 (3%)
Genital infection	10 (3%)
Nonlocalized infectious syndrome	7 (2%)
Buccodental infection	6 (2%)
Ocular infection	1 (0.5%)
Enterovirus meningitis	1 (0.5%)
Total	317

Severe infections included 5 urinary tract infections, 3 lower respiratory tract infections, 1 ocular infection, 1 enterovirus meningitis, 1 upper respiratory tract infection, 1 gastrointestinal infection, and 1 skin infection.

(range 0–8). The median follow-up after the first RTX infusion was 3.5 years (range 1–5.8), and the median number of RTX infusions 5 (range 1–9).

Eleven patients stopped RTX during the follow-up because of severe infection (n = 5), hypogammaglobulinemia (n = 1), psoriasis (n = 1), inflammatory bowel disease (n = 1), stroke (n = 1), myocardial infarction (n = 1), and toxidermia (n = 1). Eight patients were lost to follow-up.

Frequency of Reduced Levels of Igs

Before and after RTX onset, 32 (17%) and 83 (44%) of the 188 patients showed reduced IgG level <7 g/L, 14 (7.4%) and 44 (23.4%) reduced IgG level <6 g/L, 1 (0.53%) and 8 (4.2%) reduced IgG level <4 g/L, and none and 1 (0.53%) reduced IgG level <2 g/L (Figure). At baseline, 26 (14.1%) patients had an IgM level <0.4 g/L, but no patient had a level <0.2 g/L. During the follow-up, 16 (8.6%) patients had an IgM <0.2 g/L and 67 (35.8%) from 0.2 to 0.4 g/L. Reduced IgA level <0.7 g/L was uncommon at baseline (n = 10, 5.4%) and during the follow-up (n = 23, 12.3%).

Frequency of Infections After RTX Onset

After RTX onset, 133 of 188 (70.7%) and 11 of 188 (5.9%) patients had 317 symptomatic infections (grade ≥2) and 13 severe infections (grade ≥3), respectively, with a median number of symptomatic infections per patient of 1 (range 0–16) (Table). Half of the patients had at least one infection after 1.5 years. After 4 years, 24.4% of patients (95% CI 18.0–33.1) were free of any infection and 92.0% (95% CI 87.1–97.1) had not experienced a severe infection.

Predictors of Symptomatic Infection and Hypogammaglobulinemia After RTX

High IgG level was associated with the reduced risk of infection (HR = 0.86, 95% CI 0.75–0.98, $p = 0.029$), with no predictive value of age (HR = 0.89, 95% CI 0.75–1.05, $p = 0.162$), EDSS score (HR = 0.83, 95% CI 0.64–1.07, $p = 0.143$), male sex (HR = 0.86, 95% CI 0.60–1.24, $p = 0.415$), or interaction between IgG level and EDSS score (HR = 1.02, 95% CI 0.99–1.05, $p = 0.122$). Similar models for IgM did not detect any association between serum levels and infections. The risk of reduced IgG level <6 g/L increased with age (HR = 1.36, 95% CI 1.06–1.75, $p = 0.016$) but was not associated with sex (HR = 1.05, 95% CI 0.52–2.11, $p = 0.902$) or history of immunosuppressive treatment (HR = 1.17, 95% CI 0.46–3.02, $p = 0.742$). IgM level <0.4 g/L was more common in men vs women (HR = 1.98, 95% CI 1.28–3.04, $p = 0.002$) but was not associated with age (HR = 1.07, 95% CI 0.90–1.28, $p = 0.421$) or history of immunosuppressive treatment (HR = 1.33, 95% CI 0.69–2.56, $p = 0.392$). All patients with IgA level <0.7 g/L had a history of immunosuppression, but sex and age were not associated. All HRs were stable over time.

Discussion

In our study, 23.4% and 4.2% of PwMS, who received a median number of 5 RTX cycles (range 1–9), showed reduced IgG level <6 and <4 g/L. During this period, 70.7% of patients experienced at least 1 symptomatic infection and 5.9% at least 1 severe infection. Importantly, we demonstrate that IgG level interacted with the risk of infection.

Recently, data were published from the open-label extension of the phase 3 study testing ocrelizumab in relapsing-remitting MS.[9] The study revealed that at 5 years, 5.4% of the patients who completed the study had an IgG level <5.68 g/L. However, the authors did not compare the incidence of reduced IgG level between patients who received ocrelizumab from the study onset (5 years) or after 3 years. Moreover, the frequency of hypogammaglobulinemia reported at 5 years may be underestimated owing to a potential high incidence of reduced IgG level in patients who did not complete the study. In a recent retrospective study of a large sample of PwMS receiving RTX or ocrelizumab, 3.7% showed a reduced IgG value < 5 g/L after a mean exposure of 29.7 months (SD 21).[10] As we demonstrated, this study found that IgG level interacted with the risk of infection.

The observational design of this study and the absence of a control group prevent firm conclusions about the incidence of hypogammaglobulinemia and infections directly related to treatment. Moreover, the rather short observation time might have restricted the ability to detect an increase in risk of hypogammaglobulinemia with longer treatment duration. However, the present findings highlight the need to regularly monitor Ig levels in PwMS receiving B-cell depleting therapy to potentially reduce the risk of infection.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Marine Perriguey, MD	Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France	Major role in the acquisition of data
Adil Maarouf, MD, PhD	Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, 13005 Marseille, France; Aix-Marseille University, CRMBM UMR 7339, CNRS, Marseille, France	Drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, and study concept or design
Jan-Patrick Stellmann, MD	Aix Marseille Univ, APHM, Hôpital de la Timone, Département de Neuroradiologie, Marseille, France; Aix-Marseille University, CRMBM UMR 7339, CNRS, Marseille, France	Analysis or interpretation of data
Audrey Rico, MD, PhD	Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France; Aix-Marseille University, CRMBM UMR 7339, CNRS, Marseille, France	Major role in the acquisition of data and study concept or design
Clemence Boutiere, MD	Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France; Aix-Marseille University, CRMBM UMR 7339, CNRS, Marseille, France	Major role in the acquisition of data and study concept or design
Sarah Demortiere, MD	Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France; Aix-Marseille University, CRMBM UMR 7339, CNRS, Marseille, France	Major role in the acquisition of data
Pierre Durozard, MD	Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France; Aix-Marseille University, CRMBM UMR 7339, CNRS, Marseille, France	Major role in the acquisition of data
Jean Pelletier, MD, PhD	Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France; Aix-Marseille University, CRMBM UMR 7339, CNRS, Marseille, France	Major role in the acquisition of data and study concept or design
Bertrand Audoin, MD, PhD	Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France; Aix-Marseille University, CRMBM UMR 7339, CNRS, Marseille, France	Drafting/revision of the manuscript for content, including medical writing for content, study concept or design, and analysis or interpretation of data

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