Multiple Sclerosis and Related Disorders 93 (2025) 106191

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Hypogammaglobulinemia and severe infections in Multiple Sclerosis patients on anti-CD20 agents: A multicentre study

K. Smolik [a], F. Camilli [b], I. Panzera [b], A. Fiore [c], A. Franceschini [c], M. Foschi [d,e], A. Surcinelli [d], I. Pesci [f], C. Ferri [g], V. Bazzurri [h], L. Mancinelli [i], C. Zini [j], A.M. Simone [k], A. Lugaresi [b,l], F. Falzone [l], F. Granella [c,m], M.G. Piscaglia [d], A. Guareschi [f], E. Baldi [g], P. Immovilli [h], S. Montepietra [i], M. Santangelo [j], N. Poma [a], M. Cardi [a], G. De Napoli [a], F. Vitetta [m], D. Ferraro [m,*]

[a] Department of Biomedical, Metabolic and Neurosciences, University of Modena and Reggio Emilia, Modena, Italy
[b] Department of Biomedical and Neuromotor Sciences, Università di Bologna, Bologna, Italy
[c] Neurosciences Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy
[d] Department of Neuroscience, Neurology Unit, S. Maria delle Croci Hospital, AUSL Romagna, Ravenna, Italy
[e] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[f] Multiple Sclerosis Center, Neurology Unit, Vaio Hospital, Azienda Unità Sanitaria Locale, Parma, Italy
[g] Department of Neuroscience, St. Anna University Hospital, Ferrara, Italy
[h] Neurology Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy
[i] Neurology Unit, Bufalini Hospital, AUSL Romagna, Cesena, Italy
[j] Neurology Unit, Neuromotor and Rehabilitation Department, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
[k] Neurology Unit, Ramazzini Hospital, Carpi, Italy
[l] IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
[m] Multiple Sclerosis Center, Ospedale Civile Baggiovara, Azienda Ospedaliero Universitaria di Modena, Modena, Italy

ARTICLE INFO

Keywords:
Hypogammaglobulinemia
Anti-CD20
Ocrelizumab
Rituximab
Multiple sclerosis
Infections

ABSTRACT

Background: Hypogammaglobulinemia (HG) is a known side effect of treatment with anti-CD20 monoclonal antibodies, and it is associated with the risk of infections.
Objectives: Aim of this retrospective multicentre study was to assess the frequency of HG in Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder patients treated with Ocrelizumab or Rituximab and its association with the occurrence of severe infections (SI). Furthermore, predictors of HG and SI were sought.
Methods: We included 556 patients (190M, 366F, mean age: 47 years) with a mean follow-up of 28 months (range 12-90 months).
Results: IgG HG occurred in 20% and IgM HG in 34% of patients. At multivariable analysis, the risk of IgG HG was influenced by an older age (≥50 years) (OR 1.64, 95%CI: 1.06-2.54, p=0.027), and by the number of treatment cycles (OR: 1.20, 95%CI: 1.09-1.33, p<0.001).
A total of 25 SI occurred (100 person-years rate: 1.8), with a disease phenotype other than relapsing-remitting (OR 1.50, 95%CI: 1.02-2.20; p=0.039) and IgG HG (OR 2.65, 95%CI: 1.15-6.12; p=0.022) increasing its risk.
Conclusions: IgG and IgM HG occurred in a considerable proportion of patients. IgG HG increased the risk of SI, which were, nevertheless, relatively infrequent. Our results highlight the importance of monitoring immunoglobulin levels during treatment with anti-CD20 agents, to personalize treatment strategies.

1. Introduction

Anti-CD20 monoclonal antibodies (mAbs) have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for patients with Relapsing-Remitting Multiple Sclerosis (RRMS) (Ocrelizumab (OCR) and Ofatumumab (OFT)) and Primary Progressive Multiple Sclerosis (PPMS) (OCR) while Rituximab (RTX) is widely used as off-label treatment for both RRMS and Secondary Progressive Multiple Sclerosis (SPMS)/PPMS (Hauser and Cree, 2020) as well as for Neuromyelitis Optica Spectrum Disorder (NMOSD)

* Corresponding author.
E-mail address: diana.ferraro@unimore.it (D. Ferraro).

https://doi.org/10.1016/j.msard.2024.106191
Received 9 June 2024; Received in revised form 15 November 2024; Accepted 23 November 2024
Available online 24 November 2024

(Barreras et al., 2022).

Hypogammaglobulinemia (HG) is a known adverse event of treatment with anti-CD20 monoclonal antibodies (mAbs) (Avouac et al., 2021; Habek et al., 2022; Perriguey et al., 2022). Its prevalence increases with time on treatment, and it is associated with the risk of infections (Saidha et al., 2023).

According to various studies, predictors of HG might be previous immunosuppression (Habek et al., 2022; Kim et al., 2022), use of RTX versus OCR (Mears et al., 2023), greater age (Mears et al., 2023), treatment duration (Kim et al., 2022), body mass index (BMI) (Kim et al., 2022), mean annual RTX dose (Kim et al., 2022) and baseline IgG HG (Kim et al., 2022; Mears et al., 2023).

While there is accumulating data on HG on RTX in MS patients (Kim et al., 2022; Mathew et al., 2020; Perriguey et al., 2022), there is less data on OCR, and studies often include relatively short follow-up periods (Habek et al., 2022; Szepanowski et al., 2021). Information on the safety profiles of the different anti-CD20 mAbs used in the treatment of MS can be useful for therapeutic decisions and for the implementation of de-risking strategies.

In this multicentre retrospective study, we assessed the frequency of HG in MS and NMOSD patients treated for at least one year with either OCR or RTX and its association with the occurrence of SI. Our secondary aims were to identify predictors of HG and of SI.

2. Methods

This multicentre retrospective study was conducted among 10 MS centres in Emilia-Romagna, Italy.

Adult patients with a diagnosis of MS, according to the 2017 McDonald criteria, as well as patients with an NMOSD diagnosis, according to the most recent criteria available at the time of disease onset (Wingerchuk et al., 2015, 2006), with at least one year of treatment with OCR or RTX (at least 2 infusional cycles) and with an available baseline dosage of immunoglobulin (Ig) G and M were enrolled during routine clinical visits. Data on infections were collected during routine follow-up clinical visits. Exclusion criteria were unwillingness/inability to provide informed consent, previous body irradiation/bone marrow transplantation and inherited immunoglobulin deficiencies.

Demographics, clinical and laboratory data were routinely collected at the time of OCR/RTX infusions and in case of relapses or serious adverse effects (SAE).

All infections were classified according to the Common Terminology Criteria for Adverse Events v5.0 (Cancer Institute, 2017). We considered infections of grade $\geq$3 to be severe (requiring hospitalization).

Ig levels were measured, according to local clinical practice, before anti-CD20 start and at least every 6 months. IgG levels $\geq$ 700 mg/dL were considered to be normal. Corresponding levels for IgM and IgA were 40 mg/dL and 70 mg/dL, respectively.

We considered Mitoxantrone (MITO), Azathioprine (AZT), Cladribine (CLAD), Alemtuzumab (ALEM), Cyclophosphamide (CFM) and Methotrexate (MTX) as immunosuppressive therapies.

The study protocol (n. 0018647/22) was approved by the Ethical Committee of the coordinating centre (Emilia-Romagna north (AVEN)) and by the Ethical Committees of all participating centres (Emilia-Romagna centre and Romagna).

3. Statistics

Differences between groups were assessed using the Chi-squared, T-test and the Wilcoxon sum of ranks test, as appropriate. Predictive factors for HG and for SI were investigated using univariate and multivariable logistic regression. Time to HG and SI was calculated using survival analysis Kaplan-Meier curves and COX regression. We used Poisson regression to calculate the incidence rate ratio (IRR).

STATA 16 software (StataCorp, Texas) was used for statistical analysis and $p<0.050$ was considered statistically significant.

4. Results

4.1. Study population

We included 556 patients who fulfilled inclusion criteria: 533 MS patients (286 RRMS, 149 SPMS, 98 PPMS) and 23 NMOSD patients.

Of these, 399 were on OCR and 157 on RTX. Baseline clinical and demographic characteristics as well as differences between groups, are shown in Table 1.

Mean follow-up duration was 27.81 months (26.41 on OCR and 31.38 on RTX, $p<0.001$). Patients on OCR were treated with 5.12±1.93 infusional cycles, with a mean dosing interval of 6.58±1.16 months, while patients on RTX carried out 5.18±2.33 infusional cycles with a mean dosing interval of 8.22±3.69 months (*p* not significant and $p<0.001$, respectively). The majority of patients followed a standardized dosing protocol: initial dose of 1000 mg of RTX repeated after 2 weeks and thereafter dosing intervals based on CD19+ counts which were controlled 6 months after the infusion and repeated monthly until reaching CD19+ levels $\geq$1% of total lymphocytes. Sixty-seven patients (12%) were previously treated with immunosuppressive therapies.

Only 2/458 patients with available CD19+ counts had low baseline

Table 1
Demographic characteristics of patients.

Characteristics	Overall population (n=556)	OCR patients (n=399)	RTX patients (nr=157)	p value
Age, y, mean (SD)	47 (12)	45 (11)	53 (12)	<0.001
Sex, n (%)	366 (66%) female, 190 (34%) male	257 (64%) female, 142 (36%) male	109 (69%) female, 48 (31%) male	ns
Clinical phenotype, n (%)	286 (51%) RRMS 149 (27%) SPMS 98 (18%) PPMS 23 (4%) NMOSD	256 (64%) RRMS 58 (15%) SPMS 84 (21%) PPMS 1 (0%) NMOSD	30 (19%) RRMS 91 (58%) SPMS 14 (9%) PPMS 22 (15%) NMOSD	<0.001
Disease duration in years, mean (SD)	11 (9)	10 (8)	15 (11)	<0.001
No. of previous DMTs (%)	none: 87 (16%), one: 298 (54%) two: 89 (16%) Three or more: 80 (14%)	none: 67 (17%) one: 223 (56%) two: 60 (15%) three or more: 48 (12%)	none: 20 (13%) one: 75 (48%) two: 29 (19%) three or more: 32 (20%)	<0.001
Follow-up duration in months, mean (SD), [range]	27.81 (13.65), [12-90]	26.41 (11.53), [12-57]	31.38 (17.48), [12-90]	<0.001
Mean EDSS at anti-CD20 start (SD)	3.85 (2.03)	3.56 (1.88)	4.70 (2.22)	<0.001
Last DMT, n (%)	None 141 (25%), injective: 76 (14%), DMF: 63 (11%), TERI: 36 (6%), SF1: 67 (12%), MITOX: 7 (1%), AZT: 39 (7%), CLAD: 7 (1%), ALEM: 5 (1%), NAT: 104 (19%), CFM: 9 (2%), MTX: 1 (0%)	None 101 (25%), injective: 55 (14%), DMF: 53 (13%), TERI: 19 (5%), SF1: 52 (13%), MITOX: 2 (1%), AZT: 19 (5%), CLAD: 5 (1%), ALEM 5 (1%), NAT: 82 (21%), CFM: 5 (1%), MTX: 1 (0%)	None 40 (26%), injective: 21 (13%), DMF: 10 (7%), TER: 17 (11%), SF1: 15 (10%), MITOX: 5 (3%), AZT: 20 (13%), CLAD: 2 (1%), NAT: 22 (14%), MTX: 4 (3%)	<0.001

CD19+ counts (<10 cells/uL). After treatment start, as many as 67% of patients presented persistent depletion (<10 cells/uL) of CD19+ levels: 238/335 patients (71%) on OCR and 71/123 patients (58%) on RTX, p=0.007.

Forty-three patients on OCR (11%) and 53 patients on RTX (34%, p<0.001) relapsed during follow-up. Serious adverse events (SAEs) other than infections recorded during follow-up were 13 neoplasms, 9 of which were malignant: 2 cervical cancers, 2 bladder cancers, 2 melanomas, 1 bowel cancer, 1 endometrial cancer, 1 breast cancer and 4 were benign: 1 uterine fibroid,1 Becker's nevus, 1 thyroglossal duct cyst, 1 intraductal papillary mucinous neoplasm. The incidence of malignancies was 699 per 100,000 person-years.

As regards other SAEs, one case each of bullous pemphigoid, severe liver enzyme elevation, severe lymphopenia, seronegative arthritis, and severe leukopenia were reported.

4.2. Frequency of HG

Before anti-CD20 start, 51/556 patients (9%) showed slightly reduced IgG levels, comprised between 600 and 700 mg/dL, with most of them (40/50 - 80%) presenting with IgG HG also during treatment. We did not find a statistically significant difference in the proportion of patients with reduced baseline IgG levels between patients who previously underwent immunosuppressive therapy and those who did not.

As regards baseline IgM levels, 35/556 patients (6%) had reduced IgM levels (<40 mg/dL and 8 out of 481 patients, for whom data was available (2%), reduced IgA levels (<70 mg/dL).

During treatment, 111/556 patients (20%) developed IgG HG, 187/556 patients (34%) developed IgM HG and 37/481 patients (8%) IgA HG. In all cases, HG was more frequent in RTX versus OCR-treated patients (Table 2).

Among all patients with IgG HG during follow-up, 3 patients (1%) had IgG levels lower than 400 mg/dL (minimum value 359 mg/dL), 18 patients (3%) had minimum IgG levels between 400 mg/dL and 500 mg/dL, 37 patients (7%) had minimum IgG levels between 500 mg/dL and 600 mg/dL and further 53 patients (10%) between 600 mg/dL and 700 mg/dL.

Mean levels of both IgG and IgM decreased over time and the decrease was more rapid and frequent for IgM as opposed to IgG (see Figs 1 and 2).

4.3. Time to HG

We assessed the time to reach HG using Kaplan-Meier survival analysis in patients on OCR and on RTX. Log-rank tests for equality of survivor functions were performed. Curves did not differ significantly for IgG HG (fig. 3, p=0.170) but they did for IgM HG (Fig. 4, p=0.002).

As the exposure time to both drugs differed significantly, Poisson regression that corrects this data for the follow-up duration was performed. There was a near-significantly greater IRR for IgM HG in RTX-treated patients (IRR=0.76 for OCR and 1.31 for RTX, p=0.074). IRR for IgG HG was 0.83 for OCR and 1.20 for RTX (p=0.346).

4.4. Frequency of infections and SI

After anti-CD20 initiation, 213 out of 556 patients (38%) presented 357 infections. There was no significant difference in the proportion of patients who developed infections between the two drugs as 152/399 patients on OCR (38%) developed 240 infections compared to 61/157 (39%) patients on RTX who developed 117 infections. The rate of infections per 100-person years was 26.3 per 100-person years (25.9 for OCR and 27.1 for RTX; p not significant).

Twenty-five patients presented SI: 17 on OCR (4%) and 8 on RTX (5%). The rates of SI per 100-person years were respectively 1.84 and 1.86 (p not significant).

Among SI the most frequent ones were Covid19-related pneumonias (n=19, 76% of all SI, with one death) followed by viral encephalitis (n=2, 8% of all SI) (Table 3).

Table 2
Incidence of IgG/IgM/IgA HG during treatment.

Type of HG	n (% of patients)	% of OCR patients	% of RTX patients	*p* value
IgG	111/556 (20%)	71/399 (18%)	40/157 (25%)	0.041
IgM	187/556 (34%)	116/399 (29%)	71/157 (45%)	<0.001
IgA	37/481* (8%)	19/345* (6%)	18/136* (13%)	0.004

4.5. Predictors of HG

Table 1S (supplementary material) shows factors predicting IgG HG at univariate analysis.

Significantly associated variables (p<0.050) from the univariate analysis were included in multivariate analysis. The use of RTX (versus OCR) was associated with a significantly higher risk of HG in univariate analysis, which was not confirmed at multivariate analysis (OR 1.36, 95%CI: 0.86-2.16, p=0.191), while an independent association for age ≥ 50 years (OR 1.64, 95%CI: 1.06-2.54, p=0.027), and for the number of infusional cycles (OR: 1.20, 95%CI: 1.09-1.33, p<0.001) was confirmed. We did not include baseline HG in the analyses due to the substantial overlap between baseline HG and HG during treatment.

Table 2S (supplementary material) shows factors predicting IgM HG at univariable analysis. Significantly associated variables (p<0.050) were included in the multivariable analysis which confirmed an independent association only for the use of RTX versus OCR (OR 1.87, 95% CI:1.26-2.76, p=0.002), and for the number of infusional cycles (OR 1.11, 95%CI: 1.02-1.21, p=0.021).

4.6. Predictors of infections and SI

Table 4 shows the variables included in the univariate logistic regression. At multivariable analysis, only IgG HG (OR 2.65, 95%CI: 1.15-6.12; p=0.022) at any time during treatment and the disease phenotype (progressive phenotype or NMOSD versus RRMS) (OR 1.50, 95%CI:1.02-2.20; p=0.039) increased the risk of a SI (grade≥3). In particular, SI were developed by 4% of PPMS patients, 7% of SPMS patients, 3% of RRMS patients and 9 % of NMOSD patients (p=0.122).

A sub-analysis showed that severe IgG HG, defined as IgG<500 mg/dL, was the only statistically significant variable for a higher OR for SI at multivariate analysis (OR 4.75, 95%CI: 1.42-15.85, p=0.011).

While reduced IgM levels in themselves did not increase the risk of a SI (OR 1.12, 95%CI: 0.52-2.57, p=0.798), the co-occurrence of IgG and IgM HG further increased the odds of a SI (OR 3.30, 95%CI:1.32-8.24; p=0.011).

4.7. Predictors of non COVID-related SI

Table 3S (supplementary material) shows factors predicting severe non-COVID related infections. Only IgG HG turned out to be a statistically significant predictor (OR 5.51, 95%CI: 1.21-24.98, p=0.027).

4.8. Predictors of recurrent infections

At multivariate analysis only the number of treatment cycles (OR 1.31, 95%CI: 1.12-1.52, p=0.001) influenced the risk of having recurrent infections (at least 3 infections during follow-up). Results of univariate analysis are shown in table 4S (supplementary material).

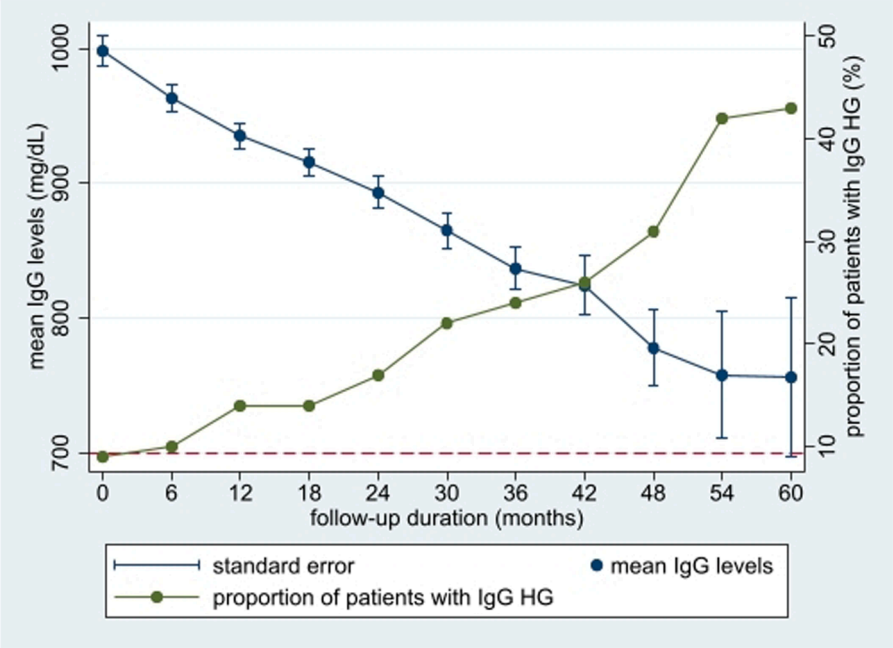

Fig. 1. Mean IgG levels and proportion of patients with IgG HG.

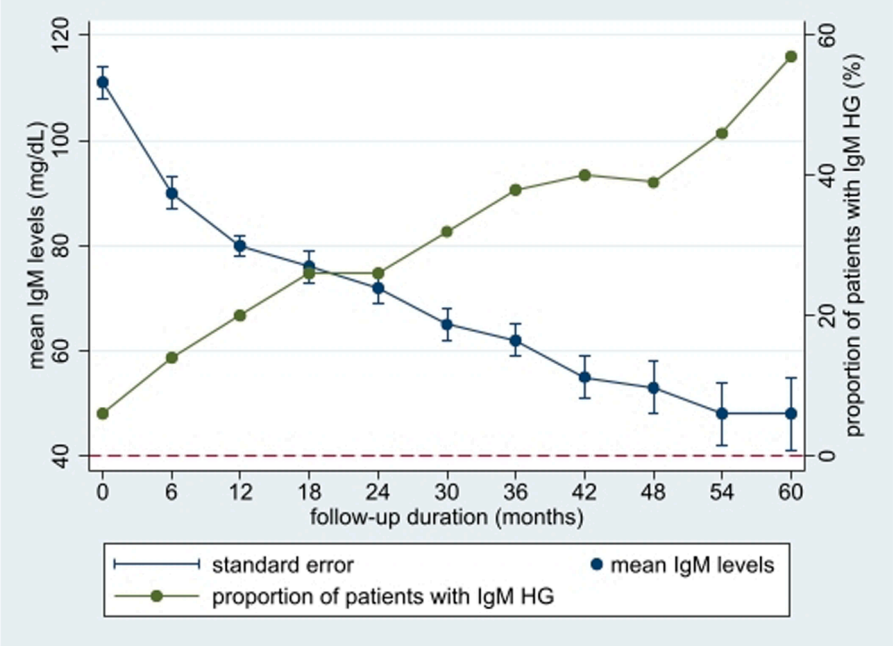

Fig. 2. Mean IgM levels and proportion of patients with IgM HG.

5. Discussion

5.1. Frequency of HG and predictors of HG

In our study, over a mean period of over 2 years, IgG/M HG occurred during treatment in 20% and 34% of patients, respectively. An older age and a greater number of infusional cycles increased the risk of IgG HG, while the use of RTX versus OCR and the number of infusional cycles increased the risk of IgM HG. Furthermore, as expected, patients with low baseline Ig levels continued to present HG during treatment.

A recent comprehensive systematic review and meta-analysis on HG and infections during treatment with anti-CD20 agents by Elgenidy et al. (2024), including data from over 20000 patients, found a cumulative frequency of HG of 11%, with RTX exhibiting the highest prevalence at 18%, followed by OCR at 11%, non-specified anti-CD20 at 10%, and OFT at 2%. However, the reduced incidence of HG compared to our study may be explained by the fact that in most of the included studies HG was defined by IgG levels lower than approximately 600 mg/dL, while our study considered a threshold of 700 mg/dL to define HG.

A large study by Langer-Gould et al. (2024) on 2482 patients treated with RTX for a median of 2.4 years also showed a lower incidence of HG compared to our study (10% vs 25%). This finding may be explained by the different dosing regimens: the most common initial maintenance dose in the cited study was 500 mg every 6 months followed by

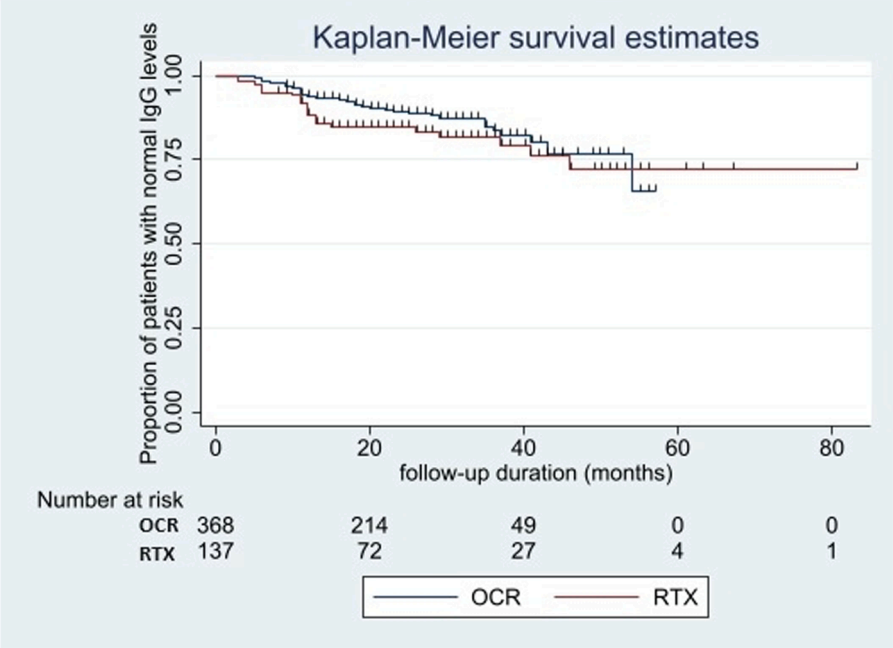

Fig. 3. Time to IgG HG.

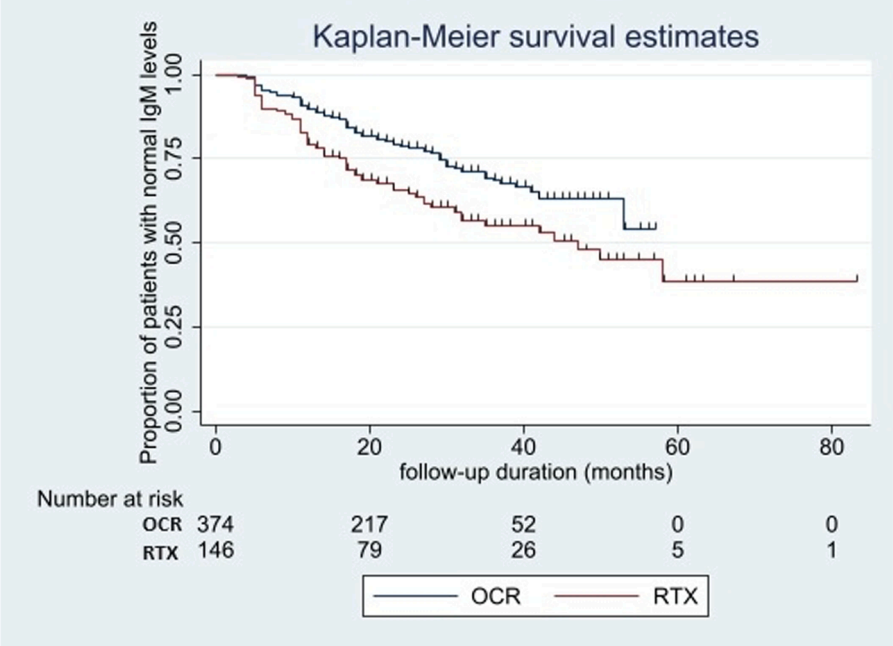

Fig. 4. Time to IgM HG.

reduction to 500 every 12 months, particularly after the third year of treatment. Furthermore, patients in the cited study had a lower mean age at treatment start compared to ours (43 versus approximately 50 years).

Our data confirm previous evidence on predictors of HG. Age was found to be a risk factor for developing IgG HG in several studies (Mears et al., 2023; Perriguey et al., 2022) as well as the number of infusional cycles (Habek et al., 2022; Kim et al., 2022) Our study did not confirm the observation from some studies which report previous immunosuppression as another predictor (Avouac et al., 2021; Kim et al., 2022). This might be because of the low proportion of patients with previous immunosuppression in our study.

Our study shows that the number of treatment cycles increases the risk of developing IgG HG. A possible strategy to avoid this effect, in clinically stable patients on anti-CD20 agents, could be to adopt extended interval dosing (EID). Even though data is still scarce, and concerns regarding an adequate control of disease activity during EID exist, our knowledge on this topic increased during Covid19 pandemic, when some of the centres were forced to adopt this strategy. An Italian multicentre experience showed that while the EID of OCR did not increase the confirmed disease progression, it affected the risk of magnetic resonance imaging (MRI) activity (Zanghì et al., 2024, 2022). Contrarily to this data, a recent study demonstrated that it might prevent IgG HG without affecting disease activity (Schuckmann et al., 2023).

Table 3
Severe infections.

Type of infection	N, % of severe infections	Infection grade
Covid19-related pneumonia	19 (76%)	1 grade 5 infection, 4 grade 4 infections, 14 grade 3 infections
Viral encephalitis	2 (8%)	grade 4
Urinary tract infections	1 (4%)	grade 3
Genital herpes	1 (4%)	grade 3
Gangrenous appendicitis	1 (4%)	grade 3
Salpingitis	1 (4%)	grade 3
Aspergillosis	1 (4%)	grade 3

Table 4
Predictive factors for SI.

Predictive factor	OR	95% CI	p value
Age	1.02	0.99-1.06	ns
Age $\geq$ 50 years	1.34	0.60-3.00	ns
Sex female versus male	0.77	0.34-1.75	ns
Drug RTX versus OCR	1.21	0.51-2.86	ns
Number of previous DMTs	1.08	0.79-1.47	ns
Number of infusions	0.96	0.78-1.17	ns
Presence of comorbidities	1.23	0.55-2.74	ns
EDSS at anti-CD20 start	1.10	0.86-1.41	ns
Progressive phenotype or NMOSD versus RRMS	**1.55**	**1.06-2.27**	**0.024**
IgG levels <700 mg/dL during treatment	**2.84**	**1.24-6.50**	**0.014**
IgM levels <40 mg/dL during treatment	1.12	0.48-2.57	ns
Baseline IgG HG	1.96	0.65-5.95	ns
Baseline IgM HG	0.61	0.80-4.64	ns
Previous Immunosuppressive therapy	0.29	0.04-2.20	ns
Persistent CD19 depletion	1.11	0.45-2.75	ns

A prospective observational study on RTX EID in MS patients did not find significant differences in relapse rates between EID and dosing intervals shorter than 8 months (Starvaggi Cucuzza et al., 2023).

Among possible de-risking strategies, another aspect that could be considered is the dosage of anti-CD20 drugs. There are some reports of patients treated with half of the approved dose of OCR (Algahtani et al., 2023) that suggest that it may maintain good efficacy, but the data is very scarce. More data is available on RTX (Mathew et al., 2020), although such studies focus on efficacy and do not consider possible benefits of reduced dosing on Ig levels. To this regard, a recent study by Kelly et al. (2023) on HG management showed that intravenous Ig supplementation yielded the largest increase in IgG per year, followed by suspension of anti-CD20 therapy and DMT switch.

A recent review by Alvarez et al. (2023) thoroughly lists possible management strategies described in literature and the current state of art on hypogammaglobulinemia, including novel anti-CD20 agents (OFT and Ublitixumab).

Other factors which should be considered, as they may impact B-cell repopulation, are patients' BMI, age and kidney function. Several studies demonstrated that high BMI increases the repopulation rate of B-cells (Abbadessa et al., 2023; Signoriello et al., 2020) and a recent single-centre retrospective observational study including 839 patients suggested that an impaired kidney function as well as an age >60 years might decrease the repopulation rate of B-cells (Welte et al., 2023).

5.2. Infections, SI and predictors of SI

The rate of SI was influenced by the disease phenotype (lower in RRMS patients) and by IgG HG. The follow-up period of our study, which found the incidence of SI to be 1.84 and 1.86 per 100-person years, for OCR and RTX respectively, overlaps with the Covid19 pandemic, therefore the real incidence of SI might be lower, although it is consistent with a large register-based study on risk of infections in MS patients (1.97 for RTX, with similar follow-up duration in the study by Luna et al. (20) and a bit lower than the one reported in a recent study by Langer-Gould et al. (2024). Although our study was conducted during the Covid19 pandemic, greater awareness on infection risks, derived from the literature might have contributed to stricter monitoring of the patients in recent years and thus to lower risk of infections (9). A recent study on infections in NMOSD patients on RTX showed the infections and SI rate to be respectively 8.18 and 1.08 per 100 person-years (7) while a recent study including both RTX and OCR patients (21) reported a SI incidence rate of 3.03 per 100 person-years, albeit over a follow-up period of 46 months.

As regards the prevention of SI, the study by Kelly et al. (2023) indicates that an anti-CD20 dose reduction may yield the largest decrease in yearly infection frequency, followed by IgG supplementation.

Moreover, our study confirms the outcomes of recent studies which showed that the progressive phenotype, especially the secondary progressive, is associated with higher risk of SI (Brand et al., 2022; Knapp et al., 2022).

The incidence rate of neoplasms that we found was very similar to the data from the Danish MS registry in patients newly treated with immunosuppressant (699 versus 675 per 100,000 person-years) and was not increased compared with the general population (Nørgaard et al., 2021).

5.3. Strengths, limitations and future directions

The main strengths of our study are the relatively high number of included patients, the comparison between two of the most widely used anti-CD20 agents, and the analysis of predictors of HG and SI, a particularly relevant aspect in an everyday clinical practice.

On the other hand, a limitation of our study is the relatively short follow-up duration which, nevertheless, highlighted a correlation between HG and SI, even in the short-medium term.

Given that the Ig level reductions seem to be time-dependent, a longer follow-up in studies would be crucial to understand the extent of the long-term risks, as only few studies with long follow-up have been published so far (Kim et al., 2022), and whether different anti-CD20 agents, such as the novel drug, OFT, harbour different HG risks. A factor which limited the possibility of finding differences in the risk profile between the two anti-CD20 agents (RTX and OCR) in our study was the difference in the two sub-populations in terms of follow-up duration, age, clinical phenotype, and disability.

Moreover, data such as the absolute lymphocyte count and the BMI which could have contributed to better characterize possible risk factors of HG/SI were not collected.

6. Conclusion

IgG and IgM HG occurred in a considerable proportion of MS patients treated with anti-CD20 mAbs. IgG HG increased the risk of SI, which were, nevertheless, relatively infrequent during treatment, although studies with a longer follow-up are necessary to provide information on the long-term risks of anti-CD20 mAbs. Our results highlight the importance of monitoring Ig levels at baseline and throughout treatment in order to personalize treatment strategies and consider de-risking strategies (such as EID, dosage reductions or treatment switches) in case of IgG HG in patients with longer treatment duration, a higher age and a progressive phenotype, This may be of particular relevance in patients with other known risk factors for infections, including comorbidities, lympho/neutropenia and previous immunosuppressive treatment.

Funding statement

The authors received no financial support for the research,

authorship, and/or publication of this article.

Data availability statement

Anonymized data, not published in the article, will be shared upon reasonable requests from a qualified investigator.

CRediT authorship contribution statement

K. Smolik: Writing – original draft, Visualization, Project administration, Formal analysis, Data curation. **F. Camilli:** Investigation, Writing – review & editing. **I. Panzera:** Investigation, Writing – review & editing. **A. Fiore:** Investigation, Writing – review & editing. **A. Franceschini:** Investigation, Writing – review & editing. **M. Foschi:** Writing – review & editing, Investigation. **A. Surcinelli:** Investigation, Writing – review & editing. **I. Pesci:** Investigation, Writing – review & editing. **C. Ferri:** Investigation, Writing – review & editing. **V. Bazzurri:** Investigation, Writing – review & editing. **L. Mancinelli:** Investigation, Writing – review & editing. **C. Zini:** Investigation, Writing – review & editing. **A.M. Simone:** Investigation, Writing – review & editing. **A. Lugaresi:** Writing – review & editing, Investigation. **F. Falzone:** Investigation, Writing – review & editing. **F. Granella:** Writing – review & editing, Investigation. **M.G. Piscaglia:** Investigation, Writing – review & editing. **A. Guareschi:** Investigation, Writing – review & editing. **E. Baldi:** Investigation, Writing – review & editing. **P. Immovilli:** Investigation, Writing – review & editing. **S. Montepietra:** Investigation, Writing – review & editing. **M. Santangelo:** Investigation, Writing – review & editing. **N. Poma:** Investigation, Writing – review & editing. **M. Cardi:** Investigation, Writing – review & editing. **G. De Napoli:** Investigation, Writing – review & editing. **F. Vitetta:** Investigation, Writing – review & editing. **D. Ferraro:** Supervision, Methodology, Conceptualization, Validation, Writing – review & editing.

Declaration of competing interest

K. Smolik: nothing to disclose, F. Camilli: nothing to disclose, I. Panzera: nothing to disclose, A. Fiore: nothing to disclose, A. Franceschini: nothing to disclose, M. Foschi has received travel and meeting support from Novartis, Roche, Biogen, Sanofi-Genzyme and Merck., A. Surcinelli nothing to disclose, I. Pesci nothing to disclose, C. Ferri: has received travel or speaker honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, Roche, and Bristol Meyer Squibb, V. Bazzurri nothing to disclose, L. Mancinelli nothing to disclose, C. Zini nothing to disclose, A.M. Simone nothing to disclose, A. Lugaresi has served as a Biogen, Bristol Myers Squibb, Horizon, Janssen, Merck Serono, Novartis, Roche, Sanofi/Genzyme Advisory Board Member. She received congress and travel/accommodation expense compensations or speaker honoraria from Alexion, Biogen, Merck Serono, Novartis, Roche, Sanofi/Genzyme, and Fondazione Italiana Sclerosi Multipla (FISM). Her institutions received research grants from Novartis and Sanofi/Genzyme., F. Falzone nothing to disclose, F. Granella has received research funding from Roche; fees for advisory boards and speaker honoraria from Biogen, Merck Serono, Novartis, Roche, and Sanofi Genzyme; travel funding from Biogen, Sanofi Genzyme, and BMS., M.G. Piscaglia nothing to disclose, A. Guareschi nothing to disclose, E. Baldi has received a grant for the organization of a scientific congress from Biogen Idec and has received travel or speaker honoraria from Biogen Idec, Sanofi Genzyme, Merck Serono, and Teva Neurosciences., P. Immovilli, S. Montepietra, M. Santangelo: nothing to disclose, N. Poma: nothing to disclose, M. Cardi: nothing to disclose, G. De Napoli: nothing to disclose, F. Vitetta has received travel grants and/or speaker/advisory board honoraria from Merck, Novartis, Sanofi, Biogen and Roche. D. Ferraro has received travel grants and/or speaker/advisory board honoraria from Biogen, Merck, Sanofi, Novartis and Roche.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.106191.

References

Abbadessa, G., Miele, G., Maida, E., Vanore, E., Cipriano, L., Coppola, C., Lavorgna, L., Bonavita, S., 2023. Immunomodulatory effects of ocrelizumab and candidate biomarkers for monitoring treatment response in Multiple Sclerosis. Mult. Scler. J. 29, 779–788. https://doi.org/10.1177/13524585221147635.

Algahtani, H., Shirah, B., Alqahtani, A., Abdelghaffar, N., Makki, S., 2023. Half-dose ocrelizumab in selected patients with relapsing–remitting multiple sclerosis. Acta Neurol. Belg. https://doi.org/10.1007/s13760-023-02303-0.

Alvarez, E., Longbrake, E.E., Rammohan, K.W., Stankiewicz, J., Hersh, C.M., 2023. Secondary hypogammaglobulinemia in patients with multiple sclerosis on anti-CD20 therapy: pathogenesis, risk of infection, and disease management. Mult. Scler. Relat. Disord. https://doi.org/10.1016/j.msard.2023.105009.

Avouac, A., Maarouf, A., Stellmann, J.P., Rico, A., Boutiere, C., Demortiere, S., Marignier, R., Pelletier, J., Audoin, B., 2021. Rituximab-induced hypogammaglobulinemia and infections in AQP4 and MOG antibody-associated diseases. Neurol. Neuroimmunol. Neuroinflamm. 8. https://doi.org/10.1212/NXI.0000000000000977.

Barreras, P., Vasileiou, E.S., Filippatou, A.G., Fitzgerald, K.C., Levy, M., Pardo, C.A., Newsome, S.D., Mowry, E.M., Calabresi, P.A., Sotirchos, E.S., 2022. Long-term effectiveness and safety of rituximab in neuromyelitis optica spectrum disorder and MOG antibody disease. Neurology. 99, E2504–E2516. https://doi.org/10.1212/WNL.0000000000201260.

Brand, J.S., Smith, K.A., Piehl, F., Olsson, T., Montgomery, S., 2022. Risk of serious infections in multiple sclerosis patients by disease course and disability status: results from a Swedish register-based study. Brain Behav. Immun. Health 22. https://doi.org/10.1016/j.bbih.2022.100470.

Cancer Institute, N., 2017. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50. accessed 14 April 2024.

Elgenidy, A., Abdelhalim, N.N., Al-kurdi, M.A.mahdi, Mohamed, L.A., Ghoneim, M.M., Fathy, A.W., Hassaan, H.K., Anan, A., Alomari, O., 2024. Hypogammaglobulinemia and infections in patients with multiple sclerosis treated with anti-CD20 treatments: a systematic review and meta-analysis of 19,139 multiple sclerosis patients. Front. Neurol. https://doi.org/10.3389/fneur.2024.1380654.

Habek, M., Piskač, D., Gabelić, T., Barun, B., Adamec, I., Krbot Skorić, M., 2022. Hypogammaglobulinemia, infections and COVID-19 in people with multiple sclerosis treated with ocrelizumab. Mult. Scler. Relat. Disord. 62. https://doi.org/10.1016/j.msard.2022.103798.

Hauser, S.L., Cree, B.A.C., 2020. Treatment of Multiple Sclerosis: a review. Am. J. Med. https://doi.org/10.1016/j.amjmed.2020.05.049.

Kelly, H., Vishnevetsky, A., Chibnik, L.B., Levy, M., 2023. Hypogammaglobulinemia secondary to B-cell depleting therapies in neuroimmunology: Comparing management strategies. Mult. Scler. J. Exp. Transl. Clin. 9. https://doi.org/10.1177/20552173231182534.

Kim, S.H., Park, N.Y., Kim, K.H., Hyun, J.W., Kim, H.J., 2022. Rituximab-induced hypogammaglobulinemia and risk of infection in neuromyelitis optica spectrum disorders: a 14-year real-life experience. Neurol. Neuroimmunol. Neuroinflamm. 9. https://doi.org/10.1212/NXI.0000000000001179.

Knapp, R., Hardtstock, F., Krieger, J., Wilke, T., Maywald, U., Chognot, C., Muros-Le Rouzic, E., Craveiro, L., 2022. Serious infections in patients with relapsing and progressive forms of multiple sclerosis: a German claims data study. Mult. Scler. Relat. Disord. 68, 104245. https://doi.org/10.1016/j.msard.2022.104245.

Langer-Gould, A., Li, B.H., Smith, J.B., Xu, S., 2024. Multiple Sclerosis, rituximab, hypogammaglobulinemia, and risk of infections. Neurol. Neuroimmunol. Neuroinflamm. 11, e200211. https://doi.org/10.1212/NXI.0000000000200211.

Mathew, T., John, S.K., Kamath, V., Murgod, U., Thomas, K., Baptist, A.A., Therambil, M., Shaji, A., Nadig, R., Badachi, S., Souza, D.D., Shivde, S., Avati, A., Sarma, G.R.K., Sharath Kumar, G.G., Deepalam, S., Parry, G.J., 2020. Efficacy and safety of rituximab in multiple sclerosis: experience from a developing country. Mult. Scler. Relat. Disord. 43, 102210. https://doi.org/10.1016/j.msard.2020.102210.

Mears, V., Jakubecz, C., Seeco, C., Woodson, S., Serra, A., Abboud, H., 2023. Predictors of hypogammaglobulinemia and serious infections among patients receiving ocrelizumab or rituximab for treatment of MS and NMOSD. J. Neuroimmunol. 377, 578066. https://doi.org/10.1016/j.jneuroim.2023.578066.

Nørgaard, M., Veres, K., Sellebjerg, F.T., Svingel, L.S., Foch, C., Boutmy, E., Sabidó, M., Magyari, M., 2021. Incidence of malignancy in multiple sclerosis: a cohort study in the Danish multiple sclerosis registry. Mult. Scler. J. Exp. Transl. Clin. 7. https://doi.org/10.1177/20552173211053939.

Perriguey, M., Maarouf, A., Stellmann, J.P., Rico, A., Boutiere, C., Demortiere, S., Durozard, P., Pelletier, J., Audoin, B., 2022. Hypogammaglobulinemia and infections in patients with multiple sclerosis treated with rituximab. Neurol. Neuroimmunol. Neuroinflamm. 9. https://doi.org/10.1212/NXI.0000000000001115.

Saidha, S., Bell, J., Harold, S., Belisario, J.M., Hawe, E., Shao, Q., Wyse, K., Maiese, E.M., 2023. Systematic literature review of immunoglobulin trends for anti-CD20

monoclonal antibodies in multiple sclerosis. Neurol. Sci. https://doi.org/10.1007/s10072-022-06582-y.

Schuckmann, A., Steffen, F., Zipp, F., Bittner, S., Pape, K., 2023. Impact of extended interval dosing of ocrelizumab on immunoglobulin levels in multiple sclerosis. Med. (N. Y.). https://doi.org/10.1016/j.medj.2023.05.001.

Signoriello, E., Bonavita, S., Di Pietro, A., Abbadessa, G., Rossi, F., Miele, G., Casertano, S., Lus, G., 2020. BMI influences CD20 kinetics in multiple sclerosis patients treated with ocrelizumab. Mult. Scler. Relat. Disord. 43, 102186. https://doi.org/10.1016/j.msard.2020.102186.

Starvaggi Cucuzza, C., Longinetti, E., Ruffin, N., Evertsson, B., Kockum, I., Jagodic, M., Al Nimer, F., Frisell, T., Piehl, F., 2023. Sustained low relapse rate with highly variable B-cell repopulation dynamics with extended rituximab dosing intervals in multiple sclerosis. Neurol. Neuroimmunol. Neuroinflamm. 10. https://doi.org/10.1212/NXI.0000000000200056.

Szepanowski, F., Warnke, C., Meyer zu Hörste, G., Mausberg, A.K., Hartung, H.P., Kleinschnitz, C., Stettner, M., 2021. Secondary immunodeficiency and risk of infection following immune therapies in neurology. CNS. Drugs. https://doi.org/10.1007/s40263-021-00863-4.

Welte, T., Westermann, L., Kappes, J., Schramm, M.A., Bemtgen, X., Staudacher, D.L., Hug, M.J., Venhoff, N., Arnold, F., 2023. Identification of covariates modulating B-cell repopulation kinetics in subjects receiving rituximab treatment. Arthritis Rheumatol. https://doi.org/10.1002/art.42625.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., De Seze, J., Fujihara, K., Greenberg, B., Jacob, A., Jarius, S., Lana-Peixoto, M., Levy, M., Simon, J.H., Tenembaum, S., Traboulsee, A.L., Waters, P., Wellik, K.E., Weinshenker, B.G., 2015. Neurology. 85 (2), 177–189. https://doi.org/10.1212/WNL.0000000000001729, 2015.

Wingerchuk, D.M., Lennon, V.A., Pittock, S.J., Lucchinetti, C.F., Weinshenker, B.G., 2006. Revised diagnostic criteria for neuromyelitis optica. Neurology. 66, 1485–1489. https://doi.org/10.1212/01.wnl.0000216139.44259.74.

Zanghì, A., Avolio, C., Signoriello, E., Abbadessa, G., Cellerino, M., Ferraro, D., Messina, C., Barone, S., Callari, G., Tsantes, E., Sola, P., Valentino, P., Granella, F., Patti, F., Lus, G., Bonavita, S., Inglese, M., D'Amico, E., 2022. Is it time for ocrelizumab extended interval dosing in relapsing remitting MS? Evidence from an Italian multicenter experience during the COVID-19 pandemic. Neurotherapeutics. 19, 1535–1545. https://doi.org/10.1007/s13311-022-01289-6.

Zanghì, A., Ferraro, D., Callari, G., Valentino, P., Granella, F., Patti, F., Lus, G., Bonavita, S., Moretti, M.C., Avolio, C., D'Amico, E., 2024. Ocrelizumab extended interval dosing in primary progressive multiple sclerosis: an Italian experience. Curr. Neuropharmacol. 22, 339–345. https://doi.org/10.2174/1570159X22666231002142709.