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Tolerability and safety of long-term rituximab treatment in systemic inflammatory and autoimmune diseases

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Abstract

Rituximab, an anti-CD20 monoclonal antibody causing selective B-cell depletion, is used for various systemic inflammatory and autoimmune diseases (SIADs). Long-term safety data on rituximab are limited. The objectives of this study were to evaluate the long-term safety and tolerability of rituximab treatment for SIADs. A retrospective, single-center observational study including all patients ≥ 16 years treated with rituximab for SIADs was performed. The electronic medical records were reviewed, and data concerning indication and duration of rituximab treatment, prior and concurrent immunosuppressive therapy, and adverse events such as infections requiring hospitalization, dysgammaglobulinemia and end organ damage, were collected. A total of 70 patients were included, with a median treatment duration of 54 months, ranging 30–138 months. The most common indications for rituximab treatment were granulomatosis with polyangiitis (22.9%), primary Sjögren's syndrome (20.0%) and systemic lupus erythematosus (14.3%). Infections and persistent dysgammaglobulinemia were the most common adverse events, occurring in 34.3% and 25.7%, respectively. A total of 64 infections were observed in 24 (34.3%) patients, including 1 case of fatal infection. Seventeen patients performed B-cell quantitation during the first 2 years following discontinuation, of which only four (19.0%) demonstrated B-cell reconstitution. End organ damage occurred in two patients, presenting as pyoderma gangrenosum and interstitial pneumonitis. No opportunistic infections were observed. Three patients died during the observational period, of which one was due to lethal infection. This study presents observational data with long treatment duration. It demonstrates that long-term rituximab treatment is relatively well tolerated, and that no cumulative side effects were observed.

Keywords Rituximab · B-cell depletion · Immunosuppression · Safety · Tolerance

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Introduction

Rituximab is a chimeric anti-CD20 monoclonal antibody which causes selective B-cell depletion through a variety of antibody-, cell- and complement-mediated mechanisms [1]. While initially introduced as an antineoplastic agent, rituximab-mediated B-cell depletion became a promising therapeutic option in B-cell-driven systemic inflammatory and autoimmune diseases (SIADs) at the beginning of the new millennium. Rituximab is now approved for treatment of rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), and is frequently used as off-label therapy for a wide variety of other SIADs when conventional treatment regimens have failed [1–8]. Clinical trials in systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) have been disappointing [9–11], but it has been argued that the instruments used to monitor disease activity and remission have

not been sufficiently sensitive to detect the clinical and biological effects of rituximab [7]. Furthermore, clinical experience and case reports indicate that rituximab has a favorable effect in some subjects, and off-label use has, therefore, been increasingly employed in patients that do not respond to conventional immunosuppressive treatment.

Adverse events related to rituximab treatment include, among others, infections, infusion reactions, dysgammaglobulinemia and cytopenia. Inflammatory end organ damage, such as interstitial pneumonitis and pyoderma gangrenosum are recognized as late-onset complications [12, 13]. Nevertheless, previous studies have demonstrated that long-term rituximab treatment in various SIADs is relatively well tolerated [14–18].

During the last 15 years, the Clinical Immunology Unit at Stavanger University Hospital have employed rituximab in more than 100 patients with difficult to treat SIADs. As several of these patients have received continuous rituximab treatment for more than 10 years, this experience can provide additional insight into the tolerability and consequences of long-term therapeutic B-cell depletion. The aim of this retrospective study was, therefore, to evaluate the long-term safety and tolerance of rituximab, with special attention to dysgammaglobulinemia, infections, and failure of B-cell reconstitution following discontinuation of rituximab treatment. Due to the retrospective nature of the design, this study did not intend to evaluate treatment efficacy.

Materials and methods

Study design

This was a single-center, retrospective observational study which included all patients ≥ 16 years treated with rituximab for SIADs at Stavanger University Hospital between 2003 and 2017. Only patients receiving rituximab for a minimum duration of ≥ 2 years were included. Patients with coexisting malignancies were excluded. Regardless of indication, all patients received an identical and standard treatment regimen consisting of two intravenous infusions of 1000 mg rituximab with two weeks interval at the start of treatment, followed by 1000 mg every 6 months, as per institution protocol. A standard pretreatment regimen consisting of paracetamol, diphenhydramine, and methylprednisolone was given to limit infusion reactions. Prior to each infusion, routine blood tests were obtained, including complete blood count, levels of immunoglobulins and immunophenotyping of lymphocytes for quantitation of CD19 + B-cells in peripheral blood. Routine biochemical and immunological analyses were performed at Stavanger University Hospital, and immunophenotyping at the Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway.

Data collection and measurements

The electronic medical records of all patients with SIADs treated with rituximab, either as monotherapy or in combination with other immunosuppressive agents, were reviewed. Data regarding gender, indication for rituximab, age at start of treatment, as well as prior and current immunosuppressive therapy were systematically collected. Results of routine blood tests, as well as treatment complications were thoroughly registered. Treatment complications included dysgammaglobulinemia (defined as subnormal levels of one or two of the three major serum immunoglobulin subclasses, IgG, IgA and IgM, and/or need for immunoglobulin substitution to maintain normal levels), hypogammaglobulinemia (defined as subnormal levels of all three major serum immunoglobulin subclasses), infection (defined as a condition requiring hospitalization with a presumed or confirmed infectious etiology and/or clinical response to antimicrobial treatment) and end organ damage (defined as a presumed non-infectious inflammatory process necessitating hospitalization which could not be attributed to activity of the underlying inflammatory condition). Persistent dysgammaglobulinemia was defined as dysgammaglobulinemia for two consecutive measurements and persisting throughout the duration of rituximab therapy. Cytopenia was defined as subnormal levels of leukocytes, neutrophils or thrombocytes for two consecutive measurements and persisting throughout the treatment duration. Days of hospitalization, as well as need for admission to an intensive care unit and mechanical ventilation was noted for all complications requiring hospital admission. Rituximab treatment duration, number of infusions, as well as reasons for discontinuation of rituximab were noted. In patients who had discontinued rituximab, data concerning immunoglobulins and CD19 + B-cells in the post-treatment period were collected to evaluate time to B-cell reconstitution.

Participants

One hundred patients were identified, of which 25 were excluded due to treatment duration of < 2 years, and 5 were excluded due to coexisting malignancies. No patients were lost to follow-up and no patients declined inclusion, leaving a total sample size of 70 patients for inclusion. There was a slight female predominance (58.6% vs. 41.4%), and the median age at initiation of rituximab treatment was 51.5 years (IQR 21.3), ranging 16–81 years. The specific diseases and conditions for which rituximab was given were diverse, with GPA, pSS and SLE being the most common (Table 1). Three patients (4.3%) received

Table 1 Indication for rituximab treatment

Diagnosis	Number of patients (%)
Granulomatosis with polyangiitis	16 (22.9%)
Primary Sjögren's syndrome	14 (20.0%)
Systemic lupus erythematosus	10 (14.3%)
Rheumatoid arthritis	5 (7.1%)
Eosinophilic granulomatosis with polyangiitis	4 (5.7%)
Antisynthetase syndrome	3 (4.3%)
Overlap syndrome	3 (4.3%)
Autoimmune thyroiditis	2 (2.9%)
Undifferentiated connective tissue disease	2 (2.9%)
Nonspecific vasculitis	2 (2.9%)
Polymyositis	2 (2.9%)
One patient each with the following diagnoses: antiphospholipid syndrome, relapsing polychondritis, polyarteritis nodosa, autoimmune polyendocrine syndrome type 1, pyoderma gangrenosum, orbital xanthogranuloma, Felty's syndrome	7 (10.0%)

Table 2 Immunosuppressive treatment given concurrently with rituximab

Immunosuppressant	Number of patients (%)
Prednisolone	63 (90.0%)
Methotrexate	24 (34.3%)
Methylprednisolone	21 (30.0%)
Hydroxychloroquine	16 (22.9%)
Azathioprine	16 (22.9%)
Mycophenolate mofetil	7 (10.0%)
Cyclophosphamide	4 (5.7%)
Cyclosporine	4 (5.7%)
Budesonide	1
None (rituximab monotherapy)	3 (4.3%)

rituximab as monotherapy only, with the most frequent concurrent immunosuppressive agents being corticosteroids (prednisolone and/or intravenous methylprednisolone) and methotrexate (Table 2).

Statistics

Categorical data are reported as counts and percentages. For continuous variables, normal distribution was tested with the Shapiro–Wilks test. Some data were not normality distributed and the results are thus presented as median and interquartile range (IQR) and minimum and maximum. In some analyses, a log transform was applied to make the data more normally distributed. The Kaplan–Meier estimator was used to estimate the probability of continuing rituximab therapy as a function of time.

Ethics

This study was approved by the Regional Ethics Committee (REK vest 2016/2195). The patients were retrospectively provided with written information and the option to deny use of medical data, as well as waiver of consent for patients that were dead.

Results

Treatment duration and discontinuation

The median number of rituximab cycles was 10 (IQR 8), ranging 6–24. Although occasional minor expedite or delays in treatment occurred, rituximab was scheduled at 0 and 2 weeks, followed by 6-month intervals. Hence, ten cycles, ranging 6–24 equate to a median treatment duration of approximately 54 months, ranging 30–138 months. At the end of the observational period, 35 patients (50.0%) had discontinued rituximab treatment. A Kaplan–Meier curve depicting the probability of continuing rituximab therapy for a given period is presented in Fig. 1. After 60 months an estimated proportion of 60.6% (CI 47.7–77.1%) of the patients are still on rituximab therapy and after 120 months the estimated proportion still on rituximab treatment is 15.1% (CI 6.6–34.7%). Sustained clinical remission, based on the treating physician's global assessment, was the most frequent cause of discontinuation ($n = 20$; 28.6%), followed by treatment-related complications ($n = 8$; 11.4%), insufficient treatment response ($n = 6$; 8.6%) and death ($n = 1$). Complications necessitating discontinuation included dysgammaglobulinemia with recurrent infections ($n = 6$), hypersensitivity/infusion reactions ($n = 1$) and pyoderma gangrenosum ($n = 1$).

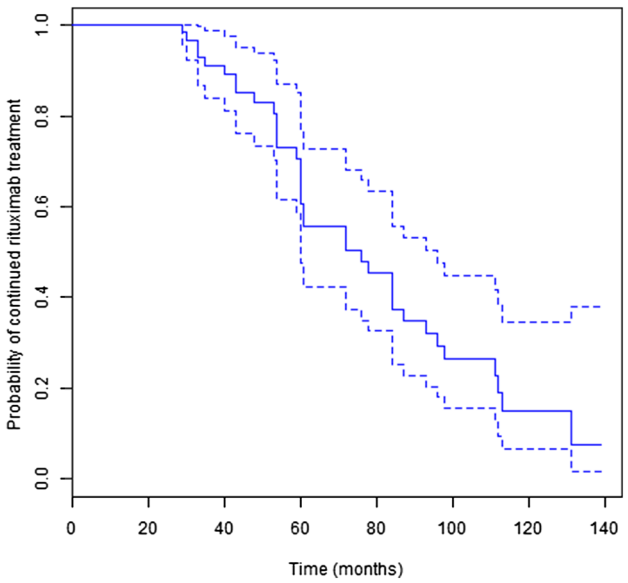

Fig. 1 Kaplan–Meier curve (solid line) with 95% pointwise confidence intervals (dashed lines) showing probability of continuing rituximab therapy beyond a given period of time (months) in the study cohort

Dysgammaglobulinemia and hypogammaglobulinemia

Levels of immunoglobulin G (IgG) for the individual patients are illustrated in Fig. 2. Persistent dysgammaglobulinemia was observed in 18 patients (25.7%), with IgG being the most commonly affected immunoglobulin subclass (Table 3). Development of subnormal IgG levels occurred after a median treatment duration of 6 months (IQR 36), ranging 6–120 months. While persistent dysgammaglobulinemia was a frequent encounter, no patients developed persistent hypogammaglobulinemia (i.e., subnormal levels of all three measured immunoglobulin classes).

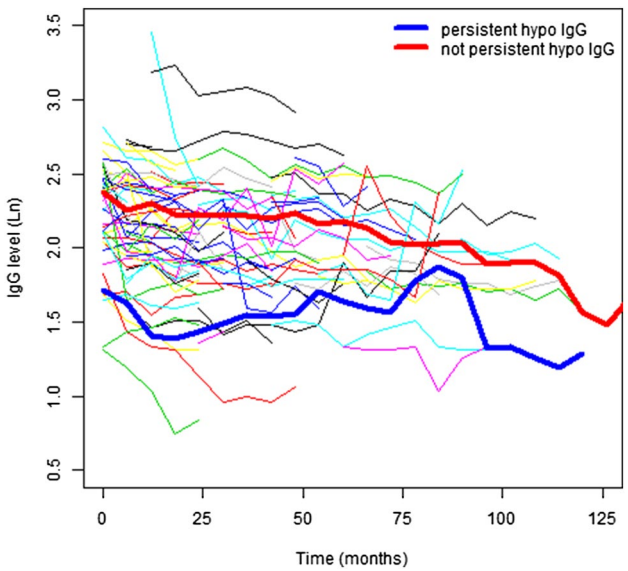

Fig. 2 Changes in serum IgG concentration during rituximab therapy for each individual patient. The changes in mean level of serum IgG for patients without persistent dysgammaglobulinemia are illustrated by the bold red line, while the mean level for patients developing persistent dysgammaglobulinemia is represented by the bold blue line

B-cell reconstitution

After discontinuation of rituximab, serial quantitation of CD19 + B-cells in peripheral blood was not implemented as a routine procedure, therefore, such data are limited. Of the 35 patients discontinuing rituximab, 17 (48.6%) had performed peripheral blood B-cell measures at 1 or more time points more than 12 months after discontinuation, and were evaluated for rate of B-cell reconstitution. Reconstitution of B-cells within the first 2 years following discontinuation, was defined as $\geq 88 \times 10^6$ CD19 + B-cells/L ($\geq 6.0\%$) in peripheral blood, occurred in four out of 17 patients (23.5%), and took place at 15, 17, 18 and 22 months after discontinuation. The remaining 13 patients had documented persistent B-cell depletion at 1 or more time points between 12 and

Table 3 Complications in the observation period

	No. of patients (%)
Cytopenia and dysgammaglobulinemia	
Persistent dysgammaglobulinemia (IgG, IgA or IgM)	18 (25.7%)
Persistent dysgammaglobulinemia (IgG) (< 5.4 g/L)	12 (17.1%)
Persistent dysgammaglobulinemia (IgA) (< 0.7 g/L)	6 (8.6%)
Persistent dysgammaglobulinemia (IgM) (< 0.2 g/L)	6 (6.8%)
Persistent leukopenia ($< 3.9 \times 10^9$/L)	1
Persistent neutropenia ($< 1.9 \times 10^9$/L)	0
Persistent thrombocytopenia ($< 176 \times 10^9$/L)	1
Infections requiring hospitalization[a]	
Infections (all)	24 (34.3%)
Upper respiratory tract infection	5 (7.1%)
Lower respiratory tract infection	14 (20.0%)
Acute pyelonephritis	4 (5.7%)
Skin/soft tissue infection	3 (4.3%)
Osteomyelitis	3 (4.3%)
Bacterial enterocolitis	1
Viral gastroenteritis	1
End organ damage	
Interstitial pneumonitis	1
Pyoderma gangrenosum	1

[a]Some patients experienced more than one type of infection

24 months after discontinuation. These 13 patients received a median of 12 cycles of rituximab (IQR 6.5), ranging 6–19 cycles. B-cell quantitation after more than 24 months following discontinuation was performed in three of these 13 patients (23.1%). None of these three patients demonstrated B-cell reconstitution, with their last quantitation performed at 30, 40 and 53 months following discontinuation, respectively. These patients received 6, 19 and 13 cycles of rituximab, respectively.

Cytopenia

Cytopenia was a rare occurrence, with persistent leukopenia, neutropenia and thrombocytopenia demonstrated in one, zero and one patients, respectively.

Infections

Infection was observed in 24 patients (34.3%). Multiple hospitalizations for infectious etiologies occurred in 14 patients (20.0%), with a median number of hospitalizations in this group being 2 (IQR 2.8), ranging 2–11, resulting in a total of 64 hospitalizations for infections. Lower respiratory tract infections were most commonly encountered (43 cases in 14 patients), followed by skin/soft tissue infections (6 cases in 3 patients), upper respiratory tract infections (5 cases in 5 patients) and pyelonephritis (5 cases in 4 patients). Proven infections with opportunistic pathogens were not observed. The median duration of hospitalization was 5 days (IQR 4.3), ranging 2–39 days. Infections necessitating admission to the intensive care unit was observed in three patients, with 1 of them requiring intubation and mechanical ventilation. This latter patient did not survive to hospital discharge, and the only case of lethal infection in this study cohort.

End organ damage

End organ damage necessitating hospitalization was observed in two patients consisting of interstitial pneumonitis and pyoderma gangrenosum. These patients carried a diagnosis of SLE and GPA, respectively, and the treating physicians considered the inflammatory end organ damage to represent an adverse event of rituximab rather than a manifestation of the underlying disease. Both these patients were admitted to the intensive care unit, with duration of hospitalization of 25 and 90 days, respectively.

Mortality

A total of three patients died during the observation period, one of these due to lethal infection, while the two others died of unknown causes (i.e., death outside the hospital without available records regarding cause of death in the electronic medical journal).

Effects of prior or concurrent cyclophosphamide treatment

A total of 20 patients (28.6%) received cyclophosphamide, either before or during treatment with rituximab. Of these, four patients received overlapping treatment in which rituximab was added while they were still receiving cyclophosphamide. These patients had GPA ($n=13$), antisynthetase syndrome ($n=2$), SLE ($n=2$), pSS ($n=1$), polyarteritis nodosa ($n=1$) and antiphospholipid syndrome ($n=1$). The association of prior or concurrent cyclophosphamide administration in the development of the aforementioned complications was evaluated. Of the 18 patients who developed persistent dysgammaglobulinemia, 9 (50.0%) had received cyclophosphamide, either prior to and/or concurrently with rituximab. Of the 24 patients who were hospitalized for infections, 10 (41.7%) had received cyclophosphamide, either prior to and/or concurrently with rituximab. This can be compared to infection occurring in 14 (28.0%) of the 50 patients not exposed to cyclophosphamide. Of the 13 patients who failed to demonstrate B-cell reconstitution within 24 months following discontinuation, 4 (30.8%) had received prior cyclophosphamide. In the group of patients in which persistent B-cell depletion for more than 24 months was documented, one of three patients had been treated with cyclophosphamide prior to rituximab treatment.

Discussion

Peripheral B-cell depletion with rituximab represents a valuable treatment modality for a variety of SIADs [1], but observational data are required to evaluate tolerance and safety of long-term treatment. This study reports experience with rituximab in a single-center cohort, with treatment duration ranging 30–138 months and a median treatment of 54 months, and are in line with other studies of long-term treatment with rituximab [14–19]. Persistent dysgammaglobulinemia and infections were the most commonly encountered adverse events, with approximately one-third of patients requiring hospitalization for infectious complications. Nevertheless, only three of these patients required intensive care unit admission, and only one patient developed infection with a fatal outcome. No opportunistic infections were noted, and particularly, there were no reported incidence of progressive multifocal leukoencephalopathy.

Inflammatory organ damage in the form of interstitial pneumonitis and pyoderma gangrenosum was a rare occurrence, with only two cases observed. Nevertheless, both patients with this type of complication experienced severe

organ damage necessitating prolonged stays in the intensive care unit. This was especially true in the case with pyoderma gangrenosum, who developed multi-organ failure requiring long-term vasopressor therapy and mechanical ventilation [20].

Persistent dysgammaglobulinemia, which can be either asymptomatic or increase risk of infection, was another commonly observed adverse event occurring after a median duration of 6 months. The mean concentration of IgG decreased progressively in patients on rituximab only, but even more in those on concurrent or prior cyclophosphamide (Fig. 3).

The rate of B-cell reconstitution following rituximab discontinuation varies between studies, and a small study on RA demonstrated a mean time to reconstitution of 8 months [21]. Prolonged B-cell depletion following rituximab treatment for SLE and AAV has been reported [22–24], and in a study of ANCA-associated vasculitides (AAV) patients, 20 of 34 patients failed to show B-cell repopulation during the observational period which ranged 9–59 months [22]. Of the total 37 patients included in that study, 92% had received cyclophosphamide, and a synergistic effect of cyclophosphamide and rituximab as a cause of prolonged B-cell depletion was suspected by the authors [22]. In our study, only 30.8% of the patients with persistent B-cell depletion had received prior cyclophosphamide, suggesting that rituximab may induce delayed repopulation of the peripheral B-cell compartment in the absence of cyclophosphamide.

The rate of reconstitution, as well as the characteristics of the reconstituting B-cell compartment may be of significance. A previous study on SLE patients showed that long-term remission following rituximab treatment was associated with a reconstituting B-cell population consisting mainly of transitional B-cells and delayed reconstitution of both switched and non-switched memory B-cells [24]. The prolonged remission was hypothesized to be due to disrupted B-cell follicles and lymphoid architecture, and/or the development of a de novo, non-autoreactive B-cell compartment demonstrating adequate immunological tolerance following treatment [24].

To detect factors associated with adverse events, we evaluated the subgroup receiving prior or concurrent cyclophosphamide therapy. Ten out of 20 patients (50.0%) required hospitalization due to infections in this group compared to 34.3% (24 of 70) in the entire study. Similarly, nine out of 20 patients (45.0%) receiving prior and/or concurrent cyclophosphamide

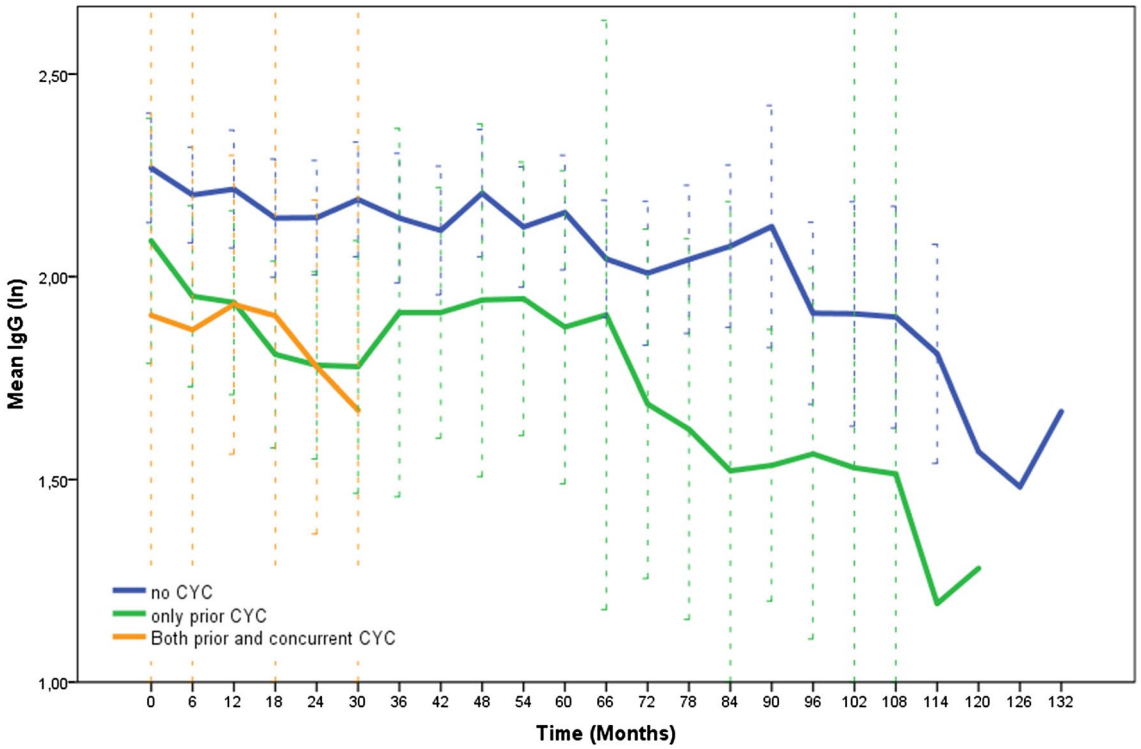

Fig. 3 Changes in mean level of serum IgG during rituximab therapy in patients receiving rituximab without prior or concurrent cyclophosphamide (blue line, $n=50$), patients who received cyclophosphamide prior to rituximab therapy (green line, $n=16$), and patients treated with rituximab and cyclophosphamide concurrently (yellow line, $n=4$). Two patients were considered as outliers and removed from this figure. One patient who received cyclophosphamide only concurrently and one patient who received both prior and concurrent cyclophosphamide for a long time (0–72 months). Dotted lines represent the 95% confidence interval

developed persistent dysgammaglobulinemia, while this was observed in 18 of 70 patients (25.7%) in the entire cohort. Figure 3 illustrates the changes in serum IgG in patients receiving prior or concurrent cyclophosphamide, compared to the patients treated with rituximab who were never exposed to cyclophosphamide. There was a tendency to more rapid decline in the cyclophosphamide group, suggesting combination therapy with cyclophosphamide may increase the risk of dysgammaglobulinemia.

Overall, our results are consistent with previous observational studies demonstrating that long-term rituximab therapy is well tolerated [25]. A retrospective study of 115 SLE patients receiving a mean number of 1.95 cycles of rituximab demonstrated dysgammaglobulinemia and severe infections in 14.9% and 7.0% of patients, respectively [26]. Van Vollenhoven et al. evaluated 3595 patients with RA receiving a mean of 4 courses (range 1–20) of rituximab, showing a serious infection event of 3.76 per 100 patient years [15].

The major limitation of this study is heterogeneity of the population, both in terms of underlying disease, as well as prior and concurrent immunosuppressive therapy. Additionally, the follow-up time differed between the subjects in the study, and the retrospective nature and single-center design adds to the list of limitations. Only infections requiring hospitalization were recorded. As such, less severe infections treated in an outpatient setting by a general practitioner, such as mild pneumonias and herpes zoster may be underreported in this study. Incomplete data on follow-up after discontinuation, in combination with one-half of the included patients still receiving rituximab therapy at the time of data collection limits the amount of data regarding B-cell reconstitution, as well as tolerability of switching from rituximab to a subsequent immunosuppressive agent.

Conclusion

This study presents observational data with long rituximab treatment duration. The results are in keeping with previous studies, demonstrating that long-term rituximab therapy confers a well-tolerated safety profile.

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Compliance with ethical standards

Conflict of interest JV has received honorarium from Novartis for participation in advisory board. RO has received honorarium from Roche for lectures and participation in advisory board.

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