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BRIEF REPORT

Idiopathic nephrotic syndrome and rituximab: may we predict circulating B lymphocytes recovery?

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Abstract

Background Rituximab (RTX) has been shown to be an efficient treatment for steroid-dependent nephrotic syndrome (SDNS). A long B cell depletion period seems to improve the duration of remission. This study reports the duration of B cell depletion after each RTX infusion in patients with nephrotic syndrome.

Methods We retrospectively report the data of 22 patients with a diagnosis of a SDNS or steroid-resistant nephrotic syndrome (SRNS) and a treatment with RTX in a single center. B cell depletion duration was compared to the first B cell depletion duration and to the previous B cell depletion duration in each patient.

Results Twenty-two patients (5 girls) were included. Seventy-six periods of B cell depletions were compared to the first B cell depletion duration and to the preceding B cell depletion duration in the same patient. Total duration of B cell depletion was 26 (6–66) months. Individual post-RTX infusion B cell depletion duration was 5.1 (1.6–14) months. Median B cell depletion duration following the first RTX cure for children who had received 1 to 2 infusions at first cure was not statistically different of those who had received 3 to 4 infusions ($p = 0.18$). Comparing the B cell depletion induced by previous RTX courses and the following B cell depletion, 89.5% of patients had a similar duration within an open interval from 2 months.

Conclusion Once the individual time interval until B cell recovery is determined, monitoring could be individualized by targeting the expected date of B cell recovery or by performing pre-emptive RTX injections.

Keywords Nephrotic syndrome · Rituximab · Children · B cell depletion

Introduction

Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, inhibits CD20-mediated B cell proliferation and differentiation [1], it was originally developed to treat patients with B cell non-Hodgkin's lymphoma and it is now used in the treatment of various autoimmune diseases [2].

In recent years, RTX has also been shown to be an efficient treatment for idiopathic nephrotic syndrome (INS) and more precisely for steroid-dependent nephrotic syndrome (SDNS) [3–5]. Kidney Disease Improving Global Outcomes (KDIGO) suggests now that RTX can be considered in children with SDNS who have continuing frequent relapse despite optimal combinations of prednisone and corticosteroid-sparing agents [6].

However, for the moment, there is no unified standard of how to use RTX, especially the duration of B cell depletion. Indeed, RTX efficiency is related to B cell depletion. It is now clear that a single infusion of RTX is an effective treatment that reduces relapse and steroid dependency [7], but several papers reported that most patients were likely to relapse with B cell recovery [7, 8]. In view of several publications, we can presume that a longer period of B cell depletion (18 months) ([3, 9]) could improve the duration of remission and also the rate of complete INS recovery.

Therefore, if we are considering a long period of B cell depletion to treat INS and that most patients were likely to relapse with B cell recovery, it seems interesting to predict the time of B cell recovery and use pre-emptive RTX injections and/or individualized monitoring to avoid B cell repletion during the target period of B cell depletion.

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The aim of our study was to evaluate the duration of B cell depletion after each RTX infusion in patients with SDNS or steroid-resistant nephrotic syndrome (SRNS), to look for ways to predict the duration of each period of B cell depletion, in order to avoid a B cell repletion and INS relapse.

Methods

We retrospectively report the data of 22 patients with a diagnosis of a SDNS or SRNS and a treatment with RTX in a single center. SDNS was defined as two consecutive relapses during tapering or within 2 weeks of discontinuation of steroid treatment. SRNS was defined as persistent proteinuria after treatment with prednisolone at 60 mg/m^2 per day for 4 weeks, and 3 methylprednisolone pulses for 1 week.

Initial RTX infusion was performed with either negative or non-nephrotic range proteinuria (< 250 mg/mmol) without significant decrease of serum albumin levels (> 30 g/L). Premedication with dexchlorpheniramine (2.5–5 mg) and methylprednisolone (0.5 mg/kg) was given prior to each RTX treatment. Cotrimoxazole (20 mg/kg, three times a week) was systematically given to all patients during the period of B cell depletion for pneumocystosis prophylaxis.

Initial RTX course was performed as 1–4 RTX infusions of 375 mg/m^2. CD19 depletion was controlled by flow cytometry assay 1 week after RTX infusion and then monthly in a prospective manner.

Data collected from each patient included the dates of B cell depletion and recovery with the duration of B cell depletion for each RTX infusion, number of relapses, previous immunosuppressive treatment, immunosuppressive treatment at first RTX infusion, the number of RTX courses, estimated glomerular filtration rate (eGFR) at first RTX infusion, the relapse number during RTX treatment, and RTX-related side effects. The 2009 Schwartz formula was used to calculate eGFR using serum creatinine and height.

B cell depletion durations were compared to the first B cell depletion duration and to the previous B cell depletion duration in each patient.

Analysis and graphs were realized with SigmaPlot 12.0 software. Data were summarized as mean and standard error of the mean (SEM) when normally distributed, and as median and range when not normally distributed. Normality test used was Shapiro-Wilk test. p values < 0.05 were considered as statistically significant.

Results

Twenty-two patients (5 girls) were included. Age at diagnosis of INS was 4.15 (1.4–14.6) years. Disease duration before first RTX infusion was 3.1 (0.4–14.8) years. Eighteen patients had SDNS and 4 patients had SRNS.

All patients received oral immunosuppressive agents before first RTX infusion: prednisone (22 patients), methylprednisolone (14, including 7 at first flare-up), levamisole (11 patients), cyclosporine A (CyA, 18 patients), mycophenolate mofetil (MMF, 17 patients), oral cyclophosphamide (9 patients, cumulative dose of 180 mg/kg for 3 months).

Age at the beginning of RTX treatment was 10.1 (4–16.6) years. At first RTX infusion, 14 patients received three immunosuppressive treatments comprising prednisone, calcineurin inhibitor, and MMF. Six patients received 2 immunosuppressive treatments: prednisone/CyA in 3 patients, prednisone/MMF in 2 patients, and one patient CyA/MMF. One patient received only prednisone and another only tacrolimus.

At the time of RTX infusion, all patients had negative proteinuria or low degree of proteinuria (< 100 mg/mmol of creatininuria).

The oral immunosuppressive regimen was the same in all patients during the course of RTX. Indeed, oral immunosuppressive treatment was stopped 2 months after the first rituximab infusion.

Renal function was normal in 20 patients. Two patients had eGFR between 60 and 90 mL/min/L 73m^2 at first RTX infusion.

CD19 depletion was obtained in all patients 1 week after RTX infusion.

Total duration of B cell depletion was 26 (6–66) months. Individual post-RTX infusion B cell depletion duration was 5.1 (1.6–14) months. Seventy-six periods of B cell depletions were compared to the first B cell depletion duration and to the preceding B cell depletion duration in the same patient.

Compared to the first B cell depletion duration, 59% of the next B cell depletions had a similar duration within an interval of ± 1 month, and 70% within an interval of ± 2 months (Fig. 1a). Comparing the B cell depletion induced by the previous RTX courses and the following B cell depletion, 58% of patients had a similar duration within an interval of ± 1 month, 79% within an interval of ± 2 months, and in 89.5% of patients within an open interval from – 2 months (Fig. 1b).

Median B cell depletion duration was 5 months (4.75–6.5) for children over 10 years old treated by RTX vs 4.25 months (3–6) for children under 10 years old at the first RTX infusion ($p = 0.15$).

Median B cell depletion duration following the first RTX cure for children who had received 1 to 2 infusions at first cure was 5 months (3.5–6.5) and those who had received 3 to 4 infusions had a median B cell depletion of 6 months (4.5–9.75). There was no statistically significant difference, $p = 0.18$. There was either no significant difference between these two groups concerning the following B cell depletion durations: 4.87 months (3.62–6.5) vs 5 months (4.62–6.38), $p = 0.5$.

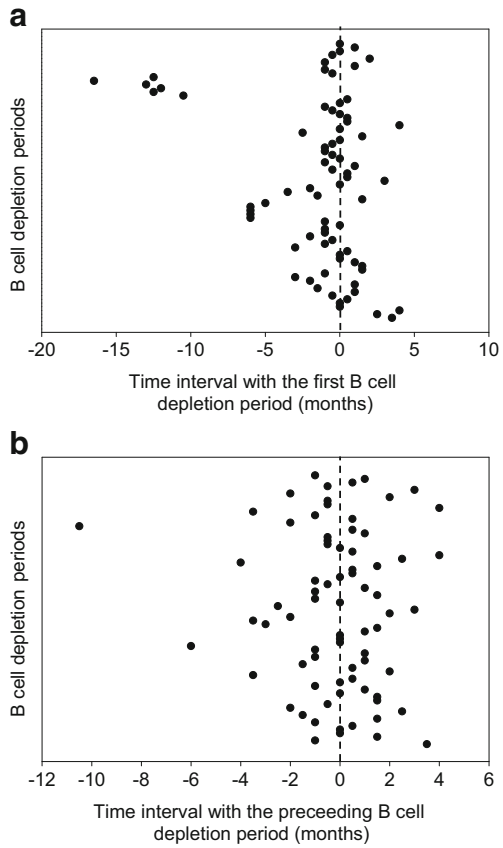

Fig. 1 **a** B cell depletion duration compared to the first B cell depletion duration after rituximab injection in patients with repeated rituximab injections to obtain a depletion period of at least 18 months. The probability of one specific patient to have a depletion period within an interval of − 1/+ 1 month compared to the first depletion period was 59%; for a − 2/+ 2 months interval, the probability was 70%. **b** B cell depletion duration compared to the previous B cell depletion duration after rituximab injection in patients with repeated rituximab injections to obtain a depletion period of at least 18 months. The probability of one specific patient to have a depletion period within an interval of − 1/+ 1 month compared to his/her previous depletion period was 58%; for a − 2/+2 months interval, the probability was 79%. 90% of a depletion periods were less than 2 months shorter than the preceding one in the same patient

Median B cell depletion duration following the first cure of RTX was not statistically different between the patients on 3 immunosuppressive agents compared with patients on 1 or 2 immunosuppressive agents: 5 months (3.25–6) vs 5 months (4–7.5), $p = 0.63$.

No serious adverse effects were observed among the patients having received RTX.

Discussion

It has been more than 10 years that RTX has been used in INS. Initially, the infusion protocol was based on what had been used in lymphoma treatment. Indeed, RTX has been given to over 300,000 lymphoma patients and the standard dose has been 375 mg/m^2 weekly for four doses. This standard dose was naturally also used for INS treatment [8, 10, 11].

However, several studies have found that a single infusion was sufficient to produce a B cell depletion [7, 12]. Thus, it seems useless to repeat RTX infusion every week to induce B cell depletion and also to have a longer B cell depletion. Indeed, our study showed that median B cell depletion duration following the first RTX cure for children who had received 1–2 RTX infusions was not statistically different from those who had received 3–4 RTX infusions. This result was also found in two other series [13, 14]. However, 17 patients received 1 or 2 infusions, while there were only 5 patients who received 3 or 4 infusions, and so, we can suppose that the absence of difference could be linked to the small sizes of the two groups.

The necessary duration of B cell depletion remains an arbitrary parameter in INS. In 2010, Sellier-Leclerc et al. found that all patients who showed B cell depletion over 15 months experienced stable remission of INS, without any ongoing oral treatment and despite the subsequent recurrence of circulating B cells for several months [13], and Ravani et al. showed that successful response to RTX was associated with older age at diagnosis and longer time to reconstitution of circulating CD20 [9].

The hypothesis that efficacy is higher if B cell depletion is longer seems confirmed by more recent studies: Kamei et al. found a very high rate of relapse (94%) in patients after a median duration of depletion under 6 months [15], while Sellier-Leclerc et al. showed that 63% percent of patients with SDNS did not relapse after definitive CD19 recovery over a follow-up of 17.4 months. In this study, the minimum CD19 depletion period was 15 months obtained by repeated RTX infusions [3]. In 2012, among 37 patients with SDNS, Kemper et al. found that the cumulative proportion of patients in long-term remission increased after repeated courses of RTX [5].

Therefore, if a long period of B cell depletion is considered, it is very interesting to predict B cell depletion duration, in order to avoid intermittent B cell repletion and relapse risk. Indeed, in previous reports and in our own clinical practice, nephrotic syndrome relapse frequently occurs just after CD19 recovery [12]. Therefore, if the B cell count is not checked frequently, B cell repletion could be missed and a relapse may occur. Such an intermittent relapse usually requires an oral steroid course, a possible hospitalization, and a delay of the next RTX infusion. Therefore, if the physician choses a longer duration of B cell depletion, undetected B cell repletion should be avoided.

The aim of our study was to compare the duration of B cell depletion in a patient to their previous depletion. There is a correlation between B cell depletion periods in the same patient. The following duration of B cell depletion can be at least partially predicted, as in 90% of cases, the next B cell depletion duration is within an interval opening from 2 months prior

to the previous depletion. For example, if the first B cell depletion lasted for 6 months, 9 times out of 10, the next RTX infusion will deplete B cells for at least 4 months. In this case, it is more efficient to focus on the period "at risk" of repletion, which means from 4 months after RTX infusion.

However, there are some disadvantages of introducing RTX without doing monthly B cell monitoring. Indeed, we can suppose that as the number of doses of RTX increases, it exposes the patient to a greater risk of infection, infusion reaction, or development of human anti-chimeric antibody.

Strictly speaking, SDNS and SRNS are not the same at all. We can thus consider that our cohort is not homogeneous. However, only patients with negative or low-degree proteinuria (< 100 mg/mmol of creatininuria) were included. And initially, our inclusion criteria for these SDNS or SRNS patients were calcineurin-inhibitor dependency. Nineteen out of twenty-two patients still had calcineurin inhibitor at the time of the first RTX infusion, and in two patients, CyA had been switched to MMF resulting in higher relapse rate, while one patient tolerated neither MMF nor CNI and was started on RTX while being on high-dose steroids.

Our study has some limitations. The influence of relapse on B cell depletion is a point that deserves to be clarified; unfortunately, our patient and relapse number was not sufficient to answer this question. The impact of oral immunosuppressive drugs on B cell depletion duration after RTX was not checked, because all immunosuppressive drugs were stopped 2 months after the first RTX injection. Our study merely proves our clinical impression, and pharmacokinetic and pharmacodynamic analyses are necessary to draw more precise conclusions on the link between RTX infusion and B cell depletion.

In conclusion, once the individual time interval until B cell recovery is determined, the monitoring could be individualized by targeting the expected date of B cell recovery or by performing pre-emptive RTX injections. This may reduce relapses and facilitate treatment management.

Compliance with ethical standards

The study complies with the Helsinki Declaration and was approved by the local institutional ethics committee.

Conflict of interest The authors declare that they have no conflict of interest.

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