Long-term follow-up after rituximab for steroid-dependent idiopathic nephrotic syndrome


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Abstract

Background. In patients with refractory steroid-sensitive nephrotic syndrome (SSNS), treatment with rituximab has shown encouraging results; however, long-term follow-up data are not available.

Methods. We performed a retrospective analysis of 37 patients (25 boys) with steroid-dependent nephrotic syndrome who were treated with rituximab (375 mg/m² given weekly for one to four courses). Long-term follow-up data (>2 years, median 36, range 24–92.8 months) are available for 29 patients (12 boys).
Results. Twenty-six of 37 (70.3%) patients remained in remission after 12 months. Relapses occurred in 24 (64.8%) patients after a median of 9.6 (range 5.2–64.1) months. Time to first relapse was significantly shorter in patients receiving one or two compared to three or four initial infusions. In the 29 patients with long-term follow-up for >2 years, 12 (41%) patients remained in remission after the initial rituximab course for >24 months, 7 (24.1%) patients without further maintenance immunosuppression. Nineteen children received two to four repeated courses of rituximab increasing the total number of patients with long-term remission to 20 (69%), remission including 14 (48%) patients off immunosuppression. The proportion of patients with long-term remission was not related to the number of initial rituximab applications. No serious side effects were noted.

Conclusion. Rituximab is an effective treatment option in the short- and long-term control of treatment refractory SSNS. Further controlled studies are needed to address optimal patient selection, dose and safety of rituximab infusions.

Introduction

Paediatric idiopathic nephrotic syndrome is characterized by steroid responsiveness in the vast majority of cases (steroid-sensitive nephrotic syndrome, SSNS) [1]. Although the initial treatment with prednisone (60 mg/m²) leads to long-term remission in a variable proportion of patients, up to 40–60% will relapse. In this situation, especially in the case of steroid dependency (i.e. relapses during steroid treatment or shortly after discontinuation), this is a major problem [2]. Some patients develop a refractory course despite the use of alternative treatments, such as levamisole, mycophenolic acid (MPA) [3, 4] and calcineurin inhibitors [5, 6]. Repeated cytotoxic treatment is one option for these patients but can be associated with significant long-term side effects [7, 8]. Therefore, SSNS is no longer regarded as a benign condition [9] because also in refractory patients, relapses occur into adulthood and long-term treatment is associated with substantial toxicity [10, 11].

The exact pathogenesis of SSNS is unknown, although immunological factors seem to play a major role. Shalhoub [12] hypothesized that lipoid nephrosis (i.e. SSNS) is a disorder of T-cell dysfunction but recently several clinical and immunological findings indicate an involvement of B-cell immunity in SSNS [13] in relapses, especially in patients with steroid dependency.

Several reports show a role of anti-B-cell treatment in steroid-dependent nephrotic syndrome (SDNS), which is difficult to control [14] including larger series from France [15], Japan [16, 17], India [18] and an international study [19]. It seems that the majority, if not all, patients with SSNS respond and in many instances, a reduction of steroids and/or maintenance immunosuppression was possible, although in the study by Sellier-Leclere et al. [20] 3 of 22 patients with SDNS did not respond. In another recently published prospective study, Ravani et al. [21] showed that rituximab and a combination of reduced dose of prednisone and calcineurin inhibitors are non-inferior in maintaining remission of the nephrotic syndrome.

Unfortunately, however, long-term follow-up data are not available. This is problematic since many patients relapse within the first 9–12 months after rituximab. We established a registry in the German Society of Paediatric Nephrology (GPN) in order to assess the effect, complications and long-term response after rituximab in SSNS. We are now able to report on 37 patients with treatment refractory SSNS, including 29 patients, in whom long-term follow-up is at least 2 years.

Materials and methods

All patients were steroid responsive at initial presentation and were treated according to the standards of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN, now GPN) [22]. A registry for patients treated with rituximab was initiated in 2007; this study was performed according to the Declaration of Helsinki and was approved by the ethical committee of the University of Hamburg and was subsequently adopted by the local ethical committees of the participating centres. Almost all German paediatric nephrology centres participated in this registry. Patient data are presented in Table 1.

Treatment of relapses of SSNS was in accordance with the APN, i.e. administration of prednisone 60 mg/m² day until urinary remission was achieved for 3 days, followed by alternate day prednisone in a dosage of 40 mg/m² for 4 weeks. After this period, steroid treatment was stopped and tapering was performed only in two individual patients.

All patients had steroid dependency as defined according to the APN standard definition as at least two relapses during alternate day (40 mg/m²) treatment with prednisone or within 14 days after stopping this treatment. Inclusion of patients was at the discretion of the local centre, but all patients continued to have frequent relapses or steroid dependency despite alternative immunosuppressive treatment except in one patient, where the parents refused alternative treatment other than rituximab. Prior to rituximab, eight children had received levamisole, 25 cyclophosphamide, 34 cyclosporine and 26 MPA, respectively (Figure 1, Table 1). Fifteen children had received at least two of these medications, 14 children received three and four children received four treatments, respectively, in varying sequence (Table 2).

### Table 1. Patient characteristics

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<th>Age at onset of NS (years)</th>
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<td>Mean (SD)</td>
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<td>Number of repeated rituximab courses</td>
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<tr>
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<td>n = 7 (six with single infusions and one with two infusions)</td>
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<tr>
<td>Two</td>
<td>n = 8 (i.e. total of 16 courses: 11 single infusions, 1 with two and three infusions, respectively, 3 with four infusions)</td>
</tr>
<tr>
<td>Three</td>
<td>n = 2 (all single infusions)</td>
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<td>Four</td>
<td>n = 2 (all single infusions)</td>
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</table>
The rituximab dose used was 375 mg/m²/week at the discretion of the local centre. Twenty-one patients received one single infusion, six patients received two infusions, one patient received three infusions and nine patients received four infusions, respectively. Patients receiving one or two infusions at their first treatment course were compared to those receiving three or four infusions. A chemoprophylaxis with trimethoprim was recommended during B-cell depletion to reduce the risk of *Pneumocystis carinii* infection.

Patient data reported to the registry included: initial dose of rituximab, occurrence of and date of relapses, response to treatment, number of repeated rituximab course, discontinuation of maintenance immunosuppression and complications.

Long-term remission was defined as remission lasting at least 2 years (on or off maintenance immunosuppression). Data on lymphocyte populations were not recorded systematically.

Data were analysed with SPSS version 13.0. Differences between groups were tested with Mann–Whitney U-test because data were not distributed normally and Fisher’s exact test. Kaplan–Meier analysis was performed with log-rank testing. A P-value < 0.05 was considered statistically significant.

Results

Short-term follow-up at 12 months

After the initial rituximab treatment, 26/37 (70.3%) patients remained in remission for 12 months. After rituximab, steroids were discontinued in 35 of 37 (94.5%) patients after a median of 1.3 (0.37–6) months. Maintenance immunosuppression was discontinued completely in 22 patients and continued at the discretion of the local centre in 15 patients (steroids *n* = 2, calcineurin inhibitor *n* = 3, MPA *n* = 10, combination *n* = 3).

Relapses

Twenty-four of 37 (64.8%) patients developed relapses at a median of 9.6 (5.2–64.1) months after the initial course of rituximab. There was no difference in time to first relapse in patients who continued maintenance immunosuppression versus those who did not (13.2 ± 7.5 versus 17.6 ± 19.2 months, *P* = 0.43). Also, time to first relapse was not different in 14 patients presenting with the nephrotic syndrome before the age of 5 years compared to children presenting after 5 years (18.6 ± 17.3 versus 11.8 ± 5.6; *P* = 0.59). Time to first relapse was 14.5 ± 8.5 months in 11 children <13.3 years at rituximab infusion compared to 14.7 ± 15.3 months in 13 patients who were >13.3 years. Time to first relapse was 10.3 ± 3.5 months in 16 patients who received one or two doses of rituximab compared to 23.3 ± 18.7 months in 11 patients who received three or four doses (*P* < 0.05).

Long-term results follow-up (>2 years)

Twenty-nine patients were followed for >2 years. Of these, 12 (41%) patients remained in remission for at least 24 months. In seven of these 10 children, maintenance immunosuppression was discontinued. Eight of these 10 children with long-term remission received one or two initial infusions and four children three or four rituximab infusions (*P* = n.s.). Kaplan–Meier analysis did not reveal a difference (*P* = 0.862) in the proportion of patients reaching long-term remission with these different regimens (Figure 2).

Repeated courses of rituximab

Nineteen (of 37) patients had a minimum of two courses of rituximab, including one patient (Patient 2) who had an initial remission of >24 months. The number of courses and infusions is presented in Table 1. Eight patients received two courses, of these, six achieved long-term remission (four off maintenance immunosuppression). Ten patients received three courses and four patients received four courses. Long-term remission was achieved in 2/10 and 1/4 patients, respectively, all off further treatment. Two patients received a fifth dose of rituximab and relapsed after 5.8 and 10.8 months, respectively. Thus, after repeated courses of rituximab, 20 of 29 patients (69%) remained in long-term remission and 20 (48%) off immunosuppression (Figure 3).

Treatment was well tolerated. Two patients experienced itching at the time of first infusion that responded to antihistamines and did not recur at repeated rituximab infusions. No infectious complications were noted and no patient experienced acute lung injury or progressive multifocal encephalopathy.

Discussion

This retrospective study provides long-term follow-up of a large cohort of patients receiving rituximab for SDNS. Although this is neither a prospective nor a controlled study, results confirm that many patients reach stable remission after rituximab. Long-term remission can be observed in up to 41% of patients, sometimes after one single dose of rituximab. Repeated courses of rituximab in patients with frequent relapses of a nephritic syndrome were well tolerated and increased the cumulative number of patients in long-term remission of >2 years. The initial dose and the continuation of maintenance immunosuppression does not seem to have an impact on long-term benefit.

The benefit of rituximab in patients with SSNS, which is relapsing despite maintenance immunosuppression with cyclosporine or other drugs, has been established. In the study of Guigonis et al. [15], patients received two to four infusions of 375 mg/m² of rituximab including seven patients who were nephrotic at the time of treatment; three of these achieved a full remission. In this study, maintenance immunosuppression (including steroids) could be reduced in 86% of patients following rituximab, but the majority of patients received some medication and median follow-up was only 9.5 months. Another recent study from Kamei et al. [17] from Japan showed that a single dose of rituximab was able to initiate steroid-free remission in all 12

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**Fig. 1.** Drug treatment prior to rituximab.
patients included. However, 75% of patients relapsed and only three had sustained remission for >1 year. Fujinaga et al. [16] addressed the response to rituximab in 10 patients who relapsed despite cyclosporine maintenance treatment, resulting in a decrease of relapse rate. However, in most patients, steroids or calcineurin inhibitors were continued. Also, a recent international study reported a superior initial response of steroid-sensitive (82%) compared to steroid-resistant patients (44%); again, median remission in this report was only 4.5 (range 1–10) months [21]. A recent series by Gulati et al. [18] following patients for a mean of 16.8 months, a good response of steroid-sensitive patients was confirmed leading to a 12-month remission rate of 83.3% comparing to our results.

In our series, rituximab was given after steroid-induced remission was achieved; in almost all patients, steroids could be discontinued relatively rapidly. Also, in most patients, maintenance immunosuppression (usually cyclosporine or MPA) was stopped as well. This aspect has not been addressed systematically in children; many studies used continuation of maintenance immunosuppression, e.g. with MPA or calcineurin inhibitors (Guignois et al. [15], Fujinaga et al. [16], Ito et al. [23]). This lead to an editorial statement, that maintenance immunosuppression with MPA is an attractive option, that deserves further study [24]. Our results, however, indicate that in many patients, a period without treatment was possible, a fact that is greatly appreciated by many patients and families since most patients have been on maintenance immunosuppression for years. Whether this is related to B-cell recovery is unknown; however, strategies to repeat rituximab in order to extend B-cell depletion did not prevent relapses either [20].

The rate of remission at 12 months was 70.3%, which is comparable to the studies by Gulati with 83.3%. The corresponding times to first relapse was also in the range published by other larger series, although maintenance treatment varied somewhat: in the study by Gulati, it was 11.2–2.7 months, while in the Kamei study, patients relapsed after a median of 129 days; whether this is solely due to the reduced dose protocol or other, e.g. ethnic, reasons is unknown. In our

Table 2. Demographic data of patients

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<th>Age at RTX (years)</th>
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<th>Initial RTX</th>
<th>Maintenance IS</th>
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</tbody>
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aPatients 1–12 are those with long-term remission after initial RTX course. RTX, rituximab; LEV, levamisole; CPO, cyclophosphamide; CI, calcineurin inhibitor; IS, immunosuppression; pred, prednisone; n.r., no relapse.
patients with one or two infusions, time to relapse in the low- 
dose group was significantly longer than in the Kamei study, 
so geographic and genetic factors may play a role. Analysis of 
risk factors in our study did not show an impact of continu-

ation of maintenance immunosuppression or young age at 
presentation. Patients with three or four infusions of rituximab 
seem to have a longer time until first relapse, but this has no 
impact on long-term remission rate. Clearly, however, these 
parameter need to be studied prospectively since individual 
variability may be wide.

Our study provides long-term follow-up data in a large 
proportion of steroid-sensitive patients. Despite the risk of 
relapses, we found a significant rate of long-term remission 
in 37% of patients who have been treated with rituximab. 
This compares to old and new data after e.g. cytotoxic 
treatment [11] although the cohort under discussion belongs 
to a higher risk group since all patients had pre-treatment with 
other drugs, often in combination. Interestingly and in con-
trast to the initial relapse free interval, the intensity of initial 
treatment (one or two versus three or four doses) does not 
seem to influence long-term remission rate: eight patients 
remained in long-term remission after only one infusion of 
rituximab. Thus, individual and unknown factors may be 
responsible for this effect.

One important issue is, whether initial intensification of 
treatment (e.g. to extend B-cell depletion) will be able to 
increase the number of patients in long-term remission. 
This may well be, but on the other hand, 41% of patients 
reached long-term remission after one initial course, often 
after a single infusion. Ideally, prognostic factors should be 
evaluated to decide which patients require repeated treat-
ment and those who do not.

Repeated infusions of rituximab have been administered 
in more than half of our patients because a frequently re-
lapsing course developed again. Interestingly, the cumulative 
proportion of patients in long-term remission increased 
after repeated courses but seems to disappear after the fifth 
treatment, raising the question how to proceed with these 
patients. Whether this phenomenon is due to an altered 
response to rituximab or disease activity cannot be solved 
by the present study.

The advantage of rituximab administration is its long-
lasting effect that is important since in some patients non-
compliance, especially with calcineurin inhibitors may 
complicate the course [25, 26]. Interestingly, most patients 
presented here are in their teens, where non-adherence be-
comes a frequent problem and interestingly, the median age 
at first rituximab administration in our cohort was 13.3 
years supporting this notion.

Recently, complications of rituximab treatment have been 
reported, including death due to pulmonary complications [27, 
28]. Also, patients with progressive multifocal leucoencephal-
opathy have been reported after rituximab in lupus nephritis 
and other disorders so that potential risks have to be balanced 
against the potential benefits. In this respect, our long-term data 
are important since no long-term side effects such as malign-
nancy or serious infections have been documented in the co-
hort treated, with follow-up ranging to >8 years.

SSNS may be an immunological disorder and especially 
T-cell immunity was thought to play a dominant role. There-
fore, the success of anti-B-cell treatment was surprising, 
although specific B-cell abnormalities have been docu-
mented in SSNS [13]. Furthermore, it is now evident that 
rituximab treatment results in multiple immunological 
changes of the immune system. Including T-cell functions 
[29, 30], explaining the effect in SSNS and other glomerular 
disorders, where a T-cell pathogenesis has been implied.

In summary, rituximab is an effective new option for pa-
tients with SSNS that continue to relapse despite multidrug 
treatment. Future studies are needed to address the immuno-
logical effects, optimal doses and short- and long-term safety, 
which will be the main issue to decide, whether rituximab 
should also be offered to less complicated cases.

Conflict of interest statement. None declared.

References

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