Pediatr Nephrol (2014) 29:1305–1311
DOI 10.1007/s00467-013-2529-1

REVIEW

Is rituximab effective in childhood nephrotic syndrome? Yes and no

Markus J. Kemper · Anja Lehnhardt · Anna Zawischa · Jun Oh

Received: 20 May 2013 / Revised: 21 May 2013 / Accepted: 22 May 2013 / Published online: 3 July 2013

Abstract The idiopathic nephrotic syndrome (i.e. MCNS and FSGS) in children has been regarded as a disorder of T-cell function. Recent studies, however, also describe abnormalities of B-cell function. This supports the use of B-cell modulating treatment for idiopathic nephrotic syndrome (INS), especially rituximab, which has been used in other glomerular disorders as well. Many studies indicate that rituximab is effective in steroid-sensitive and -dependent nephrotic syndrome, by either inducing long-term remission or reducing relapses. In most series, children with primary (and recurrent) focal segmental glomerulosclerosis (FSGS) do not respond as well. The exact mechanisms of action of rituximab (as well as those of the other treatment options) in INS are as yet unclear. In addition to hosting mechanisms a direct stabilizing effect on the podocyte may also be of relevance, especially in FSGS. Although results are encouraging especially in steroid-sensitive patients, further studies on the clinical use of rituximab and the short- and long-term immunological effects and side-effects are necessary.

Keywords Nephrotic syndrome · Steroid-sensitive · Steroid-resistant · Immunosuppression · Minimal change glomerulonephritis (MCNS) · Focal segmental glomerulosclerosis (FSGS) · Recurrent FSGS · Rituximab

Introduction

The nephrotic syndrome in children is characterized by the triad of heavy proteinuria (>1 g/m^2/day or protein/creatinine ratio> 200 mg/mmol), hypoalbuminemia (<25 g/l) and the presence of generalized edema. So-called "idiopathic" nephrotic syndrome (INS) is the most frequent cause and consists mainly of two histological subtypes, the minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). Around 80–90 % of pediatric cases show minimal change disease on histological examination and most of these children respond to steroids (steroid-sensitive nephrotic syndrome, SSNS) as shown by the International Study of Kidney Diseases in Children (ISKDC), alleviating the need for an initial renal biopsy [1].

In contrast, the definition of steroid-resistant nephrotic syndrome (SRNS) by the ISKDC as persistent proteinuria after a 4-week course of oral prednisone (60 mg/m^2/day) is still used in clinical practice. A renal biopsy is indicated in this situation and the majority of patients with SRNS will have FSGS, MCNS, or rarely diffuse mesangial proliferation (DMS). Treatment options in steroid-resistant nephrotic syndrome vary, but in the past few years considerable progress has been made by the use of calcineurin inhibitors and mycophenolate [2]. Unfortunately, a significant proportion of patients do not respond to conventional treatment, indicating the need for some alternative treatment approaches.

Treatment targeting B-cells has been used successfully in INS, e.g., oral or intravenous cyclophosphamide, but nowadays, specific B-cell-depleting antibodies are available, especially anti-CD20 (rituximab, RTX). Since the response to conventional treatment varies significantly between MCNS and FSGS, it is likely [3] that the pathogenesis of these disorders is also different (we will not discuss genetic causes of FSGS in this article). Therefore, MCNS and FSGS (including recurrent FSGS) and the discussion of the role of rituximab in the treatment of these disorders will be discussed separately.

MCNS: steroid-sensitive nephrotic syndrome

In 1974, Shalhoub [4] hypothesized that idiopathic nephrotic syndrome is a disorder of T-cell function because of the clinical

Markus J. Kemper and Anja Lehnhardt contributed equally

M. J. Kemper (✉) · A. Lehnhardt · A. Zawischa · J. Oh
Pediatric Nephrology, University Medical Center
Hamburg-Eppendorf, Martinistrasse 52,
20246 Hamburg, Germany
e-mail: kemper@uke.uni-hamburg.de

association with Hodgkin's disease, remission after measles infection, and for several other reasons. This was supported by many immunological findings [5] and also by the response to treatment with T-cell-specific immunosuppressants, e.g., calcineurin inhibitors. Recent data show that B-cell immunity is also altered in the idiopathic (mainly steroid-sensitive) nephrotic syndrome, e.g., persisting hypogammaglobulinemia in remission or an increase in the B-cell activation markers, especially in steroid dependency [6, 7]. Also, the therapeutic effect of immunosuppressants acting on B-cells (e.g., cyclophosphamide, partly mycophenolate) supports the role of altered B immunity in INS, although few studies have been performed yet in this field [8].

In our opinion, finding arguments for (or against) immunological treatment specifically for T- or B-cells in INS is difficult. First of all, despite the abundance of data, the exact immunological pathogenesis of INS is still unknown. Second, recent immunological studies show that a strict distinction of T- or B-cell responses is not useful, as there is a close network of immunological interaction between these two arms. Third, this applies to the action of immunosuppressive drugs, even if they target just one cell type. This is also true for anti-B-cell treatment with rituximab, because a variety of immunological (and non-immunological) mechanisms are involved, that go far beyond the circulating CD20+ B-cell (Fig. 1).

Rituximab effects: beyond the B-cell

B-cells do not only contribute to immune regulation by producing antibodies, but also by interacting with T-cells, producing regulatory cytokines and influencing apoptosis. It can therefore be assumed that the immune-modulatory effect of rituximab goes beyond simply reducing the number of antibody-producing and antigen-presenting B-cells. The extent and duration of rituximab's action seem to be of great inter-individual variability, especially if concomitant immunosuppressive treatment is given. After a single dose of rituximab only B-cells in the peripheral blood, but not secondary lymphoid organs, are depleted and the functional properties of the remaining B-cells are changed [9]. Different mechanisms by which rituximab influences T-cell immunity in autoimmune disorders are discussed in the literature: reducing T-cell number and proliferation [10, 11] as well as modulating T-cell subsets [12, 13]. In patients with non-Hodgkin lymphoma, rituximab administration results in a transient, dose-dependent T-cell inactivation [14]. Therefore, the fact that rituximab is a B-cell-depleting agent, it exerts beneficial effects in patients with nephrotic syndrome, does not necessarily refute the T-cell hypothesis by Shalhoub. Studies explicitly examining the effect of rituximab on the T-cell compartment and its reactivity in children with nephrotic syndrome are needed.

It is well established that the B-cell activating factor of the TNF family (BAFF) rises in response to rituximab and this may contribute to its immune-modulatory effects [15]. Systematic investigations of serum BAFF in patients with nephrotic syndrome and correlation with disease activity and response to rituximab treatment may be of interest; in this situation, repopulation of B-cells may be very interesting. For instance, in children who received rituximab for acute

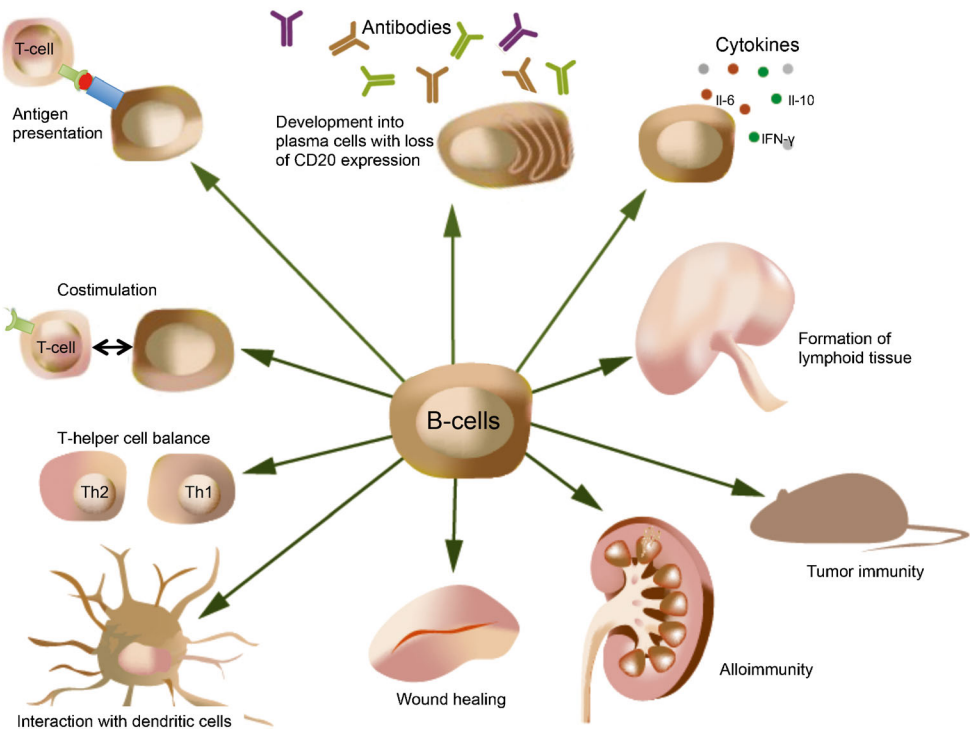

Fig. 1 B-cells are multifunctional and regulate immune homeostasis in many ways; often, these effects are antibody-independent

rejection after renal transplantation, repopulating B-cells showed a mostly naive phenotype [16].

Use of rituximab in steroid-sensitive and -dependent nephrotic syndrome: from case reports to large series

The use of rituximab in steroid-sensitive nephrotic syndrome started after the initial report by Benz et al. [14], who used this drug in a patient with nephrotic syndrome who also developed idiopathic thrombocytopenia purpura (ITP) both went into remission with rituximab therapy after other treatments had failed. Several other case reports followed, but recently larger retrospective series have been published, which showed a beneficial effect in most steroid-sensitive patients [17–28]. Importantly, mainly patients with a refractory course were included in these studies, including patients who had relapsed and remained steroid-dependent, despite intensive maintenance immunosuppression. For an overview see Table 1.

Retrospective series showed that patients were often able to reduce maintenance immunosuppression and some studies showed that patients achieved a full remission (varying between 25 and 83 %), often despite stopping all maintenance medication [17, 18, 25–28]. The international study group of Prytula et al. [21] demonstrated that maintenance immunosuppression including steroids could be reduced in most patients (86 %) following rituximab. Relapses after rituximab were related to the degree of B-cell depletion in some studies; however, some patients did not relapse, despite high CD19 counts [18, 26].

In addition to retrospective series the prospective study by Ravani et al. [23] documented the non-inferiority of rituximab compared with patients treated with prednisone and calcineurin inhibitors. Reduction of steroids was possible in almost all patients treated with rituximab, but not in the control arm, and relapses were significantly less frequent in the RTX group.

Kamei et al. [18] showed that a single dose of rituximab was able to initiate steroid-free remission in all patients. However, 75 % of patients relapsed and only 3 had sustained remission for more than 1 year. On the other hand, we reported results from a German registry and the duration of remission of patients receiving 1 or 2 vs those receiving 3 or 4 infusions of rituximab was not different [26].

While long-term remission after RTX with no further immunosuppression is the ideal outcome measure (cure of INS), steroid-sparing or reducing the number of relapses may also be deemed a success. Most patients treated with rituximab had a complicated (refractory), "difficult to treat" course and were exposed to a variety of long-term potentially toxic treatments. Previously, repeated cytotoxic treatments were used for these patients [29]. Thus, rituximab is at least an additional therapeutic option for patients with difficult-to-treat, steroid-sensitive nephrotic syndrome. Looking at the rituximab studies, however, one feels that outcome parameters should be more standardized and are often too descriptive.

Steroid-resistant nephrotic syndrome and recurrence of FSGS after renal transplantation

The pathogenesis of FSGS (except the genetic causes) is also not clear. Some data suggest a (soluble) host factor, e.g., produced by the immune system causing FSGS. This would explain, for example, the recurrence after transplantation; in this respect the sUPAR has recently become the most intensively discussed mediator [30]. The presence of a host factor is illustrated nicely by a case by Gallon et al. [31], where a living-related graft developed nephrotic syndrome after being transplanted into her brother with FSGS, but could be saved after being re-transplanted into another patient. Other studies look at structural changes, and just as an example one recent study showed increased expression of miR-193a in non-genetic FSGS, which inhibits WT1 expression [32]. Transgenic expression of the microRNA miR-193a in mice rapidly induced FSGS. As mentioned, treatment of primary non-genetic FSGS nowadays still includes immunosuppression; however, in addition to modulating the immune-response the effect of immunosuppressive treatment may be partially explained by a direct stabilizing effect on the podocyte, which has been shown nicely by Faul et al., especially for cyclosporine [33].

Rituximab and the podocyte

Non-immunological mechanisms of action on the podocyte have also been described for rituximab [34]. Fornoni et al. examined CD20 expression in kidney biopsies and suggested that rituximab has a therapeutic benefit through a non-immunological mechanism [34]. It is well known that rituximab can recognize CD20 on B-lymphocytes, but may also bind sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) protein. Kidney biopsies from patients with recurrent FSGS after transplantation had less SMPDL-3b-positive cells per glomerulus compared with the stainings from nonrecurrent FSGS patients. In podocytes rituximab was able to prevent SMPDL-3b down-regulation. Overexpression of SMPDL-3b or treatment with rituximab was able to prevent the damage of the actin cytoskeleton in podocytes and reduced podocyte apoptosis caused by the patient's sera. These remarkable data support a new model of an additional non-immunological mechanism for rituximab in (post-transplantation) FSGS.

Clinical results: rituximab in primary and recurrent FSGS

The response to rituximab in primary idiopathic FSGS or SRNS seems to be much more variable and less optimistic than in SSNS (Table 2). Initial reports were highly encouraging [35]; however, these results could not be confirmed by other series [20, 21, 26, 36–38]. An international registry [21] reported a superior initial response of steroid-sensitive (82 %) compared with steroid-resistant patients (44 %). In an American–

Table 1 Rituximab in children with steroid- or cyclosporine-dependent nephrotic syndrome

Study	*n*	Age at RTX (years)	RTX dose	Response long-term remission	Relapses	Comment
Tellier et al. [28]	18	Median 10.4	375 mg/m^2×1–4 Repeated with B-count >1 %	22 % sustained remission 44 % long-term remission	56 % in first 12 months	Repeated dose owing to B-cell recovery
Ito et al. [27]	55	Median 11.3	375 mg/m^2×1 in 85 % of patients	77 % stopped steroids 31 % stopped CNI	51 %	Fewer relapses if maintenance IS had been continued
Kemper et al. [26]	37	13.4 (range: 6.4–18)	375 mg/m^2 weekly 1–4×	Long-term remission 41 % after 2 years, 24.1 % without immunosuppression	65 %	No difference 1 or 2 vs 3 or 4 initial infusions
Sellier-Leclerc et al. [25]	39	12. ± 0.7 years	Repeated doses to keep CD19 count <1 %	63 % no relapse with repeated doses	37 %	36 % side-effects, mostly transient
Sinha et al. [24]	10	12.2 2.3	375 mg/m^2×3 or tacrolimus	No difference in relapse rate at 12 and 18 months; 67 % reduction steroids vs 43.6 in tacrolimus-treated patients		Patients pre-CNI treatment (retrospective analysis, non-inferiority)
Ravani et al. [23]	54 27 randomized	11 ± 4	375 mg/m^2×1 or 2 or continue standard therapy	70 % reduction in proteinuria. Fewer relapses and higher rate being drug-free in RTX arm	18.5 % risk of relapse (vs 48.1 %)	Randomized open label study
Ito et al. [22]	9		375 mg/m^2×1	Lower relapse rate (0.4 vs 2.3/year) in patients with MMF after RTX		MMF maintenance (historical control)
Prytula et al. [21]	28		375 mg/m^2×1 or 4 or 2×750 mg/m^2 every second week	Full remission 61 %	11 % no response	International registry/ questionnaire
Gulati et al. [20]	24	11.7 ± 2.9	400 ± 20.7×2	Remission in 83 % after 12 months Remission in 71 % after last follow-up	0.2 ± 0.3 episodes/ patient/year	
Sellier-Leclerc et al. [19]	22	Mean 13.5	375 mg/m^2 weekly 1–4×	41 % long-term remission		Retreatment in 18 patients to maintain B-cell depletion
Kamei et al. [18]	12	12.7 ± 3.9 years	375 mg/m^2×1	25 % despite B-cell recovery	75 % after 1 year	
Guigonis et al. [17]	22	14.3 (6.3–22.1)	375 mg/m^2 weekly 2–4×; additional courses if CD19 count <1 %	Response in 86 % 3 patients with non-response	20 %	Reduction of immunosuppression in 85 %; side effects 45.5 %, mostly mild

RTX rituximab; *CNI* calcineurin inhibitor

Table 2 Rituximab in children with primary steroid-resistant nephrotic syndrome

Study	*n*	Histology	RTX dose	Response	Comment
Ito et al. [27]	19		375 mg/m^2×2.3 ±1.4	−31.5 % complete remission, −31.5 % partial remission −In 29 % discontinuation of prednisone possible	1 nonresponder with WT1 mutation
Magnasco et al. [38]	31		375 mg/m^2×2	No change in proteinuria	Remission of proteinuria in 6 delayed resistant patients
Zachwieja et al. [37]	16	Steroid-resistant (14)	375 mg/m^2×4	44 % remission	
Kari et al. [36]	4	2 FSGS	375 mg/m^2×1	1 patient partial response, 3 non-response	
Gulati et al. [20]	33	MCNS 17 FSGS 16	4× 375 mg/m^2 weekly	Complete remission 20.8 %, PR 25 %	Including 3 adults Primary resistance 5
Prytula et al. [21]	27	MCNS 40.5 %, FSGS 40.5 %	375 mg/m^2×1 or 4 or 2×750 mg/m^2 every second week	Full remission 22 % Proteinuria, serum albumin >30 g/l: 22 % Proteinuria, serum albumin 20–30 g/l: 22 %	Primary resistance 34 %
Bagga [35]	5	MCNS 2 FSGS 3	375 mg/m^2×4	3/5 complete remission 2/5 partial remission	2 patients with late resistance

FSGS focal segmental glomerulosclerosis; *MCNS* minimal change nephrotic syndrome

Indian series by Gulati [20], extending their previous experience [35], response to rituximab was worse than initially described, but still 27.1 % reached full remission and 21.1 % partial remission.

A recent open-label, randomized trial comparing two doses of rituximab with standard treatment with steroids and calcineurin inhibitors [38] did not show a reduction in proteinuria after 3 months. However, at a closer look 3 patients with "delayed-resistant" response entered remission with reduction of steroids and calcineurin; this also occurred in 3 "delayed-resistant" patients in the control arm. Inclusion of "delayed-resistant" or secondarily resistant patients may explain the difference between studies, since in the initial series by Bagga [35], 2 patients with initial steroid sensitivity were included and other patients had also been successfully treated with other drugs previously. As a further example in an unpublished series of 13 children with steroid-resistant nephrotic syndrome from Germany only 23 % showed a long-term benefit of rituximab, and again those with secondary steroid resistance responded better than those with primary resistance (Kemper, unpublished). Last but not least, one should be aware of potential reporting bias, because it is much more likely that unsuccessful cases will not be published.

Recurrence after transplantation

The use of rituximab in recurrent FSGS after transplantation has been summarized in a recent review [39] describing 39 patients, including 19 children. 64 % of patients achieved complete or partial remission often together with other treatment modalities, such as plasmapheresis. Young age and normal serum albumin levels were associated with a good response. Although a reporting bias for this subgroup of patients has to be anticipated, these data show that under certain circumstances rituximab is a therapeutic rescue option after recurrence of FSGS, which is a serious event. Further studies are necessary, e.g. relating to preemptive or very early treatment, e.g. when proteinuria is still very low indicating that podocyte damage is at an early, potentially reversible stage.

Open issues: rituximab in primary and recurrent FSGS

1. In general studies on the use of rituximab in FSGS (primary and after recurrence in the renal transplant) have to be viewed critically because of a publication bias, and in addition often other treatment modalities have been performed in parallel. It seems that individual factors related to initial presentation and previous treatment need to be characterized in a better way. Steroid resistance according to the ISKDC maybe not be exact enough since a patient with a late response or severe steroid dependency may be overlooked and therefore some authors recommend pulse steroids in the event of an initial nonresponse [40]. Also, a fraction of patients with FSGS respond to steroids (partially or completely) and may have a better prognosis. Thus, there is an overlap in steroid-sensitivity and resistance as well as FSGS and MCNS that needs to be considered when evaluating the effect of any treatment. Lastly, a fraction

of patients have underlying structural (genetic) defects that respond poorly to the available treatment modalities.

2. Although treatment with rituximab in primary steroid-resistant nephrotic syndrome is not always successful, it may well be an option e.g. for late-responders or "delayed-resistant" patients as well as in patients who have gone into remission with standard treatment, but cannot be weaned or relapse on maintenance immunosuppression with rituximab, as indicated by the study by Bagga [35]. Also, optimal dosing, repetition of infusions, and other issues need to be addressed in prospective studies, although these may be difficult to perform because of the heterogeneity of these patients. It may well be that in FSGS timing (early vs rescue; preemptive in the patient after renal transplantation) of rituximab infusion (or other treatment) may well have an impact on treatment outcome.

Future use of rituximab: what about side-effects?

Briefly, although most patients seem to tolerate rituximab quite well [41], severe complications have been described, especially pulmonary complications [42], which can be fatal. In addition, progressive multifocal leukoencephalopathy (PML) has been reported after rituximab in patients with lupus nephritis. Too little is known about the long-term immunological complications after rituximab (hypogammaglobulinemia, effect on B- and T-cell function, response to vaccination, development of malignancy, etc.). Only if the risk/benefit profile proves to be equal to or even better than those of the drugs currently available, extending the indication for rituximab to less complicated patients is justified.

Summary

In summary, rituximab is an effective treatment option for children with steroid-sensitive nephrotic syndrome, but it is much less effective in primary steroid-resistant patients who are unresponsive to conventional treatment. In recurrent FSGS the effect of rituximab is not predictable; however, its use as a last resort to prevent graft loss may be an option in inducing complete or partial remission. Future studies should better define patient characteristics and entry criteria for use in SSNS and these studies need to address the effective dose, treatment modification, and ultimately the long-term risk profile. As yet, it is unclear how many patients reach long-term remission after this drug or become rituximab-dependent.

Financial disclosures None.

References

1. International Study of Kidney Disease in Children (1978) Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int 13:159–165
2. International Study of Kidney Disease in Children (1981) The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. J Pediatr 98:561–564
3. Van Husen M, Kemper MJ (2011) New therapies in steroid-sensitive and steroid-resistant idiopathic nephrotic syndrome. Pediatr Nephrol 26:881–892
4. Shalhoub RJ (1974) Pathogenesis of lipoid nephrosis: a disorder of T-cell function. Lancet 2:556–560
5. Schnaper HW (1989) The immune system in minimal change nephrotic syndrome. Pediatr Nephrol 3:101–110
6. Kemper MJ, Meyer-Jark T, Muller-Wiefel DE (1997) IgG2 deficiency in uremic children is not restricted to peritoneal dialysis treatment. Pediatr Nephrol 11:684–686
7. Kemper MJ, Meyer-Jark T, Lilova M, Muller-Wiefel DE (2003) Combined T- and B-cell activation in childhood steroid-sensitive nephrotic syndrome. Clin Nephrol 60:242–247
8. Dotsch J, Muller-Wiefel DE, Kemper MJ (2008) Rituximab: is replacement of cyclophosphamide and calcineurin inhibitors in steroid-dependent nephrotic syndrome possible? Pediatr Nephrol 23:3–7
9. Kamburova EG, Koenen HJ, Borgman KJ, Ten Berge IJ, Joosten I, Hilbrands LB (2013) A single dose of rituximab does not deplete B cells in secondary lymphoid organs but alters phenotype and function. Am J Transplant 13:1503–1511
10. Monson NL, Cravens P, Hussain R, Harp CT, Cummings M, de Pilar Martin M, Ben LH, Do J, Lyons JA, Lovette-Racke A, Cross AH, Racke MK, Stuve O, Shlomchik M, Eagar TN (2011) Rituximab therapy reduces organ-specific T cell responses and ameliorates experimental autoimmune encephalomyelitis. PLoS One 6:e17103
11. Vigna-Perez M, Hernandez-Castro B, Paredes-Saharopulos O, Portales-Perez D, Baranda L, Abud-Mendoza C, Gonzalez-Amaro R (2006) Clinical and immunological effects of rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. Arthritis Res Ther 8:R83
12. Stasi R, Del Poeta G, Stipa E, Evangelista ML, Trawinska MM, Cooper N, Amadori S (2007) Response to B-cell depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. Blood 110:2924–2930
13. Stroopinsky D, Katz T, Rowe JM, Melamed D, Avivi I (2012) Rituximab-induced direct inhibition of T-cell activation. Cancer Immunol Immunother 61:1233–1241
14. Benz K, Dotsch J, Rascher W, Stachel D (2004) Change of the course of steroid-dependent nephrotic syndrome after rituximab therapy. Pediatr Nephrol 19:794–797
15. Zarkhin V, Lovelace PA, Li L, Hsieh SC, Sarwal MM (2011) Phenotypic evaluation of B-cell subsets after rituximab for treatment of acute renal allograft rejection in pediatric recipients. Transplantation 91:1010–1018
16. Kreuzaler M, Rauch M, Salzer U, Birmelin J, Rizzi M, Grimbacher B, Plebani A, Lougaris V, Quinti I, Thon V, Litzman J, Schlesier M, Warnatz K, Thiel J, Rolink AG, Eibel H (2012) Soluble BAFF levels inversely correlate with peripheral B cell numbers and the expression of BAFF receptors. J Immunol 188:497–503
17. Guigonis V, Dallocchio A, Baudouin V, Dehennault M, Hachon-Le Camus C, Afanetti M, Groothoff J, Llanas B, Niaudet P, Nivet H, Raynaud N, Taque S, Ronco P, Bouissou F (2008) Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. Pediatr Nephrol 23:1269–1279

18. Kamei K, Ito S, Nozu K, Fujinaga S, Nakayama M, Sako M, Saito M, Yoneko M, Iijima K (2009) Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children. Pediatr Nephrol 24:1321–1328
19. Sellier-Leclerc AL, Macher MA, Loirat C, Guerin V, Watier H, Peuchmaur M, Baudouin V, Deschenes G (2010) Rituximab efficiency in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol 25:1109–1115
20. Gulati A, Sinha A, Jordan SC, Hari P, Dinda AK, Sharma S, Srivastava RN, Moudgil A, Bagga A (2010) Efficacy and safety of treatment with rituximab for difficult steroid-resistant and -dependent nephrotic syndrome: multicentric report. Clin J Am Soc Nephrol 5:2207–2212
21. Prytula A, Iijima K, Kamei K, Geary D, Gottlich E, Majeed A, Taylor M, Marks SD, Tuchman S, Camilla R, Ognjanovic M, Filler G, Smith G, Tullus K (2010) Rituximab in refractory nephrotic syndrome. Pediatr Nephrol 25:461–468
22. Ito S, Kamei K, Ogura M, Sato M, Fujimaru T, Ishikawa T, Udagawa T, Iijima K (2011) Maintenance therapy with mycophenolate mofetil after rituximab in pediatric patients with steroid-dependent nephrotic syndrome. Pediatr Nephrol 26:1823–1828
23. Ravani P, Magnasco A, Edefonti A, Murer L, Rossi R, Ghio L, Benetti E, Scozzola F, Pasini A, Dallera N, Sica F, Belingheri M, Scolari F, Ghiggeri GM (2011) Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol 6:1308–1315
24. Sinha A, Bagga A, Gulati A, Hari P (2012) Short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome. Pediatr Nephrol 27:235–241
25. Sellier-Leclerc AL, Baudouin V, Kwon T, Macher MA, Guerin V, Lapillonne H, Deschenes G, Ulinski T (2012) Rituximab in steroid-dependent idiopathic nephrotic syndrome in childhood–follow-up after CD19 recovery. Nephrol Dial Transplant 27:1083–1089
26. Kemper MJ, Gellermann J, Habbig S, Krmar RT, Dittrich K, Jungraithmayr T, Pape L, Patzer L, Billing H, Weber L, Pohl M, Rosenthal K, Rosahl A, Mueller-Wiefel DE, Dotsch J (2012) Long-term follow-up after rituximab for steroid-dependent idiopathic nephrotic syndrome. Nephrol Dial Transplant 27:1910–1915
27. Ito S, Kamei K, Ogura M, Udagawa T, Fujinaga S, Saito M, Sako M, Iijima K (2013) Survey of rituximab treatment for childhood-onset refractory nephrotic syndrome. Pediatr Nephrol 28:257–264
28. Tellier S, Brochard K, Garnier A, Bandin F, Llanas B, Guigonis V, Cailliez M, Pietrement C, Dunand O, Nathanson S, Bertholet-Thomas A, Ichay L, Decramer S (2013) Long-term outcome of children treated with rituximab for idiopathic nephrotic syndrome. Pediatr Nephrol 28:911–918
29. Neuhaus TJ, Fay J, Dillon MJ, Trompeter RS, Barratt TM (1994) Alternative treatment to corticosteroids in steroid sensitive idiopathic nephrotic syndrome. Arch Dis Child 71:522–526
30. Wei C, Trachtman H, Li J, Dong C, Friedman AL, Gassman JJ, McMahan JL, Radeva M, Heil KM, Trautmann A, Anarat A, Emre S, Ghiggeri GM, Ozaltin F, Haffner D, Gipson DS, Kaskel F, Fischer DC, Schaefer F, Reiser J (2012) Circulating suPAR in two cohorts of primary FSGS. J Am Soc Nephrol 23:2051–2059
31. Gallon L, Leventhal J, Skaro A, Kanwar Y, Alvarado A (2012) Resolution of recurrent focal segmental glomerulosclerosis after retransplantation. N Engl J Med 366:1648–1649
32. Gebeshuber CA, Kornauth C, Dong L, Sierig R, Seibler J, Reiss M, Tauber S, Bilban M, Wang S, Kain R, Bohmig GA, Moeller MJ, Grone HJ, Englert C, Martinez J, Kerjaschki D (2013) Focal segmental glomerulosclerosis is induced by microRNA-193a and its downregulation of WT1. Nat Med 19:481–487
33. Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, Chang JM, Choi HY, Campbell KN, Kim K, Reiser J, Mundel P (2008) The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. Nat Med 14:931–938
34. Fornoni A, Sageshima J, Wei C, Merscher-Gomez S, Aguillon-Prada R, Jauregui AN, Li J, Mattiazzi A, Ciancio G, Chen L, Zilleruelo G, Abitbol C, Chandar J, Seeherunvong W, Ricordi C, Ikehata M, Rastaldi MP, Reiser J, Burke GW 3rd (2011) Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med 3:85ra46
35. Bagga A, Sinha A, Moudgil A (2007) Rituximab in patients with the steroid-resistant nephrotic syndrome. N Engl J Med 356:2751–2752
36. Kari JA, El-Morshedy SM, El-Desoky S, Alshaya HO, Rahim KA, Edrees BM (2011) Rituximab for refractory cases of childhood nephrotic syndrome. Pediatr Nephrol 26:733–737
37. Zachwieja J, Silska M, Ostalska-Nowicka D, Soltysiak J, Lipkowska K, Blumczynski A, Musielak A (2012) Efficacy and safety of rituximab treatment in children with primary glomerulonephritis. J Nephrol 25:1060–1066
38. Magnasco A, Ravani P, Edefonti A, Murer L, Ghio L, Belingheri M, Benetti E, Murtas C, Messina G, Massella L, Porcellini MG, Montagna M, Regazzi M, Scolari F, Ghiggeri GM (2012) Rituximab in children with resistant idiopathic nephrotic syndrome. J Am Soc Nephrol 23:1117–1124
39. Araya CE, Dharnidharka VR (2011) The factors that may predict response to rituximab therapy in recurrent focal segmental glomerulosclerosis: a systematic review. J Transplant 2011:374213
40. Murnaghan K, Vasmant D, Bensman A (1984) Pulse methylprednisolone therapy in severe idiopathic childhood nephrotic syndrome. Acta Paediatr Scand 73:733–739
41. Tullus K, Marks SD (2013) Indications for use and safety of rituximab in childhood renal diseases. Pediatr Nephrol 28:1001–1009
42. Bitzan M, Anselmo M, Carpineta L (2009) Rituximab (B-cell depleting antibody) associated lung injury (RALI): a pediatric case and systematic review of the literature. Pediatr Pulmonol 44:922–934