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REVIEW

Indications for use and safety of rituximab in childhood renal diseases

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Abstract Rituximab was initially developed for the treatment of patients with B cell lymphoma but has during the last decade proven to be quite effective in treating a range of kidney diseases including lupus nephritis, nephrotic syndrome, and also in different situations before and after a renal transplant. We will here review the scientific basis for the use of rituximab in children with renal diseases and give recommendations both regarding its clinical use and need for further research.

Keywords Rituximab · SLE · Nephrotic syndrome · Renal transplant

Introduction

Rituximab is a monoclonal antibody against the CD20 antigen on B-lymphocytes, which was developed and successfully used as a treatment for B-cell lymphoma in adults and children. It has also over the last decade been used more frequently in children with different kidney diseases, including systemic lupus erythematosus (SLE), vasculitis, renal transplantation, and more recently in nephrotic syndrome.

This review will investigate the scientific basis for the use of rituximab, specifically looking at data for children. If there is no pediatric data available, then studies in adult patients will be extrapolated for consideration of its use in children.

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Pharmacology and immunology

Rituximab is a mouse-human chimeric monoclonal antibody of the immunoglobulin IgG1-kappa type with murine anti-CD20 variable sequence regions and human constant sequence regions, which mediates B cell lysis. Rituximab binds specifically to the CD20 antigen, which is a non-glycosylated tetra-spanning cell membrane-embedded phosphoprotein restricted to only B-cell lineage. It is expressed on pre-B cells, immature, mature naive, pre-germinal center and germinal center mature and memory B cells, but not on plasma cells (Fig. 1) [1].

Rituximab has been shown to reduce pre-B and B lymphocytes in vivo and has become an effective treatment for lymphomas and post-transplant lymphoproliferative disorders in adults and children [2, 3]. The use of rituximab has been extended with data regarding its safety and efficacy in adults with rheumatoid arthritis and other autoimmune diseases [4, 5].

Rituximab causes B cell depletion in in vitro studies by mechanisms involving antibody-dependent cell-mediated cytotoxicity, via binding of the IgG1 constant regions to B cells to generate decoy sacrificial cellular immune complexes that attract and bind Fc-γ receptor-expressing effector cells (such as monocytes, macrophages, and neutrophils). This results in reducing the recruitment of these effector cells at sites of immune complex deposition. There is also complement-dependent cytotoxicity and direct signaling leading to apoptosis (induced by hyper-crosslinking of membrane-associated CD20 molecules).

The ideal dosing schedule for intravenous rituximab is currently unknown. The initial protocols used were based on lymphoma and post-transplant lymphoproliferative disorders, utilizing a once-weekly intravenous dose of 375 mg/m^2 for 4 weeks. This has been translated into clinical practice in many centers by giving the same cumulative dose using two doses of 750 mg/m^2 2 weeks apart. However, many patients will deplete their B cells even after just one dose. Some

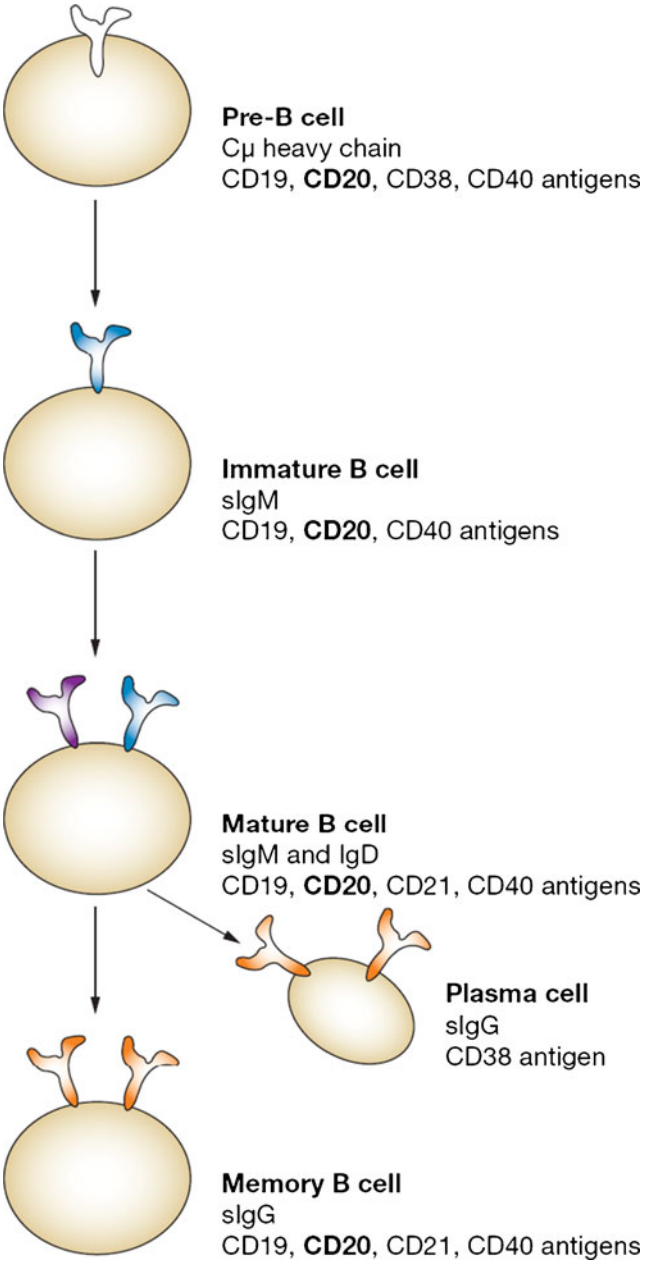

Fig. 1 B cell development and antigen expression. With permission from Salama and Pusey, Nature Clinical Practice Nephrology 2006;2:221–230

protocols utilize two doses of intravenous cyclophosphamide (usually at 375 mg/m^2) given the day after each of the two intravenous rituximab doses in order to maximize immunosuppressive properties and to reduce the formation of human anti-chimeric antibodies (HACA).

Systemic lupus erythematosus and lupus nephritis

B lymphocytes play a pathogenic role through antibody-dependent and antibody-independent mechanisms in murine models of SLE [6–8] There are quantitative and functional B cell abnormalities in humans (both adults and children) with SLE [4, 5, 9].

Antigen presentation, T cell activation and polarization, and dendritic-cell modulation appear to be important autoantibody-independent B cell functions mediated by B cell production of immunoregulatory cytokines and chemokines.

Although rituximab had been used effectively in children with non-Hodgkin lymphoma and post-transplant lymphoproliferative disease, there was little data of its use in children with SLE refractory to conventional therapy prior to 2005. The first girl with lupus that was treated with rituximab that we know of was in 2000. She had SLE and ISN/RPS Class V lupus nephritis and therapy-resistant nephrotic syndrome and had required treatment with intravenous albumin infusions twice weekly for several years. She showed a remarkable therapeutic response with normalization of her serum albumin. Subsequently, there was the first publication in the literature of a case report in 2004 on its use in a girl with SLE who had refractory autoimmune thrombocytopenia [10].

Early experiences

The first cohort on rituximab treatment of adult SLE patients was in 2004 from University College Hospital, London, where they initially reported six female adult patients with refractory SLE [11], which was then updated with their first 50 patients [12] (Table 1). Several other authors have also published cohort studies of adult patients that show good safety and efficacy with profound B lymphocyte depletion [13, 14].

The first cohort of adult patients with lupus nephritis (LN) was described in 2006 by Vigna-Perez et al. who presented 22 patients with active refractory SLE with Class III and IV lupus nephritis [15]. Disease activity and proteinuria showed a significant improvement both at 60 and 90 days. Complete remission was established at a median of 3 months from the start of treatment and sustained at 12 months in 40 % of patients. A recent large retrospective European cohort of 164 adult patients with biopsy-proven lupus nephritis showed an improvement in 103 of the patients [16].

The first seven successfully treated children were published in 2005, and then updated to include our first 19 patients in 2008 [17, 18]. The clinical response observed was impressive, with a large majority of children experiencing reduced disease activity and about 50 % going into full remission. The British Isles Lupus Assessment Group (BILAG) index improved significantly together with antibody and complement levels as well as hematological parameters and laboratory signs of renal involvement. In a further pediatric study of 11 girls (of whom eight had nephritis), remission was achieved in eight (six had nephritis) [19]. There have been subsequent

Table 1 Outcome in larger case series of rituximab treatment of children or adult patients with lupus

Authors	Number of patients	Full or partial response (%)	Side-effects
Studies in children			
Marks et al. [17]	7	7 (100 %)	No significant
Podolskaya et al. [18]	19	18 (95 %)	No significant
Willems et al. [19]	11	8 (73 %)	Severe in six
			Two cases of septicemia
			Two cases of neutropenia
			Two cases of thrombocytopenia
Studies in adult patients			
Leandro et al. [11]	6	5 (83 %)	No significant
Lu et al. [12]	50 (45 followed for at least 6 months)	40 (89 %)	Five serious adverse events
Looney et al. [14]	17 (16 possible to evaluate)	10 (63 %)	No significant
Vigna Perez et al. [15]	22	20 (90 %)	One death due to invasive histoplasmosis
Diaz-Lagarez et al. [16]	164	49 (30 %) complete response	8 infusion reactions (2 severe)
			21 infections
		54 (33 %) partial response	2 thrombosis
			3 death (septic chock, brain hemorrhage, disease progression)

pediatric and adult case series described, which was reviewed in 2010 [20].

The requirement for proper randomized controlled trials was recognized by international nephrological and rheumatological groups and recently data from two controlled trials in adult patients have become available. Surprisingly, the first randomized controlled trial, EXPLORER, did not find any difference between those patients who had treatment with rituximab compared to placebo [21]. In this study, there were 237 patients with moderate to severe extra-renal lupus who were randomized to receive 1,000 mg of intravenous rituximab or placebo at days 1, 15, 168, and 182 on a background therapy of azathioprine, mycophenolate mofetil (MMF), or methotrexate and prednisolone.

In general, the rituximab-treated patients depleted their B-cells and showed improved levels of antibodies to double-stranded DNA (dsDNA) and complement C3 and C4 levels. However, most importantly, no clinical response was recorded among 70 % and 72 % of the rituximab and placebo groups, respectively, and a major clinical response was seen in only 12 % and 16 %, respectively. Safety and tolerability was similar in patients receiving placebo and those receiving rituximab [21].

After the publications of many positive case series, it has been extensively discussed why the first randomized study did not show any benefits from rituximab with several explanations proposed. The primary endpoint was improved BILAG index at week 24 and maintaining the response without any flare of disease activity until week 52. It has been suggested that the BILAG criteria were either too strict or too complicated to accurately reflect the clinical situation of the patients in this study.

In addition, a post hoc analysis considering alternative definitions for flare was undertaken with the hypothesis that assessment of severe (BILAG A) flares may distinguish potential treatment effects with greater sensitivity than assessment of BILAG B flares, as there was no difference found between rituximab and placebo in preventing or delaying moderate to severe flares. However, when BILAG A flares alone were examined, rituximab reduced the risk of a subsequent first A flare and lowered mean annualized A flare rates [22].

A second large randomized, placebo-controlled study on rituximab, called the LUNAR trial has been published [23]. This study included 144 adult patients with histological evidence of ISN/RPS Class III or IV lupus nephritis within 12 months prior to randomization. These patients were treated with prednisone (0.75 mg/kg tapered from day 16 to 10 mg at week 16) and MMF (initiated at a dose of 1.5 g/day increased to 3 g/day at week 4. Placebo or rituximab 1,000 mg intravenously was infused at days 1, 15, 168, and 182. There were greater improvements in anti-dsDNA and complement C3 and C4 levels in those treated with intravenous rituximab but the clinical outcomes after 1 year of treatment were not improved. The rituximab-treated group had a better side-effect profile compared to those treated with placebo.

There are several reasons for the failure of this study to show a beneficial result from rituximab treatment. The investigators utilized a definition of renal remission as requiring a totally normal urine test, which is more than what would normally be expected to be seen in clinical practice. Rituximab was also used in addition to MMF and corticosteroids, which under most circumstances would have been regarded as sufficient therapy for these patients. It is also interesting to note that the non-significant improvement seen in LUNAR of 11 % may be due to lack of power. There were very similar improvement rates of 10 and 14 % reported in two Belimumab trials and in these larger trials they became statistically significant.

The evidence to date demonstrates that targeted B cell depletion therapy is safe but there is a question over its efficacy as an addition to standard immunosuppressive agents in refractory disease. However, intravenous rituximab will most likely continued to be used in children where disease activity remains after treatment with other therapies. There is a clear need for further studies to be undertaken for that indication.

Other therapies targeting B cells

Ocrelizumab is a fully humanized antibody that targets CD20-positive B cells and has been developed as a "new-generation" humanized version of rituximab. This antibody should minimize the potential problems associated with the development of HACA. Ocrelizumab has been studied in 381 adult patients with lupus nephritis [24], who were also treated with corticosteroids and MMF or cyclophosphamide followed by azathioprine. The results of this study are eagerly awaited as this has not yet been published, although the study was discontinued early due to an increased rate of serious infections.

Belimumab is another treatment targeting B cells that has recently been approved for use by the European Medicines Agency. Belimumab is a fully humanized monoclonal antibody that binds to soluble BLyS (B-lymphocyte stimulator) and acts as a specific inhibitor of its biological activity. Belimumab has shown efficacy in two large published randomized controlled trials [25, 26]. However, there is no data of its efficacy in children or young adults with lupus nephritis.

Vasculitis

There is little data on the use of intravenous rituximab in pediatric vasculitis. In adults with newly diagnosed ANCA-associated vasculitis (AAV), there is emerging data of rituximab being at least as effective as conventional therapy and obtaining remission rates of more than 80 % in refractory disease [27].

There were 197 adult patients with severe AAV (Wegener's granulomatosis or microscopic polyangiitis) recruited to a multicenter, randomized, double-blind, double-dummy, non-inferiority trial of intravenous rituximab 375 mg/m^2/week for 4 weeks) as compared with cyclophosphamide 2 mg/kg/day for remission induction. Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission but the rituximab-based regimen was more efficacious than the cyclophosphamide-based regimen for inducing remission of relapsing disease (p=0.01) [28]. In another similar trial, the rituximab-based regimen was equally effective as cyclophosphamide and not associated with reductions in early severe adverse events [29].

In addition, there is evidence that a rituximab-based cyclophosphamide-sparing regimen is effective at inducing long-term disease-free remission in adults with renal AAV and may be the platform upon which to develop a steroid-minimizing regimen to further decrease adverse events in the future [30].

We have published our use of intravenous rituximab in ten children with vasculitis, including four patients with Wegener's granulomatosis and one with polyarteritis nodosa [31]. In six of these children, rituximab was the only biologic received, and in the remaining four, rituximab was one of two or more biologics used sequentially. The commonest regimen used was two doses at 750 mg/m^2 (maximum dose 1 g) infused 14 days apart in eight patients. The remaining two children received 375 mg/m^2 weekly for 4 weeks. In most cases, the rituximab infusion was accompanied by intravenous cyclophosphamide with doses varying between 350 and 500 mg/m^2 in eight patients. In two patients, intravenous rituximab combined with cyclophosphamide therapy resulted in rapid disease control and was followed by subsequent reduced cyclophosphamide therapy used at a dosage of 500 mg/m^2 instead of 750 mg/m^2 to consolidate the remission. Five children continued adjunctive maintenance immunosuppressive therapy after rituximab using MMF, azathioprine, methotrexate, or ciclosporin.

There is a need for randomized controlled trials in children with vasculitis to determine the role, required dosage, and protocol for the use of rituximab.

Nephrotic syndrome

The first report of successful treatment of childhood nephrotic syndrome (NS) was published in 2004 [32] (Table 2). This child had been treated for many years for a frequently relapsing steroid-dependent NS and was treated with rituximab as he had developed thrombocytopenia. At the time of publication, he had had no further relapses in his NS. Subsequently, numerous case reports have been published.

Table 2 Outcome in larger case series of rituximab treatment in children with steroid-dependent or frequently relapsing nephrotic syndrome

Author	Number of children	Full or partial response (*n*) (%)	Side-effects
Benz et al. [32]	1	1	None described
Guigonis et al. [33]	22	19 (85 %)	Five mild
			Four regarded as severe
			Atrial arrhythmia stopping spontaneously
			Malaise, transient bronchospasm
			Severe rotavirus gastroenteritis
			Transient neutropenia with gingivitis
Prytula et al. [34]	28	23 (82 %)	Data not separated on different diagnosis in the publication
			19 (27 %) of 70 showed side-effect
			Most common acute reaction to infusion one was a severe and life-threatening anaphylactic reaction
			Three severe infection
			Agranulocytosis with sepsis
			Two cases of pneumonia one of which with pseudomonas
Gulati et al. [35]	24	20 (83.3 %)	Three had mild infusion reactions
Kemper et al. [36]	37	26 (70.3 %)	No serious side-effects

Frequently relapsing or steroid-dependent nephrotic syndrome

The first larger study in children with severe steroid and ciclosporin-dependent NS was published from France in 2008 [33]. They reported 15 of 22 children going into remission. We performed a large international collaborative survey of pediatric nephrologists who treated 70 children with rituximab: 28 of this cohort were steroid-dependent or frequently relapsing [34]. Ninety-three percent of these children had a full or partial response to the treatment and 82 % improved their serum albumin to above 30 g/l. A total of 61 % of the treated children went into full remission. We were unable to find any variation in the response between the different doses of intravenous rituximab (ranging from 375 to 1,500 mg/m^2). A further large cohort of 24 children with steroid-dependent NS confirmed a high remission rate of 83 % 12 months after treatment [35]. A recent retrospective study in 37 children with refractory steroid-sensitive NS showed that 70 % were still in remission after 1 year and 41 % after 2 years without any serious side-effects noted [36].

A retrospective study published earlier this year compared rituximab with tacrolimus in children with steroid-dependent nephrotic syndrome [37]. Ten children were treated with rituximab and 13 with tacrolimus. The mean number of relapses before treatment was 3.1±1.1 and 5.5±1.6 per year in the two groups. The relapse rate declined similarly in both groups and was, after 12 months, 0.8±1.0 and 0.9±1.1, respectively.

Steroid-resistant nephrotic syndrome

The first report in children with steroid-resistant NS came from New Delhi with five children treated resulting in a complete remission in three and a partial remission in the other two [38] (Table 3). In our international cohort, we reported 27 children with steroid-resistant NS [34]. In that group, 44 % showed a partial remission but only 22 % went into full remission. However, 44 % (12 of 27) children managed to increase their serum albumin level to above 30 g/l. A further case series with 33 children with steroid-resistant NS found similar figures: 27 % showed full remission and 21 % partial remission [35].

Therefore, it seems quite clear that there is a group of children with NS that benefit from treatment with rituximab. We should remember that these children had previously failed multiple therapies for their NS. If rituximab had been used as an earlier treatment alternative, the outcomes may have been

Table 3 Outcome in larger case series of rituximab treatment in children with steroid-resistant nephrotic syndrome

Authors	Number of children	Full or partial response (*n*) (%)	Side-effects
Bagga et al. [38]	5	5 (100 %)	No severe
Prytula et al. [34]	27	12 (44 %)	See Table 2.
Gulatti et al. [35]	33	16 (48.4 %)	One mild infusion reaction

better. However, there is also a potential of a publication bias that could make the figures look better than they would be in a randomized controlled trial.

Therefore, there is a strong need for pediatric randomized controlled trials to define the role of rituximab in the treatment of NS and to determine at what point it should be used. Its side-effect profile may well compare better to that of ciclosporin, which can cause nephrotoxicity if there is a requirement for many years of treatment. Rituximab may become a drug of choice early in the treatment of children with NS with a more complicated course.

Other important questions are regarding the benefit of continued treatment with MMF or ciclosporin after the rituximab infusions, which have been suggested by small open studies [39, 40]. The optimal number of rituximab doses and the optimal treatment dose is also not known. Studies suggest that a single dose works as well as several doses [34, 39, 41].

A very recent randomized controlled trial in children with steroid-resistant NS studied the addition of rituximab to the treatment with prednisone and a calcineurin inhibitor. They failed to show any benefit from the rituximab treatment [42]. There is an important need for randomized controlled trials in children with different kinds of NS comparing rituximab to standard treatments.

Relapse of nephrotic syndrome after transplant

As mentioned above, the use of rituximab for post-transplant lymphoproliferative disease (PTLD) was extrapolated from experience in lymphoma treatment in adults and children. It was because of its utilization in treating PTLD that clinicians noted that it had a positive effect in treating recurrent nephrotic syndrome in pediatric renal transplant recipients whose primary diagnosis was steroid-resistant nephrotic syndrome (NS).

The first two reported cases showed that rituximab treatment for PTLD induced complete remission of NS. The first case was in a 12-year-old boy 6 months post-renal transplantation [43] who had developed NS due to recurrence of focal and segmental glomerulosclerosis (FSGS) and the other, a 7-year-old boy with immediate FSGS recurrence who had developed Epstein–Barr virus-driven diffuse large-cell lymphoma 5 months post-transplantation [44].

After these anecdotal cases were published, contradictory data emerged showing that this therapy was not successful in other pediatric renal transplant recipients [45]. In our international survey, there were 15 patients who were treated with rituximab for post-transplant recurrence of NS [34]. Complete and partial remission was found in six (40 %) and four (27 %) patients, respectively, with five (33 %) patients demonstrating no response.

Renal transplantation

Intravenous rituximab has been utilized within the field of pediatric and adult renal transplantation for many years. Experience was initially gained in treating patients with PTLD and has now extended to post-transplant recurrence of nephrotic syndrome. However, intravenous rituximab has been advocated for induction treatment in ABO compatible [46] and incompatible [47] transplantation, desensitization [48] as well as acute and chronic antibody-mediated rejection.

Post-transplant lymphoproliferative disease (PTLD)

The mainstay of treatment of PTLD is the initial reduction of immunosuppression, which constitutes discontinuing of the anti-proliferative agent (azathioprine or MMF) and reduction of calcineurin inhibitor. In cases where this treatment is insufficient to resolve the PTLD, other treatments such as rituximab may become important, as over 90 % of PTLD cells express CD20. There are no controlled trials on rituximab in this indication but it seems to be safe and effective in treating children who develop PTLD, which may be driven by the Epstein–Barr virus (EBV). It is important to demonstrate CD20 antigen expression histologically as rituximab works by causing lysis of B-lymphocytes expressing CD20, which aborts the lytic-replicative phase of EBV-driven PTLD.

The first Phase I and Phase II multicenter studies in adult patients evaluating four weekly infusions of intravenous rituximab 375 mg/m^2 were published in 1997 showing favorable results with an improved safety profile compared to conventional chemotherapy for relapsed non-Hodgkin's lymphoma [49]. This led to the introduction of rituximab in treatment for PTLD. Rituximab therapy was included as treatment of PTLD in the European best practice guidelines for renal transplantation in 2002 [50].

Recently, an international multicenter open-label Phase 2 trial of treatment-naive adult solid-organ transplant recipients diagnosed with CD20-positive PTLD who had failed to respond to initial immunosuppression reduction was published [51]. They received four weekly doses of intravenous rituximab 375 mg/m^2 followed by 4 weeks without treatment and four cycles of CHOP every 3 weeks. Eleven percent of patients had CHOP-associated treatment-related mortality. At the time of data analysis, the median response duration in the 53 patients who had responded to treatment had not yet been reached. It should be noted that the response to PTLD to rituximab therapy can occur up to 60 days (median 25 days) after treatment.

Cytokine release syndrome is a severe side-effect of the use of rituximab in lymphoma that is rarely seen in other conditions. This side-effect seems to be related to bulky disease, and in those cases, a tumor lysis syndrome can also

be seen. Fulminant hepatitis and hepatitis B reactivation can occur after rituximab therapy for PTLD.

Antibody-mediated rejection

The role of humorally mediated rejection in causing acute and chronic renal allograft dysfunction is becoming increasingly important in the quest to increase renal allograft survival rates. Augmentation of immunosuppression is required for renal transplant recipients with the following three clinical features: renal allograft dysfunction, circulating donor-specific HLA antibodies and histological evidence of acute rejection with positive C4d staining of the peritubular capillaries. However, there is a lack of controlled studies in this field, especially since some patients may only exhibit one or two of the above clinical features. Previously, an acute rejection episode was generally thought to be a T cell-mediated event, but there is increasing evidence of the role of B cells in both humorally mediated and vascular rejection. Histologically, infiltrating B cells have been suggested to play a pivotal role [52–54].

This led to studies reporting a high prevalence of intrarenal B cell clusters in 56 % of biopsies with acute vascular rejection. The addition of intravenous rituximab to conventional treatment led to a complete depletion of intrarenal B cells [55] showing good clinical response with improvement in renal allograft function [56].

Side-effects

Most case reports have emphasized the low incidence of severe side-effects from rituximab treatment. The two placebo-controlled trials discussed confirmed this impression, although, interestingly, the LUNAR trial actually found more severe adverse events (SAEs) in the placebo group compared to the active treatment group.

Similar findings have been reported in the case series of its use in children with NS. However, one report from France did find “severe” adverse events in 45 % of their patients when they were re-treated with rituximab [57], most of which were hematological, appearing during a few days post-infusion and were quickly reversible.

However, there are some very important potential concerns regarding severe side-effects with rituximab. This includes the development of HACA, which can potentially reduce the efficacy of the treatment by neutralizing rituximab. In addition, they can cause severe allergic reactions, although this has not become a serious problem in clinical practice.

Although hypogammaglobulinemia is seen after using rituximab, infectious complications are low, but do include viral infections, such as herpes zoster. This may be because serum immunoglobulin levels are maintained by persistent plasma cells.

Another very uncommon but very serious reported side-effect is JC (a polyoma) virus, which can induce a progressive multifocal leukoencephalopathy (website address http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126519.htm accessed 14 June 2012). This complication can also occur in lupus patients that have not been treated with rituximab so it is not clear if rituximab treatment or multiple treatments confer an increased risk for this devastating disease.

A severe lung injury seems to be an unusual but highly significant complication to rituximab treatment. In 2009, a French group described a child with steroid-resistant NS that developed a rapidly progressing fatal pulmonary fibrosis of unknown etiology after treatment with rituximab [58]. The same year, Bitzan and coworkers coined the term rituximab-associated lung injury (RALI) and described one boy with FSGS who developed progressive dyspnea, hypoxemia, and fatigue 18 days after rituximab treatment and recovered within 3 weeks [59]. A review of the literature found a further 30 adult cases, with 28 patients treated for a malignancy and a mortality rate of 29 %.

Conclusions

Rituximab has been used to treat an increasing number of different conditions in pediatric nephrology over the last decade. It has proven to be quite effective with a good side-effect profile in case series, although no randomized controlled trials currently exist for children. There is now a strong need to further explore and establish the role of rituximab in children with renal disease through proper trials.

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