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The Long-term Impact of Rituximab for Childhood Immune Thrombocytopenia

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Abstract Rituximab administered at standard doses induces universal B-cell depletion. It shows good efficacy in patients with a variety of autoimmune diseases and has been licensed for use in rheumatoid arthritis. Despite prolonged B-cell depletion, side effects appear to be minimal. The use of B-cell depletion in children in whom the immune system is more immature may have other unknown complications, although the literature remains sparse. This review summarizes the available studies of rituximab in children with immune thrombocytopenia and assesses some of the short-term and potential long-term consequences of B-cell depletion. Overall, rituximab appears well-tolerated in children. The incidence of serum sickness may be higher than it is in adults, but infections remain infrequent and occur mostly in patients with an underlying predisposition to infections. Finally, although data remain limited, it is recommended to perform vaccinations before administration of rituximab or after B-cell return.

Keywords Immunodeficiency · B-cell depletion · Infection · Pediatric · Immunoglobulins · Platelets

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Introduction

Rituximab therapy at standard doses induces B-cell depletion for 3–6 months in both children and adults. After its first successful use in 1998 in a patient with autoimmunity [1] and several successful randomized controlled trials [2], it is now licensed for use in rheumatoid arthritis and is used frequently off label for a wide range of autoimmune conditions [3, 4]. Because plasma cells do not express CD20, these are not depleted with rituximab; therefore, humoral immunity, including the ability to produce immunoglobulins, seems relatively spared. However, there are increasing reports of unusual infections, including reactivation of hepatitis B and also JC virus, Cooper and Arnold BJH 2010 resulting in progressive multifocal leukoencephalopathy (PML), although the latter infection seems rare and may be the result of the underlying disease rather than use of rituximab [5••].

Most studies of the safety and efficacy of rituximab are reported in adults, both with malignant and nonmalignant conditions. Whether the efficacy and safety can be extrapolated to children, in whom the humeral immune system may not be fully mature, is not clear.

This review summarizes the studies of the use of rituximab in children with immune thrombocytopenia (ITP) and discusses some of the potential problems that may result following the use of rituximab.

Childhood Immune Thrombocytopenia

ITP in children is typically a benign disorder, with most children going into a long-term remission within weeks to months of diagnosis. Persistent and chronic ITP are uncommon. Because bleeding remains rare despite low

platelet counts, children often can be managed by observation [6]. Treatment, if needed, includes corticosteroids, immunosuppressive therapy, anti-D, and/or intravenous immunoglobulin (IVIG) [7, 8]. Splenectomy is usually reserved for those with chronic disease and bleeding. All these therapies have significant side effects, in particular long-term steroids. The enthusiasm for using rituximab in the early stages of the disease or later, when the disease has become chronic, has been the relative preservation of the immune system and establishment of a cure in some patients without the need for surgery. In effect, a removed spleen cannot be put back, but B cells will return.

Furthermore, it has traditionally been thought that the chronology and outcome of this disorder is not influenced by standard upfront treatment. However, the mechanisms of tolerance are complex, and a delay in treatment may result in epitope spreading [9] and, potentially, a higher incidence of intractable chronic disease. A recent retrospective analysis from the Intercontinental Cooperative ITP Study Group (ICIS) suggests that upfront treatment with IVIG may reduce the number of children developing chronic disease [10]. It is thereby possible that early treatment with immunomodulatory treatments such as rituximab and/or high-dose steroids may be found to be protective against the development of chronic disease in the future, although large studies will be required to ascertain this.

Clinical Studies/Response Rates to Rituximab

No randomized controlled studies have been conducted with rituximab in children (or adults) with ITP. A recent review of the literature up to July 2006 described the response rates in 4 cohort studies and 10 case reports, with an overall response rate of 43% and 70%, respectively [11•]. A summary of these four cohort studies and additional reports published since this review including a total of 150 children is outlined in Table 1. The overall response rate in these studies was 61% (92 patients), although response varied between studies from 30% [12] to 79% [13, 14], perhaps relating to a higher proportion of refractory patients in the study reported by Bennett et al. [12]. From three of the studies in which it was clearly documented, 49% of patients had a complete response (defined as platelet count > 100×10^9/L). There were reasonable number of relapses within the first year (8 of 19 in the study reported by Wang et al. [13], and 6 of 13 in the study reported by Taub et al. [15]), resulting in a 1-year response similar to that seen with adults [18•]. Long-term follow-up for two of these studies showed few further relapses, with 8 of 11 still responding at 1 year [16] and 34 of 49 continuing to respond at a median of 39.5 months [17]. One study suggested that older children and those

Table 1 Cohort studies of rituximab in children with immune thrombocytopenia

Study	Doses of rituximab (375 mg/m^2), *n*	Patients in study, *n*	Responses, *n*	% responders	Complete responders, *n*	Median follow-up	Relapses, *n*	Infectious complications?	Serum sickness, *n*	Immunoglobulins
Bennett et al. [12], Mueller et al. [16]	4	36	11	30	0	> 12 mo	3	No	2	Decreased IgG and IgM in 2 patients
Wang et al. [13]	4	24	19	79	15	9 mo	8	No	3	Decreased IgG in 4 patients, decreased IgM in 5 patients
Parodi et al. [17]	2–6	49	34	69	0	39.5 mo	13	No	0	–
Taube et al. [15]	1	22	13	59	7	–	6	No	0	–
Rao et al. [14]	4–6	19	15	79	10	18 mo	0	No	0	Decreased IgG, IgA, and IgM

with a shorter duration of disease are more likely to respond [17]. Otherwise, very few markers of response have been detected.

Side Effects

Infusion Effects

Rituximab is generally well-tolerated. As with adults, first infusion-related effects are seen, including chills; fever; headache; discomfort in the throat; and occasionally dyspnoea, nausea, pruritis, angioedema, or hypotension. These symptoms are related to the release of inflammatory cytokines caused by direct B-cell destruction, as well as by macrophage activation during clearance of antibody-coated B cells. The symptoms usually resolve completely with slowing or interruption of the infusion and can be limited by the use of premedications, including antihistamines, paracetamol, and corticosteroids [19]. Reactions are uncommon following the first infusion. Very rarely, more serious mucocutaneous syndromes have been described, including Stevens-Johnson syndrome [20], paraneoplastic pemphigus, and toxic epidermal necrolysis [11•].

Serum Sickness

A more severe reaction resembling serum sickness was described in five children from the studies in Table 1 (Bennett et al. [12], $n=2$; Wang et al. [13], $n=3$) and in an additional case report [21], occurring with any of the four infusions. It can be managed with steroids but resulted in discontinuation of treatment in these individuals. This appears to be more common than in adult-reported studies and may occur in up to 10% of children.

B-cell Depletion

B-cell depletion occurs, as with adults, at standard doses [12, 13] and with lower doses [15]. B cells return within 3 and 6 months, with normalization of the counts by 6–12 months, although the phenotype of retuning cells in children has not been fully described. Prolonged B-cell depletion is uncommon after rituximab administration and was not described in the studies in Table 1; however, it has been reported in occasional patients [22].

Immunoglobulin Levels

Despite depletion in B cells, immunoglobulin levels do not frequently fall below normal, although a slight fall has been described. In one pediatric study (age range, 2.6–18.3 years; median >10 years), there were no changes in IgG levels; IgM levels were reported to fall but stayed within the normal range in all but one patient [12]. A second study described a fall in immunoglobulin levels to below the normal range in 6 of 14 cases [13]. A third study described a fall in IgM, IgA, and IgG levels 6, 9, and 12 months after therapy, respectively, but levels remained close to if not within the normal range. Tetanus toxoid antibody titers were also measured in this study and remained detectable at all stages [14].

However, hypogammaglobulinemia has been described after multiple courses of rituximab in a child treated with cytopenias, although this was in the context of autoimmune lymphoproliferative disorder and potential immunodeficiency [23]. Hypogammaglobulinemia may occur more commonly in patients with immunodeficiency-associated ITP [24•], in the very young, and in those treated for autoimmune hemolytic anemia.

Risk of Infections

Whether rituximab results in an increased incidence of infections has not been fully resolved. Some studies in adults have reported a slight increase in infectious complications in adults treated with rituximab for rheumatoid arthritis [2, 25] or lymphoma, when additional chemotherapy is given, and following extended courses with prolonged B-cell depletion [26]. On the other hand, a systematic review of randomized controlled studies in cancer patients did not find any increase in infection [27]. In the systematic review of rituximab in adults with ITP by Arnold et al. [18•], 7 of 303 treated patients (2.3%) developed serious infections, 4 of which were fatal. However, most patients had received additional immunosuppressive therapies, and a direct association with rituximab is difficult to establish [18•]. Studies assessing the risk of infections in children treated with rituximab are even more limited. The studies in Table 1 did not describe unusual infections in the 150 children reported. However, several case reports have described unusual infections, although usually in the context of lymphoma or systemic lupus erythematosus. One case report describes enteroviral infection in a 10-year-old who had received 6 years of treatment for refractory ITP, including hematopoietic stem cell transplantation 20 months before the rituximab. T cells and IgG levels were normal before rituximab was instigated; however, neurocognitive decline occurred 18 months after the first course of rituximab and 11 months after the second course (given for relapse); the patient made a full recovery [28]. Infectious complications, including death from viral and fungal infections, have also been reported, although in the context of treatment at the age of 8 weeks for fulminant autoimmune hemolysis and with multiple immunosuppressants [29]. One adolescent boy treated with rituximab together with ciclosporin for a high-titer inhibitor developed

aspergillosis and hepatitis B infection [30]. A review of the records of 10 children treated with rituximab for a variety of autoimmune diseases described no significant change in the rate of all infections after rituximab, with 2.4 events per patient-year before rituximab therapy and 2.8 events per patient-year after rituximab therapy. Although infections requiring antimicrobials occurred in three patients after rituximab, two of these three had developed grade 3 candidemia (n=1) and grade 3 herpes and pneumonia (n=1) before therapy with rituximab, demonstrating their underlying susceptibility to infections [31].

One rare infectious complication, PML, a demyelinating disease caused by reactivation of latent JC virus in the brain, was reported after rituximab, resulting in a black box warning being issued by the US Food and Drug Administration (http://www.fda.gov/downloads/Drugs/DrugSafety/UCM169892.pdf). However, immunosuppression, systemic lupus erythematosus, and underlying lymphoma are known risk factors for PML, suggesting that underlying patient characteristics may be more important than the treatment [32, 33]. The median time to development of PML in the largest series of recent cases was 5.5 months [5••]. In children, most cases of PML have been reported in the context of HIV, immunodeficiency or following bone marrow transplantation. The risks of PML following rituximab administration in children are not known and seem extremely low in patients with ITP, but vigilance and reporting of adverse events are necessary.

Reactivation of hepatitis B virus is another recognized complication of immunosuppression or cytotoxic therapies, even without rituximab [34]. Patients with lymphoma seem to be at higher risk of hepatitis B virus reactivation than patients with other cancers [34–36]. Similarly, patients with rheumatologic disease receiving immunosuppressive therapy are also at increased risk of hepatitis B virus reactivation after treatment with rituximab or other biologics [37]. Children with ITP and a normal immune system may be at lower risk of hepatitis B virus. However, testing for hepatitis B status is necessary before considering treatment with rituximab, and if serology is indicative of past infection rather than vaccination (ie, hepatitis B surface antigen positive or hepatitis B core antibody positive), rituximab probably should be avoided. If it is still deemed an important therapy, then prophylaxis with lamivudine is recommended, even in inactive carriers [38].

Effect of Rituximab on Vaccine Response

The influence of rituximab on vaccine responses is also unclear. Two studies in patients with lymphoma suggest defects after rituximab administration. Inadequate response to T-cell-independent antigens such as pneumococcal polysaccharide with a preserved T-cell-dependent response to tetanus toxoid following rituximab was described in one study [39]. A second study described reduced recall response to tetanus and polio, with absent primary response to keyhole limpet hemocyanin and hepatitis A [40]. However, the patients in these studies had also received cytotoxic treatment for underlying lymphoma. In contrast, rituximab did not impair an adequate response to two of three influenza virus antigens in patients with rheumatoid arthritis (n=14), even during profound B-cell depletion [41].

Despite the lack of effect of rituximab on the response to influenza antigen, the manufacturer recommends that vaccines be administered 4 weeks prior to the first dose of rituximab or after B cells have returned. This may be especially relevant in patients with ITP who may undergo splenectomy.

Respiratory Symptoms

Another rare side effect following rituximab administration is respiratory distress syndrome. A teenage boy treated with rituximab for nephritic syndrome on the background of focal segmental glomerulosclerosis presented with progressive dyspnea, fever, hypoxemia, and fatigue 18 days after completion of a second course of rituximab. His symptoms started while he was still on high-dose prednisolone. Radiologic features included ground-glass infiltrates, and bronchiolar lavage showed inflammatory cells. He recovered after 3 weeks. A systematic review of the literature described 30 more cases in adults, with a median age of 64 years: 28 had been treated for B-cell malignancy, one for graft-versus-host disease, and one for ITP. Most patients (71%) had received other chemotherapy in addition to rituximab. Symptoms occurred between 11 and 22 days from rituximab administration, and high-dose steroids did not improve survival. Nine of 31 patients died (29%), with 11 being ventilated [42]. A subsequent case report described an 8-month-old girl with autoimmune hemolytic anaemia who developed interstitial pneumonia with acute respiratory distress syndrome requiring intensive care admission and extracorporeal membrane oxygenation therapy for 37 days 7 months after rituximab administration and having received high-dose steroids and cyclophosphamide [43]. The pathology behind this side effect is not known, although it has also been seen rarely with intravenous anti-D treatment.

Cytopenias After Rituximab

Cytopenias, in particular neutropenia, have been described following rituximab administration and can occur in up to 25% of adults receiving CHOP-R for B-cell lymphomas [44]. This complication occurs less frequently following

rituximab use for autoimmune conditions and has not been described frequently in children. One report described severe acute thrombocytopenia and neutropenia, respectively, a few days after rituximab infusion in two children with autoimmune hemolytic anemia. In both cases, the cytopenia was reversible in a few days [45]. Although this may not be common, we recommend concurrent therapy to maintain a "safe" platelet count during the period of treatment.

Use of Rituximab in Infants and Neonates

Although not systematically assessed, rituximab has been used without ill effect in infants as young as 12 weeks old [46]. Side effects may be more common in the younger age group, with case reports of infectious complications and death [29], but this may reflect the underlying disorder requiring treatment. It has also been used inadvertently in the fetus following emergency treatment with rituximab in pregnancy for a variety of conditions. A summary of eight case reports of rituximab given during pregnancy described no adverse events for the fetus or neonate despite passage of rituximab across the placenta. Rituximab was given at all stages of gestation (week 1-week 34) and in this series, babies were delivered around term (range, 33–41 weeks) with no adverse effects. B cells were depleted in five of six babies tested and normalized in at least two (the rest were not reported). One child had normal levels of B cells 1 month after birth when the mother had been treated at 21 weeks. Vaccination titers after 10 months were adequate in the four babies who were assessed, and immunoglobulin levels were appropriate in three children. One child, whose mother had received rituximab between weeks 30 and 34, had low immunoglobulin levels at 1–2 months but good recovery by 6 months. No infectious complications were reported [47•].

Conclusions

Rituximab treatment in children with autoimmunity has similar efficacy to that reported in adults. Depletion of B cells occurs with standard doses and may occur just as effectively with lower doses. Rituximab is well-tolerated, although serum sickness may be more prevalent in children than in adults.

Immunoglobulin levels probably fall, although not below normal in the majority of children, although repeated doses over many years may precipitate dangerously low levels, especially if there is an underlying immunodeficiency.

Infectious complications were not reported in the larger pediatric cohorts. However, case reports suggest that unusual infections do occur. Infections are also more frequently reported in patients with Evans syndrome and in patients treated with multiple agents, such as steroids. Hepatitis B, although less common in children, must be checked before this therapy is considered, and vigilance for signs of PML is needed. In addition, patients with an underlying immunodeficiency are more predisposed to infections and hypogammaglobulinemia; astute diagnosis of ITP and exclusion of secondary causes is important before considering treatment options.

Responses to vaccines may be suboptimal following rituximab administration, although this has not been systematically assessed. It has been recommended to give vaccinations before therapy with rituximab or to delay giving vaccines until B cells have returned.

Overall, in the immunocompetent child, rituximab seems safe, even in the fetus inadvertently treated with B-cell depletion, perhaps reflecting the relative use of the innate immune system in children as well as the preservation of the plasma cell.

Finally, should IVIG be given prophylactically in children who have received rituximab? This has not been appropriately investigated, and many doctors routinely give IVIG. Given the low incidence of infections and that IgG levels generally do not fall below normal, this may not be necessary, but there is little evidence to support giving or withholding infusions of IVIG. It is more likely that patients with preexisting immunodeficiency, those receiving additional chemotherapy, and very young children will benefit from IVIG. Long-term follow-up of children treated with rituximab is important, and compulsory reporting of adverse events is necessary to ensure the continued safe prescription of rituximab.

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