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Treatment with Rituximab in Benign and Malignant Hematologic Disorders in Children

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Monoclonal antibodies (mAbs) have had a major impact on the diagnosis and treatment of many disorders. First discovered in the 1980s, the original monoclonal antibodies were composed entirely of mouse protein which resulted in the development of human anti-mouse antibodies (HAMA) preventing repeated use. Advances in antibody engineering resulted in chimeric antibodies, with both human and mouse components, and more recently humanized antibodies comprised of almost all human protein (>90%)¹. The reduction in the mouse components of monoclonal antibodies has allowed for these treatments to be repeated by lessening or eliminating development of human anti-mouse antibodies. Tens of thousands of monoclonal antibodies have been produced but less than 20 have been licensed for use in patients in the United States.

Rituximab is a chimeric monoclonal antibody specific for CD20, an antigen expressed on B cells. In 1997, it was the third monoclonal antibody approved by the FDA following OKT3 and abciximab. The efficacy of rituximab for the treatment of non-Hodgkin's B cell lymphoma and its relative lack of toxicity lead to its incorporation in most standard treatment protocols for B cell lymphomas and its use in a wide spectrum of B cell disorders, including autoimmune diseases and other malignancies². Over 540,000 patients have been treated with rituximab worldwide, primarily for B cell lymphomas³. There are only two monoclonal antibodies that have been more widely used, both of which are also chimeric: abciximab, an anti-integrin used in more than one million cardiac patients, and infliximab, an anti-TNF-alpha used in approximately 770,000 patients with Crohn disease and rheumatoid arthritis⁴.

Although rituximab has been widely used in adults for 10 years, studies in the pediatric population are limited and include primarily case reports, small retrospective and small prospective cohort studies. Specifically, there have been no randomized controlled studies of

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the safety or efficacy of rituximab in children. The package insert states that rituximab has not been studied in children, however, rituximab has been explored in children for a number of hematologic conditions including autoimmune hemolytic anemia (AIHA), chronic immune thrombocytopenic purpura (ITP), antibodies to factors VIII and IX, post transplant lymphoproliferative disease (PTLD), pre B cell acute lymphoblastic leukemia (ALL), and B cell non Hodgkins lymphoma (NHL). This paper will review the current literature on these uses of rituximab in children including articles and abstracts through July 2006.

Mechanism of Effect

Rituximab is a chimeric monoclonal antibody composed of murine variable regions fused with human IgG1 heavy chains and kappa light chains. Rituximab is specific for the CD20 antigen, a 35kd transmembrane protein expressed on all normal and malignant mature B-lymphocytes. CD20 is not expressed on stem cells, pro-B-cells, most pre-B-cells, most plasma cells, or any other normal human tissue. CD20 does not circulate in plasma⁵, is not shed from or internalized by the B-cell, and is not downregulated upon antibody binding⁶. The physiologic role of CD20 is poorly understood. There is no known natural ligand and CD20 knockout mice show no significant defects in B cell function⁷. Based on structural homologies, CD20 is hypothesized to be a calcium channel subunit⁸ involved in B-cell activation, differentiation, and/or cell cycle progression⁹.

Rituximab binds to CD20 causing rapid depletion of circulating CD20+ B-cells¹⁰. Although circulating B-cells are profoundly depleted, the number of B-cells found in lymph nodes are reduced¹¹. Rituximab is postulated to induce B-cell destruction through a variety of mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-mediated lysis, apoptosis, inhibition of cell growth, and sensitization to chemotherapy¹²⁻¹⁴. The importance of the Fc gamma receptor IIIa (FcγRIIIa), a receptor found on natural killer cells and macrophages which binds to IgG1, has been well documented. A polymorphism in this receptor (specifically V/F158) has been correlated with differences in rituximab-induced ADCC and clinical response to rituximab for the treatment of NHL¹⁵, Waldenstrom's macroglobulinemia¹⁶, and systemic lupus erythematosus (SLE)¹⁷. Rituximab-induced sensitization to chemotherapy is thought to be mediated by downregulation of Bcl-2, an inhibitor of apoptosis¹⁸. As its mechanism of action is distinct from that of conventional chemotherapy, combining rituximab with standard treatment may have additive, if not synergistic, effects.

Safety Profile

The standard dose of rituximab is 375 mg/m²/dose administered intravenously on a weekly schedule for 4 weeks. This dose, however, was not chosen based on any studies of pharmacokinetics or the response to the drug, and other dosing schedules have been successfully used. Rituximab has been generally well tolerated in adult and pediatric patients. The majority of reported side effects are mild or moderate and infusion-related.

The first infusion often causes a syndrome of chills, fever, headache, and occasional dyspnea, nausea, pruritis, angioedema, or hypotension¹⁹. These symptoms are mediated by the release of inflammatory cytokines such as TNF-alpha, IL-8, and IFN-gamma both directly secondary to B cell destruction, as well as indirectly by macrophage activation²⁰. Among lymphoma patients, reactions are more common and more severe in patients with a high tumor burden. The symptoms usually resolve completely with slowing or temporary interruption of the infusion. Premedications such as antihistamines, antipyretics, and corticosteroids are commonly used and can be re-administered to mitigate the reactions.²¹ Subsequent infusions are much less likely to cause such reactions.

Among the approximately 540,000 patients who have been treated worldwide, tumor lysis syndrome and severe infusion reactions have been reported rarely, a small number of which were fatal. The most severe cases were in patients with high tumor burden, multiple rounds of previously administered chemotherapy, advanced age, and comorbid conditions, such as pulmonary or cardiovascular disease. Anaphylactoid reactions have been reported which may be exaggerated “first infusion” cytokine reactions. Severe mucocutaneous syndromes have also been reported rarely, including Stevens-Johnson syndrome²², paraneoplastic pemphigus, and toxic epidermal necrolysis¹⁹. In October 2004, the manufacturer issued a warning stating that carriers of hepatitis B are at risk for its reactivation with development of fulminant hepatitis¹⁹.

Serum sickness has been a relatively infrequent occurrence despite the fact that rituximab is chimeric rather than humanized. Two recent reports, however, suggest that serum sickness may develop in 5-10% of children receiving rituximab to treat ITP^{23,24}.

An important concern with the use of rituximab has been the risk of developing new infections which generally do not occur despite the immunologic changes. Treatment with rituximab results in immediate, marked B-cell depletion with levels remaining low for 2-6 months and returning to pretreatment levels in 6-12 months²⁵. Physicians should not administer immunizations at any age until the B-cell population has returned. Despite substantial prolonged B-cell depletion, an increased incidence of infection has not been demonstrated. Furthermore studies, primarily in adults, have looked at immunoglobulin levels and generally found very little to no change²¹. This is likely due to the persistence both of plasma cells and also of B-cells in lymph nodes¹¹. Despite the general lack of change of immunoglobulin levels, prophylactic treatment with IVIG has been employed following rituximab in younger children, as they are thought to be at higher risk of transient hypogammaglobulinemia. Studies of rituximab in combination with chemotherapy for lymphoma report a higher rate of neutropenia than with chemotherapy alone, but again without significant increases in infections²⁶. There has been a small number of case reports describing serious viral infections in patients receiving rituximab in conjunction with pre- and post- transplant chemotherapy.

Methods

A literature search of articles and abstracts published on the use of rituximab in pediatric hematologic and oncologic disorders was performed. Cohorts, case reports, and abstracts published by July 2006 were included. Reports on the use of rituximab for the following diseases were reviewed: AIHA, chronic ITP, antibodies to factor VIII/IX, PTLD, pre-B-cell ALL, and B-cell NHL. No articles were identified describing the use of rituximab in pediatric patients with thrombotic thrombocytopenic purpura. Although there have been a number of reports on the use of rituximab in other autoimmune disorders, such as SLE²⁷, they are outside the scope of this review.

Case reports were presented separately from cohort studies given their bias in favor of positive results. Case reports were arbitrarily defined as three or fewer patients. Publications were analyzed for the following variables: age, sex, diagnosis, treatment prior to rituximab, rituximab dose, response to treatment and duration of response, and adverse events. Results are summarized by treatment indication in the Table.

Results

Autoimmune Hemolytic Anemia (AIHA)

AIHA, an autoimmune disorder characterized by anti-red cell antibodies, is usually a self limited disorder treated with short courses of steroids. Resistant disease, however, has been

difficult to manage. Immunosuppressants and splenectomy are not consistently effective and may carry a risk of infection. Often children require prolonged use of high dose steroids which is associated with serious adverse effects.

Cohort studies have described the use of rituximab for AIHA in a total of 25 children, all of whom had failed conventional treatments²⁸⁻³⁰. The standard dose of rituximab was given weekly for 1-6 weeks (median = 4 doses). Remarkably, 23 of the 25 children (92%) had a complete response ongoing from 7-28 months (median = 16 months) at the time of the last follow up. Only 3 of these 23 responders had relapsed, including one patient who had had two relapses. All relapses were successfully retreated with rituximab.

There have been 14 single case reports published on the use of rituximab for AIHA in children³¹⁻⁴⁴. Ninety three percent of children demonstrated a complete response. The mean response duration was 14 months, and all patients had ongoing responses at the time of publication.

These results differ in comparison with adult studies. Adults with AIHA often have cold agglutinin disease with IgM anti-red cell autoantibodies unlike children who most commonly have warm antibody AIHA. Although some adult studies report a high response rate², the largest study of 27 adults receiving 37 courses of rituximab treatment for cold agglutinin disease reported a response in 54%, 20 out of 37 courses, with a complete response in only one patient⁴⁵.

Given the high degree of efficacy of rituximab in pediatric patients and the difficulty of treating AIHA, it seems appropriate to consider early use of rituximab in these patients, especially in steroid intolerant children. In the treatment of small children, despite the absence of data on serial immunoglobulin levels, prophylactic monthly IVIG has been used.

Chronic Immune Thrombocytopenic Purpura

Chronic ITP, characterized by autoantibodies to platelets, is treated with observation, corticosteroids, immunosuppressants, anti-D, and/or intravenous immunoglobulin (IVIG). Splenectomy and immunosuppressants are reserved for those with persistent disease.

Wang²³ (n=24), Taube⁴⁶ (n=22) and Bennett²⁴ (n=36) reported series of children with chronic ITP refractory to multiple prior treatments treated with rituximab. Children in the Wang and Bennett studies were given the standard dose of rituximab weekly for 4 weeks, whereas children in the Taube study received only a single dose. A response defined as platelet count >50,000/uL was seen in 71% in the study by Wang, most of which were a complete response (CR), and 31% in the study by Bennett. Taube reported a CR (platelets >100,000/uL) in 32% and partial response (platelets > 30,000/uL) in 27%. The lower response rate in the Bennett study was probably a result of a more severely affected patient population. All but 1 CR in the study by Wang occurred within 4 weeks of the first rituximab infusion. Case reports published on a total of 10 children with ITP receiving four doses of rituximab showed a response rate of 70%⁴⁷⁻⁵³. Neither Wang nor Bennett could identify clear predictors of response to rituximab. Of note, Bennett (2) and Wang (3) reported 5 children who experienced serum sickness, a rate which appears to be higher than in any other rituximab-treated patient group.

Bennett noted in their children (ages 2.6 to 18.3, median > 10 years of age) that IgG levels were unchanged. IgM levels fell significantly but not to levels out of the normal range. Pharmacokinetics on 14 children demonstrated that clearance of rituximab following the first infusion was more rapid than clearance following the fourth infusion.

Data in adults with ITP treated with rituximab is similar to that reported in children except that children with ITP who respond to rituximab appear to do so more quickly than adults. Conversely, 15 of 17 adults in one study who attained a CR maintained that response for > 1 year²¹ whereas in the Wang study children appeared to relapse sooner.

In conclusion, infusions of rituximab have the potential to avoid splenectomy in children with chronic ITP but apparently in not more than 50% of cases. Specific indications for rituximab and when treatment with it should be initiated remain uncertain. The development of serum sickness can be readily managed with prednisone but requires discontinuation of treatment.

Antibodies to Factor VIII/IX (Inhibitors)

Approximately 20-30% of patients with severe hemophilia A and 5% of patients with severe hemophilia B develop inhibitory antibodies. Hemophiliacs with inhibitors commonly receive bypassing agents for acute bleeds and immune tolerance in an attempt to eliminate the inhibitor.

No cohort studies have been published on the use of rituximab for inhibitors. Four case reports describe 8 children with congenital hemophilia treated with rituximab for antibodies against factors VIII and IX⁵⁴⁻⁵⁷. Five of 8 (63%) had an initial response. Two had relapses at 11mo and 8mo, only one of which responded to a second course of rituximab.

Two studies reported 14 adults, 13 with acquired hemophilia, treated with rituximab^{58,59}. A response was seen in 11 of the 13 patients with acquired hemophilia and in the patient with congenital hemophilia. The two patients who did not initially achieve remission both had inhibitor levels greater than 100 Bethesda Units; both achieved a complete response with a combination of rituximab and cyclophosphamide.

A projected single arm study of the efficacy of rituximab in 43 children and adults with inhibitors in congenital hemophilia is beginning in September 2006.

Post Transplant Lymphoproliferative Disease

Post transplant lymphoproliferative disease is a B-cell proliferative disorder induced by infection with Epstein-Barr virus in the setting of chronic immunosuppression. This is particularly prevalent in the post transplant setting. Standard treatment is withdrawal of immunosuppression, acyclovir and alpha interferon.

Seventy one children with PTLTD have been treated with rituximab⁶⁰⁻⁶⁴ including preliminary results of a phase II trial⁶⁵. Twelve patients had undergone bone marrow transplantation, 5 umbilical cord blood transplantation, and 54 solid organ transplantation. The patients who had received solid organ grafts had refractory PTLTD defined as no response to reduced immunosuppression, progressive or relapsed disease, and/or concomitant allograft rejection. The 12 children who had undergone bone marrow transplantation received rituximab as first line treatment.

The 71 children received the standard dose of rituximab weekly for 1-9 weeks. Fifty (70%) had a complete response followed for a mean of 28 months with few adverse events. Case reports on 14 children treated with rituximab describe similar results⁶⁶⁻⁷⁷. The authors of one study suggested that rituximab should be first-line treatment for refractory PTLTD after solid organ transplant⁶⁵.

Two large studies in adults reported lower response rates of 46 and 65%.^{78,79} A recent study piloted the use of rituximab in combination with cyclophosphamide and prednisone; complete responses were seen in 5 of 6 adults⁸⁰.

Overall it may be appropriate to use rituximab as first line therapy in PTLD in children in view of the high response rate.

Lymphoma

Rituximab was licensed in the United States based on of its efficacy in adults with B cell non-Hodgkin lymphoma. Treatment of children with Burkitt lymphoma has been far more restricted. This is in large part due to the much smaller number of cases of B-cell NHL in children compared to adults.

No cohort studies have been published on the used of rituximab for pediatric lymphoma. Five case reports describe the use of rituximab for six children with B-cell NHL⁸¹⁻⁸⁵. All had had relapsed disease. Rituximab was infused at the standard dose weekly for 4-8 weeks and, in one case, repeated every 6 months. Five children had a response to rituximab, which was sustained in four. Two deaths were reported, one from relapse of disease and the other from graft versus host disease related to stem cell transplant five years after rituximab treatment.

Current Children's Oncology Group protocols incorporate rituximab in first line treatment protocols for B-cell NHL (Burkitt's Lymphoma).

Leukemia

As most pre B-cells do not express CD20, the great majority of pre B-cell ALL in children is CD20 negative. Four case reports describe 6 children with relapsed, CD20+ pre B cell ALL treated with rituximab^{82,86-88}. All had been treated previously with conventional chemotherapy and subsequently relapsed. Rituximab added to a chemotherapy resulted in remission for all six patients. One patient died of a CD20 negative relapse 6 months after treatment. Five children were in remission at the time of publication.

Conclusions

Rituximab has emerged as an important new drug for the treatment of autoimmune B cell mediated disease and B-cell malignancies in both the adult and pediatric populations. Although there are relatively few published reports in children describing rituximab treatment of hematologic diseases and their sample size is typically small, they appear to demonstrate that rituximab is a safe and effective treatment especially for AIHA, chronic ITP, and PTLD. Although rituximab was generally used when conventional treatments have failed, the findings suggest a role for rituximab as first-line therapy in PTLD and, in AIHA, in cases failing or intolerant of steroids. In these diseases, and perhaps chronic ITP, rituximab appears to be more effective in children than in adults. The toxicities in children appear to be similar to those seen in adults with the exception of serum sickness in children with ITP.

Future studies should include randomized, controlled trials to examine long-term outcomes as well as pharmacokinetic and pharmacodynamic studies to help determine optimal dosing. Other questions that remain to be answered include:

1. Are there reliable predictors of response?
2. Is there a benefit to monthly IVIG infusion following rituximab, beyond infection prophylaxis, by virtue of suppression of rebound autoantibody production?
3. In cases where rituximab is effective, is there a role for maintenance infusions?
4. When is it appropriate to initiate rituximab treatment?

Given the more limited follow up available in studies of non-malignant disease, caution regarding long term potential side effects of rituximab is warranted. The effect of rituximab to

transiently deplete B-cells generally is not accompanied by infectious complications, but little to no data exists on the long-term effects on immune responses. Questions regarding reactivation of existing infections and acquisition of new infections need to be addressed. Nonetheless, early results of treatment of hematologic B cell mediated diseases with rituximab remain impressive and worthy of further investigation.

References

1. Ballou M. -ximab this and -zumab that! Has the magic bullet arrived in the new millennium of medicine and science? *Journal of Allergy & Clinical Immunology* 2005 Oct;116:738–43. [PubMed: 16210044]
2. Boye J, Elter T, Engert A. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. *Annals of Oncology* 2003 Apr;14:520–35. [PubMed: 12649096]
3. www.rituxan.com
4. www.remicade.com
5. Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a human B lymphocyte-specific antigen. *Journal of Immunology* 1980 Oct;125:1678–85.
6. Press OW, Appelbaum F, Ledbetter JA, Martin PJ, Zarling J, Kidd P, Thomas ED. Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas. *Blood* 1987 Feb;69:584–91. [PubMed: 3492224]
7. O'Keefe TL, Williams GT, Davies SL, Neuberger MS. Mice carrying a CD20 gene disruption. *Immunogenetics* 1998 Jul;48:125–32. [PubMed: 9634476]
8. Bubien JK, Zhou LJ, Bell PD, Frizzell RA, Tedder TF. Transfection of the CD20 cell surface molecule into ectopic cell types generates a Ca²⁺ conductance found constitutively in B lymphocytes. *Journal of Cell Biology* 1993 Jun;121:1121–32. [PubMed: 7684739]
9. Kanzaki M, Shibata H, Mogami H, Kojima I. Expression of calcium-permeable cation channel CD20 accelerates progression through the G1 phase in Balb/c 3T3 cells. *Journal of Biological Chemistry* 1995 Jun 2;270:13099–104. [PubMed: 7539422]
10. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, Newman RA, Hanna N, Anderson DR. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994 Jan 15;83:435–45. [PubMed: 7506951]
11. Gong Q, Ou Q, Ye S, Lee WP, Cornelius J, Diehl L, Lin WY, Hu Z, Lu Y, Chen Y, Wu Y, Meng YG, Gribbling P, Lin Z, Nguyen K, Tran T, Zhang Y, Rosen H, Martin F, Chan AC. Importance of cellular microenvironment and circulatory dynamics in B cell immunotherapy. *Journal of Immunology* 2005 Jan 15;174:817–26.
12. Shan D, Ledbetter JA, Press OW. Signaling events involved in anti-CD20-induced apoptosis of malignant human B cells. *Cancer Immunology & Immunotherapy* 2000 Mar;48:673–83. [PubMed: 10752475]
13. Flieger D, Renoth S, Beier I, Sauerbruch T, Schmidt-Wolf I. Mechanism of cytotoxicity induced by chimeric mouse human monoclonal antibody IDEC-C2B8 in CD20-expressing lymphoma cell lines. *Cellular Immunology* 2000 Aug 25;204:55–63. [PubMed: 11006018]
14. Alas S, Emmanouilides C, Bonavida B. Inhibition of interleukin 10 by rituximab results in down-regulation of bcl-2 and sensitization of B-cell non-Hodgkin's lymphoma to apoptosis. *Clinical Cancer Research* 2001 Mar;7:709–23. [PubMed: 11297268]
15. Cartron G, Dacheux L, Salles G, Solal-Celigny P, Bardos P, Colombat P, Watier H. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIa gene. *Blood* 2002 Feb 1;99:754–8. [PubMed: 11806974]see comment
16. Treon SP, Pilarski LM, Belch AR, Kelliher A, Preffer FI, Shima Y, Mitsiades CS, Mitsiades NS, Szczypek AJ, Ellman L, Harmon D, Grossbard ML, Anderson KC. CD20-directed serotherapy in patients with multiple myeloma: biologic considerations and therapeutic applications. *Journal of Immunotherapy* 2002 Jan-Feb;25:72–81. [PubMed: 11924912]
17. Anolik JH, Campbell D, Felgar RE, Young F, Sanz I, Rosenblatt J, Looney RJ. The relationship of FcγRIIIa genotype to degree of B cell depletion by rituximab in the treatment of systemic lupus erythematosus. *Arthritis & Rheumatism* 2003 Feb;48:455–9. [PubMed: 12571855]

18. Alas S, Bonavida B. Rituximab inactivates signal transducer and activation of transcription 3 (STAT3) activity in B-non-Hodgkin's lymphoma through inhibition of the interleukin 10 autocrine/paracrine loop and results in down-regulation of Bcl-2 and sensitization to cytotoxic drugs. *Cancer Research* 2001 Jul 1;61:5137–44. [PubMed: 11431352]
19. Package insert. Rituxan® (rituximab). IDEC Pharmaceuticals Corporation; San Diego CA: 2003.
20. Byrd JC, Murphy T, Howard RS, Lucas MS, Goodrich A, Park K, Pearson M, Waselenko JK, Ling G, Grever MR, Grillo-Lopez AJ, Rosenberg J, Kunkel L, Flinn IW. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *Journal of Clinical Oncology* 2001 Apr 15;19:2153–64. [PubMed: 11304767]
21. Cooper N, Stasi R, Cunningham-Rundles S, Feuerstein MA, Leonard JP, Amadori S, Bussel JB. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. *British Journal of Haematology* 2004 Apr;125:232–9. [PubMed: 15059147]
22. Lowndes S, Darby A, Mead G, Lister A. Stevens-Johnson syndrome after treatment with rituximab. *Annals of Oncology* 2002 Dec;13:1948–50. [PubMed: 12453865]
23. Wang J, Wiley J, Luddy R, Greenberg J, Feuerstein MA, Bussel JB. Chronic immune thrombocytopenic purpura (ITP) in children: Assessment of rituximab treatment. *Journal of Pediatrics* 2005 Feb;146:217–221. [PubMed: 15689912]
24. Bennett CM, Rogers ZR, Kinnamon DD, Bussel JB, Mahoney DH, Abshire TC, Sawaf H, Moore TB, Loh ML, Glader BE, McCarthy MC, Mueller BU, Olson TA, Lorenzana AN, Mentzer WC, Buchanan GR, Feldman HA, Neufeld EJ. Prospective phase 1/2 study of rituximab in childhood and adolescent chronic immune thrombocytopenic purpura. *Blood* 2006 Apr 1;107:2639–42. [PubMed: 16352811]
25. Maloney DG, Grillo-Lopez AJ, Bodkin DJ, White CA, Liles TM, Royston I, Varns C, Rosenberg J, Levy R. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *Journal of Clinical Oncology* 1997 Oct;15:3266–74. [PubMed: 9336364]
26. McLaughlin P, Hagemaster FB, Rodriguez MA, Sarris AH, Pate O, Younes A, Lee MS, Dang NH, Romaguera JE, Preti AH, McAda N, Cabanillas F. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. *Seminars in Oncology* 2000 Dec;27(6 Suppl 12):37–41. [PubMed: 11225999]
27. Willems M, Haddad E, Niaudet P, Kone-Paut I, Bensman A, Cochat P, Deschenes G, Fakhouri F, Leblanc T, Llanas B, Loirat C, Pillet P, Ranchin B, Salomon R, Ulinski T, Bader-Meunier B. French Pediatric-Onset SLE Study Group. Rituximab therapy for childhood-onset systemic lupus erythematosus. *Journal of Pediatrics* 2006 May;148:623–627. [PubMed: 16737873]
28. Quartier P, Brethon B, Philippet P, Landman-Parker J, Le Deist F, Fischer A. Treatment of childhood autoimmune haemolytic anaemia with rituximab. *Lancet* 2001 Nov 3;358:1511–3. [PubMed: 11705566]Letter
29. Motto DG, Williams JA, Boxer LA. Rituximab for refractory childhood autoimmune hemolytic anemia. *Israel Medical Association Journal. Imaj* 2002 Nov;4:1006–8. [PubMed: 12489491]
30. Zecca M, Nobili B, Ramenghi U, Perrotta S, Amendola G, Rosito P, Jankovic M, Pierani P, De Stefano P, Bonora MR, Locatelli F. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. *Blood* 2003 May 15;101:3857–61. [PubMed: 12531800]
31. Zecca M, De Stefano P, Nobili B, Locatelli F. Anti-CD20 monoclonal antibody for the treatment of severe, immune-mediated, pure red cell aplasia and hemolytic anemia. *Blood* 2001 Jun 15;97:3995–7. [PubMed: 11389047]
32. Hongeng S, Tardtong P, Worapongpaiboon S, Ungkanont A, Jootar S. Successful treatment of refractory autoimmune haemolytic anaemia in a post-unrelated bone marrow transplant paediatric patient with rituximab. *Bone Marrow Transplantation* 2002 May;29:871–2. [PubMed: 12058238]
33. Nowak-Węgrzyn A, King KE, Shirey RS, Chen AR, McDonough C, Lederman HM. Fatal warm autoimmune hemolytic anemia resulting from IgM autoagglutinins in an infant with severe combined immunodeficiency. *Journal of Pediatric Hematology/Oncology* 2001 May;23:250–2. [PubMed: 11846306]

34. Seeliger S, Baumann M, Mohr M, Jurgens H, Frosch M, Vormoor J. Autologous peripheral blood stem cell transplantation and anti-B-cell directed immunotherapy for refractory auto-immune haemolytic anaemia. *European Journal of Pediatrics* 2001 Aug;160:492–6. [PubMed: 11548187]
35. Perrotta S, Locatelli F, La Manna A, Cennamo L, De Stefano P, Nobili B. Anti-CD20 monoclonal antibody (Rituximab) for life-threatening autoimmune haemolytic anaemia in a patient with systemic lupus erythematosus. *British Journal of Haematology* 2002 Feb;116:465–7. [PubMed: 11841453]
36. McMahon C, Babu L, Hodgson A, Hayat A, Connell NO, Smith OP. Childhood refractory autoimmune haemolytic anaemia: is there a role for anti-CD20 therapy (rituximab)? *British Journal of Haematology* 2002 May;117:480–3. [PubMed: 11972537]Letter
37. Ship A, May W, Lucas K. Anti-CD20 monoclonal antibody therapy for autoimmune hemolytic anemia following T cell-depleted, haplo-identical stem cell transplantation. *Bone Marrow Transplantation* 2002 Feb;29:365–6. [PubMed: 11896436]Letter
38. Corti P, Bonanomi S, Vallinoto C, Balduzzi A, Uderzo C, Cazzaniga G, Gaipa G, Dassi M, Perseghin P, Rovelli A. Rituximab for immune hemolytic anemia following T- and B-Cell-depleted hematopoietic stem cell transplantation. *Acta Haematologica* 2003;109:43–5. [PubMed: 12486323]
39. Ng PC, Lee KK, Lo AF, Li CK, Fok TF. Anti B cell targeted immunotherapy for treatment of refractory autoimmune haemolytic anaemia in a young infant. *Archives of Disease in Childhood* 2003 Apr;88:337–9. [PubMed: 12651764]
40. Kerridge I, Hann I, Ethel M, Potter M, Prentice HG. Anti-CD20 monoclonal antibody (rituximab) therapy in a child with refractory chronic autoimmune haemolytic anaemia. *Internal Medicine Journal* 2003 Nov;33:544–5. [PubMed: 14656263]Letter
41. Raj A, Bertolone S, Cheerva A. Successful treatment of refractory autoimmune hemolytic anemia with monthly rituximab following nonmyeloablative stem cell transplantation for sickle cell disease. *Journal of Pediatric Hematology/Oncology* 2004 May;26:312–4. [PubMed: 15111785]
42. Bonduel M, Zelazko M, Figueroa C, Magaldi G, Rossi J, del Pozo A. Successful treatment of autoimmune hemolytic anemia with rituximab in a child with severe combined immunodeficiency following nonidentical T-cell-depleted bone marrow transplantation. *Bone Marrow Transplantation* 2005 Apr;35:819–21. [PubMed: 15750606]Letter
43. Jubinsky PT, Rashid N. Successful treatment of a patient with mixed warm and cold antibody mediated Evans syndrome and glucose intolerance. *Pediatric Blood & Cancer* 2005 Sep;45:347–50. [PubMed: 15704210]
44. McMahon C, Babu L, Hodgson A, Hayat A, Connell NO, Smith OP. Childhood refractory autoimmune haemolytic anaemia: is there a role for anti-CD20 therapy (rituximab)? *British Journal of Haematology* 2002 May;117:480–3. [PubMed: 11972537]Letter
45. Berentsen S, Ulvestad E, Gjertsen BT, Hjorth-Hansen H, Langholm R, Knutsen H, Ghanima W, Shammass FV, Tjonnfjord GE. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. *Blood* 2004 Apr 15;103:2925–8. [PubMed: 15070665]
46. Taube T, Schmid H, Reinhard H, von Stackelberg A, Overberg US. Effect of a single dose of rituximab in chronic immune thrombocytopenic purpura in childhood. *Haematologica* 2005 Feb;90:281–3. [PubMed: 15710595]Letter
47. Bengtson KL, Skinner MA, Ware RE. Successful use of anti-CD20 (rituximab) in severe, life-threatening childhood immune thrombocytopenic purpura. *Journal of Pediatrics* 2003 Nov;143:670–3. [PubMed: 14615744]
48. ten Cate R, Smiers FJ, Bredius RG, Lankester AC, van Suijlekom-Smit LW, Huizinga TW, Egeler RM. Anti-CD20 monoclonal antibody (rituximab) for refractory autoimmune thrombocytopenia in a girl with systemic lupus erythematosus. *Rheumatology* 2004 Feb;43:244. [PubMed: 14739467]Letter
49. Roganovic J. Rituximab treatment in refractory idiopathic thrombocytopenic purpura in children. *European Journal of Pediatrics* 2005 May;164:334. [PubMed: 15711954]Letter
50. Russo G, Licciardello M, La Spina M. Rituximab in children with idiopathic thrombocytopenic purpura: does it really work? *European Journal of Pediatrics* 2004;163:569. [PubMed: 15243812]
51. Pusiol A, Cesaro S, Nocerino A, Picco G, ZanESCO L, Bisogno G. Successful treatment with monoclonal antibody rituximab in two children refractory autoimmune thrombocytopenia. *European Journal of Pediatrics* 2004;163:305–307. [PubMed: 15346911]

52. Moschovi M, Trimis G, Pergantou H, Platokouki H, Vrachnou E, Tzortzatou-Stathopoulou F. Clinical remission following monoclonal anti-CD20 therapy in two children with chronic refractory idiopathic thrombocytopenic purpura. *Journal of Paediatrics & Child Health* 2005 Jul;41:384–6. [PubMed: 16014149]
53. Bengtson K, Skinner M, Ware R. Successful use of anti- CD20 (Rituximab) in severe, life threatening childhood immune thrombocytopenic purpura. *Journal of Pediatrics* November;2003 143:670–673. [PubMed: 14615744]
54. Fox RA, Neufeld EJ, Bennett CM. Rituximab for adolescents with haemophilia and high titre inhibitors. *Haemophilia* May;2006 12:218–222. [PubMed: 16643204]
55. Mathias M, Khair K, Hann I, Liesner R. Rituximab in the treatment of alloimmune factor VIII and IX antibodies in two children with severe haemophilia. *British Journal of Haematology* 2004 May; 125:366–8. [PubMed: 15086418]
56. Mateo J, Badell I, Forner R, Borrell M, Tizzano E, Fontcuberta J. Successful suppression using Rituximab of a factor VIII inhibitor in a boy with severe congenital haemophilia: an example of a significant decrease of treatment costs. *Thrombosis & Haemostasis* 2006 Feb;95:386–7. [PubMed: 16493502]
57. Curry N, Stanworth S, Keeling D. The use of rituximab in two children with allo-antibodies towards factor VIII. *British Journal of Haematology* 2006 Apr;133:214–6. [PubMed: 16611318]Letter
58. Wiestner A, Cho HJ, Asch AS, Michelis MA, Zeller JA, Peerschke EI, Weksler BB, Schechter GP. Rituximab in the treatment of acquired factor VIII inhibitors. *Blood* 2002 Nov 1;100:3426–8. [PubMed: 12384448]see comment
59. Stasi R, Brunetti M, Stipa E, Amadori S. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. *Blood* 2004 Jun 15;103:4424–8. [PubMed: 14996701]
60. Faye A, Quartier P, Reguerre Y, Lutz P, Carret AS, Dehee A, Rohrlach P, Peuchmaur M, Mathieu-Boue A, Fischer A, Vilmer E. Chimaeric anti-CD20 monoclonal antibody (rituximab) in post-transplant B-lymphoproliferative disorder following stem cell transplantation in children. *British Journal of Haematology* 2001 Oct;115:112–8. [PubMed: 11722420]
61. Serinet MO, Jacquemin E, Habes D, Debray D, Fabre M, Bernard O. Anti-CD20 monoclonal antibody (Rituximab) treatment for Epstein-Barr virus-associated, B-cell lymphoproliferative disease in pediatric liver transplant recipients. *Journal of Pediatric Gastroenterology & Nutrition* 2002 Apr; 34:389–93. [PubMed: 11930095]see comment
62. Berney T, Delis S, Kato T, Nishida S, Mittal NK, Madariaga J, Levi D, Nery JR, Cirocco RE, Gelman B, Ruiz P, Tzakis AG. Successful treatment of posttransplant lymphoproliferative disease with prolonged rituximab treatment in intestinal transplant recipients. *Transplantation* 2002 Oct 15;74:1000–6. [PubMed: 12394845]
63. Gong JZ, Bayerl MG, Sandhaus LM, Sebastian S, Rehder CW, Roubort M, Lagoo AS, Szabolcs P, Chiu J, Comito M, Buckley PJ. Posttransplant lymphoproliferative disorder after umbilical cord blood transplantation in children. *American Journal of Surgical Pathology* 2006 Mar;30:328–36. [PubMed: 16538052]
64. Quiros-Tejeira RE, Chang I, Karpen SJ, Bristow LJ, Scott JD, Goss JA. Post-Transplant Lymphoproliferative Disease in Pediatric Liver Transplant Recipients treated with anti CD20 monoclonal antibody: A long term outcome study. *Journal of Pediatric Gastroenterology and Nutrition*, volume June;2004 39(supplement 1):S93.
65. Webber S, Harmon W, Faro A, Green M, Sarwal M, Hayashi R, Canter C, Thomas D, Jaffe R, Fine R. Anti-CD20 monoclonal antibody (Rituximab) for refractory PTLD after pediatric solid organ transplantation: Multicenter experience from a registry and from a prospective clinical trial. *Blood* 104:213a.
66. Faye A, Van Den Abeele T, Peuchmaur M, Mathieu-Boue A, Vilmer E. Anti-CD20 monoclonal antibody for post-transplant lymphoproliferative disorders. *Lancet* 1998 Oct 17;352:1285. [PubMed: 9788467]Letter
67. Kuehnle I, Huls MH, Liu Z, Semmelmann M, Krance RA, Brenner MK, Rooney CM, Heslop HE. CD20 monoclonal antibody (rituximab) for therapy of Epstein-Barr virus lymphoma after hemopoietic stem-cell transplantation. *Blood* 2000 Feb 15;95:1502–5. [PubMed: 10666232]

68. Stachel DK, Schmid I, Schuster F, Stehr M, Baumeister FA, Muller-Hocker J. Lymphoproliferative syndrome in an infant after stem cell transplantation: successful therapy with T-lymphocytes and anti-CD20 monoclonal antibodies. *Medical & Pediatric Oncology* 2000 Nov;35:503–5. [PubMed: 11070486]
69. Skoda-Smith S, Douglas VK, Mehta P, Graham-Pole J, Wingard JR. Treatment of post-transplant lymphoproliferative disease with induction chemotherapy followed by haploidentical peripheral blood stem cell transplantation and Rituximab. *Bone Marrow Transplantation* 2001 Feb;27:329–32. [PubMed: 11277182]
70. Zilz ND, Olson LJ, McGregor CG. Treatment of post-transplant lymphoproliferative disorder with monoclonal CD20 antibody (rituximab) after heart transplantation. *Journal of Heart & Lung Transplantation* 2001 Jul;20:770–2. [PubMed: 11448808]
71. Herman J, Vandenberghe P, van den Heuvel I, Van Cleemput J, Winnepenninckx V, Van Damme-Lombaerts R. Successful treatment with rituximab of lymphoproliferative disorder in a child after cardiac transplantation. *Journal of Heart & Lung Transplantation* 2002 Dec;21:1304–9. [PubMed: 12490276]
72. Bueno J, Ramil C, Somoza I, Sanchez-Galindo A, Solar A, Arnal F, Alvarez A, Sanchez-Mozo P, Gomez M. Treatment of monomorphic B-cell lymphoma with rituximab after liver transplantation in a child. *Pediatric Transplantation* 2003 Apr;7:153–6. [PubMed: 12654058]
73. Al-Akash SI, Al Makadma AS, Al Omari MG. Rapid response to rituximab in a pediatric liver transplant recipient with post-transplant lymphoproliferative disease and maintenance with sirolimus monotherapy. *Pediatric Transplantation* 2005 Apr;9:249–53. [PubMed: 15787802]
74. Zhu K, Chen J, Chen S. Treatment of Epstein-Barr virus--associated lymphoproliferative disorder (EBV-PTLD) and pure red cell aplasia (PRCA) with Rituximab following unrelated cord blood transplantation: a case report and literature review. *Hematology* 2005 Oct;10:365–70. [PubMed: 16273722]
75. Nozu K, Iijima K, Fujisawa M, Nakagawa A, Yoshikawa N, Matsuo M. Rituximab treatment for posttransplant lymphoproliferative disorder (PTLD) induces complete remission of recurrent nephrotic syndrome. *Pediatric Nephrology* 2005 Nov;20:1660–3. [PubMed: 16133051]
76. Gokce S, Suoglu OD, Sokucu S, Gun F, Emiroglu H, Celik A, Dogan O, Cevikbas U. Primary nonresponse to anti-cd20 therapy in gastrointestinal posttransplant lymphoproliferative disorder. *Journal of Pediatric Gastroenterology & Nutrition* 2006 Mar;42:316–20. [PubMed: 16540802]
77. Codeluppi M, Cocchi S, Guaraldi G, Di Benedetto F, Bagni A, Pecorari M, Gennari W, Pinna AD, Gerunda GE, Esposito R. Rituximab as treatment of posttransplant lymphoproliferative disorder in patients who underwent small bowel/multivisceral transplantation: report of three cases. *Transplantation Proceedings* 2005 Jul-Aug;37:2634–5. [PubMed: 16182770]
78. Milpied N, Vasseur B, Parquet N, Garnier JL, Antoine C, Quartier P, Carret AS, Bouscary D, Faye A, Bourbigot B, Reguerre Y, Stoppa AM, Bourquard P, Hurault de Ligny B, Dubief F, Mathieu-Boue A, Leblond V. Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. *Ann Oncol* 2000;11:113–116. [PubMed: 10707791]
79. Choquet S, Herbrecht R, Socie G, Stoppa AM, Vandenberghe P, Feremans W, Fischer A, Morschauser F, Salles G, Vilmer E, Garnier JL, Jaccard A, Lamy T, Lang P, Lebranchu Y, Offner F, Oksenhendler E, Abraham E, Leblond V, Milpied N. Multicenter, open label, phase II trial to evaluate the efficacy and safety of treatment with rituximab in patients suffering from B-cell posttransplantation lymphoproliferative disorders (B-PTLD) (M39037 trial). *Ann Oncol* 2002;13:37.
80. Orjuela M, Gross TG, Cheung YK, Alobeid B, Morris E, Cairo MS. A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation. *Clinical Cancer Research* 2003 Sep 1;9(10 Pt 2):3945S–52S. [PubMed: 14506193]
81. Culic S, Culic V, Armanda V, Kuljis D, Pesutic-Pisac V, Jankovic S. Anti-CD20 monoclonal antibody (Rituximab) for therapy of mediastinal CD20-positive large B-cell non-Hodgkin lymphoma with a local tumor extension into the lung of a 10-year-old girl. *Pediatric Hematology & Oncology* 2003 Jun;20:339–44. [PubMed: 12746167]

82. de Vries MJ, Veerman AJ, Zwaan CM. Rituximab in three children with relapsed/refractory B-cell acute lymphoblastic leukaemia/Burkitt non-Hodgkin's lymphoma. *British Journal of Haematology* 2004 May;125:414–5. [PubMed: 15086431]Letter
83. Okur FV, Oguz A, Karadeniz C, Citak C, Poyraz A, Boyunaga O. Refractoriness to rituximab monotherapy in a child with relapsed/refractory Burkitt non-Hodgkin lymphoma. *Pediatric Hematology & Oncology* 2006 Jan-Feb;23:25–31. [PubMed: 16326409]
84. Jetsrisuparb A, Wiangnon S, Komvilaisak P, Kularbkaew C, Yutanawiboonchai W, Mairieng E. Rituximab combined with CHOP for successful treatment of aggressive recurrent, pediatric B-cell large cell non-Hodgkin's lymphoma. *Journal of Pediatric Hematology/Oncology* 2005 Apr;27:223–6. [PubMed: 15838396]
85. Imamura T, Yoshihara T, Morimoto A, Ishida H, Sugimoto T, Imashuku S. Successful autologous peripheral blood stem cell transplantation with rituximab administration for pediatric diffuse large B-cell lymphoma. *Pediatric Hematology & Oncology* 2006 Jan-Feb;23:19–24. [PubMed: 16326408]
86. Corbacioglu S, Eber S, Gungor T, Hummerjohann J, Niggli F. Induction of long-term remission of a relapsed childhood B-acute lymphoblastic leukemia with rituximab chimeric anti-CD20 monoclonal antibody and autologous stem cell transplantation. *Journal of Pediatric Hematology/Oncology* 2003 Apr;25:327–9. [PubMed: 12679650]
87. Claviez A, Eckert C, Seeger K, Schrauder A, Schrappe M, Henze G, von Stackelberg A. Rituximab plus chemotherapy in children with relapsed or refractory CD20-positive B-cell precursor acute lymphoblastic leukemia. *Haematologica* 2006 Feb;91:272–3. [PubMed: 16461321]Letter
88. Kraal K, Schalijs-Delfos N, van Buchem M, Egeler M, Ball L. Optic nerve relapse in a child with common acute lymphoblastic leukemia, treated with systemic anti-CD-20 (rituximab). *Haematologica* 2005 Nov;90(Suppl):ECR24. [PubMed: 16266915]

Abbreviations

ADCC	antibody-dependent cellular cytotoxicity
AIHA	autoimmune hemolytic anemia
ALL	acute lymphoblastic leukemia
CR	complete response
ITP	immune thrombocytopenic purpura
IVIG	intravenous immune globulin
NHL	non Hodgkins lymphoma
PTLD	post-transplant lymphoproliferative disease
SLE	systemic lupus erythematosus

Table

type	N	% Male/Female	Age range (median)	Other Diagnoses	Previous Treatment	Doses of Rituximab range (median)	Response Rate	Follow-up range (median)	Toxicity/Side Effects
cases	25	38/62	4mo-15yr (35mo)	SLE, rheumatoid arthritis,ITP	steroids, IVIG, cyclosporine, cyclophosphamide, splenectomy, azathioprine, tacrolimus	1-6(4)	92%	7 - 28mo (16 mo)	E. Coli pyelonephritis, bronchitis, varicella pneumonia, varicella zoster (2), Pneumocytis carinii pneumonia
cases	14	54/46	2mo-18yr (7yr)	Beta-thalassemia, severe combinedimmunodeficiency, SLE,ITP, diabetes mellitus, Evans syndrome	steroids, IVIG, cyclosporine,cyclophosphamide,azathioprine,	2-8 (4)	93%	1- 30 mo (14 mo)	Fatal RSV pneumonia,fungal infection
cases	82	48/52	2yr-19yr(11 yr)	Evans syndrome (n = 6)	splenectomy, IVIg, anti-D, danazol,cyclophosphamide,azothioprine, vincristine	1-4(4)	43%	3-30mo(9 mo)	Neutropenia (3),serum sickness(3), hypotensionwith 3 rd dose,primary varicella
Outcomes	10	33/67	3mo-16vr (8vr)	SLE	Anti-D, steroids, IVIg,splenectomy	3-4 (4)	70%	80d-22mo (12 mo)	none
	8	100/0	7y-17y(14y)	none	Immune tolerance	4-every 10wks (4)	63%	11- 15 mo (13 mo)	none
	71	not reported	11mo-16yr (8yr)	Transplant:bone marrow (12) umbilical cord blood (5),liver (11), small bowel(3), heart (15), kidney (11), lung (9), other (5)	reduction ofimmunosuppression,ganciclovir, CMV Ig	1-9 (4)	70%	12d-41mo (28 mo)	Fatal staphylococcalsepsis,anaphylaxis
cases	14	69/31	9mo-19yr(5yr)	Transplant:bone marrow (6),umbilical cord blood (1),heart (2), liver (3), kidney (1), small bowel (1)	reduction ofimmunosuppression,maternal lymphocytes,acyclovir	1-4(4)	93%	6mo-3yr(10mo)	none
reports	6	67/33	4-14vr (9vr)	none	conventionalchemotherapy	4-8 (4)	83%	4-5 yr	none
	6	67/33	2-12vr(6vr)	none	conventionalchemotherapy	1-5(4)	100%	6mo-4yr(12mo)	none