Rituximab Therapy for Immune Anaemia and Thrombocytopenia

a report by
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Significant morbidity and mortality are found in the immune-mediated haematological disorders autoimmune haemolytic anaemia (AIHA) and idiopathic thrombocytopenic purpura (ITP). Despite the availability of several treatment options, relapsed or refractory disease is frequently encountered and treatment-related complications are of major concern.

Rituximab, a genetically engineered chimeric monoclonal anti-CD20 antibody, has shown impressive activity in CD20-positive B-cell non-Hodgkin's lymphomas.[1] Clinical observations showed that this peripheral B-cell-depleting agent may also be promising in the growing armamentarium of immune-mediated haematological (and non-haematological) disorders.[2]

AIHA is caused by the formation of autoantibodies directed against autologous red blood cell (RBC) antigens, leading to RBC destruction (haemolysis). Based on the characteristic temperature reactivity of the autoantibody, AIHA can be divided into warm antibody AIHA, cold antibody AIHA and mixed antibody AIHA. Furthermore, AIHA can be classified into primary (idiopathic) and secondary AIHA, associated with an underlying factor such as a lymphoproliferative condition, autoimmune disorder, infection or medication regimen.[3]

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ITP is characterised by immune-mediated platelet destruction in the mononuclear phagocytic system, leading to thrombocytopenia. As with AIHA, ITP can be divided into primary (idiopathic) and secondary ITP.[4] Evans syndrome is a rare disorder defined by a combination of immune thrombocytopenia and anaemia and without any known underlying condition.[5]

Although major progress has been made during the last few decades, the pathogenesis of immune-mediated disorders remains poorly understood. The role of T cells has been established for a long time, but B cells also seem to play a major role, being responsible for the production of autoantibodies, but also by acting as antigen-presenting cells (APCs) supporting the activation of autoreactive T cells. This major contribution of B cells makes them an attractive target in the treatment of immune-mediated disorders and provides a rationale for the use of rituximab in AIHA and ITP (see *Figure 1*).[3,6]

In warm antibody AIHA, corticosteroids are the initial therapy of choice. Although the majority of patients initially respond to this therapy, only 20–35% remain in permanent remission. In cases of failure or relapse, splenectomy is considered second-line therapy, with initial complete responses of 50%. If these conventional therapies fail or are not tolerated, immunosuppressive regimens including azathioprine, cyclophosphamide, cyclosporin A or mycophenolate mofetil can be tried. Additional therapies include danazol, intravenous immunoglobulins (IVIg) and eradication of *Helicobacter pylori*, if present. In cold AIHA, corticosteroids and splenectomy are usually less effective,[3,7] and avoidance of the common cold is most important.

Initial therapy for ITP depends on whether urgent treatment to raise the platelet count is needed. In patients experiencing serious or life-threatening bleeding or who present with very low platelet counts, initial therapy consists mostly of IVIg and IV methylprednisolone. Platelet transfusions are recommended only in case of ongoing life-threatening bleeding.

In a non-urgent setting, corticosteroids remain the initial standard treatment. In cases of intolerance, IV anti-D can be considered in Rh+ patients. However, more than 70% of patients fail to achieve a lasting response with these agents. In these cases, splenectomy is the standard of care. This leads to a durable response in about two-thirds of patients. In refractory or relapsing patients, immunosuppressive therapy including azathioprine, cyclophosphamide, cyclopsporin A, mycophenolate mofetil and combinations of these products has shown variable responses.[8]

In recent years, several reports using monoclonal antibodies (MAbs) in the treatment of haematological diseases, including autoimmune disorders, have been published. Most experience has been obtained with rituximab, a chimeric murine/human antibody directed against the CD20 antigen expressed on the surface of normal and malignant B lymphocytes that was primary developed to treat patients with clonal B cell malignancies. As already mentioned, B cells play a major role in this immune-mediated disorder. They are responsible for the production of autoantibodies and they also act as APCs, supporting activation of autoreactive T cells.

Table 1: Responses with Rituximab in Autoimmune Haemolytic Anaemia

Author	Year	Number of Patients	Age (years)	Response ORR (%)	Response CR (%)
Quartier	2001	6	0.5–3	100	100
Gupta	2002	8	46–70	100	60
Zecca	2003	15	0.3–14	87	NR
Trapé	2003	5	44–66	100	60
Shanafelt	2003	5	21–79	40	40
Camou	2003	5	NR	100	20
Berentsen	2004	27 (37R-courses)	51–91	51	3
Schöllkopf	2006	20	54–86	45	4
D'Arena	2006	14	48–87	72	22
D'Arena	2007	11	23–81	100	73
Dierickx	2007	39 (53R courses)	1–87	79	NR
Total		**116**	**0.5–91**	**78**	**27**

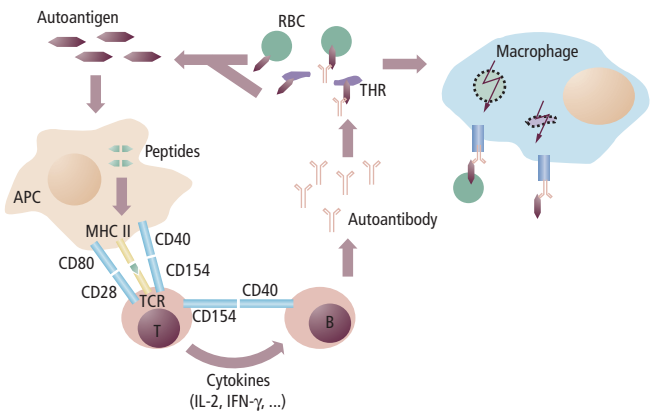
ORR = overall response rate; CRR = complete response rate; R = rituximab; NR = not reported.

Depletion of B cells by rituximab seems to be a result of complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity and induction of apoptosis.[9]

Based on the current literature, rituximab seems to have efficacy in the treatment of AIHA. Unfortunately, most of the available evidence is based on case reports or single-centre experiences. A few prospective trials have been performed, but none of them included a control group. In addition, response criteria were not uniform or were not mentioned. Nevertheless, as shown in *Table 1*, rituximab seems to be an effective and safe therapy. Overall response rates with rituximab approached 78%.

Response duration ranged from one to 96 months.[10] Especially in cold agglutinin disease, rituximab seems to be a promising agent, improving therapeutic responses compared with classic agents, with overall response rates of 45–60%. However, there were few complete remissions. Nevertheless, these are promising results due to the current lack of effective therapies in this subtype of AIHA.[11,12] Additionally, rituximab can be combined with cytotoxic agents in the treatment of AIHA secondary to CLL or other lymphoproliferative disorders.[13]

Figure 1: Pathogenetic Mechanisms in Autoimmune Haemolytic Anaemia and Idiopathic Thrombocytopenic Purpura



Platelet (THR) and red blood cell (RBC) antigens are cleaved by antigen-presenting cells (APCs) and presented as peptides on their surface via major histocompatibility complex (MHC) class II molecules. This complex is recognised by the T-cell receptor (TCR) of the CD4-positive T-helper (Th)-cell. Additional co-stimulatory signals are provided by CD80–CD28 and CD40–CD154 interactions. The activated Th cells produce activating cytokines (such as interleukin-2 and interferon-γ), which cause activation and differentiation of B-cells, leading to autoantibody production.
Autoantigens on the surface of THRs and RBCs are recognised by the Fab part of the autoantibodies. Autoantibody-coated platelets and RBCs are then recognised by macrophages of the mononuclear phagocytic system via Fc receptors on their surface, internalised and, eventually, undergo phagocytosis.

Several studies have shown that rituximab may also show impressive activity in the treatment of ITP. Recently, Arnold et al. published a systematic review of the available literature regarding the efficacy and safety of rituximab in the treatment of ITP in adult patients. Similar to rituximab in AIHA, no randomised controlled trials have yet been published. Response criteria were not always uniform and there are often insufficient data available for interpretation.[14] Nevertheless, as shown in *Table 2*, rituximab was associated with a platelet count response in approximately 64% of patients. Response duration ranged from five to 48 months.[10] Despite these promising results, prospective randomised trials are needed to determine response rates, duration of responses, prognostic factors predicting response, exact timing, doses and safety.

Although toxicity appears low, caution is needed. Most common side effects are infusion-related, such as fever, chills, headache, rash, bronchospasm and hypotension, mostly occurring during the first infusion. After administration of rituximab, peripheral B cell levels show a dramatic decrease, returning to near baseline six to 12 months after completion of therapy. Despite this profound B-cell depletion, decrease in serum Ig levels is observed in only a minority of patients. Serious infections seem to be rare and are seen only when concomitant immunosuppressive therapy is given.[15] However, rituximab needs to be used with caution in patients with a history of hepatitis B because of the risk of hepatitis activation.[16] Finally, T cells are not affected by rituximab, giving the patients no excess susceptibility to opportunistic infections compared with other MAbs such as alemtuzumab.[15]

Analogous to the use of rituximab in the treatment of B-cell malignancies, rituximab was given at a dose of 375mg/m^2/week over four consecutive weeks in most cases. Responses were mainly seen four to eight weeks after the start of rituximab administration, supporting the concept of depletion of autoreactive B cells as the main mechanism of action. However, in some cases responses were observed during the first few weeks after start of rituximab. This may have been due to saturation of Fc receptors of the mononuclear phagocytic system by

Table 2: Responses with Rituximab in Idiopathic Thrombocytopenic Purpura

Author	Year	Number of Patients	Age (years)	Prior Splenectomy (n)	Response ORR (%)	Response CR (%)
Stasi	2001	25	22–74	8	52	20
Giagounidis	2002	12	28–71	11	75	41
Zaja	2003	20	16–76	2	65	45
Narang	2003	6	30–70	6	100	67
Shanafelt	2003	12	31–79	1	50	42
Cooper	2004	57	21–79	31	54	32
Sanal	2004	15	20–83	8	87	67
Zalzaleh	2004	10	NR	NR	60	2
Jacoub	2004	11	20–79	6	91	81
Braendstrup	2005	35	17–82	16	49	20
Case	2005	22	24–83	20	59	32
Garcia-Chaves	2005	14	17–70	NR	92	36
Ahn	2005	12	22–87	3	83	50
Narat	2005	6	19–74	NR	83	67
Bennett	2006	36	2–18	7	31	NR
Penalver	2006	89	4–98	47	55	46
Dierickx	2007	29	16–89	22	64	58
Total		**370**	**2–87**	**165/340 reported**	**64**	**45**

n = number of patients; ORR = overall response rate; CRR = complete response rate; NR = not reported.

rituximab-coated B cells, similar to the mechanism of rapid response of anti-D in Rh+ patients with ITP.[8]

Currently, no pre-treatment patient or disease characteristics that predict response have been identified. So far, no consistent significant correlation between response and sex, age, prior splenectomy, platelet count or haemoglobin concentration when rituximab was started, duration of disease before start of rituximab and presence of underlying condition have been identified.

Preliminary experience suggests that re-treatment with rituximab in patients relapsing after a successful treatment with anti-CD20 therapy is beneficial, although concern has been raised. Reactivation of the disease may be attributable to the production of autoantibodies by long-lived plasma cells that are not targeted by rituximab due to the absence of CD20 expression on their surface.[2]

Apart from rituximab, other targeted immunotherapy has been described in immune-mediated haematological disorders. Alemtuzumab is a humanised rat anti-CD52 MAb that binds to most normal and malignant lymphocytes, both of T and B type. The mechanism of cell lysis is similar to that of rituximab. There has been very limited experience with alemtuzumab in autoimmune cytopenia, with only one report showing responses in 15 of 21 patients treated. Compared with rituximab, toxicity is expected to be much greater due to the profound immunosuppression that lasts for several months after cessation of treatment.[17] Humanised anti-CD154 MAb is another potentially interesting molecule in the treatment of ITP. By blocking the interaction between CD40 on APCs and CD154 (=CD40 ligand) on activated CD4-positive T cells, the autoimmune response is selectively suppressed (see *Figure 1*). Although a phase I trial showed encouraging results, no further trials were set up because of the occurrence of unacceptable adverse (thromboembolic) events.[18]

Based on growing literature and experience, rituximab has emerged as an effective and well-tolerated immunotherapeutic treatment option in patients with immune anaemia and thrombocytopenia. However, due to the lack of controlled data, no conclusions regarding the true efficacy, optimal timing, dose and safety of rituximab administration can currently be made and no valid comparison with the classic treatments of immune cytopenia is currently available. ■

1. Cheung MC, Haynes AE, Meyner RM, et al., Rituximab in lymphoma: a systematic review and consensus guideline from Cancer Care Ontario, *Cancer Treat Rev*, 2007;33(2):161–76.
2. Edwards JC, Cambridge G, B-cell-targeting in rheumatoid arthritis and other autoimmune diseases, *Nat Rev Immunol*, 2006;6(5):394–403.
3. Gehrs BC, Friedberg RC, Autoimmune haemolytic anaemia, *Am J Hematol*, 2002;69(4):258–71.
4. Cooper N, Bussel J, The pathogenesis of immune thrombocytopaenic purpura, *Br J Haematol*, 2006;133(4):364–74.
5. Norton A, Roberts I, Management of Evans syndrome, *Br J Haematol*, 2006;132(2):125–37.
6. Semple JW, Freedman J, Autoimmune pathogenesis and autoimmune haemolytic anaemia, *Semin Hematol*, 2005;42(3):122–30.
7. King KE, Ness PM, Treatment of autoimmune haemolytic anaemia, *Semin Hematol*, 2005;42(3):131–6.
8. Cines DB, Bussel JB, How I treat idiopathic thrombocytopaenic purpura (ITP), *Blood*, 2005;106(7):2244–51.
9. Maloney DG, Smith B, Rose A, Rituximab: mechanism of action and resistance, *Semin Oncol*, 2002;29(Suppl. 2):2–9.
10. Dierickx D, De Rycke A, Vanderschueren S, et al., New treatment options for immune-mediated haematological disorders, *Eur J Intern Med*, in press.
11. Berentsen S, Ulvestad E, Gjertsen BT, et al., Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients, *Blood*, 2004;103(8):2925–8.
12. Schöllkopf C, Kjeldsen L, Bjerrum OW, et al., Rituximab in chronic cold agglutinin disease: a prospective study of 20 patients, *Leuk Lymphoma*, 2006;47(2):253–60.
13. Gupta N, Kavuru S, Patel D, et al., Rituximab-based chemotherapy for steroid-refractory autoimmune haemolytic anaemia of chronic lymphocytic leukaemia, *Leukemia*, 2002;16(10):2092–5.
14. Arnold DM, Dentali F, Crowther MA, et al., Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopaenic purpura, *Ann Intern Med*, 2007;146:25–33.
15. Kimby E, Tolerability and safety of rituximab (Mabthera®), *Cancer Treatm Rev*, 2005;31(6):456–73.
16. Tsutsumi Y, Kanamori H, Mori A, et al., Reactivation of hepatitis B virus with rituximab, *Expert Opin Drugs Saf*, 2005;4:599–608.
17. Willis F, Marsh JC, Bevan DH, et al., The effect of treatment with Campath-1H in patients with autoimmune cytopaenias, *Br J Haematol*, 2001;114(4):891–8.
18. Kuwana M, Normura S, Fujimura K, et al., Effect of a single injection of humanised anti-CD154 monoclonal antibody on the platelet-specific autoimmune response in patients with immune thrombocytopaenic purpura, *Blood*, 2004;103:1229–36.