# The Use of Rituximab in Immune-mediated Anaemia

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## Abstract

Immune-mediated anaemia is a collective term describing the occurrence of anaemia due to an immune dysfunction, leading directly or indirectly to the destruction of red blood cells. In recent years, as knowledge of the immune system has progressed, these disorders have also become better understood and their management improved. Monoclonal antibodies have emerged as a powerful tool in the treatment of many different disorders, including both haematological and non-haematological disorders. Most experience has been obtained with the use of rituximab, a chimeric mouse/human anti-CD20 monoclonal antibody, showing high overall response rates with a relatively safe toxicity profile. Here we describe the currently available evidence on the use of rituximab in immune-mediated anaemia. We will also reflect on potential side effects that might hamper the initial enthusiasm for its use in these disorders.

## Keywords

Rituximab, CD20, anaemia, immune-mediated disorder, autoimmune haemolytic anaemia, cold agglutinin disease, Evans syndrome, pure red cell aplasia, thrombotic microangiopathy, thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, ADAMTS13

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Immune-mediated haematological disorders are a heterogeneous group of disorders characterised by immune-mediated destruction of blood cells, leading to anaemia, neutropenia or thrombocytopenia or to a combination of two or all of them. Immune-mediated anaemia can be caused directly by destruction of red blood cells (autoimmune haemolytic anaemia), by auto-antibodies against red blood cell precursors in the bone marrow (pure red cell aplasia) or indirectly by mechanical fragmentation of red blood cells secondary to the occurrence of auto-antibodies against other self antigens (thrombotic microangiopathy). Improving knowledge of the pathogenesis has revealed, besides the well-known role of T cells, a major role of B cells as well, making them a potential target in the treatment of immune-mediated disorders and providing a rationale for the use of B-cell-depleting therapy in these disorders. In immune-mediated cytopenia the use of rituximab has been associated with overall response rates exceeding 60%. However, most evidence is based on retrospective series with only a few prospective trials performed. Although rituximab is considered a safe treatment alternative, recent reports of severe (mainly infectious) complications need to be incorporated in therapeutic strategies.

## Mechanism of Action

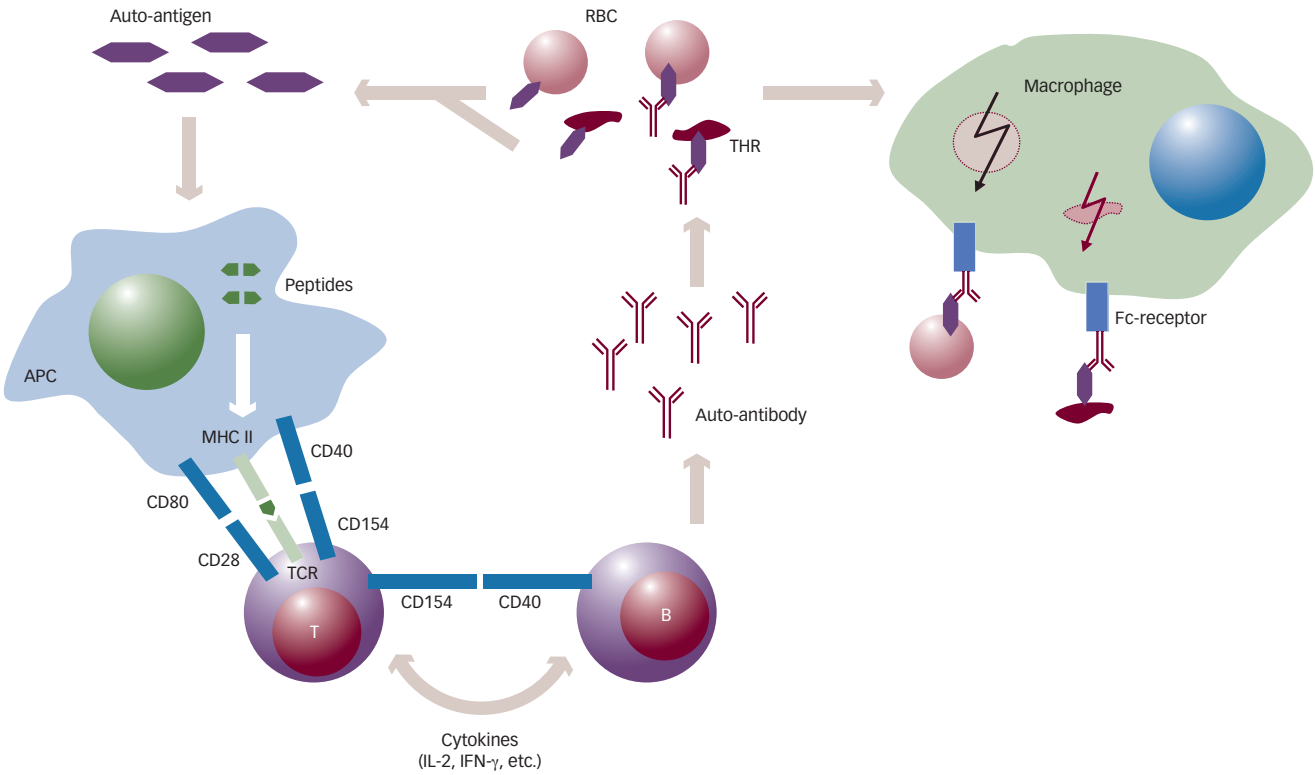
The use of monoclonal antibodies has emerged as a new and strong therapeutic platform in the treatment of haematological malignancies.[1,2] Clinical observations showed that some of these molecules may also aid in the treatment of immune-mediated haematological disorders.[3,4] Rituximab is a chimeric murine/human anti-CD20 antibody that was initially developed to treat patients with clonal B-cell malignancies. The therapeutic mechanisms of the molecule include antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity and direct apoptotic activity.[5] Both T cells and B cells play leading roles in the pathogenesis of immune-mediated disorders. The major role of B cells in producing auto-antibodies, producing inflammatory cytokines and acting as antigen-presenting cells supports the concept of B-cell-depleting therapy as an attractive target in the treatment of immune-mediated disorders (see *Figure 1*).[6] Recent findings have revealed that rituximab also influences the balance between the Th1/Th2 ratio and can cause restoration of $CD4^+$ $CD25^+$ Foxp3 regulatory T-cells (Tregs) in patients with immune thrombocytopenic purpura (ITP).[7,8]

Following 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, a decrease in serum immunoglobulin levels is observed in only a minority of the patients.[9]

## Rituximab in Autoimmune Haemolytic Anaemia

Rituximab in autoimmune haemolytic anaemia (AIHA) is an immune-mediated disorder in which B cells produce auto-antibodies against self-red blood cell antigens, leading to destruction of these cells. AIHA can be classified according to the characteristic temperature reactivity of the red blood cell auto-antibody as either warm-type or cold-type AIHA. Both types of AIHA can develop idiopathically ('primary' AIHA) as well as in association with a wide range of underlying conditions ('secondary' AIHA), including lymphoproliferative disorders, autoimmune diseases, infections, medication and immunodeficiency syndromes. Occasionally patients can have a combination of warm and cold auto-antibodies and are classified as mixed-type AIHA.[10,11]

**Figure 1: Pathogenetic Mechanisms in Autoimmune Haemolytic Anaemia and Immune 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-gamma), which cause activation and differentiation of B cells, leading to auto-antibody production. Auto-antigens on the surface of platelets and RBCs are recognised by the Fab part of the auto-antibodies. Auto-antibody-coated platelets and RBCs are then recognised by macrophages of the mononuclear phagocytic system via Fc-receptors on their surface, are internalised and eventually undergo phagocytosis.*

Evidence on the use of rituximab in AIHA is mainly based on retrospective case reports and case series, with only a few prospective trials. Nevertheless, based on these rather small series, information on about 300 patients has been reported, leading to overall response rates of more than 60%, with complete response rates exceeding 25%.[4,12] However, these numbers need to be interpreted with caution, as patients not responding are unlikely to be reported in case reports and smaller series.

Although patients experiencing warm AIHA can often be treated successfully with corticosteroids and/or splenectomy, these treatment options are very disappointing in primary cold agglutinin disease (CAD). CAD has traditionally been treated upfront with cytotoxic therapy, displaying a substantial toxicity profile. Recent findings using rituximab in CAD showing overall response rates of 50–65% in retrospective and prospective uncontrolled trials have led to the general assumption that rituximab, either in monotherapy or combined with alkylating agents or purine analogues, should be used as a first-line treatment in CAD.[12–15]

AIHA is a well-known complication of lymphoproliferative disorders, especially chronic lymphocytic leukaemia (CLL). Based on its potent activity in these disorders, either in monotherapy or combined with chemotherapeutic agents, rituximab has been used in lympho-proliferative-disorder-associated AIHA. The combined immuno-chemotherapeutic regimen rituximab–cyclophosphamide–dexa-methasone in particular seems to be associated with very high and durable responses in CLL-associated AIHA.[16,17]

Whether rituximab can be used as a splenectomy-sparing second-line therapy in warm AIHA has yet not been studied properly. However, in ITP – which can be considered the platelet analogue of AIHA – rituximab is now considered a valuable alternative in patients not fit enough to undergo or refusing splenectomy.[18,19]

Unlike ITP, identification of possible clinical or biochemical parameters able to predict outcomes following rituximab treatment have been poorly investigated. In both trials by Berentsen et al. in primary CAD and in the Belgian retrospective registry, no such parameters could be identified.[12,13,15]

Response duration in AIHA patients treated with rituximab has shown considerable variation, ranging from one month to more than eight years, with most patients showing responses exceeding more than one year. Although rituximab can induce durable responses in a proportion of patients with AIHA, most patients will eventually relapse. However, re-treatment with rituximab in previously responding patients having lost their response seems feasible, leading to comparable response rates and sometimes even longer response duration.[4,12]

## Rituximab in Evans Syndrome

Evans syndrome (ES) is a rare autoimmune disorder characterised by simultaneous or sequential occurrence of ITP and AIHA. Although initially by definition considered as an idiopathic ('primary' ES) disorder, the existence of 'secondary' ES has recently been recognised.[20,21] Michel et al. reported on a large database of 68 ES

patients, of whom 11 were treated with rituximab during the course of their disorder. Initial overall response rate in this series was 82%, with long-term response rates of 64%.[21]

## Rituximab in Pure Red Cell Aplasia

PRCA is another immune-mediated disorder, characterised by an isolated depletion of erythroid precursors in an otherwise normal bone marrow. Like AIHA, ITP and ES, PCRA can be classified as 'primary' or 'secondary', depending on the absence or presence of an underlying condition. Specific PCRA-inducing conditions include parvovirus B19 infection, thymoma and treatment with recombinant human erythropoietin.[22] As PRCA is an extremely rare disorder, evidence on the use of rituximab is limited to several case reports and very small series, showing both successes and failures.[23,24]

## Rituximab in Thrombotic Microangiopathy

TMA is a life-threatening disorder characterised by Coombs-negative micro-angiopathic haemolytic anaemia, thrombocytopenia and formation of microthrombi in different organs, especially the kidneys, heart and central nervous system. Although anaemia in TMA is caused by mechanical fragmentation of red blood cells, TMA is immune-mediated in a substantial proportion of patients.[25,26]

The term TMA comprises different entities, including thrombocytopenic thrombotic purpura (TTP) and haemolytic uremic syndrome (HUS). Broadly, TMA can be divided into three different categories:

- a disintegrin and metalloproteinase with thrombospondin type 1, 13, the member (ADAMTS13)-deficiency TTP (congenital or acquired);
- HUS (typical and atypical); and
- secondary TMA (see *Table 1*).[27,28]

Acquired ADAMTS13-deficiency TTP is a typical autoimmune disorder caused by the formation of auto-antibodies against ADAMTS13. This enzyme is responsible for cleavage of ultralarge von Willebrand factor (ULvWF) multimers. Due to these antibodies, ULvWF multimers are not or are insufficiently cleaved in patients with TTP, leading to profound platelet consumption, fragmentation of red blood cells and occlusion of small blood vessels in different organs (see *Figure 2*).[29]

Although initial treatment of TMA consists of urgent daily therapeutic plasma exchange,[30] treatment with rituximab is a promising approach in immune-mediated TMA, both as an adjunctive treatment to therapeutic plasma exchange and in case of relapse.[4] Currently, the experience with rituximab is limited to a few smaller case series and case reports on relapsing and refractory cases of TTP. Taken together, rituximab therapy seems to provide the most benefit in patients with severe ADAMTS13 deficiency due to ADAMTS13 auto-antibodies, which seems to be associated with a significantly higher relapse rate compared with patients with non-severely deficient ADAMTS13 activity levels.[31] Currently, more than 100 patients have been reported, with severe ADAMTS13 deficiency being documented in about 80% of these patients. In most of these cases, rituximab was used at the moment of relapse in adjunct to therapeutic plasma exchange, reaching response rates as high as 80–100%. Ling et al. recently reported on 13 patients with ADAMTS13 deficiency (12 patients experiencing severe deficiency) treated with rituximab, leading to durable complete response rates in 92% of the patients. Besides clinical remissions, most responses were also associated with a decrease in ADAMTS13 antibodies and an increase in ADAMTS13 activity in the plasma of the patients.[32] So far the largest series has been published by Scully et al., who described 25 patients with relapsing/refractory TMA and demonstrable auto-antibodies against ADAMTS13. All 25 patients attained complete clinical and laboratory remission within a median of 11 days after initiation of rituximab.[33]

Besides the use of rituximab as adjunctive therapy, there are a few reports on the successful use of rituximab as a monotherapy in patients with relapsing TTP. In an effort to better understand the therapeutic benefit of rituximab in relapsed/refractory TTP, the Canadian Apheresis Group recently initiated a phase II trial incorporating anti-CD20 therapy together with standard therapeutic plasma exchange.[34]

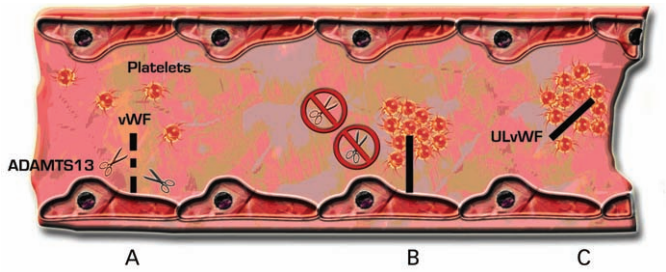
Rituximab may also be used in a prophylactic way in patients with relapsing TTP. In a multicentre, open-label, prospective trial, Fakhouri et al. treated five patients with severe relapsing TTP and persistent ADAMTS13 auto-antibodies during a period of clinical remission. In all patients, antibodies disappeared with the appearance of significant ADAMTS13 activity following rituximab admission.[35]

These promising results using rituximab in TTP have raised the question of whether rituximab should be used upfront together with therapeutic plasma exchange as standard treatment for TTP. In 2006, George et al. started a study on this specific subject, which will help to identify the place of rituximab in first-line therapy of TTP.[36]

**Table 1: Classification of Thrombotic Microangiopathy**

| |
|---|
| **ADAMTS13-deficiency Thrombocytopenia Thrombotic Purpura** |
| Congenital (mutations in ADAMTS13 gene) |
| Acquired (auto-anti-ADAMTS13 antibodies) |
| **Haemolytic Uraemic Syndrome (HUS)** |
| Typical HUS (Shiga toxin producing Escherichia coli) |
| Atypical HUS: |
| Congenital (mutations in complement regulatory proteins, thrombomodulin) |
| Acquired (auto-anti-complement regulatory proteins, antibodies) |
| **Secondary Thrombotic Micro-angiopathy Associated with:** |
| Solid organ transplantation |
| Haematopoietic stem cell transplantation |
| Pregnancy |
| Medication (clopidogrel, ticlodipin, quinine, mitomycin C, gemcitabine, calcineurin inhibitors, proliferation signalling inhibitors, etc.) |
| Auto-immune disorders (antiphopsholipid syndrome, systemic lupus erythematosus, etc.) |

**Figure 2: Pathogenetic Mechanisms in Thrombotic Microangiopathy**




*A: Normal circumstances: the endothelium produces von Willebrand factor (vWF). Afterwards, there is a rapid proteolysis of vWF by the ADAMTS13 enzyme. B: Idiopathic thrombocytopenic thrombotic purpura (TTP): unusually large von Willebrand factors (ULvWF) remain in a multimer form because of the inhibition of ADAMTS13 by auto-antibodies. C: ULvWF result in platelet aggregation; peripheral thromboembolisation develops under the influence of increased shearing stress.*

## Safety of Rituximab

Although rituximab is generally considered to be well tolerated and safe, severe and life-threatening events have been described.

### Infusion-related Complications

Most adverse events in lymphoma patients treated with rituximab are infusion-related, including fever, chills, rigour and hypotension, and in most cases are seen during the first infusion. In mostpatients these complications can be ameliorated by slowing or temporary interruption of the infusion and with pre-medication with paracetamol, anti-histamines and steroids. Although not always mentioned in the different reports, the incidence of infusion-related side effects seems to be comparable in immune-mediated disorders. Although rare, life-threatening symptoms such as bronchospasms, angioedema, hypoxia and shock have been described.[9]

### Infectious Complications

An important concern associated with the use of rituximab is the risk of developing infection. Indeed, rituximab has been associated with several severe or fatal infections, including cytomegalovirus reactivation, *Pneumocystis jiroveci* pneumonia and parvovirus B19 infection.[37] In a recent meta-analysis, Aksoy et al. reported a higher incidence of infection and neutropenia in lymphoma patients during rituximab maintenance therapy.[38] Since the introduction of rituximab, hepatitis B reactivation and hepatitis B-related complications have been increasingly reported. Pei et al. reported on 115 B-cell lymphoma patients treated with rituximab-containing therapy. Eight out of 10 HBsAg-positive patients without lamivudine prophylaxis and four out of 95 HBsAg-negative patients developed hepatitis B virus (HBV)-related hepatitis, with three patients dying from fulminant hepatitis/hepatic failure.[39] In another trial, Yeo et al. found that among HBsAg-negative/anti-HBc-positive diffuse large B-cell lymphoma patients treated with rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone (R-CHOP), 25% experienced HBV reactivation.[40] However, taking into account the fact that HBV reactivation is also a well-known complication of cytotoxic therapy, the real impact of rituximab is not entirely clear. The incidence of this complication in rituximab-treated patients with immune-mediated disorders is currently unknown.

Another emerging infectious problem in patients treated with rituximab and other monoclonal antibodies is progressive multifocal leuco-encephalopathy (PML), which is usually a fatal infection caused by JC polyomavirus. After the publication of several case reports on PML following immunomodulatory therapy, an attempt was made to document as many cases as possible following rituximab therapy. The Research on Adverse Drug Events and Reports (RADER) project reported on 57 cases, most of which were heavily pre-treated lymphoma patients. However, five patients with immune-mediated disorders were also described, of whom one ITP patient received corticosteroids and rituximab without any other immunosuppressive therapy.[41]

### Haematological Complications

Although rare, cytopenias are a well-known complication of rituximab therapy. Late-onset neutropenia in particular has emerged as an important side effect of this specific immunotherapy. Time between administration of rituximab and occurrence of late-onset neutropenia can vary widely, although most cases have been reported between two and 12 months following rituximab therapy. Several hypotheses for this phenomenon have been suggested, as reviewed by Ram et al.[37]

### Other Complications

Rituximab has been associated with several other side effects, including intestinal perforation and obstruction, although the exact contribution of the monoclonal antibody remains unknown.[37] However, the most severe and worrying complication seems to be delayed interstitial pneumonitis. Although very rare in most studies or series, Liu et al. reported on 107 lymphoma patients treated with rituximab-containing immunochemotherapy. Nine patients developed interstitial pneumonitis, which was in most cases reversible after prompt initiation of treatment with corticosteroids.[42] Recently, Bitzan et al. performed a systematic review of paediatric cases with rituximab-associated lung injury. Interestingly, of the 31 reported patients, the underlying disorder was immune-mediated in only three of the cases (one focal segmental glomerulosclerosis, one graft-versus-host disease and one ITP).[43]

## Conclusion

Rituximab, a monoclonal anti-CD20 antibody, has shown impressive activity in most B-cell non-Hodgkin's lymphomas. In recent years, clinical observations have shown that this B-cell-depleting molecule is also a potent tool in the treatment of immune-mediated disorders. In this way rituximab has become an important cornerstone in the treatment of AIHA, ES, PRCA and TMA, which are all immune-mediated disorders leading to anaemia.

However, despite the promising results, currently most evidence on rituximab's use is based on case series and retrospective studies, with only a few prospective trials being performed. Besides, most patients are treated with the classic dosage of four weekly administrations of 375mg/m², which is used in most patients with lymphoproliferative disorders. Recent studies, especially in immune TTP, showed similar response rates and B-cell depletion with lower doses of rituximab.

Further studies are needed to determine the best timing as well as the optimal schedule of rituximab administration in immune-mediated haematological disorders. Initially considered a safe therapy, caution is required based on recent reports describing sometimes severe rituximab-related complications. Although most side effects have been reported in heavily treated lymphoma patients, patients with immune-mediated disorders experiencing serious complications have also been described. By treating benign – but sometimes potentially life-threatening – immune-mediated disorders, the efficacy and toxicity of rituximab treatment should be balanced carefully. ■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