

Rituximab in the treatment of autoimmune haematological disorders

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Summary

Current treatment regimens for haematological autoimmune diseases are relatively non-selective and are often associated with considerable toxicity. Recently, it has become clear that B cells play a key role in both the development and perpetuation of autoimmunity, suggesting that B-cell depletion could be a valuable treatment approach for patients with autoimmune diseases. This article reviews data supporting the use of rituximab – an anti-CD20 monoclonal antibody that specifically depletes B cells – in four key autoimmune haematological disorders: idiopathic thrombocytopenic purpura (ITP); autoimmune haemolytic anaemia (AIHA); acquired haemophilia; and thrombotic thrombocytopenic purpura (TTP). Although treatment of ITP, AIHA, acquired haemophilia and TTP with rituximab is still relatively uncommon, results from case series and small phase II trials indicate that patients of all ages can respond to rituximab, irrespective of the number or type of prior treatments that they have received. Moreover, patients with these diseases receiving rituximab experienced predominantly mild adverse events, with only a few serious adverse events reported. These data suggest that rituximab provides an effective and well-tolerated alternative treatment option for patients with ITP, AIHA, acquired haemophilia and TTP, many of whom have limited treatment choices.

Keywords: acquired haemophilia, autoimmune haemolytic anaemia, cold agglutinin disease, idiopathic thrombocytopenic purpura, rituximab, thrombotic thrombocytopenic purpura.

Autoimmune diseases are relatively common, with a prevalence rate of 3.2% in the USA (Rose & Mackay, 1998). Such disorders are characterized by the production of antibodies against 'self' antigens, known as autoantibodies. A number of diseases are caused by autoantibodies against blood proteins or cells, giving rise to autoimmune haematological disorders.

Current treatment regimens for autoimmune disorders, particularly those of a haematological nature, tend to be relatively non-selective in their mechanism of action. Such therapies (e.g. corticosteroids and cytotoxic drugs) aim for global immunosuppression, with the intention of suppressing the autoantibody-related component of the immune system. Consequently, treatment success is often deceptive and may be associated with significant systemic toxicity. More specific and less toxic treatment options are therefore required.

The role of T lymphocytes in the pathogenesis of autoimmune diseases is well established; however, more recent data suggest that B cells also play a key role in supporting the development and perpetuation of autoimmunity (Looney, 2002; Silverman & Weisman, 2003). Thus, the elimination of B cells may be an effective treatment strategy for patients with autoimmune diseases.

Rituximab is a chimeric monoclonal antibody that specifically depletes B cells from the blood, lymph nodes and bone marrow by targeting CD20, which is expressed on the surface of premature and mature B lymphocytes but not on plasma cells or haematopoietic stem cells (Reff *et al*, 1994). Rituximab was first developed for the treatment of haematological malignancies and is indicated for the treatment of indolent and aggressive non-Hodgkin lymphoma (NHL) in both the USA and Europe; it is also used to treat patients with chronic lymphocytic leukaemia. In these settings, rituximab has been shown to be effective both as a monotherapy and in combination with chemotherapy (Cvetkovic & Perry, 2006). In addition, rituximab has a well-established safety profile through its use in haemato-oncological indications for over 10 years (Kimby, 2005). Physicians should be aware, however, that rituximab has been associated with rare cases of progressive multifocal encephalopathy, hepatitis B reactivation and other viral

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infections in NHL (Goldberg *et al*, 2002; Steurer *et al*, 2003; Aksoy *et al*, 2007; Freim Wahl *et al*, 2007; Kranick *et al*, 2007).

The central role of B cells in autoimmunity and the known mechanism of action of rituximab (selective depletion of B cells) provided a strong rationale for exploring the use of rituximab in the treatment of autoimmune diseases. Data from three recent large trials conducted in patients with active, long-standing rheumatoid arthritis have demonstrated a significant and clinically meaningful improvement in disease activity in patients treated with a combination of rituximab and methotrexate therapy compared with those receiving methotrexate alone (Edwards *et al*, 2004; Cohen *et al*, 2006; Emery *et al*, 2006). This has led to the approval of rituximab for the treatment of rheumatoid arthritis by the US Food and Drug Administration and the European Commission, and recommendation by the National Institute for Health and Clinical Excellence that rituximab should be a treatment option for patients with rheumatoid arthritis in England and Wales. In addition, data from a number of studies indicate that rituximab may also be effective in the treatment of other autoimmune diseases, such as systemic lupus erythematosus and multiple sclerosis (Rastetter *et al*, 2004).

The mechanism of action of rituximab

The mechanism of action of rituximab in autoimmune diseases may not be as straightforward as it appears at first sight. Although rituximab depletes B cells – which are the source of all immunoglobulins – clinical experience with rituximab in autoimmune diseases suggests that autoantibody levels are not always significantly affected by rituximab treatment (Taylor & Lindorfer, 2007). This suggests that B-cell depletion does more than simply remove the source of pathogenic autoantibodies. B cells are known to act as efficient antigen-presenting cells, providing important co-stimulatory signals in promoting effector T-cell expansion. In addition, B cells can produce cytokines that support the survival of other mononuclear cells (Looney, 2002; Silverman & Weisman, 2003; Carter, 2004; Martin & Chan, 2004; Cohen, 2005). Recently, Taylor and Lindorfer (2007) have suggested a different mechanism of action of rituximab in autoimmune diseases: the immune complex decoy hypothesis. They hypothesized that, as rituximab-opsonized B cells will be recognized by monocytes and macrophages, these effector cells would be diverted away from interactions with autoimmune antibody complexes. A similar theory was put forward by Stasi *et al* (2002) to explain the very rapid effect of rituximab treatment in some patients with idiopathic thrombocytopenic purpura (ITP). Although the pathogenesis of ITP is autoantibody-mediated, immunoglobulin (Ig)G autoantibodies are driven by T cell-dependent mechanisms and many reports have described several consistent T-cell abnormalities in ITP (Coopamah *et al*, 2003). The efficacy of a B-cell depleting therapy, despite the presence of autoreactive T cells, led Stasi *et al* (2007) to demonstrate that the therapeutic efficacy of rituximab may actually be due to a normalizing of the abnormal autoreactive T-cell responses in

patients with ITP. The pretreatment T-cell abnormalities, including elevated T-cell helper type 1/2 (and T cytotoxic type 1/2) cytokine ratios, elevated CD4⁺ T cell-associated *BCL2/BAX* mRNA levels and oligoclonal T-cell expansion, were completely reversed by 3 months after treatment. This was observed only in those patients who responded to rituximab therapy; these normalization changes persisted for as long as 6–12 months after therapy. These results suggest the intriguing hypothesis that rituximab therapy is effective only when T-cell subsets can be modulated. While the role of the reversal of T-cell abnormalities in ITP by rituximab therapy remains to be further elucidated, Semple (2007) has suggested that these findings may alter how we view therapeutic design in ITP. It seems likely that a combination of some or all of the above mechanisms play a role in the efficacy of rituximab in autoimmune diseases.

This review examines the evidence base supporting the use of rituximab in the treatment of four important autoimmune haematological disorders: ITP, autoimmune haemolytic anaemia (AIHA), acquired haemophilia and thrombotic thrombocytopenic purpura (TTP). A search of PubMed was conducted with each disease name and abbreviation combined with 'rituximab' up to December 2007. Additional published studies identified from the text of any of the publications identified on PubMed were also included. For each disease area, different criteria were used to determine which studies were to be included in each table, as described in the tables themselves. These criteria depended on the number of published studies in each disease area.

It is important to note that while there is published evidence that rituximab may be effective in some patients with ITP, AIHA, acquired haemophilia or TTP, it is not licensed for use in these diseases. It is imperative that physicians counsel patients about the risks associated with the off-label use of this drug so that they are able to make an informed decision about its use.

Idiopathic thrombocytopenic purpura

Disease characteristics

Idiopathic thrombocytopenic purpura is an autoimmune bleeding disorder with an incidence of approximately 30 per million persons per year in adults (Frederiksen & Schmidt, 1999; Neylon *et al*, 2003) and a similar incidence in children (Sutor *et al*, 2001; Zeller *et al*, 2005). The pathogenesis of ITP is not entirely clear, but patients develop autoantibodies against platelet surface glycoproteins. The subsequent destruction of platelets in the reticulo-endothelial system (notably the spleen) leads to a reduced peripheral blood platelet count. However, some patients with ITP lack detectable autoantibodies. It has been suggested that, in some cases, ITP may result from (i) T cell-mediated cytotoxicity or (ii) antibody-mediated complement activation causing platelet lysis or (iii) antibody-mediated suppression of megakaryocyte production (Nakhoul *et al*, 2006).

The clinical features of ITP are very different in adults and children. Whereas most cases of childhood ITP are acute, with >70% resolving spontaneously within 6 months (Bolton-Maggs, 2000), early spontaneous remissions in adults are rare and most patients progress to develop chronic ITP (George *et al*, 1994).

Current management of patients

Most treatments for adults with ITP are designed to increase platelet counts to reduce the risk of bleeding – particularly intracranial bleeding – and to manage any major bleeding episodes (Cines & Bussel, 2005; Nakhoul *et al*, 2006). Patients are usually treated with steroids and may receive intravenous immunoglobulin (IVIG) or anti-Rh(D) immunoglobulins. For those who fail to respond to these treatments or who require continued treatment, a splenectomy may be considered (Cines & Bussel, 2005; Nakhoul *et al*, 2006). Although splenectomy is an effective treatment for many patients, with approximately three-quarters achieving a durable response (Kumar *et al*, 2002; Kang *et al*, 2007), it carries with it an increased risk of infection (Kang *et al*, 2007) and a risk of death from postsplenectomy sepsis of up to 1% (Kumar *et al*, 2002).

For the 30–40% of patients with chronic ITP that is refractory to steroids and/or splenectomy, treatment options are limited. While some may tolerate very low platelet levels without serious bleeding events, many will require treatment at some point. Unfortunately, the currently available treatment options [which include danazol, vincristine, cyclophosphamide, azathioprine, ciclosporin A, IVIG and anti-Rh(D)] are not always effective and are associated with various toxicities, resulting in high rates of morbidity (Cines & Blanchette, 2002; Cines & Bussel, 2005; Nakhoul *et al*, 2006).

As the majority of children with ITP will undergo spontaneous remission within a few weeks, many clinicians recommend observation in the first instance. However, ITP can persist beyond 6 months in up to 25% of children with acute-onset ITP and approximately 5% of these will continue with severe thrombocytopenia for 1 year or longer (Blanchette & Price, 2003). For children with ITP requiring treatment, management is similar to that for adults. Splenectomy is deferred for as long as possible because of the associated lifelong increased risk of infection (Cines & Blanchette, 2002), with fatal postsplenectomy sepsis developing in 1.5–3% of children who have received a splenectomy (Aronis *et al*, 2004; Wang *et al*, 2006).

Treatment of children who relapse after splenectomy is challenging as no regimen is universally effective, although azathioprine (alone or with prednisone), cyclophosphamide, ciclosporin A or combination chemotherapy may be useful (Cines & Blanchette, 2002).

Use of rituximab in idiopathic thrombocytopenic purpura

Over the past few years, rituximab has emerged as an alternative treatment for ITP, with prospective data being

published for over 200 adults and 100 children with ITP (Table I). In most studies, over 50% of patients responded to treatment with rituximab, with between 8% and 88% of adult and paediatric patients achieving a complete response and with no obvious difference between the responses of adults and children (Table I). The majority of responses were durable and many were maintained for >1 year – the longest reported response was ongoing at 3.2 years (Cooper *et al*, 2004). These response rates were confirmed in a systematic review of rituximab for the treatment of adults with ITP. In this meta-analysis, the pooled response rate was 62.5%, with a complete response rate of 46.3% and a median duration of response of 10.5 months (Arnold *et al*, 2007).

In most studies, there were two patterns of response: the majority of responders (approximately 72%) responded to rituximab within 4 weeks, whereas, the rest did not achieve a complete response until several weeks or even months after the start of rituximab therapy (Giagounidis *et al*, 2002; Stasi *et al*, 2002; Zaja *et al*, 2003a, 2006; Cooper *et al*, 2004; Braendstrup *et al*, 2005; Wang *et al*, 2005; Parodi *et al*, 2006; Penalver *et al*, 2006; Garcia-Chavez *et al*, 2007; Schweizer *et al*, 2007). These two distinct patterns of response to rituximab in patients with ITP suggest that rituximab may operate through at least two separate mechanisms. The rituximab response in early responders is too rapid to be explained by the depletion of autoantibodies. Instead, it has been proposed that in these patients, opsonized B cells block the macrophage Fc-receptor function, reducing the sequestration of platelets in the spleen (Stasi *et al*, 2002; Taylor & Lindorfer, 2007). Further, it has been speculated that the late and sustained responses are more likely to result from a reduction in autoantibody levels. However, the lack of direct correlation between anti-platelet antibody levels and clinical response suggests that additional mechanisms may also be at work (Stasi *et al*, 2002, 2007; Martin & Chan, 2004).

Whereas, most studies using rituximab in ITP employed the same dose as is used to treat lymphoma (375 mg/m² weekly for 4 weeks), Saleh *et al* (2000) undertook a dose-ranging study, utilizing rituximab doses ranging from 50 to 375 mg/m². Although the number of patients was small, their results suggested that patients treated with lower doses of rituximab were less likely to achieve an objective response than those receiving higher doses. By contrast, in a more recent study, 11 patients with chronic ITP achieved an objective response rate of 45% after treatment with four once-weekly doses of 100 mg rituximab (El-Najjar *et al*, 2006). Furthermore, although the majority of studies treated patients with four doses of rituximab (Table I), a single dose (375 mg/m²) in 22 paediatric ITP patients resulted in an objective response rate of 59% (Taube *et al*, 2005). These data suggest that lower doses of rituximab may be an effective treatment for ITP in some circumstances.

Re-treating patients who have relapsed after an initial response to rituximab may also be an effective treatment option. Of 12 patients with ITP who initially responded to

Table 1. Studies employing rituximab to treat ITP.*

Reference	Study type	n	Population	Age (years)	ITP duration before rituximab (months)	Previous splenectomy (n)	Baseline platelet count ($\times 10^9/l$)	Doses of rituximab (n)	Response (%)	Response duration (weeks)
Saleh <i>et al</i> (2000)	Prospective phase I/II	13	Adult	21–77	NA	7	4–57	4 [†]	CR (8); PR (15) [‡]	13+–26+
Stasi <i>et al</i> (2001)	Prospective	25	Adult	22–74	9–56	8	3–25	4	CR (20); PR (20)	2–108+
Stasi <i>et al</i> (2002)	Prospective	7	Adult	20–66	10–84	3	1–19	4	CR (57); PR (29)	7–56+
Giagounidis <i>et al</i> (2002)	Prospective pilot	12	Adult	28–71	NA	11	1–29 [§]	2 (3); 4 (9)	CR (58); PR (8)	3–65+
Zaja <i>et al</i> (2003a) [¶]	Prospective	15	Adult	26–76	4–264	2	4–55	4	CR (40); PR (13)	9+–69
Shanafelt <i>et al</i> (2003) [¶]	Retrospective	12	Adult	22–79	NA	10	1–38	1 (1); 2 (3); 3 (1); 4 (7)	CR (42); PR (8)	2–48+
Cooper <i>et al</i> (2004)	Prospective	57	Adult	21–79	3–360	31	<30	4	CR** (32); PR (23)	<10–165+
Braendstrup <i>et al</i> (2005)	Retrospective	35 ^{††}	Adult	17–82	1–288	16	1–49	4	CR (18); PR (15)	8–126 ^{‡‡}
Taubke <i>et al</i> (2005)	Prospective	22	Paediatric	2.5–15.2	14–103	2	2–27	1	CR (32); PR ^{§§} (27)	9–104
Wang <i>et al</i> (2005)	Prospective	24	Paediatric	2–19	6–120	4	1–30 ^{¶¶}	2 (1); 3 (1); 4 (22)	CR** (63); PR (8)	13–130
Scheinberg <i>et al</i> (2006)	Retrospective	8	Adult and paediatric	8–51	24–180	NA	10–77	4	CR (88)	12.8+
Bennett <i>et al</i> (2006)	Prospective phase I/II	36	Paediatric	2.6–18.3	7–145	7	1–27	<4 (3); 4 (33)	Res (31)	NA
Zaja <i>et al</i> (2006) ^{***}	Prospective	37	Adult	NA	1–264	5	NA	4	CR (54); PR (19)	2–55+
Penalver <i>et al</i> (2006)	Retrospective	89	Adult and paediatric	4–98	1–305	47	1–30	1 (1); 3 (8); 4 (77); 5 (2); 6 (1)	CR (46); PR (9)	NA–52+
Parodi <i>et al</i> (2006)	Retrospective	19	Paediatric	3–16	5–73	6	2–26	2 (2); 3 (2); 4 (12); 5 (3)	CR (68)	3–43+
Godeau <i>et al</i> (2006)	Prospective	60	Adult	18–84	NA	0	16 \pm 10 ^{†††}	2 (1); 4 (59)	Success ^{***} (40)	52+
Rao <i>et al</i> (2007)	Prospective	19	Paediatric	3–18	1–48	NA	NA	6 (6); 4 (13)	CR ^{§§§} (53); PR ^{§§§} (26)	NA

Table I. (Continued).

Reference	Study type	n	Population	Age (years)	ITP duration before rituximab (months)	Previous splenectomy (n)	Baseline platelet count ($\times 10^9/l$)	Doses of rituximab (n)	Response (%)	Response duration (weeks)
Schweizer <i>et al.</i> (2007)	Retrospective	14	Adult	16–84	1–480	4	2–69	4 (8); 3 (2); 2 (4)	CR (50); PR (14)	2–156+
Garcia-Chavez <i>et al.</i> (2007)	Prospective	18	Adult	17–70	25–348	15	3–26	4	CR (28); PR (28)	NA–26+

CR, complete response (platelet count $>100 \times 10^9/l$, unless otherwise noted); ITP, idiopathic thrombocytopenic purpura; NA, data not available; PR, partial response (rise in platelet count to $50-100 \times 10^9/l$, unless otherwise noted); Res, response (sustained platelet count of $\geq 50 \times 10^9/l$ for four consecutive weeks).

*Published studies including more than or equal to seven patients are detailed in this table.

†Dose-escalation trial, with doses ranging from 50 to 375 mg/m².

‡In this study, a CR was defined as platelet count $>150 \times 10^9/l$ for >4 weeks and a PR as a platelet count $75-100 \times 10^9/l$ without maintenance steroids or $>100 \times 10^9/l$ with maintenance steroids for >4 weeks.

§Includes responding patients only.

*Data included in this table are for patients with ITP.

**In this study, a CR was defined as platelet count $>150 \times 10^9/l$.

††A total of 39 rituximab treatments were evaluated as four patients were treated twice.

‡‡Duration of response is for patients achieving a CR only; data were not available for PR.

§§In this study, a PR was defined as a rise in platelet count to $30-100 \times 10^9/l$.

**Excluding three patients receiving long-term steroid treatment to maintain their platelet counts before the start of rituximab.

***This study includes data from 15 patients that have been reported previously (Zajac *et al.*, 2003a). This report includes 30 patients with ITP, one with idiopathic thrombocytopenia and neutropenia, four with immune thrombocytopenia with undifferentiated connectivitis and two with low-grade non-Hodgkin lymphoma.

†††Median count.

‡‡‡In this study success was defined as platelet count $\geq 50 \times 10^9/l$ with at least a twofold increase in the initial value 1 year after rituximab infusion.

§§§In this study response rates were determined on a sustained response for >30 days, with a CR defined as platelet count $\geq 75 \times 10^9/l$ and a PR as platelet count $30-75 \times 10^9/l$.

rituximab but subsequently relapsed, the response rate after a second course of rituximab was roughly the same as that for the first course, with half of the patients responding to this second treatment (Stasi *et al*, 2001; Giagounidis *et al*, 2002; Braendstrup *et al*, 2005; Garcia-Chavez *et al*, 2007; Rao *et al*, 2007). This is analogous to the data in indolent NHL, where patients remain sensitive to rituximab re-treatment (Lemieux *et al*, 2004; Hainsworth *et al*, 2005).

Patients respond to rituximab regardless of the number of prior treatments they have received (Cooper *et al*, 2004; Bennett *et al*, 2006). Additionally, in most studies, patients who had not received a splenectomy fared equally as well as those who had (Stasi *et al*, 2001; Cooper *et al*, 2004; Braendstrup *et al*, 2005; Bennett *et al*, 2006; Godeau *et al*, 2006; Parodi *et al*, 2006; Penalver *et al*, 2006; Schweizer *et al*, 2007). In particular, the role of rituximab as an alternative to splenectomy has been assessed in a prospective study (Godeau *et al*, 2006). In this phase II trial, 60 adults who were candidates for splenectomy because of chronic ITP received four weekly intravenous infusions of rituximab, with patients requiring additional treatment within 1 year considered non-responders. At 1 year, 40% of patients were considered good long-term responders, with platelet levels restored to within the normal range in three-quarters of these patients. Taken together, these data suggest that rituximab treatment may obviate or delay the need for splenectomy in some patients. However, further large prospective studies are required to investigate the timing of rituximab treatment versus splenectomy, as data on the long-term outcomes and safety of rituximab in this situation are still lacking (Cooper *et al*, 2007).

Analyses demonstrate that patients benefit from rituximab regardless of the length of time between ITP diagnosis and rituximab treatment (Stasi *et al*, 2001; Zaja *et al*, 2003b; Taube *et al*, 2005; Bennett *et al*, 2006; Parodi *et al*, 2006), although patients with a disease duration of >10 years may have a reduced response rate (Cooper *et al*, 2004; Penalver *et al*, 2006).

Patients with ITP responded both to treatment with rituximab monotherapy (Stasi *et al*, 2001; Giagounidis *et al*, 2002; Shanafelt *et al*, 2003; Zaja *et al*, 2003a; Cooper *et al*, 2004; Taube *et al*, 2005; Wang *et al*, 2005; Bennett *et al*, 2006; Parodi *et al*, 2006; Penalver *et al*, 2006) and to treatment with rituximab combined with other drugs, including steroids, IVIG and cyclophosphamide (Stasi *et al*, 2002; Shanafelt *et al*, 2003; Zaja *et al*, 2003a; Cooper *et al*, 2004; Braendstrup *et al*, 2005; Penalver *et al*, 2006). In two studies, statistical comparisons indicated that there was no difference in responses between patients treated with rituximab monotherapy and those receiving rituximab in combination with steroids (Zaja *et al*, 2003a) or in combination with steroids and/or other therapies (Penalver *et al*, 2006).

Rituximab treatment of ITP was well tolerated in both adults and children, with the most common adverse events being temporary grade 1/2 infusion-related reactions (Saleh *et al*,

2000; Stasi *et al*, 2001; Giagounidis *et al*, 2002; Zaja *et al*, 2003a; Cooper *et al*, 2004; Braendstrup *et al*, 2005; Wang *et al*, 2005; Bennett *et al*, 2006; Parodi *et al*, 2006; Penalver *et al*, 2006; Garcia-Chavez *et al*, 2007; Rao *et al*, 2007). Serious toxicities resulting in treatment discontinuation were rare, but included thrombocytosis, a severe anaphylactoid reaction, serum sickness and infusion-related hypotension (Giagounidis *et al*, 2002; Braendstrup *et al*, 2005; Wang *et al*, 2005; Bennett *et al*, 2006). In the ITP studies listed in Table I, there is a single report of a serious infection during rituximab treatment – a paediatric patient who developed primary varicella after the first rituximab infusion and who recovered completely after treatment (Bennett *et al*, 2006). No long-term toxicities among these ITP patients treated with rituximab have been described. In a systematic review of the use of rituximab in ITP, Arnold *et al* (2007) reported that 10 of 306 patients for whom safety data had been reported experienced grade 3/4 adverse events, and nine patients died.

Both adult and paediatric ITP can be very expensive to treat. Patients with chronic refractory ITP often require many hospital visits and ongoing treatment for years. It has been estimated that, for a 20-kg child, each IVIG treatment costs US\$2492 (1US\$ is approximately equivalent to €0.70), while each anti-Rh(D) immunoglobulin treatment costs US\$2035 (O'Brien *et al*, 2007). Although there have been no formal economic evaluations of rituximab use in ITP, the potential benefits of rituximab treatment in terms of cost and patient outcome may outweigh the initial costs of the four weekly infusions. In a case study, Pérez-Calvo *et al* (2005) evaluated the costs associated with treating a patient with refractory ITP. The costs for this patient, associated with the eight hospital admissions, splenectomy and 41 outpatient clinic visits in the 55 months before rituximab treatment, were estimated to be €46 200, i.e. €840/month. In the 29 months after rituximab treatment, the patient had no hospital admissions and only five outpatient visits, at an estimated cost of €12 200, i.e. approximately €420/month (Pérez-Calvo *et al*, 2005). Rituximab treatment thus allowed a 50% reduction in direct costs even without considering the reduction in the patient's travel costs and discomfort. Generalized conclusions cannot be drawn from a single case-study, but the clinical characteristics of the patient described in this report could be representative of many patients with refractory ITP. Further cost-effectiveness may be achieved if, as has been suggested, therapy with lower or fewer doses of rituximab is equally safe and effective as treatment with the standard four once-weekly doses of 375 mg/m² (Taube *et al*, 2005; El-Najjar *et al*, 2006). Larger studies are warranted to further investigate the cost-effectiveness of rituximab therapy.

Conclusions

Steroid treatment, often combined with IVIG and/or anti-Rh(D) immunoglobulins, is the standard first-line treatment for both adults and children with ITP. However, although most

patients respond to steroid treatment, only 10–30% of adult patients continue in remission once therapy is halted (Cines & Bussel, 2005) and up to 75% of patients treated with glucocorticoids report unpleasant side effects (Matzdorff & Arnold, 2007). For patients requiring continued treatment, a splenectomy is usually recommended. Rituximab offers a possible alternative treatment option for patients with relapsed or refractory ITP, with studies demonstrating that more than half of all adults and children respond to rituximab therapy. As most studies show that patients fare equally well whether or not they have received a splenectomy, rituximab treatment may obviate or delay the need for a splenectomy, thus preventing or postponing a procedure that carries a lifelong risk of infection. Rituximab can also be effective in patients with ITP refractory to splenectomy, providing a well-tolerated alternative to danazol and/or toxic chemotherapeutic agents. Additional large prospective studies are required to further investigate the use of rituximab in ITP and to define the optimal position of rituximab in the therapeutic armamentarium.

Autoimmune haemolytic anaemia

General disease characteristics

Autoimmune haemolytic anaemia – disorders in which autoantibodies are directed against self red blood cells (RBC), resulting in severe anaemia – may lead to significant morbidity and mortality. The aetiology of autoantibody production is not well understood, but is thought to involve a complex dysfunction of the immune system and immune surveillance mechanisms (Semple & Freedman, 2005). Whereas most patients respond to therapy, those who are refractory to treatment have a reduced quality of life and increased mortality. Although AIHA can be idiopathic, 20–80% of patients have a suspected secondary cause of their disorder. Underlying diseases can include lymphoproliferative disorders, autoimmune disorders and infections (Gehrs & Friedberg, 2002).

Autoimmune haemolytic anaemia is a relatively uncommon disorder, with an estimated incidence of one to three cases per 100 000 persons per year (Gehrs & Friedberg, 2002). AIHA is classified as either warm AIHA or cold AIHA, depending upon the temperature at which the autoantibodies show maximal binding. Cold AIHA is subdivided into cold agglutinin disease (CAD) and paroxysmal cold haemoglobinuria. In rare cases, patients can have both warm and cold autoantibodies.

Warm autoimmune haemolytic anaemia

Warm AIHA is responsible for 48–70% of AIHA cases (Sokol *et al*, 1992; Gehrs & Friedberg, 2002). By definition, the autoantibodies – the majority of which are in the IgG1 and/or IgG3 subclasses – show maximal binding to RBC at body temperature. The IgG-coated RBC are recognized by the macrophages of the spleen, resulting in loss of a portion of cell

membrane. After multiple passages through the spleen, the surface area of the RBC is decreased to such an extent that the cell becomes spherical (a spherocyte). The rigid spherocytes are then trapped in the splenic sinusoids and removed from circulation (Sokol *et al*, 1992; Gehrs & Friedberg, 2002; Gertz, 2006).

Current management of patients

Patients with warm AIHA requiring treatment generally receive corticosteroids as first-line therapy. Approximately 70–80% of patients will improve with this treatment; however, although 15–20% of new cases will achieve a complete remission, most patients will require maintenance treatment (Gehrs & Friedberg, 2002). For those patients with an inadequate response to steroids, second-line treatment is usually splenectomy, which is associated with an initial response rate of approximately 50% (King & Ness, 2005). Treatment options for patients who fail to respond to, relapse after or are unable to undergo a splenectomy are limited. Cytotoxic and immunosuppressant drugs, such as cyclophosphamide, azathioprine and ciclosporin A, give a 40–60% response rate. However, these treatments may be associated with serious side effects, such as bone marrow suppression, nephrotoxicity and secondary malignancies, while the effectiveness of other options, such as IVIG, plasmapheresis and danazol, is controversial (Petz, 2001; Gehrs & Friedberg, 2002; King & Ness, 2005).

Cold agglutinin disease

Cold agglutinin disease or cold agglutinin syndrome represents 16–32% of all AIHA cases (Sokol *et al*, 1992; Gehrs & Friedberg, 2002). Approximately 90% of CAD cases are mediated by monoclonal antibodies of the IgM class. Fewer than 8% of cases of CAD are associated with IgG or IgA and only 6% of patients have polyclonal antibodies – mostly children with CAD secondary to a viral infection (Gehrs & Friedberg, 2002; Berentsen *et al*, 2006; Gertz, 2006). In CAD, the autoantibodies generally react best at cold temperatures, binding to the RBC when they move to the slightly cooler periphery of the body. The autoantibodies fix complement on the surface of the RBC and these complement-coated RBC are then cleared from the blood, predominantly by the macrophages of the liver or by complement-mediated intravascular lysis (Gehrs & Friedberg, 2002; Gertz, 2006).

Current management of patients

The primary treatment for CAD is avoidance of cold exposure. Unfortunately, for those patients with more severe haemolysis, medical therapy is frequently necessary but often proves inadequate. Immunosuppression with chlorambucil or cyclophosphamide may be beneficial and plasmapheresis can provide temporary improvement, although it has no effect on the underlying disease (Petz, 2001; Gehrs & Friedberg,

2002; King & Ness, 2005). Steroids are generally not helpful for CAD and splenectomy is also not usually effective, as complement-coated RBC are mainly destroyed in the liver.

As with ITP, current treatments available to patients with AIHA are far from satisfactory. Long-term use of corticosteroids is associated with many complications (Boumpas *et al*, 1993), and splenectomy has an associated mortality rate of 1.3% in adults and 1.7% in children (Bisharat *et al*, 2001). Cytotoxic immunosuppressants may be effective in some cases, but can also be associated with serious adverse events (Petz, 2001; Gehrs & Friedberg, 2002; King & Ness, 2005). Alternative safe and effective treatments are therefore required.

Use of rituximab in autoimmune haemolytic anaemia

The reported efficacy of rituximab in other autoimmune disorders provided a rationale for investigating rituximab therapy in AIHA, with encouraging results (Table II). Inter-study comparisons of response rates are difficult owing to a lack of universal agreement on the precise definition of a response, especially that of a complete response. Nonetheless, an overview of studies including five or more patients reveals that rituximab (375 mg/m² weekly for a median of 4 weeks) is effective in treating both warm AIHA and CAD, with an overall response rate ranging from 40% to 100% (median *c.* 60%), and with patients of all ages responding (Table II). Moreover, many of these responses were durable, lasting >3 years in some patients (Table II).

In a Norwegian population-based retrospective study of 86 patients receiving a variety of treatments for CAD, rituximab was the only treatment to induce a complete response in any patient (Berentsen *et al*, 2006). Moreover, rituximab was the only treatment that resulted in an overall response rate >16%. The overall response rate for patients receiving rituximab was 60%, with 10% of patients achieving a complete response and 50% a partial response. In this study, the next best treatment regimen was alkylating agents (with or without corticosteroids), which gave an overall response rate of 16%, all of which were only partial responses (Berentsen *et al*, 2006).

An overview of studies employing rituximab in AIHA demonstrated that the speed with which AIHA patients responded to rituximab treatment varied considerably, with some patients responding very quickly and others taking weeks or even months to achieve their maximum response (Gupta *et al*, 2002; Zaja *et al*, 2003b; Zecca *et al*, 2003; Berentsen *et al*, 2004; Schöllkopf *et al*, 2006; D'Arena *et al*, 2007). Responses were observed both in patients with idiopathic AIHA (Quartier *et al*, 2001; Shanafelt *et al*, 2003; Zecca *et al*, 2003; Narat *et al*, 2005; Berentsen *et al*, 2006; Schöllkopf *et al*, 2006; D'Arena *et al*, 2007) and in those with AIHA secondary to a range of conditions, including bone marrow transplant (Quartier *et al*, 2001; Zecca *et al*, 2003), autoimmune disorders (Shanafelt *et al*, 2003; Zecca *et al*, 2003), chronic lymphocytic leukaemia (Gupta *et al*, 2002; Trapè *et al*, 2003; Zaja *et al*, 2003b; Narat *et al*, 2005; D'Arena *et al*, 2006) and other lymphoproliferative

disorders (Trapè *et al*, 2003; Narat *et al*, 2005; Schöllkopf *et al*, 2006). Patients with warm AIHA responded well to rituximab treatment regardless of prior therapy (Quartier *et al*, 2001; Gupta *et al*, 2002; Shanafelt *et al*, 2003; Trapè *et al*, 2003; Zaja *et al*, 2003b; Zecca *et al*, 2003; Narat *et al*, 2005; D'Arena *et al*, 2006). Likewise, rituximab was effective in patients with CAD regardless of whether they had previously been treated with immunosuppressant drug regimens and/or corticosteroids (Berentsen *et al*, 2004; Schöllkopf *et al*, 2006). In addition, there was no difference between CAD responders and non-responders with regard to their initial haemoglobin or serum monoclonal antibody levels, cold agglutinin titre or bone marrow $\kappa:\lambda$ ratio (Berentsen *et al*, 2006).

Although most patients with AIHA receive rituximab as monotherapy, rituximab has also been used in combination with corticosteroids, immunosuppressant drugs and interferon- α (Gupta *et al*, 2002; Zecca *et al*, 2003; Berentsen *et al*, 2004; Narat *et al*, 2005; D'Arena *et al*, 2006). In patients with underlying lymphoproliferative disorders in particular, treatment with a combination of rituximab and other agents may offer additional benefits (Gupta *et al*, 2002; Narat *et al*, 2005). For example, a patient with CAD who had not responded to single-agent rituximab achieved a partial response after second-line treatment with rituximab plus interferon- α (Berentsen *et al*, 2004).

Although rituximab can induce durable responses in a substantial proportion of patients with both warm AIHA and CAD, some patients will inevitably relapse. From the preliminary data available, it appears that rituximab re-treatment may be effective for these patients. In the series of studies detailed in Table II, there are reports of 17 patients being re-treated with rituximab, with a total of 21 re-treatments. All but three of these re-treatments resulted in a further response, with five complete responses (normalization of haemoglobin levels), seven partial responses (increase in haemoglobin level of at least 20 g/l) and six 'disease remissions' (increase in haemoglobin level of at least 15 g/l; Gupta *et al*, 2002; Zecca *et al*, 2003; Berentsen *et al*, 2004; Rao *et al*, 2007). Some patients responded to re-treatment more than once; for example, one child relapsed a total of three times and responded to rituximab re-treatment after each relapse (Zecca *et al*, 2003; Berentsen *et al*, 2004).

Maintenance therapy with rituximab has been shown to prolong progression-free survival and to extend overall survival times in patients with indolent NHL (van Oers *et al*, 2006). Further investigations are needed to determine whether rituximab maintenance therapy prolongs remission duration in AIHA. In addition to the data reported above showing that patients can respond to re-treatment with rituximab, preliminary data in small series of AIHA and CAD patients show that durable responses can also be achieved after extended rituximab treatment (Quartier *et al*, 2001; D'Arena *et al*, 2006, 2007; Schöllkopf *et al*, 2006). In addition, a case report has described a patient with mantle cell lymphoma who developed acquired AIHA that was successfully treated with rituximab

Table II. Studies employing rituximab to treat AIHA.*

Reference	Study type	n	Adult/ paediatric	Type of AIHA (n)	Age (years)	Hb levels (g/l)	Doses of rituximab (n)	Response (%)	CR/PR duration (months)
Quartier <i>et al</i> (2001)	Prospective	6	Paediatric	Warm (6)	0.6–2.9	NA	4 (4); 12 (2)	CR (100)	15+–22+
Gupta <i>et al</i> (2002)	Prospective	8	Adult	Warm (8)	46–70	50–99	2 (3); 3 (2); 4 (1); 5 (2)	CR (87.5); PR (12.5)	7–23+
		5†			NA	52–81	1 (1); 2 (2); 3 (2)	CR (100)	3–9+
Trapè <i>et al</i> (2003)	Prospective	5	Adult	Warm (5)	44–66	47–98	4	CR (60); PR (40)	3–20+
Shanafelt <i>et al</i> (2003)	Retrospective	5	Adult	Warm (5)	21–79	51–83	3–8	CR (40)	4+, 13+
Narat <i>et al</i> (2005)	Retrospective	11	Adult	Warm (11)	18–81	40–90	4	CR (27); PR (36)	2.5–20+
D'Arena <i>et al</i> (2006)	Retrospective	14	Adult	Warm (14)	48–87	42–117	3 (3); 4 (11)	CR‡ (21); PR (50)§	NA
D'Arena <i>et al</i> (2007)	Retrospective	11	Adult	Warm (11)	23–81	43–110	4	CR (73); PR (27)	1+–95+
Zecca <i>et al</i> (2003)	Prospective	15	Paediatric	Warm (13); CAD (1); unclear (1)	0.3–14	35–100	2 (3); 3 (10); 4 (2)	CR (67); PR (20)	7–28+
Zaja <i>et al</i> (2003b)	Prospective	5¶	Paediatric	NA	NA	NA	NA	Response (100)	NA
Berentsen <i>et al</i> (2004)**	Prospective	5	Adult	Warm (4); CAD (1)	42–84	73–115	4	CR (40)	8+, 38+
	Prospective phase II trial	27	Adult	CAD (27)	51–91	62–123	4 (25); 8 (2)	CR‡ (4); PR (52)	2–42
	Prospective	10¶¶	Adult	NA	NA	NA	4 (10)	PR (70)	NA
Schöllkopf <i>et al</i> (2006)	Prospective phase II trial	20	Adult	CAD (20)	54–86	73–153	4	CR‡ (5); PR (40)	2–18+
Berentsen <i>et al</i> (2006)**	Retrospective	52	Adult	CAD (52)	30–92§§	45–156§§	NA	CR‡ (10); PR (50)	NA
Rao <i>et al</i> (2007)	Prospective	6	Paediatric	NA	5–17	NA	4 (5); 6 (1)	CR¶¶ (67); PR¶¶ (17)	NA
		1						Response	

AIHA, autoimmune haemolytic anaemia; CAD, cold agglutinin disease; CR, complete response (normalization of haemoglobin levels, unless otherwise noted); PR, partial response (stable increase of haemoglobin levels by >20 g/l, unless otherwise noted); NA, data not available.

*Published studies including more than or equal to five patients are detailed in the table.

†Five patients were re-treated with rituximab after relapse.

‡In this study, a CR was defined as a complete absence of anaemia and no clinical or molecular symptoms of disease.

§In two patients (one CR and one PR), rituximab therapy started within 1 week of the start of methylprednisolone treatment and therefore a firm conclusion about the cause of these responses cannot be drawn.

¶Three patients were re-treated after relapse and one patient subsequently received a third and fourth course of rituximab.

**The patients reported in the prospective study published by Berentsen *et al* (2004) are also included in the retrospective study published in 2006 (Berentsen *et al*, 2006).

¶¶Eight patients were re-treated after relapse with rituximab plus interferon- α ($n = 3$) or rituximab alone ($n = 5$), and two were re-treated with rituximab monotherapy for a second relapse.

**This study was a population-based retrospective analysis of as many patients as possible with CAD in Norway. Of 86 patients studied, 52 received rituximab – 40 as monotherapy and 12 in combination with interferon- α ($n = 5$) or fludarabine ($n = 7$).

§§This information is for all 86 patients in the analysis (not only the 52 who received rituximab).

¶¶In this study, a CR was defined as haemoglobin levels stable without transfusion ≥ 100 g/l and a PR as haemoglobin levels 75–100 g/l without transfusion.

despite extensive previous exposure to rituximab as lymphoma treatment (Fabbri *et al*, 2006). Furthermore, 6 months of rituximab treatment given as maintenance therapy was effective in one patient with CAD who failed to respond to rituximab induction (Pulik *et al*, 2002). Overall, these data indicate that maintenance therapy with rituximab may be a strategy worth pursuing in both warm AIHA and CAD.

Rituximab treatment for AIHA was well tolerated and no adverse events were reported for most patients. Adverse events that did occur were predominantly mild to moderate infusion-related side effects, including hypotension, fever and chills and upper airway oedema (Gupta *et al*, 2002; Trapè *et al*, 2003; Zecca *et al*, 2003; Schöllkopf *et al*, 2006; Rao *et al*, 2007). Of the 111 patients for whom safety data were reported, two patients were reported to have experienced grade 4 neutropenia (Gupta *et al*, 2002; Berentsen *et al*, 2004), and seven infectious events that were possibly related to rituximab therapy were noted (Quartier *et al*, 2001; Trapè *et al*, 2003; Zecca *et al*, 2003; Narat *et al*, 2005; Schöllkopf *et al*, 2006).

Conclusions

Patients with warm AIHA are usually initially treated with corticosteroids with a complete response rate of 15–20% (Gehrs & Friedberg, 2002). Those requiring further treatment generally have a splenectomy (to which approximately half of all patients respond), although some continue to require treatment with low-dose prednisone (King & Ness, 2005). Patients failing corticosteroid treatment and splenectomy are usually treated with cytotoxic drugs, such as cyclophosphamide or azathioprine. Rituximab may provide an effective alternative to splenectomy and/or chemotherapy. More than half of all patients with warm AIHA receiving rituximab responded to treatment, with a significant proportion of sustained remissions and responses being achieved by patients with primary or secondary AIHA. Rituximab may therefore prevent or delay splenectomy in some patients, removing the mortality risk associated with this procedure, and may also reduce the need for cytotoxic drugs in patients who have not responded to or who have relapsed after steroids and/or splenectomy.

Cold agglutinin disease is a difficult disease to treat. Patients for whom avoidance of cold exposure is insufficient can obtain temporary relief from plasmapheresis and may benefit from immunosuppression; however, treatment is often inadequate for patients with severe haemolysis. Recent studies have shown that rituximab infusions can be effective in obtaining durable responses in patients with CAD, offering an additional treatment choice to a group of patients with limited options.

Acquired haemophilia

Disease characteristics

Acquired haemophilia is a very rare disease, with an incidence of approximately 1.5 per million persons per year (Collins

et al, 2005). The disease occurs when patients develop autoantibodies, or 'inhibitors', directed against the factor VIII (FVIII) clotting factor. Patients who develop such acquired FVIII inhibitors may present with catastrophic bleeding episodes, despite having no prior history of a bleeding disorder (Ma & Carrizosa, 2006). It is associated with considerable morbidity, as demonstrated by a survey of 215 non-haemophilic patients who had developed inhibitors to FVIII; in this study major bleeding occurred in >80% of patients, with a mortality rate of approximately 20% (Green & Lechner, 1981).

In acquired haemophilia, autoantibodies prevent FVIII from binding to von Willebrand factor (VWF), to activated FIX or to negatively charged phospholipids (Boggio & Green, 2001), resulting in haemorrhage (principally in soft tissues) and systemic bleeding episodes. The underlying mechanisms leading to the production of FVIII autoantibodies are not completely understood and, in almost half of all cases, no associated pathology can be identified. However, approximately 18% of cases of acquired haemophilia are associated with autoimmune diseases, while approximately 7% of cases occur during pregnancy or in the immediate postpartum period (Green & Lechner, 1981).

Current management of patients

Although approximately one-third of patients with acquired haemophilia will experience a spontaneous remission (Green & Lechner, 1981; Lottenberg *et al*, 1987), the high risk of a fatal haemorrhage necessitates immediate treatment once the condition is diagnosed. The two primary treatment objectives are to stop acute bleeding episodes and to eliminate FVIII autoantibodies (Sallah & Aledort, 2005).

Acute bleeding episodes in patients with low-titre autoantibodies can be treated with plasma-derived or recombinant human FVIII, whereas FVIII-bypassing agents, such as activated prothrombin complex or recombinant FVIIa, are recommended for patients with high-titre autoantibodies (Sallah & Aledort, 2005; Hay *et al*, 2006). The long-term goal of therapy is to eliminate the FVIII autoantibodies and thus cure the disease. To this end, it is recommended that immunosuppressant therapy be initiated as soon as acquired haemophilia is diagnosed (Sallah & Aledort, 2005; Hay *et al*, 2006). Prednisone with or without cyclophosphamide is generally the treatment of choice for initial immunosuppressant therapy, with elimination of inhibitors being achieved in approximately 70% of patients (Hay *et al*, 2006). For those patients who do not respond to initial therapy and the 20% of patients who relapse after a first response, second-line therapy may include 2-chlorodeoxyadenosine, ciclosporin A, azathioprine or IVIG (Sallah & Aledort, 2005; Hay *et al*, 2006).

Although prednisone and/or cyclophosphamide may be effective in eliminating autoantibodies, time to resolution of the antibody is usually slow and prolonged treatment with corticosteroids and cytotoxic drugs may be associated with considerable morbidity and mortality (Delgado *et al*, 2003;

Collins *et al*, 2005). The toxicity of these treatments is particularly pertinent as most patients with acquired haemophilia are elderly (Green & Lechner, 1981).

Use of rituximab in acquired haemophilia

Several case reports and one small trial have described treatment of acquired haemophilia with rituximab (Table III). The data demonstrate that rituximab is a possible treatment option for acquired haemophilia.

Rituximab has been used successfully to eliminate FVIII autoantibodies in patients ranging in age from 18 to 81 years, both as a first-line treatment and as a salvage therapy (Table III). Although patients were treated with rituximab at 375 mg/m² per dose in most studies, four once-weekly doses of 400 mg and two, two-weekly doses of 1000 mg have also been effective (Jy *et al*, 2003; Clatworthy & Jayne, 2006). In a number of cases, patients with long-standing disease refractory to conventional immunosuppressant therapy have achieved durable responses after treatment with rituximab (Kain *et al*, 2002; Abdallah *et al*, 2005; Santoro *et al*, 2007), while durable remissions have also been attained by patients receiving rituximab as first-line therapy (Table III). Although single-agent rituximab can treat acquired haemophilia rapidly and effectively in many cases, patients with high autoantibody titres may only achieve partial responses or may attain a complete response only very slowly (Table III). However, improved responses can be achieved by increasing the number of doses of rituximab or by combining rituximab with cyclophosphamide and/or corticosteroids (Stasi *et al*, 2004; Aggarwal *et al*, 2005).

The time taken to achieve a response with rituximab ranged from 1 to 65 weeks (Table III). This is in comparison to a median of 8, 7 and 30 weeks to complete response in patients treated with steroids, steroids plus cyclophosphamide and cyclophosphamide alone respectively (Collins *et al*, 2005).

Re-treatment with rituximab may also be effective. Six patients who initially responded to rituximab treatment but who subsequently relapsed responded to rituximab re-treatment, achieving sustained remissions (Stasi *et al*, 2004; Aggarwal *et al*, 2005; Field *et al*, 2007).

Although corticosteroids alone or in combination with cyclophosphamide are recommended as initial therapy for the treatment of acquired haemophilia (Sallah & Aledort, 2005; Hay *et al*, 2006), immunosuppressant and cytotoxic therapies are not always suitable for elderly patients or those with co-morbidities. Moreover, in young female patients, such treatment can compromise fertility (Maillard *et al*, 2006). In contrast, rituximab was well tolerated with few side effects and no infectious complications reported in patients with acquired haemophilia (Wiestner *et al*, 2002; Fischer *et al*, 2003; Jy *et al*, 2003; Stasi *et al*, 2004; Aggarwal *et al*, 2005; Clatworthy & Jayne, 2006; Maillard *et al*, 2006; Santoro *et al*, 2007), and was an effective alternative for patients unable to receive cytotoxic therapy (Jy *et al*, 2003; Marietta *et al*, 2003; Stasi *et al*, 2004; Berezne *et al*, 2006; Maillard *et al*, 2006).

Aggarwal *et al* (2005) have proposed an algorithm for the treatment of autoimmune haemophilia. They suggested that patients with minimal bleeding and inhibitor levels below 5 Bethesda Units (BU) should be treated with prednisone alone; those with an inhibitor level <30 BU but with serious bleeding should receive rituximab in combination with prednisone; and those with an inhibitor level ≥30 BU should be treated with rituximab, prednisone and cyclophosphamide. They also proposed that patients not responding to – or relapsing after – these therapies may benefit from repeated courses of rituximab or rituximab maintenance therapy.

Rituximab treatment of acquired haemophilia may be cost-effective. Bypassing haemostatic agents are extremely expensive; the average cost of the resolution of a single minor-to-moderate bleed can be as much as US\$32 150 (Joshi *et al*, 2006). Kain *et al* (2002) documented the case of a patient with acquired haemophilia who required admission to hospital with severe bleeding episodes on four occasions in the year before rituximab therapy. The estimated cost of treating these episodes with recombinant FVIIa was AUD 823 000 (1 AUD is approximately equivalent to €0.64). In contrast, since treatment with rituximab (which cost AUD 15 000) the patient experienced no significant bleeds and the inhibitor had disappeared.

Conclusions

Acute bleeding episodes in patients with acquired haemophilia are not only associated with considerable morbidity and mortality but are also very expensive to treat. Consequently, the long-term goal of treatment is to eradicate FVIII autoantibodies. Although prednisone (with or without cyclophosphamide) is effective in eliminating autoantibodies in the majority of patients, some are refractory to – or relapse after – such treatment. For these patients, second-line treatment is usually effective, although a number of patients may require long-term maintenance immunosuppression (Hay *et al*, 2006). A number of case studies and one small trial have indicated that rituximab may be a useful alternative or addition to existing therapies. Available data indicate that rituximab can induce durable remissions in a wide range of patients and may be of particular benefit to those patients for whom corticosteroid and/or cytotoxic therapy are unsuitable or those who are refractory to conventional immunosuppressant therapy.

Thrombotic thrombocytopenic purpura

Disease characteristics

Thrombotic thrombocytopenic purpura is a rare disease with a prevalence of approximately four per million and occurs mainly in adults, with more women than men being affected (George *et al*, 2002; Moake, 2002; Veyradier & Meyer, 2005). About one-third of cases of TTP are idiopathic, whereas the other two-thirds of patients develop TTP associated with a

Table III. Case reports of treatment of acquired haemophilia with rituximab.

Reference	n	Age (years)	Rituximab doses to maximum benefit (n)	Previous immunosuppressive treatment	Treatment concurrent with rituximab	Inhibitor titre	Response (n)	Time to response (weeks)	CR/PR duration (months)
Wiestner <i>et al</i> (2002)	3	38–79	4	None	PDN+CPM (1) PDN (2)	5–23	CR (3)	3–12	7+–12+
	1	39	2	None	PDN (1)	60	CR/PR (1)*	1	
Kain <i>et al</i> (2002)	1	28	4	PDN, CPM, AZA, CSA, IVIG	None	268	CR (1) [†]	17	11+
Marietta <i>et al</i> (2003)	1	71	2	Cs, CPM, FVII	None	2–3	PR [‡] (1)	2	1
Fischer <i>et al</i> (2003)	1	71	2	Cs, FVII, CPM, V, PE	Cs+PE	633	None	–	–
Jy <i>et al</i> (2003)	1	81	4	IVIG, CPM, M, V, Cs, PE	None	400	PR (1)	2	6+
Stasi <i>et al</i> (2004)	8	27–78	4	None (5); PDN+CPM (3)	None (7)	4–96	CR (8)	3–12	2–3–42+
	2	62, 70	8	None (1); PDN, CVP, CPM, PE (1)	CPM (2)	160, 250	CR (2)	6, NA	NA
Aggarwal <i>et al</i> (2005)	4	60–81	4–8	None (1); PDN (1); PDN + CPM (2)	None (1); PDN (3)	7–525	CR (3)	2–35	3–5–10+
	2 [§]	60, 73	4	PDN(1); PDN+CPM(1)	PDN (2)	70, NA	PR (1)	2–8	5, 5+
Abdallah <i>et al</i> (2005)	2	47, 80	4	PDN (1)	None	148, 5–5	CR (2)	10, 65	18+, 30+
	1	53	8	PDN + AZA (1)	None	24	CR (1)	22	NA
Holme <i>et al</i> (2005)	2	64, 94	4	PDN	None	1350, 42	CR (1)	13	NA
Maillard <i>et al</i> (2006)	1	18	4	CVP, CSA (1); none (1)	None	94	CR (1)	48	12+
Clatworthy and Jayne (2006)	1	48	2	PDN, IVIG	None	1–1	CR (1)	1	3
Bereznié <i>et al</i> (2006)	2	74, 81	4	Cs	PDN (1); none (1)	440, 88	CR (2)	39, 43	9+, 10+
Onitilo <i>et al</i> (2006)	6	24–76	3–9	None	PDN (1); none (1)	11–3075	CR (6)	1–52	4–36+
	1	61	4	AZA, CVP (1); PDN, CPM (4); PDN, Solu-Medrol [¶]	Cs	2–0	CR	2	12+
Oliveira <i>et al</i> (2007)	1	61	4	Cs, mycophenolate mofetil, prothrombin	Cs	2–0	CR	2	12+
Field <i>et al</i> (2007)	4	40–71	4	PE, FVII, FVIII, CVP (1); FVII, CVP (1); CVP, CPM (1); FVII, CVP (1)	CPM (3); none (1)	249–725	PR (4)	6–5–11	5–14
Santoro <i>et al</i> (2007)	1	25	4	Dexamethasone, IVIG, CPM, FVII, PDN	PDN	206	CR	39	29+

Table III. (Continued).

Reference	n	Age (years)	Rituximab doses to maximum benefit (n)	Previous immunosuppressive treatment	Treatment concurrent with rituximab	Inhibitor titre	Response (n)	Time to response (weeks)	CR/PR duration (months)
Alvarado <i>et al</i> (2007)	2	61, 73	4	Cs, VII (1); desmopressin acetate, FVII, PDN (1)	PDN (2)	1:1, 7:2	CR (2)	6–35	3–24+

AZA, azathioprine; BU, Bethesda unit; CR, complete response (normal FVIII level, inhibitor not detectable or <1 BU); Cs, corticosteroids; CSA, ciclosporin A; CPM, cyclophosphamide; CVP, cyclophosphamide, vincristine and prednisone; FVII, recombinant activated factor VIIa; FVIII, factor VIII; IVIG, intravenous immunoglobulin; M, mitoxantrone; NA, data not available; PDN, prednisone; PE, plasmapheresis; PR, partial response (inhibitor titre decline >50%, factor VIII level >25%, no further bleeding); V, vincristine.

*Patient with mild haemophilia A; FVIII activity recovered and autoantibody resolved, but alloantibody persisted for >2 months.

†Inhibitor titre fell to <1 BU; FVIII level not reported.

‡Although the activated partial thromboplastin time returned to normal after two doses of rituximab, the patient died shortly afterwards.

§Two patients relapsed and were re-treated.

*Treatments include immunosuppressive therapy given previously or concurrently with rituximab.

range of clinical situations, including bacterial or viral infection, pregnancy, drug ingestion, autoimmune disorders, disseminated malignancy and bone marrow transplantation (Veyradier & Meyer, 2005).

Thrombotic thrombocytopenic purpura was first described in 1924 by Eli Moschcowitz and is characterized by a pentad of clinical and laboratory features consisting of microangiopathic haemolytic anaemia, thrombocytopenia, central nervous system abnormalities, renal impairment and fever (Lämmle *et al*, 2005). It is now thought that most cases of TTP are caused by a deficiency in a plasma metalloprotease, ADAMTS13, which cleaves a specific peptide bond in plasma VWF (George *et al*, 2002; Tsai, 2003). VWF is a protein essential for platelet adhesion and aggregation at the elevated levels of fluid shear stress found in microvessels, and it forms multimers, which are cleaved by the ADAMTS13 protease. In patients with TTP – who lack ADAMTS13 activity – the unfolded VWF multimers are not cleaved into these smaller, less active forms. Consequently, the plasma of patients with TTP contains abnormally large multimers of VWF, which are thought to lead to spontaneous platelet clumping in the microcirculation (George *et al*, 2002; Tsai, 2003; Sadler *et al*, 2004; Veyradier & Meyer, 2005). These platelet-rich microvascular thrombi in the arterioles and capillaries result in thrombocytopenia, ischaemic cerebral, renal and other organ damage and intravascular fragmentation of RBC (George *et al*, 2002; Lämmle *et al*, 2005). If untreated, TTP is associated with a mortality rate of >90%. However, treatment with plasma infusion or plasma exchange has reduced the mortality to approximately 25% (George *et al*, 2002; Veyradier & Meyer, 2005).

The ADAMTS13 deficiency in patients with sporadic TTP usually results from the presence of inhibitory IgG autoantibodies, which have been detected in 70–80% of such patients (Tsai, 2003). At present, the reason for the occurrence of ADAMTS13 inhibitory autoantibodies is not understood.

Current management of patients

The initial treatment for patients with acute TTP is daily plasma exchange (George, 2000; George *et al*, 2002; Brunskill *et al*, 2007). Patients who fail to respond quickly and completely to plasma exchange, or in whom exacerbation occurs after initial recovery, require more intensive treatment. These patients are generally treated with glucocorticoids (George, 2000; George *et al*, 2002). Those with more severe disease or who do not respond well to glucocorticoids in combination with plasma exchange may receive other immunosuppressive agents, such as vincristine, cyclophosphamide, ciclosporin A or splenectomy (Moake, 2002; Sadler *et al*, 2004; Kappers-Klunne *et al*, 2005; Lämmle *et al*, 2005; Outschoorn & Ferber, 2006). Over one-third of patients with TTP who achieve a remission will relapse at least once, with a subset developing chronic TTP requiring long-term plasma exchange (George *et al*, 2002; Tsai, 2003; Sadler *et al*, 2004). Although prompt plasma exchange is undeniably the best course of

action for patients presenting with acute TTP, it does not come without risk. In one study of 71 patients treated for clinically suspected TTP-haemolytic uraemic syndrome, 21 patients had major complications, resulting in the death of two patients; major complications included 12 systemic infections, seven episodes of catheter thrombosis and two episodes of haemorrhage after subclavian line insertion (Rizvi *et al*, 2000).

Use of rituximab in TTP

The successful use of rituximab to treat patients with a variety of autoimmune diseases, including ITP, has led to a number of case reports and two small trials of rituximab in TTP. Analysis of the literature has demonstrated that patients ranging in age from 14 to 77 years have responded to treatment with rituximab at the standard dose of 375 mg/m² (Table IV).

There is some difficulty in directly comparing the outcome of different cases of TTP treated with rituximab because of inconsistencies in the definitions of complete and partial responses, and agreement of standard response criteria would be beneficial. Nonetheless, of the patients described in the studies listed in Table IV, only two did not respond at all to rituximab, according to the authors (Ahmad *et al*, 2004; Sallah *et al*, 2004), with 59 of the 75 patients (79%) achieving a complete response. All 36 patients treated with rituximab in two prospective trials in TTP achieved a complete response (Fakhouri *et al*, 2005; Scully *et al*, 2007). The remissions induced by rituximab in patients with TTP were generally durable, with a number of patients remaining in remission for over a year and one patient continuing in remission for nearly 3 years (Table IV; Scully *et al*, 2007). In a small retrospective study comparing patients receiving rituximab-containing treatment for relapsed or refractory TTP with those receiving conventional therapy, patients receiving rituximab had a significantly longer median progression-free survival (45.8 vs. 0.9 months; $P = 0.0025$; Heidel *et al*, 2007).

The time taken for patients with TTP to respond to rituximab ranges from <1 week to 13 weeks (Heidel *et al*, 2007; Kameda *et al*, 2007), with one patient achieving a rapid neurological response just 12 h after rituximab therapy (Ozdogu *et al*, 2007). Furthermore, in some cases, rituximab is effective in patients with TTP with normal ADAMTS13 activity (Reddy *et al*, 2005; Kameda *et al*, 2007). These data suggest that rituximab cannot simply be decreasing levels of ADAMTS13 autoantibody production by depleting B cells, but must be functioning by at least one other mechanism. Kameda *et al* (2007) have suggested that B-cell depletion by rituximab therapy may reduce excessive cytokine production in patients with secondary TTP and therefore contain the level of VWF multimers to within the normal range.

Although the majority of patients received the standard once-weekly dose of rituximab (375 mg/m²) for 4 weeks, some patients required more prolonged treatment to realise the full benefit (Heidel *et al*, 2007; Scully *et al*, 2007), whereas others responded to treatment with only one or two doses of

rituximab (Chemnitz *et al*, 2002; Chow *et al*, 2007; Heidel *et al*, 2007; Kameda *et al*, 2007; Scully *et al*, 2007). Furthermore, in patients who initially responded to rituximab treatment but then relapsed, re-treatment with rituximab appeared effective, with durable responses induced again (Ahmad *et al*, 2004; Fakhouri *et al*, 2005; Galbusera *et al*, 2005; Reddy *et al*, 2005; Herbei & Venugopal, 2006; Heidel *et al*, 2007; Patino & Sarode, 2007). Herbei and Venugopal (2006) have suggested that rituximab maintenance may be beneficial for some patients. They described a patient who, after her second course of rituximab treatment for TTP, remained in remission while receiving rituximab maintenance therapy consisting of one dose of rituximab every 2 months for 1 year.

Most of the patients treated with rituximab to date have had long-standing TTP that has relapsed after and/or is refractory to a number of conventional treatments. Among the cases summarized in Table IV, patients with long-standing TTP appear to respond as well to rituximab treatment as those being treated during their first acute episode. In addition, in two prospective trials, patients treated with rituximab during an acute refractory episode of TTP and those receiving rituximab for severe relapsing TTP achieved complete responses (Fakhouri *et al*, 2005; Scully *et al*, 2007).

The majority of TTP patients received rituximab and plasma exchange concurrently, at least until disease symptoms stabilized. However, there is some debate in the literature as to how long plasma exchange should be delayed after rituximab treatment. Boctor and Smith (2006) have drawn attention to the reported mean half-life of rituximab of 4.4 days, and have recommended delaying plasma exchange for 72 h after rituximab treatment to maximise the effect of the drug. In contrast, Hull and Eichbaum (2006) maintain that an interval of 24 h between rituximab treatment and plasma exchange appeared adequate. The controversy was discussed in some detail by Darabi and Berg (2006), who concluded that a standard dose of rituximab would be expected to have a rapid effect on CD20⁺ cells and therefore plasma exchange can be resumed within 24–36 h of rituximab treatment. In rare cases where plasma exchange is not possible, rituximab treatment may play an important role in alternative treatment (Martin *et al*, 2007).

In the majority of reports in which safety and tolerability are mentioned, rituximab was well tolerated, with few side effects noted during follow-up (Chemnitz *et al*, 2002; Zheng *et al*, 2003; Ahmad *et al*, 2004; Stein *et al*, 2004; Yomtovian *et al*, 2004; Fakhouri *et al*, 2005; Gianfaldoni *et al*, 2005; Kosugi *et al*, 2005; Koulova *et al*, 2005; Benetatos *et al*, 2006; Schleinitz *et al*, 2007). Rituximab infusion reactions were reported in some studies, but were generally mild in nature and did not warrant the discontinuation of rituximab (Sallah *et al*, 2004; Heidel *et al*, 2007; Scully *et al*, 2007). One serious adverse event has been reported during the use of rituximab for TTP. A 20-year-old female patient developed acute biventricular cardiogenic shock in response to treatment with a single dose of rituximab for refractory TTP. She later recovered with a complete resolution of her heart failure (Millward *et al*, 2005).

Table IV. Treatment of thrombotic thrombocytopenic purpura with rituximab.*

Reference	n	Age (years)	Previous treatments	Treatment concurrent with rituximab	Doses of rituximab (n)	TTP duration before rituximab (weeks)	ADAMTS-13 activity	Response (n)	Response duration (months)
Chemnitz <i>et al</i> (2002)	2	39, 37	PEx (2), PDL (2), V (2)	PEx (2), PDL (1), V (2)	4, 2	2, 2	<1%, NA	CR (2)	2+, 12+
Gutterman <i>et al</i> (2002)	3	40–62	PEx (3), Cs (2), AZA (2), CPM (2), V (2), CSA (1) S (1), A (1), DPD (1), PDL (1), IVIG (1)	PEx (3)	8 (2), 4 (1)	135–521	NA, <0.1 U/ml (2)	CR (2); PR (1)	3–23+
Salliah <i>et al</i> (2004)	5	25–52	PEx (5), PDL (5), V (5), S (3) CPM (2), CSA (2)	PEx (5)	4	15–100	<1–4%	CR [‡] (4)	9+–13+
Ahmad <i>et al</i> (2004)	4	53–61	PEx (4), Dex (2); PDL (2); V (2); CPM (1); Cs (1); S (1)	PEx (3), V (2), PDL (2)	4 (3), 2 (1)	150–1400	NA–15%	CR (3)	13–14+
Reddy <i>et al</i> (2005)	1 [†] 5	56 27–70	PEx, Cs (5); S (4); V (3), A (3), AZA (2)	PEx (5)	4	35–103	<10–100%	CR CR (5)	6+ 6–15 [§]
Koulova <i>et al</i> (2005)	2	40, 45	PEx (2), S (1), Cs (1), V (1)	PEx (1)	4	22, 60	NA	CR	21+
Fakhouri <i>et al</i> (2005)	11	21–60	PEx (11), V (8), S (5), R (3) IVIG (2), CSA (1), none (1)	Cs (6)	4	1–1460	NA	CR (11)	5+, 11+ 6–11+
Darabi and Berg (2006)	2	39, 62	PEx (2), Cs (2), V (1)	PEx (2), Cs (2), V (1)	4	1–6	NA, <4%	PR (2)	NA
Niewold <i>et al</i> (2006)	2	32, 69	PEx (2), Cs (2)	PEx (2)	4, 2	105, 7	<4%, NA	PR (2)	NA
Scully <i>et al</i> (2007)	25	17–67	PEx (24), V (12), CSA (4), defibrotide (3), PDL (1), CPM (1)	PEx (24)	8 (1), 6 (3), 4 (20), 2 (1)	NA	<5–64%	CR (25)	1–33+
Heidel <i>et al</i> (2007)	8	21–77	PEx (8), Cs (8), C (5), IVIG (1)	PEx (8), Cs (8)	8 (1), 6 (1), 4 (3), 2 (1), 1 (2) 4 (1), 1 (1)	NA	<6.25–22%	Res (8)	2–51+
Patino and Sarode (2007)	2 [†]	14, 41	PEx (2), Cs (1), PDL (1)	PEx (8), Cs (8)	4 (2)	208, 256	<10%, <10%	Res (2)	37, 21
Chow <i>et al</i> (2007)	2	36, 60	PEx (2), V (2), Cs (1)	PEx (2)	4			CR (2)	3+, 6+
Kameda <i>et al</i> (2007)	2	26, 38	PEx (2), Cs (2), CSA (1)	PEx (2), IVIG (1) Cs (2)	2 (1), 1 (1) 2 (2)	8, 3 4, 5	NA 110%, 93%	CR (2) PR, CR	16+, 18+ 5+, 3+

A, aspirin; AZA, azathioprine; BU, Bethesda unit; C, cytotoxic agents; CR, complete response (normalization of clinical and laboratory values, unless otherwise noted); Cs, corticosteroids; CSA, ciclosporin; CPM, cyclophosphamide; Dex, dexamethasone; DPD, dipyrindamole; IVIG, intravenous immunoglobulin; NA, data not available; PDL, prednisolone; PDL, prednisolone; PDL, plasmapheresis; PEx, plasma exchange; PR, partial response (platelet count $>100 \times 10^9/l$ but persistence of some symptoms); R, rituximab; Res, complete absence of clinical symptoms, plus platelet count $>100 \times 10^9/l$, haemoglobin level $>100 \text{ g/l}$, lactate dehydrogenase $<1.5 \times$ upper limit of normal and haptoglobin $>0.3 \text{ g/l}$; S, splenectomy; V, vincristine.

*Published studies including more than or equal to two patients are detailed in the table.

[†]Patient(s) was re-treated with rituximab after relapse.

[‡]In this study a CR was defined as an increase in platelet count to $>150 \times 10^9/l$ and decrease in lactate dehydrogenase to $<420 \text{ U/l}$.

[§]With a median follow-up of 15 months, all patients remain in CR.

At present there are no reports of economic analyses regarding the use of rituximab in TTP.

Conclusions

Although the mortality of patients with TTP has reduced more than threefold with the introduction of plasma exchange therapy, TTP is still a serious disease with a mortality of approximately 25%. Moreover, plasma exchange and therapy with steroids or cytotoxic agents (such as vincristine or cyclophosphamide) or splenectomy are not without risk. In the subset of patients who develop chronic TTP and require continued plasma exchange therapy, this risk may be even higher. Although plasma exchange is the most appropriate treatment for patients with acute TTP, rituximab offers an additional treatment option for those patients who do not respond to conventional treatment or who have experienced multiple relapses. Rituximab has been shown to produce robust remissions in a wide range of patients, including those with acute episodes of refractory TTP and those with severe relapsing TTP.

In summary, rituximab as a single agent or in combination with other agents appears to be a well-tolerated and much-needed additional therapeutic option for patients with haematological disorders such as ITP, AIHA, acquired haemophilia or TTP. Reports of the use of rituximab in these (and other autoimmune haematological) disorders are limited, however. It is essential that large, prospective studies are carried out to investigate the use of rituximab in all these disorders. In particular, it will be important to establish the safety profile of rituximab in haematological autoimmune disorders and to ascertain whether there are any consequences of long-term B-cell depletion. This is especially important in children, where B-cell depletion may have different or additional consequences to those seen in adult patients (Giulino *et al*, 2007).

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