Rituximab for the treatment of adults with refractory idiopathic thrombocytopenic purpura

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Summary

- Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterised by persistent thrombocytopenia (platelet count < 150 x 10^9/L). Standard first line treatment consists of corticosteroids and intravenous immunoglobulins. Those who fail to respond to first line therapy, or require unacceptably high doses of steroids to maintain a safe platelet count are classified as having refractory disease; the proportion affected ranges from 11% to 35%. Treatments that have been tried in this setting with varying success including high dose steroids, high dose IVIG, anti D, vinca alkaloids, danazol, immunosuppressants, combination chemotherapy and dapsone. Splenectomy is another second line treatment option and normalises platelet count in two-thirds of patients. The treatment options in those who fail second line therapy are limited and include α-interferon, Campath, mycophenolate and rituximab.

- A systematic review on the efficacy and safety of rituximab for the treatment of adults with ITP identified 19 eligible reports on efficacy (313 patients), of which 9 were published in abstract form, and 29 on safety (306 patients). Of these, there was one dose finding phase II study and 18 single arm cohort studies. After a median follow up of 9.5 months, the weighted means for complete response (platelet count > 150 x 10^9 cells/L) and overall response (platelet count > 50 x 10^9 cells/L) with rituximab were 43.6% (95% CI, 29.5% to 57.7%) and 62.5% (CI, 52.6% to 72.5%), respectively. Median response duration was 10.5 months. Overall, the quality of the evidence in support of rituximab in this setting was poor; efficacy compared with standard treatments could not be determined due to lack of control groups in the studies, and the optimal timing and dose remained uncertain. The review concluded that until RCTs have demonstrated the efficacy of rituximab, the indiscriminate use of this treatment for ITP should be discouraged.

- A subsequent multicentre, prospective, phase II study has assessed rituximab in an extended population of adults with chronic ITP and low platelet counts who were candidates for splenectomy. The study involved 60 patients with a mean platelet count at inclusion of 16 ± 10 x 10^9/L who received 4 weekly intravenous infusions of 375 mg/m². Of the 60 patients, 36 initially responded to treatment with rituximab, for a 60% response rate, and 24 (40%) had a significant durable response. Patients who were younger and had undergone few previous treatments had significantly better responses.

- Of the 29 reports (n = 306) on safety covered by the systematic review, 66 (21.6%) patients experienced mild or moderate adverse events (grade 1-2), of which 55 were infusional reactions. Ten patients (3.7%) experienced severe or life threatening events and 9 (2.5%) patients died.

- The cost of 500mg/50ml is £873.15 and 375mg costs £655- cost in adult of average body surface area (1.73m²) is £1133 for dose 375mg/m² (= £4530 for 4 doses administered at weekly intervals), which would be £1746 if rounded up to 2 vials (= £6984 for 4 doses at weekly intervals), the number of vials used to obtain dose.

- In the absence of data from controlled trials, and no consensus on standard treatment for refractory ITP, the place in therapy of rituximab is unclear but trials are unlikely to be carried out as this condition is relatively uncommon, and thus not of sufficient commercial interest for Roche to pursue. Therefore does rituximab represent a good balance of risk vs. benefit based on currently available data if the alternative is supporting patients with low platelet counts through transfusions or splenectomy in those with pronounced bleeding tendencies?
Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterised by persistent thrombocytopenia (platelet count < 150 x 10^9/L), which arises from the binding of autoantibodies to platelet antigen(s) leading to their premature destruction. Symptoms in adults range from mild bruising and mucosal bleeding through to frank haemorrhage. Bleeding symptoms are uncommon unless the ITP is severe (platelets < 30 x 10^9/L). The need for treatment depends on factors such as clinical status (asymptomatic, bruising, bleeding or planned intervention likely to induce bleeding), balanced against the risks of infection due to use of immunosuppressive therapy.1

The standard first line treatment consists of corticosteroids and intravenous immunoglobulins (IVIG). About two-thirds of patients will respond to prednisolone, of which one third can expect a long term response. However, relapse is common after the dose is decreased. IVIG can increase platelet count in 75% of patients, of which 50% will achieve a normalised count, but responses are transient and platelet counts drift back towards pre-treatment levels 3 to 4 weeks after start of treatment. Those who fail to respond to first line therapy, or require unacceptably high doses of steroids to maintain a safe platelet count are classified as having refractory disease; the proportion affected ranges from 11% to 35%. A variety of treatments have been tried in this setting with varying success. Choice of therapy depends on age of patient, severity of presentation, platelet count, whether disease is primary refractory or relapsed, and length of time prior to relapse.1

Second line conventional treatments could involve the initial first line therapies, but for patients who are not suitable for further conventional treatment with standard dose steroids, there are many therapeutic options, such as high dose steroids, high dose IVIG, anti D, vinca alkaloids, danazol, immunosuppressants (e.g. azathioprine, cyclophosphamide), combination chemotherapy and dapsone. Splenectomy is another second line treatment option and normalises platelet count in two-thirds of patients; even those who do not achieve a complete response can expect some improvement in counts.1 The decision to undergo this procedure is determined in large part by patient preference, but with the availability of other therapeutic options that may defer splenectomy, patients may decide to wait.2 In those who fail first and second line therapies, the treatment options are limited; they include agents such as a-interferon, Campath, mycophenolate and rituximab.1

**Epidemiology**

The incidence of ITP in adults is 5.8 to 6.6 per 100,000. The disease affects mainly women of child bearing age.1

**Efficacy**

Data up to April 2006 were analysed in a systematic review on the efficacy and safety of rituximab for the treatment of adults with ITP.1 Descriptive and comparative studies in any language that met predefined inclusion criteria were eligible and the efficacy analysis was restricted to studies enrolling 5 or more patients.

Exclusion criteria were secondary causes of thrombocytopenia, including splenomegaly, hepatitis B or C infection, HIV infection, lupus, APS, bone marrow failure syndromes, and drug induced thrombocytopenia; malignancy, including CLL and lymphoma; the Evan syndrome and rituximab re-treatments.

Nineteen eligible reports on efficacy (313 patients), of which 9 were published in abstract form, and 29 on safety (306 patients) were identified. Of these, there was one dose finding phase II study and 18 single arm cohort studies. The efficacy studies consisted of 7 prospective, 7 retrospective and 5 of uncertain type.

Patients were 16 to 89 years of age, had had ITP for 12 to 360 months and platelet counts in the range 1.0 to 89 x 10^9 cells/L before rituximab treatment. Most (99%) had received steroids, half had had a splenectomy and most were refractory to multiple treatments. Other previous treatments included cyclosporine, azathioprine or mycophenolate (n=26); cyclophosphamide (n=12); vinca alkaloids (n=18) and danazol (n=17). Rituximab was administered as a weekly infusion of 375mg/m^2 for 4 consecutive weeks in 16 of 19 studies.

After a median follow up of 9.5 months, the weighted means for complete response (platelet count ≥ 150 x 10^9 cells/L) and overall response (platelet count > 50 x 10^9 cells/L) with rituximab were 43.6% (95% CI, 29.5% to 57.7%) and 62.5% (CI, 52.6% to 72.5%), respectively. Median response duration was 10.5 months. Interpretation of the data from this review is limited by the following factors:

- None of the studies included a control group
- None of the studies met all predetermined methodological quality criteria for observational studies
- Many of the reports were published in abstract form
- Relatively few patients with ITP treated with rituximab have been described in the literature.

The review noted that overall, the quality of the evidence in support of rituximab in this setting is poor; efficacy compared with standard treatments could not be determined due to lack of control groups in the studies, and the optimal timing and dose remained uncertain. It concluded that until RCTs have demonstrated the efficacy of rituximab, the indiscriminate use of this treatment for ITP should be discouraged.2

Since publication of the systematic review, a multicentre, prospective, phase II study has assessed the safety and efficacy of rituximab in an extended population of adults with chronic ITP and low platelet counts who were candidates for splenectomy.2 The study involved 60 patients (mean age, 48 years) with a mean platelet count at inclusion of 16 ± 10 x 10^9/L. They received 4 weekly intravenous infusions of 375 mg/m^2 of rituximab. All other treatments were stopped. Success was defined as a platelet count ≥ 50 x 10^9/L, with at least a two-fold increase of the initial value at 1 year after the first rituximab infusion. Patients given another treatment during follow-up were considered non-responders.

All but one patient received 4 infusions. Of the 60 patients, 36 initially responded to treatment with rituximab, for a 60% response rate, and 24 (40%) had a significant durable response. Of the 34 failures at 1 year, 21 patients underwent splenectomy, of which 11 were successful. Among the 21 patients with an initial response and with...
platelet counts > $150 \times 10^9/L$, 18 maintained a long-term response; of the 15 patients with platelet counts $50–149 \times 10^9/L$, only 6 maintained a response at 1 year, for a statistically significant difference between these types of patients ($p < 0.01$). Patients who were younger and had undergone few previous treatments had significantly better responses as well.4

**Safety**

Of the 29 reports (n = 306) on safety covered by the systematic review, 66 (21.6%) patients experienced mild or moderate adverse events (grade 1-2), of which 55 were infusional reactions. Ten patients (3.7%) experienced severe or life threatening events and 9 (2.5%) patients died.3 In the phase II study, 15 experienced transient side effects that did not lead to treatment discontinuation, and no patient was lost to follow-up. Five patients developed a rash, but only one case of serum sickness was reported, which resolved upon treatment interruption.4

**Cost Implications for NHS**

The cost of 500mg/50ml is £873.15 (MIMS Sept 2007); 375 mg costs £655, cost in adult of average body surface area (1.73m²) is £1133 for 375mg/m² (= £4530 for 4 doses administered at weekly intervals), which would be £1746 if rounded up to 2 vials (= £6984 for 4 doses at weekly intervals) as this is the number of units used to obtain dose. The 375mg/m² dose reflects that licensed for other indications and is the dose used in most of the studies included in the systematic review though optimal dose and duration of treatment remain to be established.

**Points for consideration**

- In the absence of data from controlled trials, and no consensus on standard treatment for refractory ITP, what is the place in therapy of rituximab? Other treatments used in this setting also lack supporting RCT data.
- Does rituximab represent a good balance of risk vs. benefit based on currently available data if the alternative is supporting patients with low platelet counts through transfusions or splenectomy in those with pronounced bleeding tendencies?
- What is the optimal dose and duration of rituximab treatment?
- As refractory ITP is relatively uncommon, it is not of sufficient commercial interest for Roche to pursue, and licensing any product in this area would be difficult in view of the lack of standard treatment pathways. Should rituximab be rejected for use because of the lack of "gold standard" evidence

**References**


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