Rituximab for the treatment of Immune (Idiopathic) Thrombocytopenic Purpura (ITP)

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Summary

- Rituximab (MabThera®, Roche) is a monoclonal antibody that targets the CD20 antigen expressed on the surface of B-lymphocytes. Rituximab is not licensed for the treatment of ITP, and it is not currently under regulatory review for this indication.

- The off-label use of rituximab as a second-line therapy for ITP has been recommended in two recent international guidelines, and has been acknowledged in the NICE appraisal of romiplostim for ITP as being acceptable current practice.

- The majority of evidence for the efficacy of rituximab in ITP is derived from observational studies, with no comparator arm. Only a few RCTs have been performed. The populations included in these studies varied, as did the definition of the primary outcome measures, concomitant medications, and the point at which rituximab was used in the treatment pathway.

- The results of studies are inconsistent, and efficacy compared to other treatments could not be determined. The limited data suggest that rituximab treatment can induce a significant and durable response in many patients with ITP. However, the optimal regimen and precise place in therapy of rituximab in the treatment of ITP remain uncertain. Whether rituximab therapy is best positioned before or after splenectomy or thrombopoietin receptor agonists has not been established.

- Response rates in adults were up to 63%, and complete responses were seen in up to 44% of patients. Relapse frequently occurs and rituximab failed to significantly reduce the rate of treatment failure compared to placebo in two double-blind RCTs.

- The evidence for efficacy in children and young people with ITP is limited. A systematic review drawn from case series and one observational cohort study found a pooled response rate of 68%, and a complete response rate of 39%.

- Rituximab has been available as a licensed medicine in the UK since 1998 and the overall safety and tolerability has been well described. The safety data on the use of rituximab in the treatment of ITP is poorly reported. Adverse events associated with rituximab were generally mild to moderate in severity; with infusion-related reactions and infections the most frequently reported adverse events.

- Rituximab is a high cost PbR excluded drug. In most studies rituximab was used at a dose of 375 mg/m2 body surface area once a week for four weeks. Using an average adult body surface area of 1.82 m2 the estimated cost per four week course would be £4,889.63 per patient, and for a child (BSA 0.9 m2) £2,444.80 per patient (assuming wastage and excluding VAT). A lower fixed dose of rituximab of 100 mg weekly for four weeks appears to provide similar efficacy to the standard four week regimen. The estimated cost using this fixed dose would be £698.50 per patient (excluding VAT).
Introduction and background

Immune (idiopathic) thrombocytopenic purpura (ITP) is an acquired autoimmune disorder most commonly resulting from auto-antibody mediated peripheral platelet destruction and, in many cases, impaired platelet production. The condition is characterised by isolated thrombocytopenia (platelet count <100 x 10^9/L) in the absence of any obvious underlying cause, and an increased risk of bleeding and bruising.¹,²

ITP occurs in both adults and children. In adults ITP generally follows a chronic course, while in children it is typically acute in nature (<six months). Most children with acute ITP do not require treatment, and the condition generally resolves spontaneously. In the majority of adults, treatment is indicated only in those with very low platelet counts (<30 x 10^9/L), or significant bleeding.²

The goal of treatment is to achieve a platelet count associated with adequate haemostasis, rather than restoring the platelet count to normal levels. For adults with chronic ITP who require treatment, first-line options include: corticosteroids (dexamethasone, methylprednisolone and prednisolone), intravenous immunoglobulin and in a few instances intravenous anti-D immunoglobulin. Response to these agents is usually transient, and over two thirds of patients will either become refractory or experience intolerable long term side effects. Second-line therapy is individualised to according to patient and clinician preference and individual tolerability. Second-line options include: immunosuppressive agents (azathioprine, ciclosporin, danazol, dapsone, and mycophenolate), cytotoxic agents (cyclophosphamide and vinca alkaloids), rituximab and thromboprotein receptor agonists (romiplostim and eltrombopag). Not all of these treatments are licensed in the UK for ITP. Most patients will require continuous treatment, with some experiencing intermittent relapses that can be managed with rescue treatment. Only a minority of patients will experience a sustained off-treatment response. A splenectomy is a viable second-line treatment choice, but is rarely performed before 12 months from diagnosis in the UK. Although around two thirds of splenectomised patients achieve a normal platelet count, there is an increased risk of infection and mortality from post-splenectomy sepsis.²-⁴

In children with ITP, treatment should be considered by specialists on a case by case basis in those with moderate to severe bleeding symptoms, or those at increased risk of bleeding. Treatment options are comparable to those in adults.²,³

NICE has not issued clinical guidelines on ITP. However, two single technology appraisal have been undertaken, both covering the use of thromboprotein receptor agonists within their licensed indications. NICE TA 221 and TA 205 recommend romiplostim and eltrombopag, respectively, as an option for the treatment of chronic ITP in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated and only if: their condition is refractory to standard active treatments and rescue therapies, or they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies, and the manufacturer makes romiplostim or eltrombopag available with the discount agreed in their respective patient access scheme.⁵,⁶
Rituximab (MabThera®, Roche) is a monoclonal antibody that targets the CD20 antigen expressed on the surface of B-lymphocytes. Rituximab is currently licensed in the UK for the treatment of non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis. It is not licensed for the treatment of ITP, and it is not currently under regulatory review for this indication. However, rituximab was considered to be a standard active treatment in the evidence reviewed by NICE in TA 221, romiplostim for chronic ITP.6,7

This document will review the evidence for the efficacy and safety of rituximab as second-line treatment for ITP in adults and children.

**Clinical evidence**

The majority of evidence for the use of rituximab in ITP is derived from observational studies, with no comparator arm. Only a few randomised controlled studies have been performed. The populations included in these studies varied, as did the definition of the primary outcome measures, concomitant medications, and the point at which rituximab was used in the treatment pathway. The evidence considered in this report includes a meta-analysis (Auger et al., 2012) and a systematic review (Arnold et al., 2007) examining the efficacy and safety of rituximab in adults with ITP, and an additional five studies published since the meta-analysis. This report also includes a systematic review of studies undertaken in children and young people with ITP (Liang et al., 2012).

**Adults with ITP**

**Auger et al., 2012.**

A meta-analysis incorporating data up to May 2011 investigated the efficacy of rituximab before splenectomy in adults with ITP.5 Searches were restricted to articles published in English and French. Descriptive and comparative studies were included if they met pre-defined inclusion criteria and enrolled more than five subjects. Exclusion criteria included secondary causes of thrombocytopenia, hepatitis C or B infection, bone marrow failure syndromes, malignancies such as CLL and lymphoma, Evan syndrome, and patients <18 years of age or who had undergone splenectomy.

Of the 364 records identified, 19 (n=368) were included in the meta-analysis, four randomised trials, nine prospective and six retrospective studies. Subjects in the included studies varied with respect to duration of ITP, age, sex and previous treatment. Rituximab was generally administered by intravenous infusion at 375 mg/m² body surface area once weekly for four weeks. The schedule was different in three studies (1 to 4 cycles), while two studies used a fixed lower dose of 100 mg weekly for four weeks, and one study used dose escalation from 35 to 375 mg/m². The primary outcome measures were overall response rate (ORR) and complete response (CR). The definition of ORR was consistent across the included studies (platelet count >50 x 10⁹/L), while the definition of CR differed. In seven studies the CR was defined as a platelet count of >100 x 10⁹/L (CR100) and for the remaining
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...studies as >150 x 10^9/L (CR150). Therefore, the primary analysis used the CR rate as reported in each study, according to study design. Secondary efficacy outcomes included ORR and CR at one year, response time, mean platelet count at response, and duration of response.

After a median follow-up of nine months (range 2.3 to 65 months, n=368, 95% CI: 48-65) after rituximab treatment (time point not defined), the ORR was 57% (n=157, 95% CI: 53–71). The CR was 41.5% (n=346, 95% CI: 33-50) after rituximab treatment (time point not defined), and at one year was 40% (n=108, 95% CI: 35–76). Pooled CR150 was 36% (n=153, 95% CI: 24–59), and CR100 was 45.6% (n=193, 95% CI: 34.5–57). Mean time to response was 6.34 weeks (n=36, 95% CI: 2.83–9.85). The mean platelet count increased to 200 x 10^9/L (n=54, 95% CI: 129–271 x 10^9/L) at response, and the median duration of response was 49 weeks (n=36, 95% CI: 17–60). Heterogeneity was moderate to high in all analyses, except for those providing individual data, in which there was no heterogeneity. ORR and CR were significantly associated with differences in average age and sex.

Arnold et al., 2007

...An earlier systematic review investigated the efficacy and safety of rituximab in the treatment of ITP in splenectomised and non-splenectomised adults. Subjects in the included studies varied with respect to duration of ITP, age, sex and previous treatment. Just over half the study population had undergone a splenectomy. Of the 599 records identified, 19 (n=313) were included in the evaluation of efficacy, and 29 (n=306) were included in the assessment of safety. None of the studies included a control group. In 16 out of 19 studies, rituximab was given at a dose of 375 mg/m^2 once weekly for four weeks.

After a median follow-up of 9.5 months, the weighted means for CR (platelet count >150 x 10^9/L) and ORR (platelet count >50 x 10^9/L) with rituximab were 43.6% (95% CI, 29.5%–57.7%) and 62.5% (CI, 52.6%–72.5%), respectively. The median duration of response was 10.5 months (range 2 - 48 months).

Ghanima et al., 2015

...A newly published randomized, double-blind, placebo-controlled trial (n=122) investigated the long-term efficacy and safety of rituximab as a splenectomy-sparing treatment in adult patients with ITP who were previously treated with corticosteroids. The study population included unsplenectomised adult patients >18 years of age with ITP who had a platelet count <30 x 10^9/L, or 30-50 x 10^9/L and concomitant bleeding symptoms. The main exclusion criteria were previous administration of any second-line treatment for ITP, HIV, hepatitis C or B infection, and underlying malignancies.

Patients were randomised to receive rituximab 375 mg/m^2 body surface area (n=58) or placebo (n=54) once weekly for four weeks. Patients were allowed to continue taking corticosteroids tapered to the lowest dose that kept platelet counts >20 x 10^9/L. The amended primary endpoint was rate of treatment failure within 78 weeks – a composite of splenectomy or meeting the criteria for a splenectomy after week 12. Criteria for splenectomy were platelet count <20 x 10^9/L, or a need for...
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corticosteroids at doses >7.5 mg/day. The original primary endpoint was amended from splenectomy within 78 weeks because romiplostim and eltrombopag were approved, and it became unethical to deny patients this option; and because a splenectomy was occasionally not done because of patients’ refusal or contraindication. Secondary outcomes were response rates, duration of response, and corticosteroid consumption. Response to treatment was assessed according to international guidelines: CR, platelet count ≥100 x 10^9/L, and OR >30 x 10^9/L, with at least a doubling of the platelet count from baseline without administration of any platelet increasing therapy, except stable or decreasing doses of corticosteroids. Relapse was defined as platelet counts platelet count <30 x 10^9/L, after achieving a response. The Kaplan-Meier method was used for all efficacy outcomes.

Baseline characteristics were generally well balanced between groups, except for the duration of ITP, which was longer in the placebo group, and for the number of patients actively receiving corticosteroids, which was higher in the rituximab group. The median age of patients was 46 years and 40% were female. Three patients in the rituximab group did not receive treatment and were excluded from the final analysis. There was no significant difference between the rituximab and placebo group in the primary outcome measure of treatment failure within 78 weeks, with an estimated cumulative incidence of 46% vs. 52%, respectively (HR 0.89, 95% CI 0.55–1.45, p=0.65). Of these patients, eight (15%) had a splenectomy in the rituximab group vs. 14 (26%) in the placebo group (p=0.12). There were no significant differences in the cumulative incidence of CR: 58% vs. 50%, respectively (p=0.12), and OR: 81% vs. 73%, respectively (p=0.15). In those patients achieving a CR, 50% relapsed in the rituximab group vs. 62% in the placebo group, and of those achieving an OR, 68% vs. 78% relapsed, respectively. Time to relapse in the rituximab group was significantly longer in patients who achieved an OR (36 vs. 49 weeks; p=0.01) but not a CR (76 vs. 49 weeks; p=0.19). The total cumulative corticosteroid dose received during the study did not differ in the two study groups (p=0.33), and there was no significant difference in the probability of receiving rescue treatment (platelet transfusion or intravenous immunoglobulin) between the groups (p=0.09).

Arnold et al., 2012

A randomized, double-blind, placebo-controlled trial (n=60) evaluated the efficacy of adjuvant rituximab in adults with ITP who had not received a splenectomy. This pilot study was designed to explore the feasibility of recruitment, protocol adherence, and blinding of a larger trial of rituximab. The study population included adult patients 18 to 80 years of age with newly diagnosed or relapsed primary ITP who had a platelet count <30 x 10^9/L and had begun standard treatment at the discretion of their doctor. Relapsed ITP was defined as a platelet count <30 x 10^9/L after previous therapy lasting at least one month. Exclusion criteria included significant cardiac, pulmonary or liver disease, uncontrolled hypertension, thrombosis, HIV, hepatitis C or B, and acute infection.

Patients were randomised to receive rituximab 375 mg/m^2 body surface area (n=33) or placebo (n=27) once weekly for four weeks. Randomisation was stratified by ITP stage (newly diagnosed or relapsed). Standard treatments that included one or more of corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, romiplostim or platelet transfusions were permitted for up to eight weeks. The primary efficacy
outcome was treatment failure, defined as a composite of: any platelet count <50 x 10^9/L; significant bleeding, or the administration of rescue treatment because of severe thrombocytopenia, bleeding or a planned invasive procedure. Significant bleeding was defined as grade 2 severity (marked bleeding) at any site as per the ITP bleeding scale. Secondary efficacy outcomes included quality of life, proportion of patients with CR (platelet count ≥100 x 10^9/L) and ORR (≥30 x 10^9/L with doubling from baseline) without rescue treatment at six months.

Baseline characteristics were balanced between groups with a median age of 40 years, 58% were female, median platelet count was ≤15 x 10^9/L, and patients had ITP for a median of one year. Median duration of ITP among newly diagnosed (=28) and relapsed patients (n=32) was one month and 36 months, respectively. One patient in each group withdrew consent before receiving treatment. After six months, there was no statistically significant difference between rituximab and placebo groups for the composite outcome of treatment failure (65.6% vs. 80.8%, respectively; relative risk 0.81, 95% CI, 0.59% -1.11%). The proportion of patients meeting each of the components of the composite outcome was also similar between groups. There was no statistically significant difference between the groups for CR (53.1% vs. 46.2%, respectively; relative risk 1.15, 95% CI, 0.68% -1.95%) or ORR (62.5% vs. 73.1%, respectively; relative risk 0.86, 95% CI, 0.60% -1.22%). No statistically significant treatment effect was found for change in quality of life summary scores.

Gudbrandsdottir et al., 2013

An open-label, randomized, controlled trial (n=137) evaluated the efficacy of rituximab plus dexamethasone compared with dexamethasone in adults with ITP who had not received a splenectomy. The study population included adult patients >18 years of age with newly diagnosed ITP who had a platelet count ≤25 x 10^9/L, or ≤50 x 10^9/L and concomitant bleeding symptoms. Exclusion criteria included very low performance status (WHO score ≤2), previous rituximab therapy or other immunomodulating therapy within one month, HIV, hepatitis C or B, cytomegalovirus or Epstein-Barr virus.

Patients were randomised to receive rituximab 375 mg/m^2 body surface area once weekly for four weeks plus dexamethasone 40 mg daily for four days (n=63) or dexamethasone alone (n=74) with up to four years follow up. A subsequent protocol amendment allowed ‘non-responders’ in both groups to receive supplemental dexamethasone every one to four weeks for up to six cycles. Premedication included paracetamol and intravenous antihistamine. The primary efficacy outcome was sustained partial response (platelet count ≥50 x 10^9/L), or CR (≥100x 10^9/L), at six months. Secondary efficacy outcomes included time to relapse, time to rescue treatment, and rates of splenectomy.

Baseline characteristics were well balanced between groups. In the rituximab group 31% of patients received more than two cycles of dexamethasone during treatment compared to 44% of patients in the dexamethasone group (p=0.09). The median follow-up time was 922 days, with no significant differences between the groups. Four participants did not have complete data available for analysis. At six months follow-up in the ITT population, the primary end point of sustained partial response or CR was achieved in 57% of patients in the rituximab plus dexamethasone group.
versus 35\% in the dexamethasone group (p=0.01). At 12 months follow-up, sustained partial response or CR was achieved in 53\% of patients in the rituximab plus dexamethasone group versus 33\% in the dexamethasone group (p<0.05).

During a three-year observational period, there was a significantly longer time to relapse (P=0.03), and longer time to rescue treatment (p=0.007) following an initial partial or CR in the rituximab plus dexamethasone group vs. the dexamethasone group. The median time to rescue treatment was 7.4 months in the dexamethasone group, and not reached after 48 months in the rituximab plus dexamethasone group. There was no difference in the rates of splenectomy between the two groups (10\% vs. 7\%, respectively, p=0.08). A final report on the full four year follow-up data is expected in 2015.

Khellaf et al., 2104

A recently published retrospective French registry-based cohort study evaluated the efficacy of rituximab in adults with ITP outside of a clinical trial.14 A total of 248 patients >18 years of age with a diagnosis of primary ITP and who received rituximab were included, with a planned follow-up of five years. The choice of the rituximab regimen was based on the physician’s preference and not patient characteristics. In France ITP is treated in haematology or internal medicine departments. The staff in the internal medicine departments are more familiar with the ‘RA-like’ rituximab regimen (two fixed 1 g infusions on days 1 and 15) used to treat other autoimmune diseases such as RA or SLE, rather than the ‘standard regimen’ of 375 mg/m² body surface area once weekly for four weeks used to treat lymphoma. Premedication with paracetamol, diphenhydramine and methylprednisolone was recommended before each rituximab infusion.

Response to treatment was assessed according to international guidelines: CR (platelet count ≥100 x 10⁹/L) and response (≥30 x 10⁹/L with doubling from baseline) without rescue treatment at six months. Patients requiring another treatment, including a new rituximab cycle, were considered non-responders, regardless of platelet count: only rescue therapy with a short course of corticosteroids or intravenous immunoglobulin infusions administered eight weeks after the date of the first rituximab infusion was allowed.

All patients had previously received corticosteroids or intravenous immunoglobulin as first-line treatment, and 25\% had undergone a splenectomy. The mean age was 51 years, 64\% were female, median platelet count preceding rituximab treatment was <17 x 10⁹/L, and patients had ITP for a median of 16 months. In total, 173 patients (70\%) received the ‘standard regimen’ (375 mg/m² once weekly for four weeks) and 72 (29\%) received the ‘RA-like’ regimen (two fixed 1 g infusions two weeks apart). Three patients received only a one infusion regimen. At a median follow-up of 24 months, 96 patients (39\%) showed a lasting response, including 76 (30\%) with a complete response. Among 152 initial responders, the median time to relapse was 25 months. On multivariate analysis, the probability of sustained response at one year was significantly associated with ITP duration <1 year (p=0.02) and previous transient complete response to corticosteroids (p=0.05). The pattern of response was similar with the two rituximab regimens.
Moullis et al 2013
A further retrospective registry-based cohort study compared the efficacy and safety of rituximab with splenectomy in adults with ITP. A total of 105 adult patients >18 years of age with a diagnosis of primary ITP and who had undergone a splenectomy or had received rituximab were included. The primary outcome was composite of death from haemorrhage or from infection, and hospitalisation for bleeding or for infection. Secondary outcomes were overall mortality, hospitalisation for bleeding, hospitalisation for infection, as well as response and CR according to international guidelines (platelet count ≥30 x 10^9/L and ≥100 x 10^9/L, respectively).

Patients treated with rituximab (n=43) were older and had more co-morbidities than the splenectomised patients (n=62). Platelet count at diagnosis and frequency of mucosal bleeding did not differ between the groups. All patients received rituximab 375 mg/m² body surface area once weekly for four weeks. Fourteen patients were lost to follow-up in the splenectomy group and two in the rituximab group. Mean follow-up was 8.4 (± 4.7) and 3.0 (± 1.9) years, respectively. After adjustment on the propensity score, there was no difference between the two groups regarding the primary and other clinical outcomes. Response rates at three months were 91.4% after splenectomy vs. 69.8% after rituximab (p=0.005). At 12 months, the response rates were 87.9% versus 59.0% (p=0.001), respectively. Complete response rates were 82.8% versus 39.5% at three months (p<0.0001) and 81.0% versus 35.9% at 12 months (p<0.0001), respectively. Maintenance of response and maintenance of CR remained significantly higher in the splenectomy group (adjusted p<0.0001 for both).

Tran et al., 2014
The efficacy of a fixed-dose rituximab schedule was explored in phase II, open label, single arm study in adult patients with refractory ITP. Patients received two doses of rituximab (1000 mg) on days one and 15 and were followed-up for 52-weeks. A total of 122 patients were included in the safety population; efficacy was analysed in 108 patients. The primary outcome was to determine if the ORR was ≥50%. The ORR was defined as the proportion of patients achieving a CR (platelet count ≥150 x 10^9/L) or partial response (platelet count ≥50 x 10^9/L).

At week 8, the ORR was 43.5% (95% CI 34.0% -53.4%). While this study failed to meet its primary endpoint, the efficacy of two fixed doses of rituximab appears to provide similar efficacy to the standard schedule of 375 mg/m2 once weekly for four weeks.

Children with ITP
A systematic review incorporating data up to January 2012 investigated the efficacy and safety of rituximab in the treatment of ITP in children and younger people. Clinical studies published in full text or abstract only in any language that met predefined inclusion criteria were eligible. Efficacy analysis was restricted to studies enrolling five or more patients. Safety was evaluated from all studies that reported
data of toxicity. The studies included participants aged less than 18 years of age with a diagnosis of primary or secondary ITP, having platelet counts <30 x 10⁹/L. Studies that included both children and adults were excluded if data of children could not be extracted separately. Patients were treated with rituximab irrespective of dosage and schedule.

Of the 1,280 records identified, 18 (n=352) were included in the efficacy analysis, 17 were case series and one was an observational cohort study. The subjects were 0.5 to 19 years old with a duration of ITP from 0.2 to 175 months, and a platelet count of 1 to 75 x 10⁹/L before rituximab treatment. A total of 304 subjects were diagnosed with primary ITP and 48 with secondary ITP. Doses of rituximab varied both within and between the included studies. The majority of subjects (84.5%, 14 studies) received intravenous rituximab at 375 mg/m² body surface area once weekly for 1-6 doses. Two studies used a fixed lower dose of 100 mg weekly for four weeks, one study a dose escalation to 750 mg/m², and one study 500 mg/m² every two weeks. Treatments before rituximab varied between and within studies, and included corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin and splenectomy. Efficacy outcomes included response and CR according to international guidelines (platelet count ≥30 x 10⁹/L and ≥100x 10⁹/L, respectively), time to response and duration of response. Results were reported separately for subjects with primary and secondary ITP.

A total of fourteen studies (n=312) were included in the efficacy analysis of subjects with primary ITP. The response rate reported in the primary studies ranged from 33% to 100% and the pooled rate was 68% (95% CI, 58% to 77%). The CR rate ranged from 14% to 67% and the pooled rate was 39% (95% CI, 30% to 49%). There was statistically significant heterogeneity between studies for both response (p<0.001) and CR (p=0.005). The median time to response was three weeks (n=40, two studies) and duration of response was 12.8 months (n=62, four studies).

Summary of evidence

The majority of evidence for the use of rituximab in ITP is derived from observational studies, with no comparator arm. Only a few randomised controlled studies have been performed. The populations included in these studies varied, as did the definition of the primary outcome measures, concomitant medications, and the point at which rituximab was used in the treatment pathway. The results of studies included in this review are inconsistent, and efficacy compared to other treatments could not be determined. The limited data suggest that rituximab treatment can induce a significant and durable response in many patients with ITP. However, the optimal regimen and precise place in therapy of rituximab in the treatment of ITP remain uncertain. Whether rituximab therapy is best positioned before or after splenectomy or thrombopoietin receptor agonists (TRAs) has not been established.

In a well-conducted meta-analysis in adults with ITP the CR and OR with rituximab were 41.5% and 57%, respectively, after a median of follow-up of nine months. Median time to response was 6.3 weeks, with a median duration of response of 49 weeks. However, there was a large variation in the reported response rates in
individual studies, and heterogeneity was moderate to high in all analyses. In an earlier systematic review (n=313) in which just over half the study population had been splenectomised, the complete response and overall response with rituximab were 43.6% and 62.5%, respectively, after a median follow-up of 9.5 months. The median time to response was 5.5 weeks, with a median duration of response of 10.5 months. Important differences in the definition of response among studies were noted, and none of the studies met the predefined methodological quality criteria or included a control group.

In the largest double-blind RCT to date, rituximab treatment failed to significantly reduce the rate of treatment failure compared to placebo in patients previously treated with corticosteroids. Despite numerically higher response rates and a significantly longer duration of response with rituximab, the study failed to show a statistically significant difference in overall or complete response rates compared to placebo. As a result, the authors of the study concluded that the data cannot support a general recommendation for use of rituximab monotherapy in patients with ITP who did not respond to corticosteroids. The amendment of the primary endpoint from splenectomy rate to the less stringent outcome of treatment failure is a notable limitation of this study. In addition, the duration of ITP was longer in the placebo group, and the number of patients actively receiving corticosteroids was higher in the rituximab group which could have potentially biased the treatment outcome in favour of rituximab. A small pilot RCT also found no statistically significant difference between rituximab and placebo for the composite outcome of treatment failure, or in the ORR and CR rates at six months. In a larger open-label RCT there was a significantly higher response rate with rituximab plus dexamethasone than with dexamethasone alone. At six months follow-up a sustained partial response or CR was achieved in 57% of patients in the rituximab plus dexamethasone group versus 35% in the dexamethasone group (p=0.01). However, it is important to note that dexamethasone is not widely used in the UK for the treatment of ITP, and corticosteroids are principally used first-line prior to rituximab treatment.

A large retrospective registry-based cohort study in which a quarter of participants had undergone a splenectomy reported a CR of 30% at a median follow-up of 24 months. The median time to relapse was 25 months, with the probability of sustained response significantly associated with ITP duration and previous response to corticosteroids. A further retrospective registry-based cohort study comparing rituximab with splenectomy found no significant difference between the two groups for the primary composite outcome of death from haemorrhage or from infection, and hospitalisation for bleeding or for infection. However, response rate and CR at three and 12 months were statistically significantly greater with rituximab.

The evidence for efficacy in children and young people with ITP is limited. A systematic review (n=352) drawn from case series and one observational cohort study found a pooled response rate and CR rate of 68% and 39%, respectively. The median time to response was three weeks and duration of response 12.8 months. There was statistically significant heterogeneity noted between studies for both outcomes, and the study included patients who had undergone a splenectomy.
In the majority of studies, rituximab was used at a dose of 375 mg/m$^2$ once weekly for four weeks which was developed and licensed for the treatment of NHL. However, some studies have investigated the use of fixed doses of rituximab of 100 mg weekly for four weeks, and 1000 mg on days one and 15. The efficacy of these two fixed dose regimens appears to provide similar efficacy to the standard four week regimen.$^8,16,17$

An international consensus report on the management of ITP recommend rituximab as an option for second-line therapy, with the choice of treatment tailored to the individual patient. The American Society of Haematology guidelines on ITP conclude that rituximab may be considered for adults at risk of bleeding who have failed one line of therapy such as corticosteroids, immunoglobulins or splenectomy. Rituximab May be considered for children with ITP who have significant ongoing bleeding and/or have a need for improved quality of life despite conventional treatment. Also may be considered as an alternative to splenectomy in children with chronic ITP or as therapy in those who have failed splenectomy.$^3,4$

**Safety**

Rituximab has been available as a licensed medicine in the UK since 1998 and the overall safety and tolerability has been well described. The safety profile of rituximab is generally consistent across doses and regimens as well as the different patient populations and subgroups. The safety of rituximab in children below 18 years of age has not been established.$^7$

The published safety data on the use of rituximab in the treatment of ITP is limited. The majority of data is derived from observational studies, with no comparator arm. Only a few randomised controlled studies have been performed. The populations included in these studies varied with respect to severity and duration of ITP, age, sex and previous treatment.

**Adults with ITP**

Among the 29 reports (n=306) on safety covered by the systematic review by Arnold et al., (2007), a total of 66 (21.6%) patients experienced mild or moderate adverse events, of which 55 (18%) were infusion-related reactions (IRRs). Ten patients (3.7%) experienced severe or life threatening events including anaphylaxis, bronchospasm and infections. Nine (2.5%) patients died, but the number of deaths considered to be possibly related to rituximab therapy is not reported.$^9$ No safety data were included in the meta-analysis reported by Auger et al., (2012).$^8$

In the largest double-blind RCT of patients with ITP, the overall incidence of adverse events was comparable between treatment groups, and the majority were mild to moderate in nature. Influenza, headache, pyrexia, bronchitis, rash, throat irritation, URTI and abdominal pain occurred more frequently in the patients receiving rituximab than placebo (p values not reported). One or more infections occurred in the 40% of patients receiving rituximab vs. 24% with placebo, but time to first infection was not significant (p=0.09). Rates of bleeding were similar in the two groups at 38% vs. 50%, respectively, with no significant difference in the time to first bleeding event (p=0.08). In a small pilot RCT reported by (Arnold et al., 2012), IRRs
including sore throat, nasal congestion, cough, pruritus, skin rash, chest pain, and dyspnea were more common in the rituximab group than with placebo (20 vs. 10, respectively). Two serious adverse events occurred in patients receiving rituximab (serum sickness and accidental fall). In the open-label RCT (Gudbrandsdottir et al., 2013), adverse events were, in general, mild and balanced between the two groups. The most common adverse events reported in either group were fatigue, dizziness, headache, epigastritis, and anxiety. Only muscle/joint pain and fever were significantly more common in the rituximab plus dexamethasone group, whereas only anxiety was more common in the dexamethasone monotherapy group (all p<0.05). All the adverse events reported in this study had previously been described in the respective summary of product characteristics for rituximab and dexamethasone. There were 16 reported serious adverse events in the rituximab plus dexamethasone group, including one death, as compared with eight serious adverse events in the dexamethasone group, including three deaths (p=0.04). None of the deaths were considered to be treatment-related.

In the registry-based cohort study reported by Khellaf et al., (2014), a total of 87 adverse events were reported in 44 patients (19%), 66 of which were deemed to be possibly related to rituximab treatment. Infusion-related reactions (IRRs) were the most frequent adverse event, with 49 events observed in 38 patients (15%). All IRRs were mild in nature, except for three which required interruption of treatment because of severe hypotension, dyspnea with laryngeal discomfort, and reversible serum sickness. IRRs occurred mainly at the first infusion, (n=30), but some were observed during or after the second (n=16) or third infusion (n=3). Most patients received premedication with methylprednisolone, which may explain the why rituximab infusions were generally well tolerated and no sever IRRs were observed. Eleven cases of infection in seven patients (3%) were reported, corresponding to an incidence of 2.3 infections per 100 patient years. No case of progressive multifocal encephalopathy (PML) or any other opportunistic infections were reported, except one case of transient aspergillosis sinusitis. Most cases of infection recovered without sequelae. Three episodes of infection were fatal, but they occurred at least one year after rituximab infusions in older adults concomitantly receiving corticosteroids for refractory ITP. Apart from the severe infections, three patients experienced late non-fatal severe adverse events possibly related to rituximab, requiring hospitalisation (asymptomatic neutropenia, transient heart failure and inflammatory demyelinating polyneuropathy). In all thirteen patients died during follow-up; apart from the three deaths previously described, only one other death was deemed to be possible related to rituximab therapy. In a second registry-based cohort study (Moullis et al., 2013) the frequency of hospitalisations for infection did not differ between treatment groups. Seven patients treated with rituximab were hospitalised for infection (five pneumonia, one Staphylococcus septicemia, and one hepatitis E virus infection) compared with six patients in the splenectomy group (two with septicaemia, and four with enterobacteria infections).

Children with ITP

In the systematic review of rituximab in the treatment of children reported by Liang et al., (2012), 23 studies reported a total of 108 adverse events in 91 patients. The majority (84.3%) of adverse events were mild to moderate in nature, with the most
frequently reported events being mild allergic reactions, including pruritus, urticaria, chills and fever. Seven patients developed serum sickness, of which, three cases were severe. Other severe adverse events included immediate hypersensitivity reaction requiring termination of treatment in two patients; common variable immunodeficiency in one patient; headache with white matter changes on brain MRI in one patient, and infections which included varicella in two patients, pneumonia in one patient, and life-threatening enteroviral meningoencephalitis in one patient. No death associated with rituximab was reported.\textsuperscript{17}

**Warnings and precautions with rituximab**

Rituximab administration can result in serious, including fatal, adverse reactions and should only be administered in an area where full resuscitation facilities and close monitoring are available. In the treatment of ITP, rituximab should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.\textsuperscript{7}

The summary of product characteristics for rituximab describes IRRs as very common in patients receiving rituximab. Signs and symptoms suggestive of IRRs were reported in more than 50% of patients in clinical trials of intravenous rituximab in patients with NHL and CLL. These consisted primarily of fever, headache, rigors, flushing, nausea, rash, and URTI symptoms. Severe IRRs with fatal outcome have been reported during post-marketing use of rituximab intravenous formulation, with an onset ranging from 30 to 120 minutes after starting the first rituximab infusion. Premedication with an anti-pyretic and an antihistamine, e.g. paracetamol and diphenhydramine, should always be given before administration of intravenous rituximab. In addition, premedication with intravenous methylprednisolone is used in many patients receiving rituximab for ITP.\textsuperscript{7}

Rituximab is a powerful immunosuppressant that eliminates mature circulating B-cells for up to nine months. Serious infections, including fatalities, can occur during therapy with rituximab. Rituximab should not be administered to patients with an active severe infection or severely immunocompromised patients. Caution is advised when using rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Cases of hepatitis B virus (HBV) reactivation, including those with a fatal outcome, have been reported. All patients should be screened for HBV infection before treatment initiation.\textsuperscript{7}

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, has been reported in patients receiving rituximab therapy. Patients must be closely monitored for cognitive, neurological, or psychiatric signs and symptoms that may be suggestive of PML.\textsuperscript{7}

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported. In case of such an event with a suspected relationship to rituximab, treatment should be permanently discontinued.\textsuperscript{7}
Cost analysis

No published economic analyses on the use of rituximab in the treatment of ITP were identified.

Rituximab (MabThera®, Roche) is available as a solution for intravenous infusion, and as a subcutaneous injection. In the treatment of ITP, it is administered as an intravenous infusion through a dedicated line over several hours. It should only be administered in an area where full resuscitation facilities and close monitoring are available. This can usually be done on an out-patient basis.

Rituximab is a high cost PbR excluded drug. Rituximab 10 mg/ml concentrate for solution for intravenous infusion costs £349.25 for two 10 ml vials, and £873.15 for one 50 ml vial (excluding VAT; eMIMS January 2015). Once prepared the infusion solution should be used immediately, or it may be stored for a maximum of 24 hours at 2°C to 8°C.

The majority of studies reported in this review used a rituximab dose of 375 mg/m² body surface area once a week for four weeks. Using an average adult body surface area of 1.82 m² the estimated cost per four week course would be £4,889.63 per patient (assuming wastage and excluding VAT). For a child with a body surface area of 0.9 m² the estimated cost per four week course would be £2,444.80 per patient (assuming wastage and excluding VAT). This does not include administration costs or the cost of any premedication.

Some studies in both adults and children have investigated the use of a lower fixed dose of rituximab of 100 mg weekly for four weeks. The estimated cost per four week course using this fixed dose would be £698.50 per patient (excluding VAT). A recent study in adults used a fixed dose of 1000 mg on days one and 15. The estimated cost per four week course using this fixed dose would be £1,746.30 per patient (excluding VAT). These costs do not include administration costs or the cost of any premedication.

Accurately estimating the number of patients who might be eligible for treatment with rituximab for ITP is difficult as reports of the incidence and prevalence of ITP in adults and children are inconsistent and their methodology is variable.

A systematic review on ITP epidemiology suggests a UK incidence of ITP in adults in the order of 1.6 to 3.9 per 100,000 per year. The majority of incident cases will go on to become chronic. A study of the prevalence of adult ITP using the General Practice Research Database (GPRD) suggest an age- and gender- adjusted prevalence of 50 per 100,000 in the UK. Based on an adult population (≥18 years) of 2.6 million, this equates to approximately 1,300 patients with ITP in the NTAG area. The NICE costing template for romiplostim estimates that 60% (780) of these will require treatment. Of these patients, 67% (523) would be expected not to respond to first line therapy. Of these non-responders, around 40% (209) would need long term treatment and therefore may be eligible for treatment with rituximab.

References: 8,16,17
The estimated childhood incidence of ITP in the UK is in the order of 3.0 to 4.8 per 100,000 children per year, of which 15 to 20% will go on to develop the chronic form. A conservative estimate based on the most recent surveys suggests the prevalence of chronic childhood ITP is around 4.6 per 100,000 children. However, the majority of children with chronic ITP do not need treatment, and therefore, it has not been possible to estimate the number of children who might be eligible for treatment with rituximab.19,20

Comparing the potential costs of rituximab with other treatments for ITP is difficult. Rituximab is typically given as single four week course with the aim of inducing a long-term remission. The only other one-off treatment aimed at inducing long-term remission in ITP is splenectomy. The cost of an elective splenectomy on the NHS is in the range of £3,500 to £4,500 depending upon the complexity of the procedure.

It is likely that some of the cost of rituximab could be offset against potential savings realised through a reduction in blood transfusions, nursing time and rescue therapy compared to other second-line options.
Points to consider

Rituximab is not licensed for the treatment of ITP. The off-label use of rituximab as a second-line therapy for ITP has been recommended in two recent international guidelines, and has been acknowledged in the NICE appraisal of romiplostim for ITP as being acceptable current practice.

The majority of evidence for the efficacy of rituximab in ITP is derived from observational studies, with no comparator arm. Only a few RCTs have been performed. The populations included in these studies varied, as did the definition of the primary outcome measures, concomitant medications, and the point at which rituximab was used in the treatment pathway.

Overall, the results of studies are inconsistent, and the efficacy of rituximab compared to other established treatments for ITP could not be determined. The limited data suggest that rituximab treatment can induce a significant and durable response in many patients with ITP. However, the optimal regimen and precise place in therapy of rituximab in the treatment of ITP remain uncertain. Whether rituximab therapy is best positioned before or after splenectomy or thrombopoietin receptor agonists has not been established.

In adults with ITP, response rates with rituximab ranged from 44% to 63%, and complete responses were seen in 30% to 44% of patients. However, relapse frequently occurs and rituximab failed to significantly reduce the rate of treatment failure compared to placebo in two double-blind RCTs. The evidence for efficacy in children and young people with ITP is limited. A systematic review drawn from case series and one observational cohort study found a pooled response rate of 68%, and a complete response rate of 39%.

The safety data on the use of rituximab in the treatment of ITP is poorly reported. Adverse events associated with rituximab were generally mild to moderate in severity; with infusion-related reactions and infections the most frequently reported adverse events. Progressive Multifocal Leukoencephalopathy has been reported in patients receiving rituximab therapy, although this complication appears to be rare in patients with ITP receiving rituximab therapy.

Rituximab is a costly therapy. In most studies rituximab was used at a dose of 375 mg/m$^2$ body surface area once a week for four weeks. Using an average adult body surface area of 1.82 m$^2$ the estimated cost per four week course would be £4,889.63 per patient, and for a child (BSA 0.9 m$^2$) £2,444.80 per patient (assuming wastage and excluding VAT). A lower fixed dose of rituximab of 100 mg weekly for four weeks has been used in some studies and appears to provide similar efficacy to the standard four week regimen. The estimated cost using this fixed dose would be £698.50 per patient (excluding VAT). These costs do not include administration costs or the cost of any premedication.

Comparing the cost of rituximab with other treatments for ITP is difficult. Rituximab is typically given as single four week course with the aim of inducing a long-term remission. The only other one-off treatment aimed at inducing long-term remission in ITP is splenectomy (£3,500 to £4,500 depending upon the complexity of the procedure).
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