

Immune (idiopathic) thrombocytopenic purpura: rituximab

Evidence summary

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Key points from the evidence

The content of this evidence summary was up-to-date in October 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Most of the evidence for using rituximab in adults with immune thrombocytopenic purpura comes from observational studies, with no comparator arm. The populations in the included studies varied, as did the platelet count considered to represent an overall response or complete response. The [randomised controlled trials \(RCTs\)](#) discussed in this evidence summary had a number of limitations, including small numbers of participants. All of these factors make it difficult to draw firm conclusions from the evidence.

The evidence for efficacy of rituximab in children and young people is weaker, drawn from case series and 1 cohort study with no comparator arm.

Regulatory status: off-label. This topic was prioritised because there was a high volume of requests from the NHS.

Effectiveness	Safety
<ul style="list-style-type: none"> • A systematic review of mainly observational studies (n=368) suggests that rituximab can increase platelet levels in adults with immune thrombocytopenic purpura; although response rates varied significantly between individual studies. No comparisons with other treatments were made. • An RCT (n=137) suggests that rituximab plus dexamethasone may be better than dexamethasone alone for achieving a sustained response in terms of increased platelet levels in adults with newly diagnosed primary immune thrombocytopenic purpura. • Another RCT (n=60) shows that rituximab is no better than placebo for preventing treatment failure in adults with immune thrombocytopenic purpura once standard treatment was stopped. • A retrospective cohort study (n=105) suggests that there is no difference between rituximab and splenectomy for the composite outcome of death from, or hospitalisation for, bleeding or infection in adults with immune thrombocytopenic purpura. • In children and young people with immune thrombocytopenic purpura, a systematic review (n=352) suggests that rituximab can increase platelet levels. However included studies were all observational, limiting the conclusions 	<ul style="list-style-type: none"> • The <u>summary of product characteristics (SPC) for rituximab</u> describes that infusion related reactions are very common in people treated with intravenous rituximab. Severe infusion related reactions with a fatal outcome have been reported in post-marketing use. • Serious infections, including fatalities, can occur during rituximab therapy, and rituximab is contraindicated in people with an active, severe infection, and in people who are severely immunocompromised. • Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after use of rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition.

<p>that can be drawn.</p>	
<p>Patient factors</p> <ul style="list-style-type: none"> • Rituximab is administered as an intravenous infusion over several hours. • Rituximab is usually given as a 4-week course of treatment aimed at inducing a long-term response, whereas some other treatments might need to be taken continuously. • Second-line treatment options include splenectomy, which some people may prefer to avoid. 	<p>Resource implications</p> <ul style="list-style-type: none"> • Most of the studies in this evidence summary used rituximab at a dosage of 375 mg/m² body surface area weekly for 4 weeks: <ul style="list-style-type: none"> – The cost for a 4-week course based on an adult with a body surface area of 1.86 m² is estimated to be £4889.60 (assuming wastage and excluding VAT; MIMS September 2014). – The cost for a 4-week course based on a child with a body surface area of 0.89 m² is estimated to be £2794 (assuming wastage and excluding VAT; MIMS September 2014). • Some studies used a lower fixed dose of rituximab 100 mg weekly for 4 weeks. The cost for a 4-week course using this lower fixed dose is £698.50 (excluding VAT; MIMS September 2014).

Introduction and current guidance

Immune (idiopathic) thrombocytopenic purpura is an autoimmune condition characterised by increased platelet destruction and, in many cases, inadequate platelet production. The condition can result in low platelet counts and bleeding ([Eltrombopag for treating chronic immune \[idiopathic\] thrombocytopenic purpura \[review of technology appraisal 205\]](#); [NICE technology appraisal guidance 293: final scope](#)).

For adults that need treatment, first-line options include corticosteroids, intravenous immunoglobulin and intravenous anti-D immunoglobulin (although specialist opinion suggests this is rarely used in the UK). Second-line options include azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate, rituximab, vinca alkaloids, and splenectomy. Not all of these drug treatments are licensed for treating immune thrombocytopenic purpura in adults and most of the evidence for using these agents is from non-randomised or descriptive studies ([International consensus report on the investigation and management of primary immune thrombocytopenia \[2010\]](#)).

Newer therapies for immune thrombocytopenic purpura include the thrombopoietin receptor agonists eltrombopag and romiplostim. The NICE technology appraisal on [eltrombopag for treating chronic immune \(idiopathic\) thrombocytopenic purpura](#) recommends eltrombopag as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, 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 provides eltrombopag with the discount agreed in the patient access scheme.

Similarly, the NICE technology appraisal on [romiplostim for the treatment of chronic immune \(idiopathic\) thrombocytopenic purpura](#) recommends romiplostim as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, 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 available with the discount agreed in the patient access scheme.

For children that need treatment, first-line options include corticosteroids, intravenous immunoglobulin and intravenous anti-D immunoglobulin (although specialist opinion suggests this is rarely used in the UK). Second-line treatments include corticosteroids, rituximab, immunosuppressants, cytotoxic drugs and splenectomy, and are usually considered by specialist paediatricians on a case by case basis ([International consensus report on the investigation and management of primary immune thrombocytopenia \[2010\]](#)).

Rituximab is available as a solution for intravenous infusion, and as a subcutaneous injection. Studies included in this evidence review used the intravenous formulation of rituximab, therefore only this formulation is reviewed in this evidence summary.

[Full text of Introduction and current guidance.](#)

Product overview

Rituximab concentrate for solution for intravenous infusion ([MabThera](#), Roche Products Limited) is licensed in adults for treating non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. It is administered as an intravenous infusion, which can take several hours, depending on the dose and rate of infusion.

Rituximab is not licensed for treating immune thrombocytopenic purpura and so use for this indication is off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using rituximab outside its authorised indications.

Rituximab 10 mg/ml concentrate for solution for intravenous infusion ([MabThera](#), Roche Products Limited) costs (excluding VAT, [MIMS](#) September 2014):

- 2×10 ml=£349.25
- 1×50 ml=£873.15

[Full text of Product overview.](#)

Evidence review

- The evidence reported in this summary for adults includes a systematic review and meta-analysis ([Auger et al. 2012](#)), 2 RCTs ([Arnold et al. 2012](#) and [Gudbrandsdottir et al. 2013](#)) that have been published since the systematic review, and a retrospective cohort study ([Moulis et al. 2013](#)) comparing rituximab with splenectomy. Also included in the evidence summary is a systematic review ([Liang et al. 2012](#)) of studies carried out in children and young people.
- [Auger et al. \(2012\)](#) included 19 studies (n=368) in adults who had immune thrombocytopenic purpura and were receiving rituximab before splenectomy. Only 4 of the included studies were randomised. The remaining studies were prospective and retrospective observational studies with no comparator arm. Consequently, no comparisons of rituximab with other treatments were made in the review. Most studies used rituximab at a dosage of 375 mg/m² body surface area weekly for 4 weeks. Pooled overall response rate (defined as a platelet count of greater than 50×10⁹ per litre) was 57% (n=368, 95% confidence interval [CI] 48 to 65%) after rituximab treatment (time point 'after' not further defined), and 57% (n=157, 95% CI 35 to 76%) at 1 year after rituximab treatment. However, there was a large variation in the reported overall response rates in the individual studies (16–100% after rituximab, and 33–85% at 1 year after rituximab treatment). Pooled complete response rate (defined as either a platelet count of greater than 100×10⁹ per litre, or greater than 150×10⁹ per litre depending on the individual study) was 41.5% (n=346, 95% CI 33 to 50%) after rituximab treatment (time point 'after' not further defined), and 40% (n=108, 95% CI 31 to 49%) at 1 year after rituximab treatment. However, again there was a large variation in the reported complete response rates in the individual studies (0–86% after rituximab, and 0–48.4% at 1 year after rituximab treatment). Heterogeneity was moderate or high in most analyses.
- [Arnold et al. \(2012\)](#) was a pilot double-blind, placebo-controlled randomised trial of adjuvant rituximab or placebo in 60 adults with newly diagnosed or relapsed primary immune thrombocytopenic purpura who had not received a splenectomy, and who had a platelet count of less than 30×10⁹ per litre (median baseline platelet count 15×10⁹ per litre). Participants received intravenous rituximab 375 mg/m² body surface area (n=33) or saline placebo (n=27) once weekly, for 4 weeks. Participants also received standard treatment for up to 8 weeks with 1 or more of: corticosteroids; intravenous immunoglobulin; intravenous anti-D immunoglobulin; romiplostim; or platelet transfusions. For the primary outcome of treatment failure (defined as the composite of any of: platelet count below 50×10⁹ per litre; significant bleeding or administration

of rescue treatment because of severe thrombocytopenia; bleeding; or a planned invasive procedure) there was no statistically significant difference between the rituximab and placebo groups (treatment failure: 65.6% in the rituximab group compared with 80.8% in the placebo group; relative risk [RR] 0.81, 95% CI 0.59 to 1.11).

- Gudbrandsdottir et al. (2013) was an open-label RCT of rituximab plus dexamethasone, compared with dexamethasone alone in 137 adults with newly diagnosed primary immune thrombocytopenic purpura who had not had a splenectomy, and who had a platelet count of 25×10^9 per litre or less, or 50×10^9 per litre or less and concomitant bleeding symptoms. Participants received a combination of rituximab 375 mg/m^2 body surface area once weekly for 4 weeks plus dexamethasone 40 mg daily (n=63) for 4 days, or the same dosage of dexamethasone alone (n=74). In an intention-to-treat analysis, the primary outcome of sustained partial (defined as a platelet count of at least 50×10^9 per litre) or complete (defined as a platelet count of at least 100×10^9 per litre) response at 6 months' follow-up was achieved in 57% of people in the rituximab plus dexamethasone group, compared with 35% of people in the dexamethasone monotherapy group (p=0.01).
- Moulis et al. (2013) was a retrospective cohort study comparing rituximab 375 mg/m^2 body surface area weekly for 4 weeks with splenectomy for treating 105 adults with primary immune thrombocytopenic purpura. The primary outcome (a composite of death from bleeding or infection and hospitalisation for bleeding or infection) occurred in 14/43 (32.6%) people in the rituximab group, and 11/62 (17.7%) people in the splenectomy group. After adjusting for propensity score, there was no difference between the groups for the primary outcome (p=0.7).
- Liang et al. (2012) included 18 studies (n=352) that contributed to efficacy analyses, including 17 case series, and 1 observational cohort study. The participants in the studies had an age range of 0.5 to 19 years. Most participants (84.5%) received intravenous rituximab at a dosage of 375 mg/m^2 body surface area weekly for 1–6 doses (14 studies). When the results from 14 studies (n=312) were pooled, response to rituximab (defined as a platelet count of at least 30×10^9 per litre and at least double that of baseline) was achieved in 68% of participants (95% CI 58% to 77%). Complete response (defined as a platelet count of at least 100×10^9 per litre; 14 studies, n=243) was achieved in 39% of participants (95% CI 30% to 49%). There was statistically significant heterogeneity between the included studies for these outcomes (p<0.001 for response, and p=0.005 for complete response) and there was a large variation in the reported response and complete response rates in the individual studies (33–100% for response rate and 14–67% for complete response

rate).

- The [SPC for rituximab](#) (MabThera, Roche Products Limited) lists contraindications and adverse events separately for each licensed indication (see the SPC for more information).
- The [SPC for rituximab](#) describes that infusion-related reactions are very common in people treated with intravenous rituximab for any licensed indication. Severe infusion-related reactions with a fatal outcome have been reported in post-marketing use. Serious infections, including fatalities can occur during rituximab therapy, and rituximab is contraindicated in people with an active, severe infection (for example, tuberculosis, sepsis and opportunistic infections), and in people who are severely immunocompromised. Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in people receiving rituximab. Hepatitis B virus screening should be performed in all people before starting treatment with rituximab and people with active hepatitis B infection should not be treated with the drug. Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after use of rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition. See the [SPC for rituximab](#) for full details of warnings, contraindications and adverse events.
- Most of the evidence for using rituximab in adults with immune thrombocytopenic purpura comes from observational studies, with no comparator arm. The populations in the included studies varied, as did the platelet count considered to represent an overall response or complete response. The RCTs discussed in this evidence summary included relatively small numbers of people and had other limitations. All of these factors make it difficult to draw firm conclusions from the evidence.
- The evidence for efficacy of rituximab in children and young people is weaker, drawn from 17 case series and 1 cohort study; none of the studies included UK populations. The observational nature of the studies and lack of comparator arm make it difficult to draw any conclusions about using rituximab to treat immune thrombocytopenic purpura in children and young people.
- Further evidence is needed to determine the efficacy and safety of rituximab for treating immune thrombocytopenic purpura, particularly in children and young people.

[Full text of Evidence review.](#)

Context and estimated impact for the NHS

Most of the studies in this evidence summary used rituximab at a dosage of 375 mg/m² body surface area weekly for 4 weeks. As an approximate guide, the cost for a 4-week course based on an adult with a body surface area of 1.86 m² is estimated to be £4889.60 (assuming wastage and excluding VAT; [MIMS](#), September 2014). The cost for a 4-week course based on a child with a body surface area of 0.89 m² is estimated to be £2794 (assuming wastage and excluding VAT; [MIMS](#) September 2014).

Two studies in adults in the systematic review by [Auger et al. \(2012\)](#), and 3 studies in children and young people in the systematic review by [Liang et al. \(2012\)](#) investigated using a lower fixed dose of rituximab of 100 mg weekly for 4 weeks. The cost for a 4-week course using this lower fixed dose is £698.50 (excluding VAT; [MIMS](#) September 2014).

Comparing the cost of rituximab with other second-line drug treatments is difficult because rituximab is usually given as only 1 course of treatment and is intended to induce long-term remission. Other second-line drug treatments usually need to be given continuously. Specialist opinion suggests that further treatment with rituximab may be given to people whose immune thrombocytopenic purpura initially responds to treatment with rituximab, but then relapses. Rescue treatment may also be needed in people whose condition relapses after receiving rituximab. Both of these factors may increase the costs associated with using rituximab for treating immune thrombocytopenic purpura.

The only other treatment for immune thrombocytopenic purpura that is a one-off treatment aimed at inducing long-term remission is splenectomy. By comparison, the cost to commissioners of an elective splenectomy is estimated to be in the range of £3252 to £4548, depending on the complexity of the procedure.

[Full text of Context and estimated impact for the NHS.](#)

Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with immune thrombocytopenic purpura who are thinking about trying rituximab.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

Immune (idiopathic) thrombocytopenic purpura is an autoimmune condition characterised by increased platelet destruction and, in many cases, inadequate platelet production. The condition can result in low platelet counts and bleeding. In a blood test, a normal platelet count is between 150 and 400×10^9 per litre. Bleeding does not usually occur until the platelet count is below 30×10^9 per litre ([Eltrombopag for treating chronic immune \[idiopathic\] thrombocytopenic purpura \[review of technology appraisal 205\]](#); [NICE technology appraisal guidance 293: final scope](#)).

Immune thrombocytopenic purpura can be classified according to duration of the condition as newly diagnosed, persistent (lasting between 3 and 12 months) and chronic (lasting 12 months or more). In adults, the condition typically has a gradual onset with no preceding viral or other illness, and it is usually chronic. In children, the condition is normally short-lived and around two-thirds of children recover spontaneously within 6 months ([International consensus report on the investigation and management of primary immune thrombocytopenia \[2010\]](#)).

The UK incidence of adult immune thrombocytopenic purpura is estimated to be around 120 per year and 3000–3500 people are affected at any one time in England and Wales. In children, it is estimated that around 4 in every 100,000 develop immune thrombocytopenic

purpura each year. People with the condition maybe asymptomatic or have symptoms including spontaneous bruising, mucosal bleeding and, in severe cases, gastrointestinal or intracranial bleeding. Diagnosis is based on excluding other possible causes of thrombocytopenia ([Eltrombopag for treating chronic immune \[idiopathic\] thrombocytopenic purpura \[review of technology appraisal 205\]](#); NICE technology appraisal guidance 293: final scope and [The ITP Support Association: What is childhood ITP?](#)).

An international working group report ([Rodeghiero et al. 2009](#)) states that the major goal of treatment for immune thrombocytopenic purpura is providing a safe platelet count that prevents major bleeding, rather than trying to correct the platelet count to normal levels. The report suggests that suitable primary end points in studies in immune thrombocytopenic purpura should include complete response (defined as a platelet count of at least 100×10^9 per litre and the absence of bleeding) and response (defined as a platelet count of at least 30×10^9 per litre and double that of baseline, and the absence of bleeding). Secondary outcomes suggested in the report include adverse events, need for rescue treatments, rates of splenectomy, bleeding scales, and health-related quality of life assessment.

An [international consensus report on the investigation and management of primary immune thrombocytopenia](#) states that treatment is rarely needed for adults with platelet counts of greater than 50×10^9 per litre in the absence of bleeding, trauma, surgery, certain comorbidities, anticoagulant therapy, or a lifestyle or profession that puts a person at risk for bleeding. For adults that need treatment, first-line options include corticosteroids, intravenous immunoglobulin and intravenous anti-D immunoglobulin (although specialist opinion suggests this is rarely used in the UK). Second-line options include azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate, rituximab, vinca alkaloids, and splenectomy. Not all of these drug treatments are licensed for treating immune thrombocytopenic purpura in adults and most of the evidence for using these agents is from non-randomised or descriptive studies.

Newer therapies for immune thrombocytopenic purpura include the thrombopoietin receptor agonists eltrombopag and romiplostim. The NICE technology appraisal on [eltrombopag for treating chronic immune \(idiopathic\) thrombocytopenic purpura](#) recommends eltrombopag as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, 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 provides eltrombopag with the discount agreed in the patient access scheme.

Similarly, the NICE technology appraisal on romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura recommends romiplostim as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, 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 available with the discount agreed in the patient access scheme.

The international consensus report on the investigation and management of primary immune thrombocytopenia states that it is necessary to treat all children with severe bleeding symptoms, and treatment should be considered in children with moderate bleeding or those at an increased risk of bleeding. First-line options include corticosteroids, intravenous immunoglobulin and intravenous anti-D immunoglobulin (although specialist opinion suggests this is rarely used in the UK). Second-line treatments include corticosteroids, rituximab, immunosuppressants, cytotoxic drugs and splenectomy, and are usually considered by specialist paediatricians on a case by case basis.

Rituximab is available as a solution for intravenous infusion, and as a subcutaneous injection. Studies included in this evidence review used the intravenous formulation of rituximab, and so the evidence summary focuses on the intravenous formulation only.

Product overview

Drug action

Rituximab ([MabThera](#), Roche Products Limited) is a monoclonal antibody that targets the CD20 surface antigen, which is expressed on normal and malignant B cells. Rituximab binds to the CD20 surface antigen on B cells mediating cell lysis, and inducing cell death by apoptosis ([summary of product characteristics for rituximab \[MabThera\]](#)).

The effect of rituximab in immune thrombocytopenic purpura is thought to be related to B-cell depletion leading to inhibition of B-cell activities such as production of platelet autoantibodies. Rituximab has also been shown to up-regulate regulatory T cells ([Auger et al. 2012](#)).

Regulatory status

Rituximab concentrate for solution for intravenous infusion ([MabThera](#), Roche Products Limited) is licensed in adults for treating non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. It is administered as an intravenous infusion which can take several hours, depending on the dose and rate of infusion.

Rituximab is not licensed for treating immune thrombocytopenic purpura and so use for this indication is off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using rituximab outside its authorised indications.

Cost

Rituximab 10 mg/ml concentrate for solution for intravenous infusion ([MabThera](#), Roche Products Limited) costs (excluding VAT; [MIMS](#) September 2014):

- 2×10 ml=£349.25
- 1×50 ml=£873.15

Evidence review

Clinical effectiveness

This summary discusses the best available evidence for using rituximab for treating immune thrombocytopenic purpura in children, young people and adults.

The evidence that is reported in this summary for adults includes a systematic review and meta-analysis ([Auger et al. 2012](#)), 2 [randomised controlled trials](#) (RCTs; [Arnold et al. 2012](#) and [Gudbrandsdottir et al. 2013](#)) that have been published since the systematic review, and a retrospective cohort study ([Moulis et al. 2013](#)) comparing rituximab with splenectomy.

Also included in the evidence summary is a systematic review ([Liang et al. 2012](#)) of studies in children and young people.

Immune thrombocytopenic purpura in adults

A systematic review and meta-analysis investigated using rituximab before splenectomy in adults with primary immune thrombocytopenic purpura ([Auger et al. 2012](#)).

The review included 19 studies (n=368) in adults who had immune thrombocytopenic purpura and were receiving rituximab before splenectomy. Only 4 of the included studies were randomised. The remaining studies were prospective and retrospective observational studies with no comparator arm. Consequently no comparisons of rituximab with other treatments were made in the review.

Participants in the included studies differed in the duration of their immune thrombocytopenic purpura, their age, sex and previous treatments they had received.

Most studies used rituximab at a dosage of 375 mg/m² body surface area weekly for 4 weeks, 1 study used dose escalation from 35 to 375 mg/m², and 3 studies used different schedules (1–4 cycles). Two studies used a lower fixed dose of 100 mg weekly for 4 weeks.

Overall response rate and complete response rate after treatment with rituximab were reported in the primary assessment. Overall response was defined as a platelet count of greater than 50×10⁹ per litre. The definition of complete response varied in the included

studies and was considered as either a platelet count of greater than 100×10^9 per litre, or greater than 150×10^9 per litre. Overall response and complete response at 1 year, response time, mean platelet count at response, and duration of response were also reported. Median follow-up was 9 months (range 2.3 to 65 months).

Pooled overall response rate was 57% (n=368, 95% confidence interval [CI] 48 to 65%) after rituximab treatment (time point 'after' not further defined), and 57% (n=157, 95% CI 35 to 76%) at 1 year after rituximab treatment. However there was a large variation in the reported overall response rates in the individual studies (16–100% after rituximab, and 33–85% at 1 year after rituximab treatment). Heterogeneity was moderate or high in all analyses, except for the analysis including only studies that provided individual data, which had no heterogeneity.

Pooled complete response rate was 41.5% (n=346, 95% CI 33 to 50%) after rituximab treatment (time point 'after' not further defined), and 40% (n=108, 95% CI 31 to 49%) at 1 year after rituximab treatment. However, there was a large variation in the reported complete response rates in the individual studies (0–86% after rituximab, and 0–48.4% at 1 year after rituximab treatment). Again, heterogeneity was moderate or high in all analyses, except for the analysis including only studies that provided individual data, which had no heterogeneity.

Mean time to response was 6.34 weeks (n=36, 95% CI 2.83 to 9.85 weeks). The mean platelet count increased to 200×10^9 per litre (n=54, 95% CI 129 to 271×10^9 per litre), and the median duration of response was 49 weeks (n=36, 95% CI 17 to 60 weeks).

Arnold et al. (2012) reported a pilot double-blind, placebo-controlled randomised trial of adjuvant rituximab or placebo in 60 adults (median age 40 years) with newly diagnosed or relapsed primary immune thrombocytopenic purpura who had not received a splenectomy, and who had a platelet count of less than 30×10^9 per litre (median baseline platelet count 15×10^9 per litre).

Participants were randomised in a 1:1 ratio to intravenous rituximab 375 mg/m^2 body surface area (n=33) or saline placebo (n=27) once weekly, for 4 weeks. Allocation was concealed. Participants also received standard treatment for up to 8 weeks with 1 or more of: corticosteroids; intravenous immunoglobulin; intravenous anti-D immunoglobulin; romiplostim; or platelet transfusions. One participant in each group withdrew consent after randomisation, before receiving any study treatment.

The primary outcome was treatment failure, defined as the composite of any of: platelet count below 50×10^9 per litre; significant bleeding or administration of rescue treatment because of severe thrombocytopenia; bleeding; or a planned invasive procedure. Significant bleeding was defined as bleeding of grade 2 severity (based on assessment of bleeding symptoms in [Page et al. \(2007\)](#), where grade 0=no bleeding, grade 1=mild bleeding, and grade 2=marked bleeding) from any site that occurred since the last study visit. Secondary outcomes included quality of life, complete response rate (defined as a platelet count of at least 100×10^9 per litre) and overall response rate (defined as a platelet count of at least 30×10^9 per litre with doubling from baseline) and without rescue treatment at 6 months.

For the primary composite outcome of treatment failure, there was no statistically significant difference between the rituximab and placebo groups (65.6% of people in the rituximab group compared with 80.8% people in the placebo group; relative risk [RR] 0.81, 95% CI 0.59 to 1.11). At 6 months, there was no statistically significant difference between the groups for complete response rate (53.1% in the rituximab group and 46.2% in the placebo group; RR 1.15, 95% CI 0.68 to 1.95) and overall response rate (62.5% in the rituximab group and 73.1% in the placebo group; RR 0.86, 95% CI 0.60 to 1.22). No statistically significant treatment effect for change in quality of life summary scores was found ($p=0.45$ for physical domains; $p=0.32$ for mental domains).

[Gudbrandsdottir et al. \(2013\)](#) reported an open-label RCT of rituximab plus dexamethasone, compared with dexamethasone alone, in 137 adults (median age 51 years in the rituximab plus dexamethasone group, and 58 years in the dexamethasone alone group) with newly diagnosed primary immune thrombocytopenic purpura who had not received a splenectomy, and who had a platelet count of 25×10^9 per litre or less, or 50×10^9 per litre or less and concomitant bleeding symptoms.

Participants were randomised 1:1 to a combination of rituximab 375 mg/m^2 body surface area once weekly for 4 weeks plus dexamethasone 40 mg daily for 4 days ($n=63$) or to the same dosage of dexamethasone alone ($n=74$). A protocol amendment allowed 'non-responders' in both arms to repeat dexamethasone treatment every 1 to 4 weeks for a total of 6 cycles. The method of randomisation was not described in enough detail to determine if allocation was concealed.

The primary outcome was sustained partial (defined as a platelet count of at least 50×10^9 per litre) or complete (defined as a platelet count of at least 100×10^9 per litre) response at 6 months' follow-up. Secondary outcomes included time to relapse, time to

rescue treatment, and rates of splenectomy.

In an intention-to-treat analysis (total number of participants not reported; included participants that had died or withdrawn from the study because of adverse events), the proportion of people whose condition achieved a sustained partial or complete response at 6 months' follow-up (the primary outcome) was 57% in the rituximab plus dexamethasone group, compared with 35% in the dexamethasone monotherapy group ($p=0.01$).

At 12 months' follow-up, sustained partial or complete response was achieved in 53% of people in the rituximab plus dexamethasone group, compared with 33% of people in the dexamethasone monotherapy group ($p<0.05$). There was a statistically significantly longer time to rescue treatment in the rituximab plus dexamethasone group compared with the dexamethasone monotherapy group ($p=0.007$). In people who had initially achieved a partial or complete response, median time-to-rescue treatment was 7.4 months in the dexamethasone monotherapy group, and was not reached in the rituximab plus dexamethasone group after 48 months of follow-up. There was no difference between the groups in number of people who had a splenectomy (6/62 [10%] people in the rituximab plus dexamethasone group compared with 5/71 [7%] in the dexamethasone monotherapy group, $p=0.8$).

A retrospective cohort study ([Moulis et al. 2013](#)) compared rituximab 375 mg/m² body surface area weekly for 4 weeks with splenectomy for treating primary immune thrombocytopenic purpura in 105 adults. Rituximab was mainly used to treat persistent immune thrombocytopenic purpura (lasting from 3 to 12 months), whereas splenectomy was mainly used to treat chronic immune thrombocytopenic purpura (lasting more than 12 months). People treated with rituximab were older and had more comorbidities than people treated with splenectomy. The primary outcome was a composite of death from bleeding or infection, and hospitalisation for bleeding or infection. Secondary outcomes included overall mortality, mortality from bleeding, hospitalisation for bleeding, hospitalisation for infection, response and complete response rate at 3 and 12 months, loss of response and loss of complete response. Mean follow-up was 8.4±4.7 years in the splenectomy group and 3.0±1.9 years in the rituximab group.

The primary composite outcome occurred in 14/43 (32.6%) people in the rituximab group, and 11/62 (17.7%) people in the splenectomy group. After adjusting for propensity score, there was no difference between the groups for the primary outcome ($p=0.7$), overall mortality, or hospitalisation for bleeding (p values not reported).

Response rate (defined as a platelet count of at least 30×10^9 per litre and the absence of bleeding and absence of other treatments for immune thrombocytopenic purpura) was statistically significantly greater in the splenectomy group than in the rituximab group at 3 months (91.4% compared with 69.8% respectively, $p=0.005$) and 12 months (87.9% compared with 59.0% respectively, $p=0.001$). Complete response rate (defined as a platelet count of at least 100×10^9 per litre and the absence of bleeding and absence of other treatments for immune thrombocytopenic purpura) was also statistically significantly greater in the splenectomy group than in the rituximab group at 3 months (82.8% compared with 39.5% respectively, $p<0.0001$) and 12 months (81.0% compared with 35.9% respectively, $p<0.0001$). Maintenance of response and complete response was statistically significantly higher in the splenectomy group compared with the rituximab group (adjusted $p<0.0001$ for both comparisons).

Immune thrombocytopenic purpura in children and young people

A systematic review investigated using rituximab to treat immune thrombocytopenic purpura in children and young people ([Liang et al. 2012](#)).

The review included 18 studies ($n=352$) that contributed to efficacy analyses. A total of 17 of the studies were case series, and 1 was an observational cohort study. Five of the included studies were published in abstract form only. The studies included participants with an age range of 0.5 to 19 years, and a duration of immune thrombocytopenic purpura for between 0.2 to 175 months. Participants had platelet counts ranging from 1 to 75×10^9 per litre before rituximab therapy, and included children and young people who had received a splenectomy. A total of 304/352 (86.4%) participants had primary immune thrombocytopenic purpura. Results were reported separately for participants with primary and secondary immune thrombocytopenic purpura.

Most participants (84.5%) received intravenous rituximab at a dosage of 375 mg/m^2 body surface area weekly for 1–6 doses (14 studies). The remaining participants received dosages of 100 mg weekly for 4 weeks (2 studies), 500 mg/m^2 body surface area every 2 weeks for 2 doses (1 study), or 1 dose of 375 mg/m^2 body surface area for 4 doses or 100 mg per dose for 4 doses (1 study).

Outcomes included response (defined as a platelet count of at least 30×10^9 per litre and at least double that of baseline) and complete response (defined as a platelet count of at least 100×10^9 per litre).

In children and young people with primary immune thrombocytopenic purpura, when the results from 14 studies (n=312) were pooled, response to rituximab was achieved in 68% of participants (95% CI 58% to 77%). Complete response (14 studies, n=243) was achieved in 39% of participants (95% CI 30% to 49%). There was statistically significant heterogeneity between the included studies for these outcomes ($p < 0.001$ for response, and $p = 0.005$ for complete response) and there was a large variation in the reported response and complete response rates in the individual studies (33%–100% for response rate and 14%–67% for complete response rate).

Safety and tolerability

In the RCT reported by [Arnold et al. \(2012\)](#), 2 serious adverse events (serum sickness and accidental fall) were reported in the rituximab group, and 1 serious adverse event (adrenal haemorrhage) was reported in the placebo group. Infusion reactions were more common with rituximab than with placebo (20 reactions reported in the rituximab group, compared with 10 in the placebo group).

In the RCT reported by [Gudbrandsdottir et al. \(2013\)](#), the most common adverse events reported in either group were fatigue, dizziness, headache, epigastritis and anxiety. Muscle or joint pain, and fever were statistically significantly more common in the rituximab plus dexamethasone group, whereas anxiety was more common in the dexamethasone monotherapy group (all comparisons $p < 0.05$). There were statistically significantly more serious adverse events in the rituximab plus dexamethasone group, compared with the dexamethasone monotherapy group (16 events [including 1 death], compared with 9 events [including 3 deaths] respectively, $p = 0.04$). One person in the rituximab plus dexamethasone group and 2 people in the dexamethasone monotherapy group withdrew from the study because of adverse events.

In the retrospective cohort study reported by [Moulis et al. \(2013\)](#), 7 people in the rituximab group were hospitalised for infection (5 people with pneumonia, 1 with staphylococcus septicaemia, and 1 with hepatitis E virus infection), compared with 6 people in the splenectomy group (2 with septicaemia and 4 with enterobacteria infections). The authors report that there was no significant difference between the groups in hospitalisations for infection; however no statistical analysis was reported.

In the systematic review reported by [Liang et al. \(2012\)](#) a total of 108 adverse events were reported in 91 children and young people in 23 studies. Most (84.3%) of these adverse events were reported as mild to moderate, with the most frequently reported reactions

being mild allergic reactions including pruritus, urticaria, chills and fever. The more serious adverse events reported included serum sickness (7 participants); immediate hypersensitivity reaction during rituximab infusion which required stopping treatment (2 participants); infections including varicella (2 participants), pneumonia (1 participant) and life-threatening enteroviral meningoencephalitis (1 participant); common variable immunodeficiency (1 participant); and headache with white matter changes on brain magnetic resonance imaging (1 participant).

The [summary of product characteristics \(SPC\) for rituximab](#) (MabThera, Roche Products Limited) lists contraindications and adverse events separately for each licensed indication (see the SPC for more information).

The [SPC for rituximab](#) describes that infusion-related reactions are very common in people treated with intravenous rituximab, reported in 12% to more than 50% of participants in clinical trials across rituximab's licensed indications. Severe infusion-related reactions with a fatal outcome have been reported in post-marketing use. Premedication with an anti-pyretic and an antihistamine (for example, paracetamol and diphenhydramine) should always be given before administration of intravenous rituximab. In addition, premedication with a glucocorticoid should be given (except in people with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia who are receiving rituximab in combination with glucocorticoid-containing chemotherapy).

Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after use of rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition ([SPC for rituximab](#)).

Serious infections, including fatalities can occur during rituximab therapy, and rituximab is contraindicated in people with an active, severe infection (for example, tuberculosis, sepsis and opportunistic infections), and in people who are severely immunocompromised. In addition, cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in people receiving rituximab. Hepatitis B virus screening should be performed in all people before starting treatment with rituximab and people with active hepatitis B infection should not be treated with the drug ([SPC for rituximab](#)).

Severe skin infections, such as toxic epidermal necrolysis and Stevens–Johnson syndrome (some with fatal outcome), have been reported in people receiving rituximab. Treatment with rituximab should be stopped if such an event occurs ([SPC for rituximab](#)).

All people treated with rituximab for rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis must be given the patient alert card with each infusion. The alert card contains important safety information for patients about potential increased risk of infections, including progressive multifocal leukoencephalopathy ([SPC for rituximab](#)).

See the [SPC for rituximab](#) for full details of warnings, contraindications and adverse events.

Evidence strengths and limitations

Most of the evidence for using rituximab in adults with immune thrombocytopenic purpura comes from observational studies, with no comparator arm. The populations in the included studies varied, as did the platelet count considered to represent an overall response or complete response, and the place of rituximab in the treatment pathway. The RCTs discussed in this evidence summary were in relatively small numbers of people and had other limitations such as being open-label, or participants being able to guess treatment allocation. All of these factors make it difficult to draw firm conclusions from the evidence.

Results of the studies that are included in this evidence summary varied. [Arnold et al. \(2012\)](#) found no statistically significant difference between rituximab and placebo for the composite outcome of treatment failure. In addition, no statistically significant difference between the rituximab and placebo groups was found for overall and complete response rates at 6 months, and no treatment effect on quality of life was found. The study was limited because it was planned as a double-blind study but many participants were able to correctly guess treatment allocation (70%; 95% CI 57% to 83%). This could have affected patient-reported outcomes such as quality of life. In addition, the study was limited by a small sample size (which may have been insufficient to detect differences in efficacy between the groups) and a relatively short evaluation period.

The RCT by [Gudbrandsdottir et al. \(2013\)](#) did find a statistically significant benefit for rituximab plus dexamethasone compared with dexamethasone alone in terms of sustained partial or complete response at 6 months' follow-up. This study again was relatively small (n=137), and was open-label which could have affected the reliability of the results. In addition, corticosteroids are often used first-line, whereas rituximab is usually a second-line treatment; therefore comparing rituximab plus corticosteroids with corticosteroid monotherapy may not be appropriate. The corticosteroid used in the study was dexamethasone. Specialist opinion suggests that prednisolone is the most widely used

corticosteroid for treating immune thrombocytopenic purpura in the UK. Therefore the relevance of these findings to UK practice is unclear.

The study reported by [Moulis et al. \(2013\)](#) compared rituximab with splenectomy and found that there was no difference between the groups for the composite primary outcome (death from bleeding or infection and hospitalisation for bleeding or infection). However, response rate and complete response rate at 3 months and 12 months were statistically significantly greater in the splenectomy group compared with the rituximab group. The study was limited by its observational nature and retrospective design, as it may have been subject to selection bias. In addition, rituximab was mainly used to treat persistent immune thrombocytopenic purpura (lasting from 3 to 12 months), whereas splenectomy was mainly used to treat chronic immune thrombocytopenic purpura (lasting more than 12 months). People treated with rituximab were older and had more comorbidities than people treated with splenectomy. These differences between people treated with rituximab and those treated with splenectomy could have affected the comparability of the two groups. The study was completed in a single centre and so may not be representative of people with immune thrombocytopenic purpura being treated outside of this centre.

The systematic review and meta-analysis in adults with immune thrombocytopenic purpura by [Auger et al. \(2012\)](#) was limited because it did not compare rituximab with placebo or active treatments, therefore no conclusions about the effect of rituximab compared with other treatments could be made. Although the review pooled results for overall response rate and complete response rate, there was a large variation in the reported response rates in the individual studies ranging from 0 to 100%. This, in addition to the moderate to high heterogeneity noted in the analyses, could have affected the results.

The evidence for efficacy of rituximab in children and young people is weaker. The systematic review by [Liang et al. \(2012\)](#) in children and young people with immune thrombocytopenic purpura was drawn from case series and 1 cohort study. Five of the included studies were only published in abstract form. There was statistically significant heterogeneity between the included studies and none of the studies included UK populations. In addition, the studies included participants who had received a splenectomy. The observational nature of the included studies, lack of comparator arm, and significant heterogeneity between the included studies make it difficult to draw any conclusions about using rituximab to treat immune thrombocytopenic purpura in children and young people.

Most of the studies included in this evidence summary were poorly reported. Further evidence is needed to determine the efficacy and safety of rituximab for treating immune thrombocytopenic purpura, particularly in children and young people.

Context and estimated impact for the NHS

Cost effectiveness

Most of the studies in this evidence summary used rituximab at a dosage of 375 mg/m² body surface area weekly for 4 weeks. Costs would vary depending on the height and weight of a person. As an approximate guide, the cost for a 4-week course based on an adult with a body surface area of 1.86 m² is estimated to be £4889.60 (assuming wastage and excluding VAT; [MIMS](#) September 2014). The cost for a 4-week course based on a child with a body surface area of 0.89 m² is estimated to be £2794.00 (assuming wastage and excluding VAT; [MIMS](#) September 2014).

Two studies in adults in the systematic review by [Auger et al. \(2012\)](#), and 3 studies in children and young people in the systematic review by [Liang et al. \(2012\)](#), investigated using a lower fixed dose of rituximab of 100 mg weekly for 4 weeks. The cost for a 4-week course using this lower fixed dose is £698.50 (excluding VAT; [MIMS](#) September 2014).

Comparing the cost of rituximab to other second-line drug treatments is difficult because rituximab is usually given as only 1 course of treatment and is intended to induce long-term remission. Other second-line drug treatments usually need to be given continuously. Specialist opinion suggests that further treatment with rituximab may be given to people whose immune thrombocytopenic purpura initially responds to treatment with rituximab but then relapses. Rescue treatment may also be needed in people whose condition relapses after receiving rituximab. Both of these factors should be borne in mind as they may increase the costs associated with using rituximab for treating immune thrombocytopenic purpura.

The only other treatment that is a one-off treatment aimed at inducing long-term remission is splenectomy. By comparison, the cost to commissioners of an elective splenectomy is estimated to be in the range of £3252 to £4548 depending on the complexity of the procedure.

Current drug usage

Estimating current drug usage of rituximab for treating immune thrombocytopenic purpura is difficult because rituximab is used to treat various conditions. No information on prescribing rituximab for immune thrombocytopenic purpura was available at the time this evidence summary was prepared.

Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with immune thrombocytopenic purpura who are thinking about trying rituximab.

Relevance to NICE guidance programmes

This use of rituximab for immune thrombocytopenic purpura is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued the following technology appraisals relating to immune thrombocytopenic purpura:

- [Eltrombopag for treating chronic immune \(idiopathic\) thrombocytopenic purpura \(review of technology appraisal 205\)](#) (NICE technology appraisal guidance 293)
- [Romiplostim for the treatment of chronic immune \(idiopathic\) thrombocytopenic purpura](#) (NICE technology appraisal guidance 221).

NICE has published several technology appraisals relating to licensed indications for the intravenous formulation of rituximab. NICE has also issued several pieces of guidance including recommendations on the use of the intravenous formulation of rituximab.

References

Arnold DM, Heddle NM, Carruthers J et al. (2012) [A pilot randomized trial of adjuvant rituximab or placebo for nonsplenectomized patients with immune thrombocytopenia](#). Blood 119: 1356–62. doi 10.1182/blood-2011-08-374777

Auger S, Duny Y, Rossi JF et al. (2012) [Rituximab before splenectomy in adults with primary idiopathic thrombocytopenic purpura: a meta-analysis](#). *British Journal of Haematology* 158: 386–98. doi: 10.1111/j.1365-2141.2012.09169.x

Gudbrandsdottir S, Birgens HS, Fredericksen H et al. (2013) [Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia](#). *Blood* 121: 1976–81. doi: 10.1182/blood-2012-09-455691

Liang Y, Zhang L, Gao J et al. (2012) [Rituximab for children with immune thrombocytopenia: a systematic review](#). *PLoS ONE* 7: doi: 10.1371/journal.pone.0036698

Moulis G, Sailler L, Sommet A et al. (2013) [Rituximab versus splenectomy in persistent or chronic adult primary immune thrombocytopenia: an adjusted comparison of mortality and morbidity](#). *American Journal of Haematology* 89: 41–6. doi: 10.1002/ajh.23580

National Institute for Health and Care Excellence (2013) [Eltrombopag for treating chronic immune \(idiopathic\) thrombocytopenic purpura \(review of technology appraisal 205\)](#). NICE technology appraisal guidance 293

National Institute for Health and Clinical Excellence (2012) [Eltrombopag for the treatment of chronic immune \(idiopathic\) thrombocytopenic purpura \(review of technology appraisal 221\) final scope](#)

National Institute for Health and Clinical Excellence (2011) [Romiplostim for the treatment of chronic immune \(idiopathic\) thrombocytopenic purpura](#). NICE technology appraisal guidance 221

Page L, Psaila B, Provan D et al. (2007) [The immune thrombocytopenic purpura \(ITP\) bleeding score: assessment of bleeding in patients with ITP](#). *British Journal of Haematology* 138: 245–8. doi 10.1111/j.1365-2141.2007.06635.x

Provan D, Stasi R, Newland AC et al. (2010) [International consensus report on the investigation and management of primary immune thrombocytopenia](#). *Blood* 115: 168–86. doi: 10.1182/blood-2009-06-225565

Roche Products Limited (2014) [MabThera 100mg and 500mg concentrate for solution for infusion summary of product characteristics \[online; accessed 20 August 2014\]](#)

Rodeghiero F, Stasi R, Gernsheimer T et al. (2009) Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 113: 2386–93. doi: 10.1182/blood-2008-07-162503

Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

Expert advisers

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Declarations of interest

Dr Lester has received honoraria for speaking at educational meetings supported by pharmaceutical companies that market thrombopoietin receptor agonists.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

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