NICE advice

Autoimmune haemolytic anaemia: rituximab

Evidence summary
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www.nice.org.uk/guidance/esuom39

Key points from the evidence

The content of this evidence summary was up-to-date in February 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Limited high-quality evidence was identified that investigated how well rituximab works for treating autoimmune haemolytic anaemia. One randomised controlled trial suggested that after 12 months, prednisolone plus rituximab was more effective than prednisolone monotherapy for inducing a complete response to treatment in adults with newly diagnosed and previously untreated warm autoimmune haemolytic anaemia. Other uncontrolled studies suggested some effectiveness of rituximab in warm and cold autoimmune haemolytic anaemia, but limitations of these studies make it difficult to draw any firm conclusions.

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

Effectiveness	Safety
• A randomised controlled trial (RCT) in 64 adults with newly diagnosed and previously untreated warm autoimmune haemolytic anaemia suggested that after 12 months, prednisolone plus rituximab was statistically significantly more effective than prednisolone monotherapy for inducing a complete response to treatment (complete response rate 75% compared with 36% respectively; p=0.003). • Uncontrolled studies in people with warm autoimmune haemolytic anaemia (4 studies; n=101 in total) reported complete response rates ranging from 27% to 67%. • Uncontrolled studies in people with cold haemagglutinin disease (5 studies; n=142 in total) reported complete response rates ranging from 4% to 54%. • The non-randomised nature of the uncontrolled studies, differing populations, and lack of standard definitions for response to treatment make it difficult to draw any firm conclusions from this evidence.	• The summary of product characteristics (SPC) for rituximab describes that infusion-related reactions are very common (more than 1 in 10) 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 using rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition. • In the RCT, the most commonly reported adverse events in people in the prednisolone monotherapy and prednisolone plus rituximab groups were dyspnoea (16.7% compared with 13.3% respectively), fatigue (13.3% in both groups), headache (13.3% compared with 6.7% respectively), dyspepsia (13.3% compared with 3.3% respectively) and insomnia (10% in both groups).

Patient factors	Resource implications
• Rituximab is administered as an intravenous infusion over several hours, or subcutaneously. • All the studies in this evidence summary used intravenous rituximab.	• Most studies in this evidence summary used intravenous rituximab at a dosage of 375 mg/m^2 body surface area weekly for 4 weeks: — The cost for a 4-week course based on an adult with a body surface area of 1.86 m^2 is estimated to be £4889.60 (assuming wastage and excluding VAT; MIMS January 2015). — The cost for a 4-week course based on a child with a body surface area of 0.89 m^2 is estimated to be £2794 (assuming wastage and excluding VAT; MIMS January 2015). • One study 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 January 2015).

Introduction and current guidance

Autoimmune haemolytic anaemia is a relatively rare condition caused by autoantibodies directed against a person's own red blood cells. The condition has warm and cold antibody types. Warm antibody type can be idiopathic or secondary to other conditions such as systemic lupus erythematosus, lymphoma, chronic lymphocytic leukaemia or Evans syndrome. Cold antibody types include cold haemagglutinin disease and paroxysmal cold haemoglobinuria (Zanella and Barcellini 2014; and haemolytic anaemia; patient.co.uk).

There are currently (January 2015) no evidence based guidelines for treating autoimmune haemolytic anaemia. The British Committee for Standards in Haematology is in the process

of producing a guideline on autoimmune haemolytic anaemia (see guidelines in progress for more information).

For warm autoimmune haemolytic anaemia, first-line treatment is normally with corticosteroids which are effective in 70–85% of people. Splenectomy and off-label conventional immunosuppressive drugs have been traditionally used as second-line treatments, and recently rituximab has also been used as a second-line treatment option. If treatment is required in cold haemagglutinin disease, corticosteroids, splenectomy and conventional immunosuppressants are much less effective, and over the last 10–15 years, on the basis of limited published data, rituximab has become first-line treatment (Zanella and Barcellini 2014).

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.

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 autoimmune haemolytic anaemia and so use for this indication is off-label.

NICE has published an evidence summary on another off-label use of rituximab: Immune (idiopathic) thrombocytopenic purpura: rituximab (ESUOM 35).

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 January 2015):

- 2×10 ml=£349.25
- 1×50 ml=£873.15

Full text of product overview.

Evidence review

- Only 1 RCT was identified that investigated using rituximab for autoimmune haemolytic anaemia. This evidence summary therefore also includes the largest uncontrolled studies that provide the best available evidence for using rituximab for treating autoimmune haemolytic anaemia. A meta analysis (Reynaud et al. 2014) of the 1 RCT and 20 uncontrolled studies of rituximab in autoimmune haemolytic anaemia has recently been published. However, it has a number of limitations.
- Most studies used rituximab at a dosage of 375 mg/m^2 body surface area weekly, usually for 4 doses. One study used the same dose of rituximab but at an interval of every 28 days for 4 doses, and another study used a lower fixed dosage of 100 mg weekly for 4 weeks.
- The RCT by Birgens et al. 2013 compared prednisolone monotherapy with prednisolone plus rituximab therapy in 64 adults aged 18 years and over (median age 65–67 years) with newly diagnosed and previously untreated warm autoimmune haemolytic anaemia. At 3 and 6 months after treatment, there was no statistically significant difference in complete response (defined as normalised haemoglobin concentration without any ongoing immunosuppressive treatment) or any response (complete or partial [defined as normalised haemoglobin concentration but requiring ongoing treatment with less than 10 mg daily prednisolone]) between the prednisolone monotherapy and the prednisolone plus rituximab groups. After 12 months, participants reported only a complete response or persistent disease. The complete response rate was 36% (95% confidence interval [CI] 19 to 56%) in the prednisolone monotherapy group compared with 75% (95% CI 55 to 89%) in the prednisolone plus rituximab group. The difference between the groups was statistically significant (p=0.003). Relapse-free survival in people whose condition had shown any response to treatment (complete or partial) was statistically significantly lower in the prednisolone monotherapy group compared with the prednisolone plus rituximab group (hazard ratio [HR] 0.33, 95% CI 0.12 to 0.88, p=0.02).
- The uncontrolled studies in warm autoimmune haemolytic anaemia reported in this

evidence summary (Dierickx et al. 2009; Maung et al. 2013; Barcellini et al. 2013 and Zecca et al. 2003) included a total of 101 children, young people and adults. The overall response rate (complete and partial) to rituximab reported in these studies ranged from 71% to 94%. Complete response rate ranged from 27% to 67%.

- The results from the recently published meta-analysis (Reynaud et al. 2014) were that the overall response rate to rituximab in warm autoimmune haemolytic anaemia was (despite methodological limitations) in line with the larger individual studies at 79% (95% CI 60 to 90%; 11 studies, n=154). The complete response rate was 42% (95% CI 27 to 58%; 11 studies, n=154).

- The uncontrolled studies in cold antibody types of autoimmune haemolytic anaemia reported in this evidence summary (Berentsen et al. 2004; Berentsen et al. 2006; Berentsen et al. 2010; Schollkopf et al. 2006 and Barcellini et al. 2013) included a total of 142 adults. The overall response rate (complete and partial) to rituximab reported in these studies ranged from 45% to 85%. Complete response rate ranged from 4% to 54%.

- In the recently published meta-analysis (Reynaud et al. 2014), the overall response rate to rituximab in cold antibody types of autoimmune haemolytic anaemia was 57% (95% CI 47 to 66%; 6 studies, n=109). The complete response rate was 21% (95% CI 6 to 51%; 7 studies, n=118).

- The uncontrolled studies included small numbers of participants and did not compare rituximab with any other treatment for autoimmune haemolytic anaemia. The studies are difficult to compare because the populations differed and included participants with primary, secondary, newly diagnosed, and relapsed autoimmune haemolytic anaemia. Some studies included people taking concomitant treatment with corticosteroids and some included people with lymphoproliferative diseases. Most studies reported outcomes such as complete, partial and overall response rates to treatment. However, there was no standardised definitions of these and they varied in the individual studies.

- In the RCT by Birgens et al. (2013) there was no statistically significant difference between the prednisolone monotherapy and prednisolone plus rituximab groups in any adverse event in adults with warm autoimmune haemolytic anaemia. There were 8 non-fatal serious adverse events in 5 people in the prednisolone plus rituximab group: pneumonia (3 events), fever (2 events), urinary tract infection (2 events) and *Clostridium difficile* enteritis (1 event). In the prednisolone monotherapy group there were 4 non-fatal serious adverse events in 4 people: pneumonia (2 events), urinary

tract infection (1 event) and pulmonary embolism (1 event). There was 1 fatal serious adverse event (pneumonia) in the prednisolone plus rituximab group that was possibly treatment-related.

- In the uncontrolled studies in warm and cold autoimmune haemolytic anaemia that discussed safety, treatment with rituximab was generally reported as being well tolerated. Adverse events that were described included haematological toxicity and infections.

- The SPC for rituximab describes that infusion-related reactions are very common (more than 1 in 10) 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.

Full text of evidence review.

Context and estimated impact for the NHS

Comparing the cost of rituximab with other therapies for autoimmune haemolytic anaemia is difficult because there is a lack of evidence to confirm the optimal dose, guide the use of recurrent courses in refractory cases, and confirm the advice on other aspects of the clinical pathway such as combination with other treatments.

Most of the studies in this evidence summary used rituximab at a dosage of 375 mg/m^2 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 m^2 is estimated to be £4889.60 (assuming wastage and excluding VAT; MIMS January 2015). The cost for a 4-week course based on a child

with a body surface area of 0.89 m^2 is estimated to be £2794.00 (assuming wastage and excluding VAT; MIMS January 2015).

One study 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 January 2015).

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 autoimmune haemolytic anaemia 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

Autoimmune haemolytic anaemia is a relatively rare condition caused by autoantibodies directed against a person's own red blood cells. Diagnosis is usually based on the presence of blood markers indicating haemolysis, review of a blood smear with features

consistent with the diagnosis and evidence of anti-erythrocyte antibodies (autoantibodies), detectable by the direct antiglobulin test (Zanella and Barcellini 2014).

The condition is normally divided into warm and cold antibody types. Warm antibody type can be primary or secondary to other conditions such as systemic lupus erythematosus, lymphoma, chronic lymphocytic leukaemia or Evans syndrome. Cold antibody type is more often secondary to another condition, such as lymphoma. Cold antibody types include cold haemagglutinin disease and paroxysmal cold haemoglobinuria. In warm antibody type, autoantibodies react at 37ºC. In cold antibody type, autoantibodies react at lower temperatures of 20ºC or below (haemolytic anaemia; patient.co.uk).

There are currently (January 2015) no evidence based guidelines for treating autoimmune haemolytic anaemia. The British Committee for Standards in Haematology is in the process of producing a guideline on autoimmune haemolytic anaemia (see guidelines in progress for more information).

For warm autoimmune haemolytic anaemia, first-line treatment is normally with corticosteroids which are effective in 70–85% of people. Splenectomy and off-label conventional immunosuppressive drugs have been traditionally used as second-line treatments, and recently rituximab has also been used as a second-line treatment option. If treatment is required in cold haemagglutinin disease, corticosteroids, splenectomy and conventional immunosuppressants are much less effective, and over the last 10–15 years, on the basis of limited published data, rituximab has become first-line treatment (Zanella and Barcellini 2014).

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 [SPC] for rituximab [MabThera]).

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 autoimmune haemolytic anaemia and so use for this indication is off-label.

NICE has published an evidence summary on another off-label use of rituximab: Immune (idiopathic) thrombocytopenic purpura: rituximab (ESUOM 35).

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 January 2015):

- 2×10 ml=£349.25
- 1×50 ml=£873.15

Evidence review

Only 1 randomised controlled trial (RCT) was identified that investigated using rituximab for autoimmune haemolytic anaemia. This evidence summary therefore also includes the largest uncontrolled studies that provide the best available evidence for using rituximab for treating autoimmune haemolytic anaemia. A meta-analysis (Reynaud et al. 2014) of the 1 RCT and 20 uncontrolled studies of rituximab in autoimmune haemolytic anaemia has recently been published. However, it has a number of limitations. Most studies used rituximab at a dosage of 375 mg/m^2 body surface area weekly, usually for 4 doses. One study used the same dose of rituximab but at an interval of every 28 days for 4 doses, and another study used a lower fixed dosage of 100 mg weekly for 4 weeks.

Clinical effectiveness

Warm autoimmune haemolytic anaemia

A Danish multicentre, phase 3, open-label RCT (Birgens et al. 2013) compared corticosteroid monotherapy with corticosteroid plus rituximab therapy in 64 adults aged 18 years and over (median age 65 to 67 years) with newly diagnosed and previously untreated warm autoimmune haemolytic anaemia. The RCT included people with primary autoimmune haemolytic anaemia, as well as those who had concomitant autoimmune disease, or low-grade B-cell lymphoproliferative neoplasia. People with autoimmune haemolytic anaemia that was drug induced, or secondary to autoimmune disease in the previous 6 months; and people with other serious diseases such as malignancy were excluded.

Participants were randomised 1:1 to prednisolone 1.5 mg/kg daily for 2 weeks, gradually reduced over the next 6–10 weeks to the lowest dose that maintained a normal haemoglobin level (n=32); or to the same dosage and schedule of prednisolone plus rituximab 375 mg/m^2 body surface area as an intravenous infusion once weekly for 4 weeks (n=32). All participants received folic acid 5 mg daily, and those in the rituximab group also received premedication with paracetamol and clemastine 30–60 minutes before their rituximab infusion. Randomisation was not described in sufficient detail to determine if allocation was concealed.

The primary objective of the study was to determine differences between the groups in treatment response at 3, 6 and 12 months after treatment was initiated. Response to treatment was considered as complete if haemoglobin concentration normalised without any ongoing immunosuppressive treatment and without any biochemical signs of haemolytic activity; or partial if the same criteria as complete response were met, but ongoing treatment with low-dose prednisolone (less than 10 mg daily) was required, or appearing as compensated haemolytic anaemia with a stable acceptable haemoglobin concentration without the need for treatment except for less than 10 mg daily of prednisolone. No response was considered if people required more than 10 mg of prednisolone daily, other immunosuppressive treatment, or splenectomy. Secondary objectives included differences in relapse-free survival, need for red blood cell transfusion after treatment, need for splenectomy and safety up to 12 months after enrolment.

At 3 and 6 months after treatment, there was no statistically significant difference in complete response or any response (complete or partial) between the prednisolone

monotherapy and the prednisolone plus rituximab groups. After 12 months, participants reported only a complete response or persistent disease. The complete response rate was 36% (95% confidence interval [CI] 19 to 56%) in the people still alive at 12 months in the prednisolone monotherapy group, compared with 75% (95% CI 55 to 89%) in the people still alive at 12 months in the prednisolone plus rituximab group. The difference between the groups was statistically significant (p=0.003).

Relapse-free survival in people whose condition had shown any response to treatment (complete or partial) was statistically significantly lower in the prednisolone monotherapy group compared with the prednisolone plus rituximab group (hazard ratio [HR] 0.33, 95% CI 0.12 to 0.88, p=0.02). After 36 months, approximately 70% of people who had shown either a complete or partial response to treatment were still relapse-free in the prednisolone plus rituximab group compared with around 45% in the prednisolone monotherapy group. There was no statistically significant difference between the groups in the number of red blood transfusions after treatment, and the number of people needing splenectomy (4 people in the prednisolone plus rituximab group compared with 3 people in the prednisolone monotherapy group).

A Belgian retrospective study (Dierickx et al. 2009) examined the effect of rituximab in people with autoimmune haemolytic anaemia (warm and cold antibody types) and immune thrombocytopenic purpura. The study included 53 participants (median age when starting rituximab 65 years; range 1 to 87 years) with autoimmune haemolytic anaemia, 36 of whom had warm antibody type. Rituximab was administered as an intravenous infusion mainly at a dosage of 375 mg/m^2 body surface area weekly for 4 weeks. Most people (77%) also received concomitant therapies including corticosteroids.

In people with warm autoimmune haemolytic anaemia, complete response rate (achievement of normal haemoglobin concentration without immunosuppressive therapy and no haemolysis) after the first course of rituximab (time point 'after' not further defined) was 50% and partial response rate (no requirement for blood transfusion in a previously transfused person, or increase in haemoglobin concentration of at least 20 g/litre) was 33%. This represented an overall response rate (complete and partial) of 83%. In the whole study population (including people with both warm and cold forms of autoimmune haemolytic anaemia), 9 people were retreated with a further 2 to 5 courses of rituximab.

An Irish multicentre retrospective study (Maung et al. 2013) investigated the efficacy and safety of rituximab in 34 young people and adults (median age 59 years; range 14 to

83 years) with primary or secondary warm autoimmune haemolytic anaemia who had received at least 1 prior treatment for their condition. All participants received rituximab at a dosage of 375 mg/m^2 body surface area weekly for 4 weeks.

Participants were followed up for a median of 36 months. Around 71% (24/34) of participants had a response to rituximab (defined as an increase in haemoglobin concentration of at least 20 g/litre from baseline, or maintenance of haemoglobin above 100 g/litre for at least 6 months after treatment) including 9/34 people (27%) who had a complete response (defined as normalisation of haemoglobin, bilirubin or lactate dehydrogenase sustained for at least 6 months). Most people (21/24) whose condition responded to treatment experienced a response within 28 days of receiving the first dose of rituximab, and the remaining 3 people responded by 3 months.

Participants whose condition responded to treatment were followed up for a median of 30 months, during which time 50% (12/24) of participants experienced a relapse (defined as a fall in haemoglobin below 100 g/litre and requirement for new treatment; median time to relapse 16.5 months).Three people who experienced a relapse were retreated with rituximab 375 mg/m^2 body surface area weekly for 4 weeks, and all 3 responded to treatment.

An Italian multicentre, single-arm prospective study by Barcellini et al. (2013) investigated using low-dose rituximab for treating idiopathic autoimmune haemolytic anaemia in adults. The study included people with warm (n=18) and cold (n=14) antibody types with either newly diagnosed disease, or people whose condition had relapsed after first-line treatment with prednisolone. Rituximab was given by intravenous infusion at a fixed dose of 100 mg on day 7, 14, 21 and 28 along with oral prednisolone 1 mg/kg daily from day 1 to 30 followed by gradual tapering. Participants were followed up for a median of 25 months (range 6 to 54 months).

In people with warm autoimmune haemolytic anaemia, a complete response to treatment (haemoglobin concentration greater than 120 g/litre and normalisation of haemolytic markers in the absence of any treatment) was achieved in 12/18 (67%) people at 6 months, 10/14 (71%) people at 12 months, 11/12 (92%) people at 24 months and 6/7 (86%) people at 36 months. Overall response (including people whose condition had a complete response or partial response [haemoglobin concentration of 100 g/litre or more or an increase of at least 20 g/litre in the absence of any treatment]) was achieved in 17/18 (94%) people at 6 months, 14/14 (100%) people at 12 months, 12/12 (100%) people at 24 months and 7/7 (100%) people at 36 months. Relapse-free survival was 89% at 6 and 12 months, and 76%

at 24 and 36 months.

An Italian, single-arm prospective study (Zecca et al. 2003) investigated using rituximab for treating refractory autoimmune haemolytic anaemia in children. The study included 15 children and young people with a median age of 2 years (range 0.3 to 14 years) at diagnosis; 9 of whom had autoimmune haemolytic anaemia, and 6 had Evans syndrome. A total of 13 children had warm antibody type, 1 had cold antibody type and antibody type could not be determined in 1 child. Rituximab was administered as an intravenous infusion at a dosage of 375 mg/m^2 body surface area weekly for 2 to 4 weeks. Median follow-up was 14 months (range 7 to 28 months).

A response to treatment (defined as at least a 15 g/litre increase in haemoglobin concentration and more than 50% reduction in reticulocyte count) was reported in 13/15 (87%) participants. Of the 13 participants whose condition responded to rituximab treatment, 10 were alive and not on any immunosuppressive treatment at a median of 13 months after treatment. The other 3 participants experienced a relapse of their condition and received a second course of rituximab therapy. All 3 achieved remission of their condition, but 1 participant experienced another 2 relapses, both which responded to a further course of rituximab.

A meta-analysis of the efficacy and safety of rituximab in autoimmune haemolytic anaemia has recently been published (Reynaud et al. 2014). This included the RCT described above (Birgens et al. 2013) and 20 uncontrolled (8 retrospective and 12 prospective) studies (n=409 in total). All the uncontrolled studies described in this evidence summary were included except Berentsen et al. (2010) which investigated combination therapy with rituximab and fludarabine in chronic cold haemagglutinin disease with clonal B-cell lymphoproliferation. The meta-analysis included studies in both warm and cold types of autoimmune haemolytic anaemia, but reported results separately. For warm autoimmune haemolytic anaemia, the overall response rate to rituximab was 79% (95% CI 60 to 90%; 11 studies, n=154). The complete response rate was 42% (95% CI 27 to 58%; 11 studies, n=154; Reynaud et al. 2014).

Cold autoimmune haemolytic anaemia

A Norwegian multicentre, single-arm, prospective study (Berentsen et al. 2004) investigated using rituximab for treating primary chronic cold haemagglutinin disease in 27 adults (mean age 71 years; range 51 to 91 years). Rituximab was administered as an intravenous infusion at a dosage of 375 mg/m^2 body surface area weekly for 4 weeks.

People whose condition did not respond to treatment within 3 months, or who had relapses during the study were offered second-line treatment with a combination of rituximab (at the same dosage as used previously) and subcutaneous injections of interferon at a dosage of 5 million units 3 times weekly for 20 weeks, started 2 weeks before the first rituximab infusion.

Complete response (defined as absence of anaemia, no signs of haemolysis, disappearance of symptoms of cold haemagglutinin disease, undetectable monoclonal serum protein, and no signs of clonal lymphoproliferation as assessed by various methods) to the first course of rituximab was reported in 1/27 (4%) people. Partial response (defined as stable increase in haemoglobin concentration of at least 20 g/litre or to the normal range, combined with reduction of serum immunoglobulin M concentrations by at least 50% of the initial level or to the normal range, improvement of clinical symptoms and transfusion independence) was reported in 13/27 (48%) people, giving an overall response rate of 52% (14/27 people). A total of 13/27 (48%) people did not report a response to first-line treatment with rituximab. Two of these people received retreatment with rituximab and interferon, 1 of who had a partial response and 1 who had no response. Of the 14 people who had an initial response to treatment, 8 relapsed and were retreated with rituximab plus interferon (n=3) or rituximab monotherapy (n=5). As a result of retreatment, 5 of these people experienced a partial response to treatment, and 3 had no response. Two people who responded to retreatment with rituximab monotherapy relapsed again and received further retreatment which achieved a partial response in both participants. Median time to response including all courses of rituximab therapy (initial and retreatment courses) was 1.5 months.

A further Norwegian multicentre, retrospective study (Berentsen et al. 2006) included 86 adults with cold haemagglutinin disease who had been treated with various therapies. Rituximab monotherapy was given to 40 people; whereas 5 people received rituximab in combination with interferon alfa and 7 people received rituximab in combination with fludarabine. Definitions of complete and partial response were the same as those in Berentsen et al. 2004 reported above. Complete response to treatment was achieved in 2/40 (5%) people who had received rituximab as monotherapy and 3/12 (25%) people who had received rituximab as combination therapy. Partial response to treatment was achieved in 21/40 (53%) people who had received rituximab as monotherapy and 5/12 (42%) people who had received rituximab as combination therapy.

Berentsen et al. (2010) reported a Norwegian prospective single-arm study investigating combination therapy with rituximab and fludarabine in 29 adults (median age 73 years;

range 39 to 87 years) with chronic cold haemagglutinin disease and the presence of a clonal B-cell lymphoproliferation. Participants received intravenous infusions of rituximab 375 mg/m^2 body surface area once every 28 days for 4 doses on day 1, 29, 57 and 85. Participants also received oral fludarabine 40 mg/m^2 body surface area on days 1–5, 29–34, 57–61 and 85–89. Definitions of complete and partial response to treatment were the same as those in Berentsen et al. 2004 reported above.

A total of 22/29 (76%) people had a response (complete or partial) to treatment, including 6/29 (21%) who experienced a complete response and 16/29 (55%) who had a partial response. Median time to response was 4 months (range 0.3 to 6 months). Fifteen people in the study had previously received rituximab monotherapy at least once prior to enrolment, of which 10 had not had a response. Of these 10 people, 6 had a response with combination treatment of fludarabine and rituximab during the study (1 complete response and 5 partial responses).

The median duration of follow-up in people who responded to treatment during the study was 33 months (range 3 to 66 months). At this point, 5 people (23% of all responders, and 31% of partial responders) had relapsed, whilst 77% of responders remained in remission. The estimated median response duration was more than 66 months.

Schollkopf et al. (2006) reported a Danish, multicentre, prospective single-arm study in 20 adults (median age 75 years; range 54 to 86 years) with chronic cold haemagglutinin disease, 11 of whom had received previous treatments for their condition. Participants included those with idiopathic cold haemagglutinin disease as well as those with lymphoproliferative diseases. Rituximab was administered as an intravenous infusion at a dosage of 375 mg/m^2 body surface area weekly for 4 weeks.

In total 1/20 (5%) people had a complete response (defined as normalisation of haemoglobin concentration, absence of signs of haemolysis, and disappearance of symptoms of their cold haemagglutinin disease), and 8/20 (40%) had a partial response (defined as an increase in haemoglobin levels of at least 10 g/litre for a minimum of 1 month, no need for erythrocyte transfusions, improvement in clinical symptoms, and, in the case of elevated immunoglobulin M concentrations, at least a 50% reduction). This gave an overall response rate (complete and partial response) of 45% (9/20 people). Median time to maximal response was 3 months (range 1 to 5 months). Two people whose condition improved after rituximab therapy, but who did not achieve the criteria for partial response, were retreated with rituximab. One person showed a further response to retreatment, whilst the other person showed no response. In the 9 people whose condition

responded to rituximab therapy, 6 relapsed during 48 weeks of follow-up. Three people were still in remission at the end of follow-up, 2 of who subsequently relapsed 14 months after demonstrating a response. Median duration of response was 6.5 months (range 2 to 10 months).

The Italian multicentre, single-arm prospective study by Barcellini et al. (2013) included 14 adults with cold haemagglutinin disease and investigated using low-dose rituximab (100 mg weekly for 4 weeks). Further studies details are provided above. Complete response to treatment was achieved in 7/13 (54%) people at 6 months, 5/7 (71%) people at 12 months, 4/5 (80%) people at 24 months and 0/7 people at 36 months. Overall response (people whose condition had a complete or partial response to treatment) was achieved in 11/13 (85%) people at 6 months, 7/7 (100%) people at 12 months, 5/5 (100%) people at 24 months and 1/2 (50%) people at 36 months. Relapse-free survival was 85% at 6 months, 67% at 12 months, and 57% at 24 and 36 months.

In the recently published meta-analysis of the efficacy and safety of rituximab in autoimmune haemolytic anaemia (Reynaud et al. 2014), the overall response rate to rituximab in cold antibody types of autoimmune haemolytic anaemia was 57% (95% CI 47 to 66%; 6 studies, n=109). The complete response rate was 21% (95% CI 6 to 51%; 7 studies, n=118).

Safety and tolerability

In the RCT by Birgens et al. (2013) there was no statistically significant difference between the prednisolone monotherapy and prednisolone plus rituximab groups in any adverse event in adults with warm autoimmune haemolytic anaemia. The most commonly reported adverse events in people in the prednisolone monotherapy and prednisolone plus rituximab groups were dyspnoea (16.7% compared with 13.3% respectively), fatigue (13.3% in both groups), headache (13.3% compared with 6.7% respectively), dyspepsia (13.3% compared with 3.3% respectively) and insomnia (10% in both groups); several of which were probably related to prednisolone. There were 8 non-fatal serious adverse events in 5 people in the prednisolone plus rituximab group: pneumonia (3 events), fever (2 events), urinary tract infection (2 events) and *Clostridium difficile* enteritis (1 event). In the prednisolone monotherapy group there were 4 non-fatal serious adverse events in 4 people: pneumonia (2 events), urinary tract infection (1 event) and pulmonary embolism (1 event). There was 1 fatal serious adverse event (pneumonia) in the prednisolone plus rituximab group that was possibly treatment-related.

In the Irish retrospective study by Maung et al. (2013), treatment with rituximab was reported as being well tolerated in young people and adults with warm autoimmune haemolytic anaemia. There was 1 case of severe neutropenic sepsis that required ventilation and treatment for possible fungal sepsis in a person who was not on any other immunosuppressive agent at the time.

In the Italian, single-arm prospective study (Zecca et al. 2003) that investigated using rituximab for treating refractory autoimmune haemolytic anaemia in children and young people, treatment was reported as being generally well tolerated. Three participants experienced adverse events; 2 cases of fever and 1 case of upper airway oedema. A further participant developed primary varicella zoster virus 2 months after rituximab treatment.

In the Norwegian prospective study by Berentsen et al. 2004, no serious infusion-related adverse events were reported in adults with chronic cold haemagglutinin disease. One person experienced muscular pain during the first infusion. Another participant had transient neutropenia, fever and infection related to rituximab.

In the Norwegian prospective study by Berentsen et al. (2010) that investigated combination therapy with rituximab and fludarabine, adverse events including grade 1–2 cytopenias without clinical manifestations were reported in 22/29 (76%) adults with chronic cold haemagglutinin disease. Haematological toxicity grade 3–4 occurred in 12/29 (41%) people; neutropenia being responsible for all cases of grade 4 toxicity. A total of 17/29 (59%) experienced grade 1–3 infections which were successfully treated in all but 1 person who died of pneumonia after 9 months. Another person died of cerebral stroke after 7 months. Three people experienced herpes zoster reactivation, and 2 people were reported as having a reduced quality of life for months after completing treatment because of recurrent respiratory infections. Treatment in this study was with a combination of fludarabine and rituximab, and the authors state that more significant toxicity was observed in this study compared with some previous studies using rituximab monotherapy.

Schollkopf et al. (2006) reported that in adults with cold haemagglutinin disease, treatment with rituximab was well tolerated and no severe infusion-related reactions were noted. A total of 8/20 (40%) people reported adverse events including fever, cough, headache, nausea, diarrhoea, shivers and dizziness. Three people developed hypotension that responded to treatment with a saline infusion.

The recently published meta-analysis of the efficacy and safety of rituximab in autoimmune haemolytic anaemia collected available data on side effects from the included studies (Reynaud et al. 2014). The authors stated that 19 of the 21 included studies reported 38 adverse events in 364 patients. Sixteen of the adverse events were infusion-related side effects, mostly chills and fever. They reported that 22 events were more severe, including 4 neutropenias and 18 severe infections.

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). It 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 a 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

Limited high-quality evidence was found that investigated how well rituximab works for treating autoimmune haemolytic anaemia. Only 1 RCT was identified therefore this evidence summary also includes the largest uncontrolled studies that provide the best available evidence for using rituximab for treating autoimmune haemolytic anaemia. A meta-analysis (Reynaud et al. 2014) of the 1 RCT and 20 uncontrolled studies of rituximab in autoimmune haemolytic anaemia has recently been published.

The RCT (Birgens et al. 2013) had strengths in the fact that it was a randomised study, and compared rituximab plus prednisolone to standard monotherapy with prednisolone in people with newly diagnosed warm autoimmune haemolytic anaemia. Limitations included the relatively small number of participants included in the trial (n=64), although the authors report that in a power analysis the study demonstrated over 80% power to detect a difference between the treatment groups in complete response rate at 12 months after treatment. The trial was open-label, and randomisation was not described in sufficient detail to say if allocation was concealed. These factors could have introduced bias to the findings.

The uncontrolled studies included in the evidence summary contained only small numbers of participants (between 13 and 36 participants in warm autoimmune haemolytic anaemia; and between 14 and 52 participants in cold autoimmune haemolytic anaemia). None of the studies compared rituximab with any other treatments, including splenectomy, and they had limitations inherent in their non-randomised design. In addition, the populations in the studies differed and included participants with primary, secondary, newly diagnosed, and relapsed autoimmune haemolytic anaemia; as well as people with lymphoproliferative diseases. Most studies reported outcomes such as complete, partial and overall response rates to treatment. However, there was no standardised definitions of these and they varied in the individual studies. These limitations make it difficult to compare the reported response rates in the studies, or to draw any firm conclusions from the evidence.

The recently published meta-analysis provides a useful summary of the efficacy and

safety of rituximab in autoimmune haemolytic anaemia. However, it has several limitations inherent in the methodology which combines results from the inclusion of only 1 RCT and 20 small, uncontrolled, heterogeneous studies. The heterogeneity related to differences in types of autoimmune haemolytic anaemia, age, disease duration, prior treatment, combinations of treatments, inconsistencies in definitions of outcomes across the studies, and history of splenectomy. Publication bias was also a possibility, and there was only limited long-term follow up for both efficacy and safety.

Context and estimated impact for the NHS

Cost effectiveness

No studies were identified which examined the cost effectiveness of rituximab for this condition.

Comparing the cost of rituximab with other therapies for autoimmune haemolytic anaemia is difficult because there is a lack of evidence to confirm the optimal dose, guide the use of recurrent courses in refractory cases, and confirm the advice on other aspects of the clinical pathway such as combination with other treatments.

Most of the studies in this evidence summary used rituximab at a dosage of 375 mg/m^2 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 m^2 is estimated to be £4889.60 (assuming wastage and excluding VAT; MIMS January 2015. The cost for a 4-week course based on a child with a body surface area of 0.89 m^2 is estimated to be £2794.00 (assuming wastage and excluding VAT; MIMS January 2015).

One study 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 January 2015).

Current drug usage

Estimating current drug usage of rituximab for treating autoimmune haemolytic anaemia is difficult because rituximab is used to treat various conditions. No information on prescribing rituximab for autoimmune haemolytic anaemia 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 autoimmune haemolytic anaemia who are thinking about trying rituximab.

Relevance to NICE guidance programmes

NICE has published several technology appraisals relating to licensed indications for the intravenous formulation of rituximab. This use of rituximab for autoimmune haemolytic anaemia is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

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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.

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Declarations of interest

No relevant interests declared.

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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