RITUXIMAB FOR CYTOPENIA FROM PRIMARY IMMUNE DEFICIENCY

QUESTION(S) TO BE ADDRESSED:

What is the evidence for the clinical and cost effectiveness for rituximab for the management of auto-immune cytopenia arising as a complication of primary immune deficiency?

SUMMARY:

Background

- A number of primary autoimmune disorders can result in diminished numbers of circulating blood cells. One treatment of this is rituximab, but there is uncertainty about the clinical and cost effectiveness of this approach.

Clinical effectiveness

- We found no systematic reviews or controlled studies.

- We found two studies of the effectiveness of rituximab in the treatment of immunodeficiency-associated immune cytopenia:

    - Gobert et al reported a study of 33 people (29 adults) with common variable immunodeficiency complicated by cytopenia. The participants experienced 34 episodes of immune thrombocytopenia and/or autoimmune haemolytic anaemia, of which 24 (74%) responded completely to rituximab, and four (12%) responded partially. Half of the responses lasted more than a year.
    - Kim et al reported a smaller study of eight children with various primary immunodeficiency disorders and cytopenia. Seven (88%) responded fully, and the eighth child's haemolytic anaemia responded, though the thrombocytopenia did not. During follow-up, participants nearly all relapsed, but their relapses responded to a further course of rituximab.

Cost effectiveness

- We found no health economic studies of rituximab for cytopenia from primary immune deficiency.

Safety

- The use of rituximab has been associated with severe infection, pancytopenia and hypogammaglobulinemia.

1 Context

1.1 Introduction

A number of primary autoimmune disorders can result in diminished numbers of circulating blood cells. One treatment of this is rituximab, but there is uncertainty about the clinical and cost effectiveness of this approach.

1.2 Existing national policies and guidance

We found no national policies or guidance about the treatment of cytopenia arising from primary immune deficiency

2 Epidemiology

Primary immunodeficiency disorders occur when the normal immune response is less than fully effective because the cells and/or proteins which deliver it do not work normally. There are more than 250 such disorders; all are rare.

Although the main symptoms of these disorders arise from an inadequate immune response, patients may also have abnormal immunoregulation, leading to the development of autoantibodies in about a fifth of cases.[1]. These antibodies are often directed at blood cells, leading to autoimmune cytopenias, particularly immune thrombocytopenia and autoimmune haemolytic anaemia.[2] Autoimmune cytopenia can be treated with corticosteroids, intravenous immunoglobulin, vinca alkaloids, danazol and splenectomy.

3 The intervention

Another treatment option is rituximab. Rituximab is a chimeric monoclonal antibody directed against CD20, an antigen found on the surface of B-cells. Administration leads to a rapid and sustained depletion in circulating CD20-positive B-cells. Although this may be effective in blunting the autoimmune attack on other blood cells, this must be considered alongside the risk of exacerbating the underlying immunodeficiency and increasing the risk of infection.

4 Findings

In October 2015, we searched TRIP, NICE Evidence Search, Medline, Embase and Cochrane Library for research published since 2000 in English. We excluded letters, comment, editorials and conference papers. We used the Immune Deficiency Foundation's definitions of primary immunodeficencies[3] and therefore excluded papers reporting the use of rituximab in lymphoma, leukaemia, myeloma, immunoproliferative disorders, immune thrombocytopenia, auto-immune haemolytic anaemias, systemic lupus erythematosus, rheumatoid arthritis and post-transplant lymphoproliferative disease, unless these were the result of a primary immunodeficiency disorder. We also excluded single case reports.

4.1 Evidence of effectiveness

We found no systematic reviews or controlled studies.

We found two uncontrolled studies of the effectiveness of rituximab in the treatment of immunodeficiency-associated immune cytopenias (Table 1):

- Gobert et al reported a study of 33 people (29 adults) with common variable immunodeficiency complicated by cytopenia.[4] The participants experienced 34 episodes of immune thrombocytopenia and/or autoimmune haemolytic anaemia, of which 24 (74%) responded completely to rituximab, and four (12%) responded partially. Half of the responses lasted more than a year.

- Kim et al reported a smaller study of eight children with various primary immunodeficiency disorders and cytopenia.[5] Seven (88%) responded fully, and the eighth child's haemolytic anaemia responded, though the thrombocytopenia did not. During follow-up, participants nearly all relapsed, but their relapses responded to a further course of rituximab.

Table 1:

Study	Patients	Intervention	Comparator	Outcomes	Comments
Gobert et al [4] Several hospitals in France and the United States	33 people (29 adults) with common variable immunodeficiency (CVID) complicated by immune thrombocytopenia (ITP) (12, 36%), autoimmune haemolytic anaemia (AHA) (3, 9%) or both (18, 55%). Mean age at diagnosis of CVID: adults 35 years, children 8 years.	Intravenous rituximab 375mg/m^2 weekly for 4 weeks. Two patients received rituximab 1g on days 1 and 15, and 1 patient received rituximab only once because of a severe pancytopenia after infusion.	Uncontrolled	Complete response* 25/34** (74%) (21 adults). Partial response† 4/34 (12%) (4 adults). No response 5/34 (15%) (5 adults), of whom 3 had a response to subsequent splenectomy. Response for more than a year: 17/34 (50%). Mean follow-up: 39 months.	Participants were also receiving corticosteroids, IV immunoglobulins and romiplostim. Corticosteroids were withdrawn in 13 of the 19 participants receiving them when rituximab was first administered.
Kim et al [5] London	8 children with primary immune deficiency: CVID (2), Wiskott Aldrich syndrome (2), autoimmune lymphoproliferative syndrome (2), combined immunodeficiency with significant autoimmunity (1), undefined immunodeficiency (1). They received 14 courses of rituximab for 21 cytopenias (5 AHA, 10 ITP, 6 autoimmune neutropenia (AIN)). Median age 7 years.	Intravenous rituximab 375mg/m^2 weekly for 4 weeks.	Uncontrolled	Response††: 7/8 (88%). One child showed response of AHA but not ITP. Relapse†††: 6/8 (75%). Median time to relapse 54 weeks. One patient had a bone-marrow transplant before relapse, and one had not relapsed after 24 weeks.	Seven children had not responded to corticosteroids and/or high-dose IV immunoglobulins; the eighth child had responded to steroids.

Study	Patients	Intervention	Comparator	Outcomes	Comments
				Relapsed participants were retreated. Overall response rate to retreatment was 90% after a median of 3 weeks. Overall relapse rate 78% after a median of 53 weeks. Mean follow-up not reported.	

* For ITP, platelets > $100x10^9$/l; for AHA, Hb ≥ 120g/l without transfusion or persistent haemolysis.
** 34 episodes of cytopenia were treated, with one participant being treated for immune thrombocyopaenia and later for autoimmune haemolytic anaemia.
† For ITP, platelets > $30x10^9$/l and more than twice the pre-treatment level; for AHA, Hb ≥ 100g/l and at least 20 g/l more than the pre-treatment level, with haemoglobin stable if haemolysis persistent.
†† For ITP, platelets > $50x10^9$/l; for AHA, Hb ≥ 80g/l; for AIN, neutrophil count > $1x10^9$/l; all without transfusion.
††† No longer meeting criteria for response.

4.2 Trials in progress

We searched clinicaltrials.gov but found no studies of rituximab for cytopenia from primary immune deficiency

4.3 Evidence of cost-effectiveness

We found no health economic studies of rituximab for cytopenia from primary immune deficiency.

4.4 Safety

Gobert et al reported no immediate adverse reactions to rituximab.[4] Eight participants experienced a total of eleven severe infections after rituximab, and one had a severe pancytopenia. The authors suggest that concurrent administration of intravenous immunoglobulins mitigates this risk. Two participants died, ten and four months after receiving rituximab, but the deaths did not seem directly attributable to the drug.

Kim et al reported no significant infections, but all of the children in that study were either already receiving immunoglobulin or started it with rituximab.[5]

Diwakar et al reported two adults who developed severe hypogammaglobulinaemia after treatment with rituximab.[6] One had common variable immune deficiency and the other probably did. Both received immunoglobulins after the hypogammaglobulinaemia had developed; one responded, but the other developed fatal fulminant hepatic failure, ascribed at post-mortem to chronic infection. The authors suggest that rituximab can aggravate pre-existing antibody deficiency.

4.5 Summary of section 4

Evidence of the use of rituximab in patients with primary immune deficiency and cytopenia is very limited, with two uncontrolled studies reporting a total of only 29 adults and 12 children. These studies report that most patients show an improvement in their cytopenia after treatment, which lasts on average for about a year. When patients relapse, the drug appears to be effective in producing a second response. The drug can lead to hypogammaglobulinaemia, and the use of concurrent intravenous immunoglobulins is advised by some authors.

5 Discussion and conclusions

What is the evidence for the clinical and cost effectiveness for rituximab for the management of auto-immune cytopenia arising as a complication of primary immune deficiency?

Primary immune deficiency complicated by cytopenia arises rarely, and in some cases responds to treatment other than rituximab. The evidence about the use of rituximab is limited both in quantity and quality. However, it suggests that the drug does bring about an improvement in the cytopenia in most cases. This lasts for about a year on average, with relapse likely but re-treatment apparently successful, at least at first.

We found no evidence about the effect of rituximab on quality or duration of life, or any other outcomes.

The cost effectiveness of this treatment is unknown.

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from NHS England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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6 References

1. Bousfiha A, Jeddane L, Al-Herz WJ, et al. The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies. *Clin Immunol* 2015; 35: 727-38.
2. Wang J, Cunningham-Rundles C. Treatment and outcome of autoimmune hematologic disease in common variable immune deficiency (CVID). *J Autoimmun* 2005; 25: 57-62.
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5. Kim JJ, Thrasher AJ, Jones AM, et al. Rituximab for the treatment of autoimmune cytopenias in children with immune deficiency. *Br J Haematol* 2007; 138: 94-6.
6. Diwakar L, Gorrie S, Richter A, et al. Does rituximab aggravate pre-existing hypogammaglobulinaemia? *J Clin Pathol* 2010; 63: 275-7.

7 Search Strategy

Table 6: Population, Intervention, Comparator and Outcomes (PICO)

P- Patients/ population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	People with cytopaenia arising as a complication of primary immune deficiency (PID). This excludes people with immune thrombocytopenia and lymphoproliferative disorders.
I - Intervention Which intervention, treatment or approach should be used?	Rituximab
C - Comparison What is/ are the main alternative/s to compare with the intervention being considered?	Any including: Corticosteroids conventional immunosuppressants e.g. azathioprine splenectomy
O - Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Clinical effectiveness Mortality QoL Morbidity Respiratory or GI failure Safety/ Adverse events Longer term outcomes Cost effectiveness
Assumptions/ limits applied to search	Published 2000 onwards Systematic reviews/metaanalysis RCTs Uncontrolled studies Case series Case studies Excluding: Conference reports Abstracts Posters Unpublished reports

Search date: 9th October 2015
Databases searched: TRIP, NICE Evidence Search, Medline, Embase and Cochrane Library and limited to 2000 and English language.
Limited to studies published in English and last 10 years
Conference papers, letters, commentary and editorials excluded. Animal studies excluded

Medline strategy

1	Thrombocytopenia/
2	Pancytopenia/
3	(pancytopeni* or pancytopaeni* or cytopeni* or cytopaeni* or thrombocytopeni* or thrombocytopaeni*).ti,ab.
4	1 or 2 or 3
5	immunologic deficiency syndromes/ or agammaglobulinemia/ or ataxia telangiectasia/ or common variable immunodeficiency/ or exp dysgammaglobulinemia/ or exp lymphopenia/ or exp phagocyte bactericidal dysfunction/ or exp severe combined immunodeficiency/ or wiskott-aldrich syndrome/
6	((primary or combined or common or variable or congenital) adj3 (immune deficien* or immunodeficien*)).ti,ab.
7	((wiskott aldrich or digeorge or chediak higashi or barth or blau or muckle wells) adj3 (disease? or syndrome?)).ti,ab.
8	((adenosine deaminase or selective iga or complement or nemo) adj2 deficien*).ti,ab.
9	(x linked lymphoproliferative disorder* or x linked lymphoprolipherative disorder* or granulomatous disorder?).ti,ab.
10	5 or 6 or 7 or 8 or 9
11	((autoimmune* or auto-immune*) adj3 (cytopaeni* or cytopeni* or thrombocytopeni* or thrombocytopaeni*)).ti,ab.
12	10 or 11
13	*Antibodies, Monoclonal/ or *Antibodies, Monoclonal, Murine-Derived/
14	(rituximab or mabthera or rituxan or zytux).ti,ab.
15	((monoclonal antibod* or mab) adj5 cd20).ti,ab.
16	(monoclonal antibod* or mab).ti.
17	13 or 14 or 15 or 16
18	4 and 17
19	12 and 17
20	18 or 19
21	limit 20 to (english language and yr="2005 -Current" and "reviews (maximizes specificity)")
22	4 and 12 and 17
23	limit 22 to (english language and yr="2005 -Current")
24	(rituximab or mabthera or rituxan or zytux).ti.
25	(pancytopeni* or pancytopaeni* or cytopeni* or cytopaeni* or thrombocytopeni* or thrombocytopaeni*).ti.
26	24 and 25
27	limit 26 to (english language and yr="2005 -Current")
28	12 and 19
29	limit 29 to (english language and yr="2005 -Current")