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Rituximab for eradicating inhibitors in people with acquired haemophilia A

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ABSTRACT

Background

Acquired haemophilia A is a rare bleeding disorder caused by the development of specific autoantibodies against coagulation factor VIII. Rituximab may be an alternative approach to the treatment of acquired haemophilia by eradicating FVIII autoantibodies.

Objectives

To assess and summarise the efficacy and adverse effects of rituximab for treating people with acquired haemophilia A.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's trials registers, comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and conference proceedings.

Date of last search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's trials registers: 01 March 2016.

Selection criteria

Randomised and quasi-randomised controlled trials of rituximab for people with acquired haemophilia A, with no restrictions on gender, age or ethnicity.

Data collection and analysis

No trials matching the selection criteria were eligible for inclusion.

Main results

No trials matching the selection criteria were eligible for inclusion.

Authors' conclusions

No randomised clinical trials of rituximab for acquired hemophilia A were found. Thus, based on the highest quality of evidence, we are not able to draw any conclusions or make any recommendations on rituximab for eradicating inhibitors in people with acquired haemophilia A. Given that undertaking randomised controlled trials in this field is a complex task, the authors suggest that, while planning such trials, clinicians treating the disease continue to base their choices on alternative, lower quality sources of evidence. The authors plan, for a future update of this review, to appraise and incorporate any randomised controlled trials, as well as other high-quality non-randomised studies.

PLAIN LANGUAGE SUMMARY

Rituximab for eradicating inhibitors in people with acquired haemophilia A

Review question

We reviewed the evidence about the effect of rituximab for treating people with acquired haemophilia A.

Background

Acquired hemophilia A is a rare but severe bleeding disorder caused by the autoantibody directed against factor VIII (FVIII, a blood clotting protein) in people with no previous history of a bleeding disorder. This bleeding disorder occurs more frequently in the elderly and may be associated with several other conditions (e.g. solid tumours and autoimmune diseases), or with drugs and is sometimes associated with pregnancy. However, in about half of the cases the causes are unknown. Bleeding occurs in the skin, mucous membranes, and muscles; with joint bleeds being unusual. The goals of management are to stop acute bleeding episodes and to eliminate factor VIII autoantibodies. Corticosteroid treatment (prednisone), with or without, cyclophosphamide is regarded by most clinicians as the most effective standard first line intervention for eradicating inhibitors; however, up to one third of people do not respond to this therapy.

Search date

The evidence is current to: 01 March 2016.

Key results

We were not able to identify any randomised controlled trials to include in this review. We have not been able to draw a definitive conclusion on the best available treatment. Randomised controlled trials are needed to evaluate the precise role of rituximab in acquired hemophilia A, but the rarity of the condition is hindering their planning and execution. While waiting for better evidence, people with haemophilia and clinicians need to base treatment decisions on the largest and better conducted observational studies.

BACKGROUND

Description of the condition

Acquired haemophilia A (AHA) is a autoimmune haemorrhagic disorder caused by an inhibitory autoantibody to factor VIII (FVIII) (Boggio 2001; Buczma 2007; Delgado 2003; Franchini 2005; Franchini 2008a; Green 1981; Hay 1998; Sakurai 2014), with an incidence of approximately 1.48 per million per year (Collins 2007a). It typically affects older people with a median age at diagnosis of approximately 78 years (Collins 2007a). Well-

recognised risk factors for AHA are autoimmune disorders (systemic lupus erythematosus and rheumatoid arthritis), solid tumours, lymphoproliferative diseases, and pregnancy (typically appearing in the postpartum period); however, approximately 50% of cases are idiopathic (Baudo 2004; Baudo 2007; Collins 2007a; Delgado 2003; Franchini 2008b; Green 1981; Knoebl 2012; Meiklejohn 2001; Tengborn 2012).

When an individual with no previous history of bleeding presents with bleeding and an unexplained prolonged activated partial thromboplastin time, AHA should be suspected. The diagnosis is confirmed in the laboratory by the subsequent identification of a

reduced FVIII:C level (the pro-coagulant activity of factor VIII measured by one stage factor VIII assay) with evidence of FVIII inhibitor activity (Baudo 2010; Collins 2010; Coppola 2009; Delgado 2003; Huth-Kühne 2009).

Haemorrhages in people with AHA usually occur suddenly and spontaneously, although approximately 25% of cases occur after surgery, trauma or other invasive procedures (Baudo 2003; Collins 2010). While bleeding at presentation is usually severe or life-threatening, requiring haemostatic treatment and transfusion; it can also be mild, with approximately 25% of individuals not requiring haemostatic treatment (Baudo 2004; Franchini 2008a). The mortality rate resulting from bleeding or otherwise complications related to AHA is high and reported to be between 8% and 22% (Green 1981; Baudo 2004; Collins 2007a; Franchini 2008a; Baudo 2007).

Description of the intervention

The therapeutic approach for AHA is aimed at stopping acute bleeds (via haemostatic agents) and to eradicate FVIII autoantibodies (via immunosuppressive treatment) (Baudo 2010; Baudo 2012; Collins 2007b; Collins 2010; Collins 2011; Collins 2012b; Coppola 2009; Hay 2006; Holme 2005; Huth-Kühne 2009; von Depka 2004; Tiede 2015).

The eradication of inhibitors is necessary to restore normal haemostasis and to prevent the risk of future bleeding episodes. However, inhibitors may spontaneously remit or resolve following treatment of the underlying condition in approximately 30% of individuals (Green 1981; Lottenberg 1987). Although spontaneous remissions may occur in people with AHA, it is generally accepted that individuals should be treated with immunosuppression to reduce the length of time for which they are at risk of severe bleeding.

Steroids alone, or in combination with cyclophosphamide, are regarded by most clinicians as the most effective standard first line immunosuppressive therapy (Collins 2012a; Franchini 2008a; Green 1993). The use of corticosteroids has been associated with inhibitor resolution in 30% to 70% of individuals, and when they are added to cyclophosphamide the remission rate approaches 60% to 80% (Collins 2007a; Green 1993). Nevertheless, up to one third of these people do not respond to this therapy. In addition, chronic use of corticosteroids is often associated with significant adverse affects. Alternative treatment options that have become available are high-dose immunoglobulin, cyclosporine, or cladribine. However, all these treatment modalities have shown only limited efficacy (Franchini 2008a).

More recently, increasing evidence suggests rituximab may be a useful alternative or addition to existing therapies. Available observational data indicate that rituximab can induce durable remissions in a wide range of individuals. It may be of particular benefit to those for whom corticosteroid or cytotoxic therapy (or both) are unsuitable or those who are refractory to conventional

immunosuppressant therapy (Abdallah 2005; Aggarwal 2005; Alvarado 2007; Banse 2015; Berezné 2006; Boles 2011; Bonfanti 2015; Braunert 2011; Cermáková 2013; Chaari 2012; Chiba 2013; Clatworthy 2006; Collins 2012a; Conte 2011; Cretel 2009; De Langhe 2015; de Palencia Espinosa 2013; Drobiecki 2013; Fernández 2013; Fischer 2003; Fletcher 2014; Franchini 2006; Franchini 2007; García-Chávez 2011; Holme 2005; Ichikawa 2009; Imashuku 2012; Jy 2003; Kain 2002; Kalro 2012; Lozier 2014; Machado 2008; Maillard 2006; Marietta 2003; Millet 2007; Muzaffar 2012; Oliveira 2007; Onishi 2013; Onitilo 2006; Riachy 2012; Saito 2012; Stachnik 2006; Stasi 2004; Wermke 2010; Wiestner 2002; Xu 2013; Yamamoto 2015; Zhang 2012; Zhou 2011).

How the intervention might work

Rituximab is a chimeric mouse-human monoclonal antibody against CD20 that binds to cells expressing CD20 surface antigen, such as B-cell lymphocytes. At most stages of cell development, CD20 is highly expressed on the surface of B-cells, including pre-B lymphocytes and activated mature cells (Pescovitz 2006; Silverman 2003). These B-cells have been shown to be essential in the development of autoimmunity or an acquired immune response, acting as antigen-presenting cells and promoting the production of cytokines and of antibodies (immunoglobulins) by plasma cells. Selective elimination or depletion of B-cells by rituximab may therefore be an effective approach to the treatment of autoimmune disorders such as acquired haemophilia (Garvey 2008). A dose of 375 mg/m² given weekly for up to four weeks, has generally been used for treatment of AHA. This is the same dose approved for treatment of CD20-positive, B-cell non-Hodgkin's lymphoma (Virgolini 2004).

Why it is important to do this review

A literature review of 65 people with AHA treated with rituximab found a response rate of more than 90%, but the investigators caution the over-interpretation of these data as they are derived from case reports or small non-randomised trials (Franchini 2007). A further literature review reported that 42 people with AHA treated with rituximab had similar outcomes to 44 controls treated with cyclophosphamide and steroids (Sperr 2007). Treatment with rituximab resulted in an overall rate of complete remission (CR) of 78.6%. The median time to CR was 8.3 weeks. At follow up, 66% of the individuals were still in CR after two years. Among the 44 individuals treated with cyclophosphamide and prednisone reported in the literature, the CR rate was 84.1%, which was slightly higher than that for rituximab. The median time to CR with cyclophosphamide and prednisone treatment was 6.3 weeks, which was similar to that in the rituximab-treated individuals; the probability of continuous CR at two years was 94%. Data from EACH2,

a prospective, large-scale, pan-European database, support these findings: 30 of 51 (59%) people treated with rituximab-based regimens achieved a stable remission. The 12 individuals treated with rituximab alone had only a 42% response rate, whereas those treated with rituximab and another agent had a 64% stable CR, similar to 70% stable CR observed for those treated with steroids and cyclophosphamide (Collins 2012a). Rituximab has not been shown to result in a more rapid remission and may be associated with slower remissions. The 51 rituximab-treated individuals in the EACH2 registry had a median time to a negative inhibitor of 65 days compared with other regimens, in which the median time was 32 to 34 days (Collins 2012a). Based on the published non-randomised trials, rituximab may be an effective treatment and a well-tolerated option for people with AHA. This Cochrane review aims to identify and summarise the available randomised evidence regarding the impact of rituximab on treating people with AHA, which is currently lacking.

OBJECTIVES

To assess and summarise the efficacy and adverse effects of rituximab for treating people with AHA.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

People with AHA, with no restrictions on gender, age or ethnicity.

Types of interventions

Interventions

- rituximab alone
- rituximab plus steroids
- rituximab plus a cytotoxic agent
- rituximab plus steroids and cytotoxic agent

Comparators

- steroids alone
- cytotoxic agent alone
- steroids plus a cytotoxic agent

Types of outcome measures

Primary outcomes

1. Stable complete remission (sCR) (defined as no reported relapse during follow up)
2. Complete remission (CR) (defined as a negative inhibitor test and a normal FVIII level)

Secondary outcomes

1. Bleeding control (yes or no)
2. Time to response (weeks)
3. Duration of response (months)
4. Overall survival (OS) (defined as the time interval from randomisation or study entry to death from any cause or to last follow up)
5. Adverse effects

Search methods for identification of studies

We will not adopt any language or publication restrictions.

Electronic searches

The Cystic Fibrosis and Genetic Disorders (CFGD) Group searched for relevant trials in the Group's Coagulopathies Trials Register using the terms: haemophilia* AND acquire* AND rituximab*.

The Coagulopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*) and weekly searches of MEDLINE and the prospective hand-searching of one journal - *Haemophilia*. Unpublished work is identified by searching the abstract books of major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Congress of the World Federation of Hemophilia; the European Association for Haemophilia and Allied Disorders, the American Society of Gene and Cell Therapy and the International Society on Thrombosis and Haemostasis. For full details of all searching activities for the register, please see the relevant section of the [Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of the last searched of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register: 01 March 2016.

Bibliographic databases

- the Cochrane Central Register of Controlled Trials (CENTRAL) - searched Issue 2, 2016 on 01 March 2016 (Appendix 1);
- MEDLINE (Ovid 1948 to present) - searched 01 March 2016 (Appendix 2).

Electronic searches in databases of ongoing trials:

- We searched the metaRegister of Controlled Trials (mRCT) to identify ongoing trials (<http://clinicaltrials.gov/>) using the terms: acquired hemophilia A AND rituximab.

Date of last search: 01 March 2016.

Searching other resources

We searched the conference proceedings of relevant conferences of the following societies for the years that were not included in CENTRAL:

- ASH (American Society of Hematology) 1994 to 2015;
- European Hematology Association 1994 to 2015;
- ISTH (International Society on Thrombosis and Haemostasis) 2002 to 2015;
- EAHAD (European Association for Haemophilia and Allied Disorders) 2009 to 2015;
- WFH (World Federation of Haemophilia) 2009 to 2015.

Data collection and analysis

Selection of studies

Two authors (ZY, ZR) independently checked the titles and abstracts identified from the searches. We obtained the full text of all trials that were possibly relevant for inclusion. The two authors were to decide which trials fit the inclusion criteria and aimed to resolve any disagreements by discussion. For future updates, if necessary, we will contact the principal trial investigators to clarify data and obtain any additional information needed.

Data extraction and management

For future updates of the review, if we include eligible trials, two review authors (ZY, ZR) will independently extract data according to chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* by using a standardised data extraction form containing the following items (Higgins 2011a).

- General information: title; authors; journal or source; contact address; country of origin; language; publication type; year of publication; setting of trial.

- Trial characteristics including: design; sample size; setting; location of trial; randomization method; concealment of allocation; blinding of participants and clinicians; withdrawals; median length of follow up; funding; conflict of interest statement.

- Interventions (basic information): disease(s) and stage(s) studied; category of treatment investigated; inclusion criteria; exclusion criteria; experimental intervention; control intervention; type of control; additional treatment; compliance; outcomes assessed; subgroup(s) evaluated; confounders.

- Baseline characteristics of participants: number of participants; age; ethnicity; gender; diagnosis; definition of diagnosis; extent of disease; organ involvement; additional diagnoses in group; stage; previous treatment; concurrent conditions.

- Interventions: setting; dose and duration of hemostatic therapy; supportive treatment; additional treatment.

- Outcomes: OS; bleeding control; adverse events.

If necessary, we will contact the principal trial investigators to clarify data and obtain any additional information needed.

Assessment of risk of bias in included studies

For future updates of the review, if we include trials, two authors (ZY and ZR) will independently assess the risk of bias of each included trial as per the recommendations in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* using the following criteria (Higgins 2011b):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

We will assess each item as having either a low, unclear or high risk of bias. We will resolve any disagreements by discussion with a third author (LD).

Measures of treatment effect

For future updates, if we include trials, we will use the Review Manager software to conduct the analysis (RevMan 2014). For dichotomous (binary) outcomes (sCR, CR, bleeding control, OS, adverse effects), we plan to present the risk ratio (RR) with 95% confidence intervals (CI). For continuous outcome data (time to response, duration of response), we plan to present the mean difference (MD) with 95% CIs, except where continuous data are reported using different units. In such cases we will calculate a standardised MD (SMD) and corresponding CIs. For survival data, we plan to use the hazard ratios (HR) to measure time-to-event data (Parmar 1998; Tierney 2007).

Unit of analysis issues

Cross-over trials

We do not expect to find trials with a cross-over design, as the effect of the drug in the first period is assumed to continue through the second period.

Multiple observations at different time points for the same outcome

For meta-analyses for time-to-event data, we plan to use data from the longest follow-up period. For dichotomous data we plan to analyse outcome data at 12 months separately to data at 60 months, if available. We plan to analyse adverse events at the end of drug treatment, up to 12 months and, if data are available, at 60 months. We plan to analyse response rates only at the end of drug treatment and up to 12 months.

Events that may recur

Adverse events may occur more than once in the same individual, mainly during different treatment cycles. We plan to extract the number of participants in each treatment arm and the number of participants who experienced at least one event. We plan to count each participant once even if repeated events occurred and analyse the data as dichotomous data.

Dealing with missing data

For future updates, if we include trials and data are missing or unavailable, we will contact the corresponding trial authors to obtain further information. This may include missing outcomes (primary or secondary), missing participants due to dropout, and missing statistics such as standard deviations (SD) or correlation co-efficients. If this is not possible and if we assume that these data are 'missing at random', we will perform an available-case analysis (i.e. ignoring the missing data) and discuss the impact of missing data on our results. When we assume the missing outcome data are not 'missing at random', we will conduct an intention-to-treat (ITT) analysis by imputing the missing data with replacement values, and treating these as if they were observed (e.g. imputing an assumed outcome such as assuming all were poor outcomes, imputing the mean, imputing based on predicted values from a regression analysis).

Assessment of heterogeneity

For future updates of the review, if we include trials, we will assess any heterogeneity by inspecting the forest plots and using the Chi² test and I² statistic with a statistical significance level of $P < 0.10$ and interpret I² as follows (Higgins 2003):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

For future updates, if we include several trials in any meta-analysis, we plan to explore potential publication bias by generating a funnel plot and statistically testing by means of a linear regression test. We consider a P value of < 0.1 as significant for this test (Sterne 2011). If we detect asymmetry, we plan to explore causes other than publication bias.

Data synthesis

For future updates, if we include trials, we plan to perform analyses according to the recommendations of chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will use aggregated data for analysis. For statistical analysis, we will enter data into the Review Manager software (RevMan 2014). One review author will enter data into the software and a second review author will check it for accuracy. We will perform meta-analyses using a fixed-effect model (e.g. the generic inverse variance method for survival data outcomes, the inverse variance method for continuous outcomes, and the Mantel-Haenszel method for dichotomous data outcomes). We will use the random-effects model in terms of sensitivity analyses. We will explore causes of heterogeneity by subgroup analyses.

Subgroup analysis and investigation of heterogeneity

For future updates, if several trials are included in the review, we plan to test the robustness of the results with the following subgroup analysis:

- high-titer inhibitors versus low-titer inhibitors.

Sensitivity analysis

We plan to undertake the following sensitivity analyses if possible:

1. quality components, including full text publications or abstracts, preliminary results versus mature results;
2. high versus low levels of dropouts;
3. random-effects modelling;
4. imputation of missing values.

Summary of findings table

For future updates, if we include trials in the review, for each comparison we plan to create a 'Summary of findings' table using the following outcomes: stable complete remission; complete remission; bleeding control; time to response; duration of response; overall survival; and adverse effects. We will use the five GRADE

considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence (studies that contribution data for the pre-specified outcomes). Methods and recommendations are described in chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will use GRADEpro software (GradePro 2014). We will justify all decisions to downgrade or upgrade the quality of evidence using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

Please refer to the [Characteristics of excluded studies](#) table.

Results of the search

A total of 2476 references were identified by the search. Of these, 2432 were discarded as not being relevant and 44 were selected for closer inspection, but were ultimately excluded. Therefore, no RCTs were identified which met the inclusion criteria for this review.

Excluded studies

Of the excluded studies, a total of nine references were review articles, editorials or comments and 35 related to non-randomised studies (see [Figure 1](#)).

Figure 1. Study flow diagram.

Risk of bias in included studies

No trials were identified which were eligible for inclusion in the review.

Effects of interventions

No trials were identified which were eligible for inclusion in the review.

DISCUSSION

Summary of main results

No randomised controlled trials (RCTs) assessing rituximab for eradicating inhibitors in people with AHA were identified. This may be due to the rarity of acquired haemophilia (AHA) and the lack of development of consistent treatment protocols. Therefore, no conclusions and recommendations for clinical practice can currently be provided based on RCT-derived evidence.

Potential biases in the review process

We anticipate the development of guidelines from the Cochrane Cystic Fibrosis and Genetic Disorders Group, which will enable the inclusion of non-randomised studies in a future update of this review. We therefore plan to appraise and incorporate evidence from any future randomised controlled trials, as well as from other high-quality non-randomised studies.

Agreements and disagreements with other studies or reviews

Treatment guidelines and treatment decisions will continue to be supported by lower-quality observational evidence (case-series and a large prospective registry), which have been summarized in the [Background](#) section of this review and suggest that rituximab could cautiously be considered as the effective treatment used for eradicating inhibitors in AHA. While caution and careful consideration on a case-by-case basis is needed, it has been noted that the recent prospective data collection of the EACH2 registry, while confirming the role of rituximab in eradicating inhibitors, has found that treatment for haemorrhage is required less commonly than previously expected ([Collins 2012a](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Due to an absence of RCTs eligible for inclusion, no implications for practice are generated by this review for or against any form of treatment. Therefore, the research evidence in this area is based on case reports or case series, with the existing systematic reviews based on observational studies only.

Implications for research

This systematic review has identified the lack of well-designed, adequately-powered RCTs to assess the benefits and risks of the use of rituximab as a means of eradicating inhibitors in people with AHA. However, formidable barriers exist to the proper planning and co-ordination of comparative trials. Due to the low absolute number of participants, trials of similar design can only be conducted over a long period of time and across several centres in order to achieve the requisite statistical power. Also, ethical considerations make designing such trials very complex ([Temple 1982](#)). Nonetheless, any active drug could be compared with alternative treatment modalities, and specific controlled study designs (risk allocation designs, sequential design, parallel cohort design) can be used to address particular issues of safety and efficacy ([Lilford 1995](#); [National Academies Press 2001](#)). Meanwhile, international prospective registries, collecting and maintaining data in agreement with high scientific standards, would be beneficial, as long as they allow the evaluation of patient-important outcomes ([Dreyer 2009](#)). Simultaneously, patient registries designed explicitly to examine questions of comparative effectiveness could provide epidemiological, safety, comparative effectiveness and cost-effectiveness data and could serve a wide spectrum of decision-making purposes ([Lipscomb 2009](#); [Temple 1982](#)). This review highlights to need randomised controlled trials to evaluate the effectiveness of rituximab in eradicating inhibitors in people with AHA. Future trials need to be rigorous in design and delivery, with subsequent reporting to include high quality descriptions of all aspects of methodology to enable appraisal and interpretation of results.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdallah 2005	Case report of 2 refractory people with AHA treated with rituximab
Aggarwal 2005	Case report of 4 people with AHA treated with rituximab.
Aljasser 2014	Case report of a 73-year-old person with AHA treated with prednisone, cyclophosphamide, rituximab and intravenous immunoglobulin
Berezné 2006	Case report of 2 people with AHA treated with rituximab.
Boles 2011	Not a RCT. Case series of 15 people with AHA treated with rituximab
Bonfanti 2015	A systematic review of postpartum AHA treated with rituximab
Chen 2012	Case report of a 69-year old male with AHA treated with rituximab
Clatworthy 2006	Case report of a 48-year old male with AHA treated with rituximab
D'arena 2015a	A review of the literature on rituximab to treat AHA.
D'Arena 2015b	Case report of a 60-year old male with AHA treated with rituximab
Daikeler 2011	Case report of 2 people with AHA treated with rituximab.
Dedeken 2009	Case report of 3 people with AHA treated with rituximab.
Delgado 2003	A systematic review and meta-analysis about AHA therapy.
EACH2 2012	Not a RCT. Prospective analysis of 51 people with AHA treated with rituximab
Field 2007	Case series of 4 people with AHA with very high-titre acquired factor VIII inhibitors treated with rituximab
Fischer 2003	Case report of 4 people with AHA treated with rituximab.
Franchini 2006	Review article about inhibitor-associated haemostatic disorders treated with rituximab
Franchini 2007	Not a RCT. A systematic literature review of 65 people with AHA treated with rituximab alone or in combination with other immunosuppressive agents
Franchini 2008b	A systematic review of acquired factor VIII inhibitor in oncohematology
Franchini 2010	A systematic review of AHA in pediatrics.

(Continued)

Franchini 2014	Review article about rituximab in AHA.
Grahammer 2015	Case series of 2 people with AHA treated with rituximab.
Herman 2005	Case report of a 53-year old man with AHA treated with rituximab
Holme 2005	Case report of 2 people with AHA treated with rituximab.
Huang 2015	Not a RCT. A retrospective analysis of 65 people with AHA in Taiwan
Jy 2003	Case report of a female with AHA treated with rituximab.
Kain 2002	Case report of a male with AHA treated with rituximab.
Karwal 2001	Case report of 3 people with AHA treated with rituximab.
Maillard 2006	Case report of a 18-year old female with AHA treated with rituximab
Mei-Dan 2009	Case report of a postpartum woman with AHA treated with rituximab
Onitilo 2006	Not a RCT. Case series of 6 people with AHA treated with rituximab
Santoro 2008	Case report of a 25-year old female with AHA treated with rituximab
Singh 2011	Not a RCT. Case series of 8 people with AHA treated with rituximab
Sperr 2007	Not a RCT. Comparative analysis of 42 people with AHA treated with rituximab and 44 with cyclophosphamide and prednisone
Stachnik 2006	A review of the literature on rituximab to treat AHA.
Stasi 2004	Not a RCT. Case series of 10 people with AHA with rituximab.
Tamponi 2002	Case series of 2 people with AHA treated with rituximab.
Tay 2009	Retrospective analysis of 25 people with AHA in South Australia
Tiede 2009	Retrospective analysis of 73 people with AHA with immunosuppressive treatment in Germany, Austria and Switzerland
Wermke 2010	Case report of an 66-year-old male with AHA treated with rituximab
Wiestner 2002	Case series of 4 people with AHA treated with rituximab.
Wilson 2011	Case report of a 74-year old man with AHA treated with rituximab
Yang 2015	Retrospective analysis of 3 people with AHA treated with rituximab

(Continued)

Yao 2014	Case report of a 88-year-old with AHA treated with low-dose rituximab
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AHA: acquired hemophilia A

ARDS: acute respiratory distress syndrome

CNL: chronic neutrophilic leukaemia

RCT: randomised controlled trial

TTP: thrombotic thrombocytopenic purpura

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL search strategy

Strategy
<ol style="list-style-type: none">1. MeSH descriptor hemophilia, factor VIII, inhibitor explode all trees2. MeSH descriptor hemophilia, A, acquired, factor VIII, inhibitor explode all trees3. (hemo*phi* NEAR/1 A*)4. (factor VIII* NEAR/3 inhibitor*) or (factor VIII* NEAR/3 autoantibodies*) or (factor VIII* NEAR/3 antibodies*)5. (acquire*)6. (haemo*phi*) or (hemo*phi*)7. (#5 AND (#3 OR #6))8. (AH or AHA)9. (#1 OR #2 OR #4 OR #7 OR #8)10. MeSH descriptor Antibodies, Monoclonal explode all trees11. (antibod* near/2 monoclonal*)12. (rituximab*)13. (CD20 NEAR/3 antibod*) or (CD-20 NEAR/3 antibod*) or (CD 20 NEAR/3 antibod*)14. (ANTI-CD20 or ANTI CD20)15. (#10 OR #11 OR #12 OR #13 OR #14)16. (#9 AND #15)

Appendix 2. MEDLINE search strategy

Strategy
<ol style="list-style-type: none">1. exp HEMOPHILIA A/2. exp ACQUIRED HEMOPHILIA A/3. ((hemo?phi\$ or haemo?phi\$) adj (A)).tw,kf,ot.4. (acquire\$).tw,kf,ot.5. 3 and 46. AH.tw.7. AHA.tw.8. or/6-79. 1 or 2 or 5 or 810. exp ANTIBODIES, MONOCLONAL/11. (antibod\$ adj2 monoclonal\$).tw,kf,ot.12. 10 or 11

(Continued)

13. rituximab\$.tw,kf,ot,nm.
14. ((CD20 or CD-20 or CD 20) adj3 antibod\$).tw,kf,ot,nm.
15. (ANTI-CD20 or ANTI CD20).tw,kf,ot,nm.
16. or/13-15
17. 9 and (12 or 16)
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. drug therapy.fs.
23. randomly.ab.
24. trial.ab.
25. groups.ab.
26. or/18-25
27. humans.sh.
28. 26 and 27
29. 17 and 28

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	WHO WILL UNDERTAKE THE TASK?
Protocol stage: draft the protocol	Zeng Yan
Review stage: select which trials to include (2 + 1 arbiter)	Zeng Yan, Zhou Ruiqing
Review stage: extract data from trials (2 people)	Zeng Yan, Long Dan
Review stage: enter data into RevMan	Zhou Ruiqing, Long Dan
Review stage: carry out the analysis	Zeng Yan,Duan Xin
Review stage: interpret the analysis	Zeng Yan, Duan Xin
Review stage: draft the final review	Zeng Yan, Zhou Ruiqing
Update stage: update the review	Zeng Yan

DECLARATIONS OF INTEREST

All authors declare no conflict of interest.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Autoantibodies; Factor VIII [*immunology]; Hemophilia A [*drug therapy]; Immunologic Factors [*therapeutic use]; Rituximab [*therapeutic use]

MeSH check words

Humans