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[Intervention Review]

# Rituximab for treating inhibitors in people with inherited severe hemophilia

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## ABSTRACT

### Background

Hemophilia A and B are inherited coagulation disorders characterized by a reduced or absent level of factor VIII or factor IX respectively. The severe form is characterized by a factor level less than 0.01 international units (IU) per milliliter. The development of inhibitors in hemophilia is the main complication of treatment, because the presence of these antibodies, reduces or even nullifies the efficacy of replacement therapy, making it very difficult to control the bleeding. People with inhibitors continue to have significantly higher risks of morbidity and mortality, with considerable treatment costs. Given the wide 'off-label' use of rituximab for treating people with hemophilia and inhibitors, its efficacy and safety need to be evaluated. This is an update of a previously published Cochrane Review.

### Objectives

To assess the efficacy and safety of rituximab for treating inhibitors in people with inherited severe hemophilia A or B.

### Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We searched the reference lists of relevant articles and reviews and also searched for ongoing or unpublished studies. We also undertook further searches of other bibliographic databases and trial registries.

Date of last search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Coagulopathies Trials Register: 16 February 2017.

### Selection criteria

Randomized controlled trials and controlled clinical trials investigating the efficacy and safety of rituximab for treating inhibitors in people with hemophilia.

### Data collection and analysis

No randomized controlled trials matching the selection criteria were eligible for inclusion.

### Main results

No randomized controlled trials on rituximab for treating inhibitors in people with hemophilia were identified.

**Rituximab for treating inhibitors in people with inherited severe hemophilia (Review)**

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## Authors' conclusions

We were unable to identify any relevant trials on the efficacy and safety of rituximab for treating inhibitors in people with hemophilia. The research evidence available is from case reports and case series. Randomized controlled trials are needed to evaluate the efficacy and safety of rituximab for this condition. However, prior to the publication of any possible future randomized controlled trials, meta-analysis of case reports and case series may provide some evidence.

## PLAIN LANGUAGE SUMMARY

### Rituximab for treating inhibitors in people with inherited severe hemophilia

#### Review question

We reviewed the evidence available to see if rituximab is effective and safe when treating clotting factor inhibitors in people with severe hemophilia. This is an update of a previously published Cochrane Review.

#### Background

Hemophilia A and B are inherited conditions in which there is either reduced levels (or none at all) of factor VIII (hemophilia A) or factor IX (hemophilia B) in the blood. In severe forms there are undetectable levels of these factors (less than 0.01 international units (IU) per milliliter). People with hemophilia are at risk of bleeding events which can occur spontaneously or after trauma or invasive medical procedures. Therefore, they need to be treated with factor concentrates, either in reaction to these events or preventatively. Unfortunately, about 30% of people with severe hemophilia A and 1% to 6% of people with severe hemophilia B can develop antibodies (inhibitors) against factor VIII or factor IX, because the factors are not recognized by the immune system. The development of inhibitors is the main complication of hemophilia treatment, because their presence reduces or cancels out the beneficial effects of replacement therapy, making it very difficult to control bleeding. Moreover, when inhibitors are present, it is impossible to start preventative treatment with factor VIII or factor IX concentrates. Therefore, it is important to eliminate the inhibitors and allow treatment to proceed successfully. The 'off-label' use (currently unapproved for treating people with hemophilia) of rituximab, has shown in some studies an effect on eliminating inhibitors in people with hemophilia. Therefore, we wanted to see whether using rituximab was better than the standard treatment or other therapies without rituximab, and whether it is safe, and could save these people from life-threatening hemorrhage and huge financial expense.

#### Search date

The evidence is current to: 16 February 2017.

#### Key results

We did not find any randomized controlled trials assessing rituximab in people with severe hemophilia. Well-designed controlled trials are needed to assess the benefits and risks of using rituximab in people with hemophilia. Until controlled trials are published, only limited and low-level evidence, based on individual cases, can guide physicians in making clinical decisions.