Autoimmunity Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Efficacy and safety of rituximab in auto-immune hemolytic anemia: A meta-analysis of 21 studies

Quitterie Reynaud [a,*], Isabelle Durieu [a,d], Marine Dutertre [a], Stanislas Ledochowski [b], Stéphane Durupt [a], Anne-Sophie Michallet [c], Denis Vital-Durand [a], Jean-Christophe Lega [a,d]

[a] Department of Internal and Vascular Medicine, Centre Hospitalier Lyon Sud, Claude Bernard University Lyon 1, France
[b] Anesthesiology and Critical Care Department, Centre Hospitalier Lyon Sud, Claude Bernard University Lyon 1, France
[c] Department of Hematology, Centre Hospitalier Lyon Sud, Claude Bernard University Lyon 1, France
[d] UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, CNRS, Claude Bernard University Lyon 1, France

ARTICLE INFO

Article history:
Received 20 November 2014
Accepted 26 November 2014
Available online xxxx

Keywords:
Rituximab
Autoimmune hemolytic anemia
Overall response rate
Complete response
Warm autoimmune hemolytic anemia
Cold agglutinin disease

ABSTRACT

Objective: This study aims to evaluate the response to rituximab (RTX) treatment in auto-immune hemolytic anemia (AIHA) patients.
Methods: Studies were selected from MEDLINE up to March 2014. Two investigators independently extracted data on study design, patient characteristics, clinical features (AIHA type, disease duration, previous treatments), dose-schedule of rituximab, duration of treatment follow-up, and toxicities. Pooled overall response rate (ORR) and complete response (CR) rates were evaluated to determine RTX efficacy and toxicity by calculating the weighted mean proportion with fixed or random-effects models in case of heterogeneity ($p < 0.1$ or $I^2 > 50\%$).
Results: Twenty-one studies encompassing 409 patients were included in the meta-analysis. The characteristics of the entire analyzed cohort reported were as follows: mean male proportion: 43%, mean age: 50 years, splenectomized patients range: 0–50%. Warm AIHA, primary AIHA and adults were mostly represented. With the random-effect model, the overall response rate (ORR) was 73% (95% CI 64–81%, 20 studies encompassing 402 patients). CR rate was 37% (95% CI 26–49%, 20 studies including 397 patients). The ORRs were close to 70% for warm AIHA (79%, 95% CI 60–90%, 11 studies, 154 patients), primary AIHA (67%, 95% CI 49–81%, 10 studies, 161 patients), and secondary AIHA (72%, 95% CI 60–82%, 8 studies, 66 patients). The ORR was 57% (95% CI 47–66%, 6 studies, 109 patients) for cold agglutinin disease (CAD). The CR rate was 42% (95% CI 27–58%, 11 studies, 154 patients) for warm AHAI, 32% (95% CI 17–51%, 11 studies, 176 patients) for primary AIHA, 46% (95% CI 30–62%, 9 studies, 87 patients) for secondary AIHA and only 21% (95% CI 6–51%, 7 studies, 118 patients) for CAD. Definitive response rates were evaluated during follow-up. CR rate was the highest within 2 to 4 months after RTX (13 studies, 203 patients, CR = 70% [57–80%]). As for toxicities, 38 adverse events in 364 patients were noted (14% (95% CI 9-21%)). Sixteen events were infusion-linked side effects, mostly chills and fever, whereas twenty-two were severe. Only one opportunistic *Pneumocystis jiroveci* pneumonia was reported. Seventeen patients out of 364 (4.6%) died during follow-up.
In univariate mixed-effect meta-regressions, ORR and CR were significantly associated with warm AIHA ($p = 0.002$) and mean age ($p < 0.001$), and marginally associated with disease type ($p = 0.06$ and 0.005, respectively).
Conclusions: Rituximab seems to be a safe and effective therapy for AIHA in this meta-analysis of observational studies. The authors suggest that it could be used at an earlier point in therapy, before more toxic immunosuppressive drugs, or in place of splenectomy in some cases.

Contents

* Corresponding author at: Department of Internal and Vascular Medicine, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, 69495 Pierre-Bénite, France. Tel.: +33 4 78 86 13 55; fax: +33 4 78 86 32 64.

http://dx.doi.org/10.1016/j.autrev.2014.11.014
1568-9972/

1. Introduction

Auto-immune hemolytic anemia (AIHA) often leads to significant morbidity and mortality. It is a rare disorder with an estimated incidence of one to three cases per 100,000 persons per year [1]. AIHA is classified as either warm (50–70%) [2,3] or cold AIHA, depending upon the temperature at which the autoantibodies show maximal binding. Warm AIHA (WAIHA) is mediated by warm reactive autoantibodies, which are usually of the immunoglobulin G class. Cold AIHA, namely cold agglutinin disease (CAD), represents 10–20% of AIHA [4]. Almost 90% of CAD is mediated by monoclonal antibodies of the IgM class [5,6]. Although AIHA can be idiopathic (primary AHAI), a subset of patients has a suspected secondary cause to their disorder (mostly lymphoproliferative disorders, autoimmune disorders such as lupus [7], and infections) defining secondary AHAI [8]. Secondary AIHA represents 50% of WAIHA [9].

Patients with WAIHA generally receive corticosteroids as first line therapy; 70–80% of patients improve with this treatment. For those with inadequate response, i.e. patients refractory to corticosteroids in 15% or dependent to corticosteroids in approximately 60%, second line treatment is usually splenectomy [10]. Treatment options forpatients who relapse or are unable to undergo splenectomy are azathioprine or cyclophosphamide, with an overall response estimated to one-third of patients [11]. The efficacy of other immunosuppressive drugs including mycophenolate mofetil and cyclosporine is uncertain probably overestimated due to selection bias [11]. In CAD, corticosteroids are generally ineffective, just as splenectomy. Immunosuppression with chlorambucil or cyclophosphamide may be beneficial [12].

Thus, current available treatments for patients with AIHA are far from satisfactory [13]. Long-term use of corticosteroids is known to be associated with many complications. On the other hand, the sustained response rate after splenectomy is approximately 60–70% according to the most recent data [14,15] with a peri-operative risk and a mortality rate of less than 1% [14]. However, overwhelming sepsis and postoperative thromboembolic complications are not infrequent. Furthermore, cytotoxic immunosuppressants can also be associated with serious adverse events: immediate increase of infection rate and delayed risk such as neoplasia with cyclophosphamide or hypersensitivity syndrome with azathioprine.

Rituximab (RTX), a monoclonal antibody directed against the CD20 antigen expressed on B-lymphocytes, has been successfully used as a second line treatment in both refractory adults and children, or in patients who are medically unsuited for splenectomy. Presumably, it targets B-lymphocytes that produce anti-red blood cells antibodies. Although many reports indicate that rituximab in an effective drug in CAD [5,16] and in WAIHA [17,18], studies assessing anti-CD20 antibodies in AIHA were mostly case reports and small retrospective studies and did not allow to draw firm conclusions on efficacy and safety.

Henceforth, we conducted a meta-analysis to evaluate the efficacy and safety of rituximab in adults and children with AIHA.

2. Methods

2.1. Data sources and searches

We followed the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines during all stages of design, implementation, and reporting of this meta-analysis [19,20]. We identified all relevant published and unpublished observational studies that specifically examined rituximab treatment efficacy in AIHA. Selection criteria were determined before data collection.

An exhaustive literature search was performed on the MEDLINE and Cochrane Library electronic databases. The search criteria were Autoimmune Hemolytic Anemia (Medical Subject Heading, MeSH) and Rituximab/Rituxan® with human as limits. We manually checked the references of all identified articles, while also searching Google Scholar and conference proceedings in the fields of hematology and internal medicine to find additional documents.

2.2. Study selection

Observational studies that included adults or children with primary or secondary AIHA treated with rituximab were selected. Refractory AIHA was defined by hemolytic anemia, a positive direct antiglobulin test, and steroid inefficacy or dependence. AIHA was classified as either primary (idiopathic AHAI), or secondary when a secondary cause of AHAI was identified. Studies were classified according to the type of AIHA (WAIHA or CAD). A distinction was made between the described populations, i.e. adults or children. Studies concerning patients with Evan's syndrome were excluded. Studies that included both warm AIHA or CAD and primary or secondary AIHA were included if data could be extracted separately.

Searches were restricted to articles published in English or French, up to march 2014. There was no restriction in study design and reports in abstract form or letters were included. Studies enrolling less of five patients were not included because of the risk of extreme bias.

2.3. Data extraction and quality assessment

Data from eligible studies was independently extracted by two authors (Q.R. and J.C.L.). In the event of discrepancy, a consensus was reached. The extracted study characteristics included the first author's name, study acronym, year of publication, design (prospective or retrospective) and population. Autoimmune hemolytic anemia was classified as primary or secondary, WAIHA or CAD. Baseline demographical data,

Please cite this article as: Reynaud Q, et al, Efficacy and safety of rituximab in auto-immune hemolytic anemia: A meta-analysis of 21 studies, Autoimmun Rev (2014), http://dx.doi.org/10.1016/j.autrev.2014.11.014