Seminars in Arthritis and Rheumatism ▮ (2013) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

Biological therapy for systemic vasculitis: A systematic review☆,☆☆,★

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ARTICLE INFO

Keywords:
ANCA-associated vasculitis
Large vessel vasculitis
Biological therapy
Systematic review

ABSTRACT

Objective: Relapses and failure are frequent in systemic vasculitis (SV) patients. Biological agents have been prescribed as rescue therapies. The aim of this systematic review is to analyze the current evidence on the therapeutic use of biological agents for SV.
Methods: MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials were searched up to the end of April 2013. Systematic reviews and meta-analysis, clinical trials, cohort studies, and case series with >3 patients were included. Independent article review and study quality assessment was done by 2 investigators with consensus resolution of discrepancies.
Results: Of 3447 citations, abstracts, and hand-searched studies screened, 90 were included. Most of the studies included ANCA-associated vasculitis (AAV) patients and only a few included large vessel vasculitis (LVV) patients. Rituximab was the most used agent, having demonstrated efficacy for remission induction in patients with AAV. A number of studies used different anti-TNFα agents with contrasting results. A few uncontrolled studies on the use of abatacept, alemtuzumab, mepolizumab, and tocilizumab were found.
Conclusion: Current evidence on the use of biological therapies for SV is mainly based on uncontrolled, observational data. Rituximab is not inferior to cyclophosphamide for remission induction in AAV and might be superior in relapsing disease. Infliximab and adalimumab are effective as steroid-sparing agents. Etanercept is not effective to maintain remission in patients with granulomatosis with polyangiitis, and serious adverse events have been reported. For LVV, both infliximab and etanercept had a role as steroid-sparing agents, and tocilizumab might be effective also for remission induction in LVV.

Introduction

Systemic vasculitis refers to a heterogeneous group of inflammatory diseases of blood vessels with multisystem manifestations. These are relatively uncommon disorders, with a reported annual incidence of 40–54 cases per 1 million persons [1]. The incidence appears to be affected by geography, age, and seasonal challenges. Numerous classifications of vasculitis have been proposed based on their involvement of specific groups of blood vessels of different sizes, their tropisms for certain organ systems, and in some cases, their characteristic pathologic features. In 1994, the Chapel Hill Consensus Conference proposed a nomenclature defining 10 primary vasculitides based on vessel size (large, medium, and

☆Source of support: Spanish Foundation for Rheumatology.
☆☆Role of Funding Source: This study was supported by the Spanish Foundation of Rheumatology (FER) with an unrestricted educational grant from Roche Farma, SA. The FER and Roche Farma had no role in the extraction and interpretation of data or in the draft of the manuscript. All authors had full access to all the data included in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr L. Silva-Fernández is supported by an educational grant from Instituto de Salud Carlos III, Madrid. Dr J.M. Pego-Reigosa is supported by the grant 316265 (BIOCAPS) from the European Union 7th Framework Programme (FP7/REGPOT-2012-2013.1).
★VMM-T: Research grants, speaking fees, advisory boards or participation in clinical trials for Roche, Pfizer, MSD and Abbott.
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http://dx.doi.org/10.1016/j.semarthrit.2013.07.010

small) [2]. This nomenclature also stresses the importance of antineutrophil cytoplasmic antibodies (ANCA) testing in the diagnosis of vasculitis, particularly in differentiating granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in persons with pulmonary and renal involvement [3,4]. The treatment of systemic vasculitides is based, for most patients, on the combination of corticosteroids (CS) with different immunosuppressants. Despite the improvement obtained with this strategy, relapses and failure are frequent [5,6], and the cumulative toxicity of some immunosuppressants like cyclophosphamide (CYC) limits its usefulness in the long-term treatment of patients [7]. In recent years, different biological agents have been prescribed as rescue therapies for vasculitis in a number of studies. The aim of this systematic review is to analyze the current evidence on the therapeutic use of biological agents for systemic vasculitis.

Methods

Literature search and study selection

We systematically searched MEDLINE (from 1940), EMBASE (from 1972), and the Cochrane Central Register of Controlled Trials (from 1993) up to the end of April 2013 using a comprehensive search strategy that combined MeSH terms and free text for "Vasculitis," "Biological Therapy," "Efficacy," and "Safety" (Appendix 1). We also hand searched abstracts from scientific meetings of the American College of Rheumatology (ACR) 2011 and 2012 and the European League against Rheumatism (EULAR) 2011–2013. Reference lists of all relevant studies, reviews, and letters were also searched to identify additional studies. The searches were limited to humans and adults.

Our inclusion criteria were broad and included prior systematic reviews and meta-analysis, clinical trials, cohort studies, and case series with more than 3 patients. The selection criteria were predefined by protocol. In order to incorporate a study, the following criteria were established: (1) the studied population had to include adult patients with a systemic vasculitis; (2) at least one group of patients had to have received treatment with a biological therapy; and (3) outcome should be a measure of efficacy (such as remission indicated by the Birmingham Vasculitis Activity Score (BVAS), time to remission, relapses, acute phase reactants, or ANCA titers) or safety (infections, cancer, demyelinating disease, cytopenia, etc.). Studies including patients with Behçet disease, cryoglobulinemia, secondary vasculitis, studies on animals, and basic science research were excluded.

Data extraction

Two reviewers (L.S.-F. and E.L.) independently screened all titles and abstracts to identify potentially relevant articles. This process was done in 20 min sessions. Disagreements were resolved by repeated review and discussion. They independently extracted data from the full-text articles using structured review forms that included inclusion/exclusion criteria, outcome measures, and study quality. Articles that did not fulfill all the inclusion criteria were excluded from the systematic review. The quality of studies to be included was assessed using the Oxford CEBM Levels of Evidence document [8].

Results

The result of the search strategies is presented in Appendix 1 by specific terms and in total in Figure 1. A total of 3408 articles were identified, of which, 107 underwent full-text review and 63 met the inclusion criteria for biologic therapy in systemic vasculitis. We identified 7 additional studies by hand search. Thirty-two congress

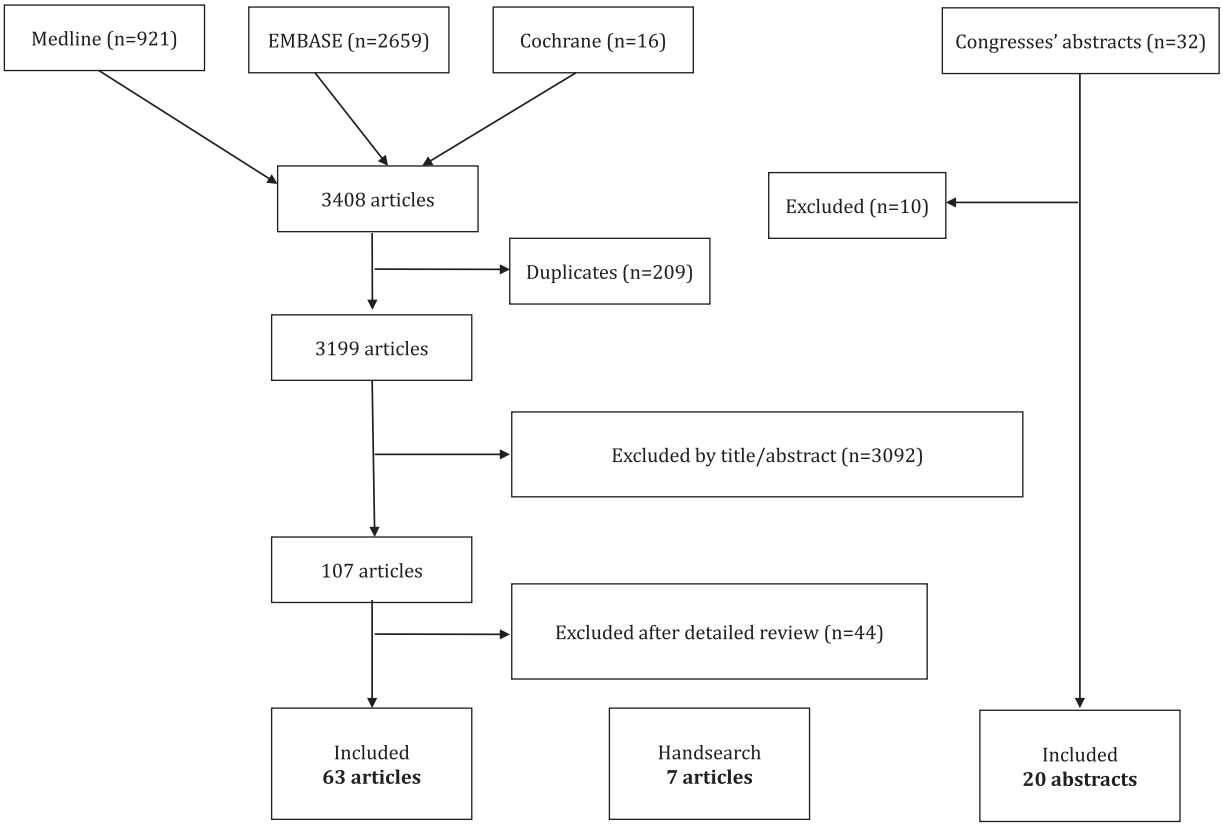

Fig. 1. Articles retrieved by different search strategies and result of selection and appraisal process.