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Review

Intravenous immunoglobulins and antiphospholipid syndrome: How, when and why? A review of the literature

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ABSTRACT

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-β2 glycoprotein-I (β2GPI) antibodies. The current mainstay of treatment for thrombotic APS is heparin followed by long-term anticoagulation, while in obstetric APS, the accepted first-line treatment consists in low-dose aspirin (LDA) plus prophylactic unfractionated or low-molecular-weight heparin (LMWH). Recently, new emerging treatment modalities, including intravenous immunoglobulins (IVIG), have been implemented to manage APS refractory to conventional therapy. The objective of this review is to summarize the currently available information on the IVIG therapy in APS, focusing on the use of IVIG in the obstetric form, CAPS and on primary or secondary thromboprophylaxis. We analyzed 35 studies, reporting the effects of IVIG in APS patients, and we discussed their results. IVIG in obstetric APS seem to be very useful in selected situations (patients not responsive to the conventional treatment, concomitant autoimmune manifestations or infections or patients in whom anticoagulation is contraindicated). IVIG treatment represents an important component of the combination therapy of CAPS and they could be useful, in addition to the standard therapy, to prevent recurrent thrombosis in APS patients refractory to conventional anticoagulant treatment. Anyway, in some cases we also found controversial results that claim the need of further well-designed studies to definitely state the efficacy and tolerability of IVIG in CAPS, obstetric and non-APS.

Contents

1. Introduction

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses, often multiple, and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-β2 glycoprotein-I (β2GPI) antibodies [1]. Preliminary classification criteria (Sapporo criteria) were developed in the 1999 international consensus meeting and updated in 2006 [2]. APS can occur either as a primary condition (primary APS) or in association with other autoimmune diseases, usually systemic lupus erythematosus (SLE) [3]. Also, a rare and severe subset

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of APS, defined catastrophic APS (CAPS), has been described and it's characterized by multiorgan failure originated by widespread thrombotic disease, which usually affects small vessels over a short period of time and is associated with high mortality rates [4].

APS is recognized as the most common cause of acquired thrombophilia in the general population; some estimates indicate that the incidence of the APS is around 5 new cases per 100,000 persons per year and the prevalence around 40–50 cases per 100,000 persons [5].

There is a wide spectrum of clinical manifestations in APS that ranged from non-criteria aPL manifestations in persistent aPL-positive patients (livedo reticularis, thrombocytopenia, hemolytic anemia, skin ulcers, aPL-associated nephropathy, and heart valve disease), to APS with only pregnancy morbidity, APS with vascular events, and to life-threatening CAPS. Considering the heterogeneity of APS clinical manifestations, it's likely that more than one pathological process may play a role [6]. Despite the exact pathogenetic mechanisms have not been fully elucidated, aPL seem to promote the activation of the endothelial cells, monocytes and platelets, leading to a procoagulant state. Furthermore, aPL could act through anticoagulation factor inactivation and activation of the complement cascade [7]. The current mainstay of treatment for thrombotic APS is heparin followed by long-term anticoagulation with vitamin K antagonists, which is problematic because of numerous drug and food interactions that necessitate frequent monitoring; furthermore, anticoagulation is not effective for all aPL manifestations [8]. In obstetric APS, the accepted first-line treatment consists in low-dose aspirin (LDA) plus prophylactic unfractionated or low-molecular-weight heparin (LMWH). However, a sufficient control of the activity disease is actually not achieved in approximately 20% of pregnant APS patients [9].

Recent studies, based on newly understood mechanisms, suggest new treatments for aPL-positive patients that target new coagulation and immunomodulatory pathways. Furthermore, new emerging treatment modalities, such as hydroxychloroquine (HCQ), statins, rituximab, eculizumab and intravenous immunoglobulins (IVIG), have been implemented to manage APS refractory to conventional therapy [8]. IVIG are blood products prepared from the serum of a large number of donors and they are currently used to treat a wide variety of immune-driven diseases, such as immune thrombocytopenic purpura, Guillain–Barré syndrome, Kawasaki disease and polymyositis/dermatomyositis [10]. Data on the use of IVIG in patients with APS focused on the obstetric complications and on CAPS, while only few reports showed the efficacy of IVIG as an adjuvant to conventional therapy in primary and secondary APS [11].

The objective of this review is to summarize the currently available information on the IVIG therapy in APS, focusing on the use of IVIG in the obstetric form, CAPS and on primary or secondary thromboprophylaxis. We also discuss the protocols therapy adopted in the different studies, the tolerability and the possible mechanisms of action.

2. Methods

We conducted a review of the literature concerning clinical studies about IVIG therapy in APS in October 2015. First of all, the strategy to select the clinical studies consisted in a detailed search in scientific databases Pubmed, Scopus, Cochrane Library and EMBASE. The keywords were “intravenous immunoglobulin”, “intravenous immunoglobulin therapy” in combination with “antiphospholipid syndrome”, “antiphospholipid antibodies”, “recurrent miscarriage”, “recurrent pregnancy loss”, “catastrophic APS” and “thrombotic events”. Studies were considered eligible if they met the following criteria: (i) patients had a diagnosis of APS, according to the 2006 updated APS criteria [2]; (ii) original articles or case reports whose main objectives were to analyze the effect and tolerability of IVIG therapy in patients with obstetric APS; (iii) original articles or case reports that evaluated the effects of IVIG in CAPS; (iv) original articles or case reports about the efficacy of IVIG in preventing thrombosis relapses in APS patients. We applied no date restrictions, so the period examined was 1990 (year of the first publication in this field) — October 2015 (date of our search). Articles written in languages other than English were excluded.

3. Results

In total, 235 potential studies were found; no additional papers were obtained by hand searching of references. Of these, 37 studies were excluded because they were written in a language other than English. Based on the title and the abstract content, 79 of these articles were not included in our review. The full texts of the remaining 119 studies were read, and a further 66 studies were excluded because review articles and 13 because not clinical trials (Fig. 1). We identified 35 assessable articles, 14 case reports, 9 case series and 12 clinical trials (9 open-label, 3 randomized controlled), reporting the effects of IVIG in APS patients, including a total number of patients of 802 (Tables 1, 2, 3, 4, 5). The 99% of the participants in the studies were women (795 women and 7 men).

4. IVIG in Obstetric APS

Most of the reports about the use of IVIG in human APS focused on its obstetric complications, mainly recurrent pregnancy loss. The first description of a case of obstetric APS patient treated with IVIG was that by Carreras et al. in 1988 [12]. The authors presented the story of a pregnant 28-years-old woman who had had nine early spontaneous abortions, two intrauterine deaths and a perinatal death at 26 weeks.

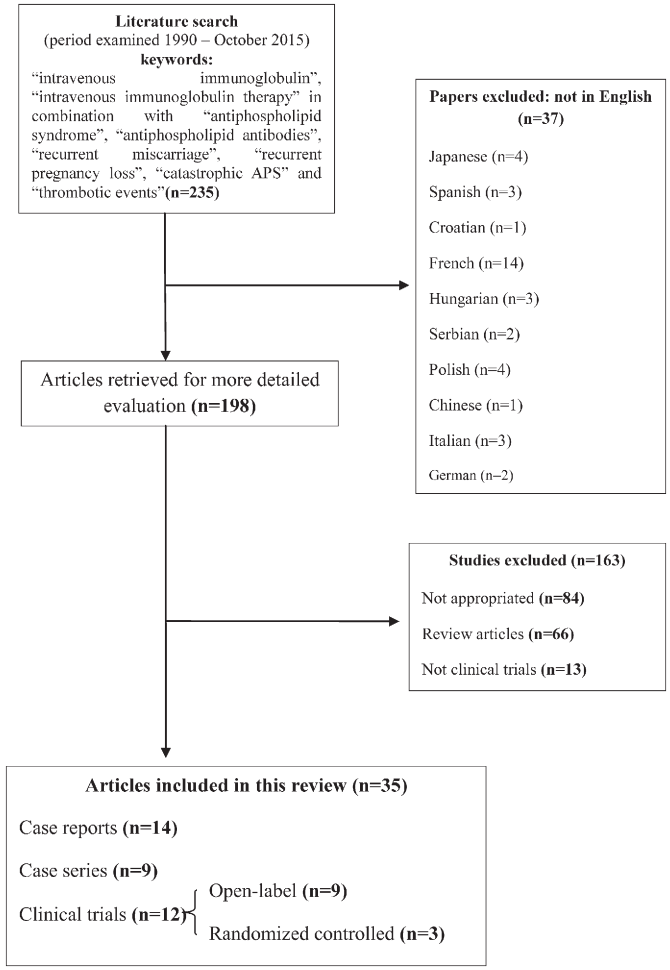

Fig. 1. Study flow diagram.