Autoimmunity Reviews 12 (2013) 1085–1090

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

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

Review

Rituximab use in the catastrophic antiphospholipid syndrome: Descriptive analysis of the CAPS registry patients receiving rituximab

Horacio Berman [a], Ignasi Rodríguez-Pintó [a], Ricard Cervera [a], Nathalie Morel [b,e], Nathalie Costedoat-Chalumeau [b,e], Doruk Erkan [c], Yehuda Shoenfeld [d], Gerard Espinosa [a,*], for the Catastrophic Antiphospholipid Syndrome (CAPS) Registry Project Group (European Forum on Antiphospholipid Antibodies) [1]

[a] Department of Autoimmune Diseases, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Catalonia, Spain
[b] Université Paris 5, Paris, France
[c] The Barbara Volcker Center for Women and Rheumatic Disease, Hospital for Special Surgery, Weill Medical College of Cornell University, New York, NY, USA
[d] The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
[e] AP-HP, Service de Médecine Interne, Centre des Maladies Rares, Hôpital Cochin, Paris, France

ARTICLE INFO

Article history:
Received 8 May 2013
Accepted 20 May 2013
Available online 15 June 2013

Keywords:
Catastrophic antiphospholipid syndrome
Refractory
Rituximab
Anti-CD20

ABSTRACT

The catastrophic variant of the antiphospholipid syndrome (APS) is characterized by thrombosis in multiple organs developing over a short period of time. First-line treatment for the catastrophic APS is the combination of anticoagulation plus corticosteroids plus plasma exchange and/or intravenous immunoglobulin. Despite this regimen, the mortality remains high and new treatment options are needed. By a systematic review of the Catastrophic APS Registry (CAPS Registry), we identified 20 patients treated with rituximab. The purpose of this study is to describe the clinical manifestations, laboratory features, and outcomes of rituximab-treated CAPS patients. In addition, the rationale for using rituximab in catastrophic APS is discussed.

Contents

1. Introduction

The antiphospholipid syndrome (APS) is characterized by venous and arterial thrombosis and/or pregnancy morbidity occurring in patients with persistently positive antiphospholipid (aPL) antibodies [1]. The catastrophic variant of the APS is characterized by thrombosis in multiple organs developing over a short period of time [2].

* Corresponding author at: Servei de Malalties Autoimmunes, Hospital Clínic, Villarroel 170, 08036 Barcelona, Catalonia, Spain. Tel.: +34 93 227 5774; fax: +34 93 227 1707.
E-mail address: gespino@clinic.cat (G. Espinosa).
[1] See complete list of members of the CAPS Registry at the end of the article.

1568-9972/$ – see front matter
http://dx.doi.org/10.1016/j.autrev.2013.05.004

Unfortunately, the current knowledge of the pathogenic mechanisms of this variant of APS is scarce in part due to the lack of studies on the pathophysiological mechanisms of catastrophic APS. In this context, it has been hypothesized that some of the features of catastrophic APS may be due to the development of systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive cytokine release from injured tissues [3].

Besides identification and treatment of any precipitating factor, the current treatment of catastrophic APS is based on two underlying pathophysiologic events, thrombosis and SIRS. First line therapies include the combination of anticoagulation (AC) against thrombosis plus glucocorticoids (GCs) against manifestations of SIRS plus plasma exchange (PE) and/or intravenous immunoglobulins (IVIGs) against both aPL and SIRS [4]. Our group demonstrated that the combined treatment of AC plus GC plus PE followed by AC plus GC plus PE and/or IVIG achieved the higher recovery rate [5].

Despite this reduction of mortality from 53% in patients diagnosed before 2001 to 33% in those diagnosed between 2001 and February 2005 ($p < 0.005$), refractory patients who die despite first-line treatments or those suffering from recurrent episodes of catastrophic APS exist. Due to the existence of these refractory cases, other medications such as rituximab have been used together with conventional combined therapy [6].

Rituximab is a chimeric monoclonal antibody against a surface antigen expressed by the B cells named CD20. Rituximab is approved for relapsed or refractory $CD20^+$, B-cell non-Hodgkin lymphoma and rheumatoid arthritis [7] and it may play a role in the treatment of autoimmune diseases. Although, two randomized controlled trials failed to demonstrate its effectiveness as add-on therapy in SLE [8,9], the global analysis of all cases reported to date supports the off-label use of rituximab in severe, refractory SLE cases, whereas its use as a first-line therapy or in patients with a predominantly mild form of the disease is not advised [10].

Regarding APS, a recent open label phase II trial has shown the safety of rituximab use in patients with APS and some benefits in controlling non-criteria manifestations such as thrombocytopenia, skin ulcers, nephropathy, and cognitive dysfunction [11]. Moreover, Erre et al. [12] described 12 patients with primary and SLE-associated APS who were treated with rituximab.

The aim of this review is to describe the clinical manifestations, laboratory features, and outcome of patients with catastrophic APS treated with rituximab. In addition, the rationale for using rituximab in catastrophic APS is discussed.

2. Patients and methods

2.1. Data collection

We reviewed the web-based international Catastrophic APS Registry ("CAPS Registry") for rituximab-treated patients. This registry was created by the European Forum on Antiphospholipid Antibodies, a study group devoted to the development of multicenter projects with large populations of APS patients. The source of information for the CAPS Registry is: a) periodic Medline search of published CAPS reports; and b) personal communication with physicians of CAPS patients for the unpublished cases (physicians fill out a standardized data form collecting demographic, clinical, therapeutic, and outcome information). The registry documents the clinical, laboratory and therapeutic data of all reported cases of catastrophic APS, and general data can be freely consulted through the Internet (http://infmed.fcrb.es/en/web/caps).

For the purpose of this study, data from selected patients were summarized using a standardized data form, including sex, age, and diagnosis of the underlying condition, precipitating factors, main thrombotic and non-thrombotic clinical manifestations, immunologic features, treatment, and disease evolution. In addition, we contacted by email the physicians who sent the cases as personal communications in order to obtain all the required information.

Results from continuous variables are presented as mean ± standard deviation (SD) or median (interquartilic range [IQR]) and categorical data as percentages.

3. Results

3.1. General characteristics

Of the 441 patients included in the "CAPS Registry" as of May 2013, 20 (4.6%) were treated with rituximab. Ten patients were previously published [13–21] and 10 additional patients were identified based on personal communications. The main demographic features, precipitating factors, and clinical manifestations are depicted in Table 1. In 6 (30%) patients, the catastrophic event was the first manifestation of APS.

In nine (45%) patients, precipitating factors were identified. The most frequent precipitating factor, found in six (30%) patients, was infection. Problems related to anticoagulation treatment were identified in three (15%) cases (noncompliance in two and anticoagulation withdrawal due to Cesarean section in one, respectively).

Kidney involvement was present in 14 (70%) patients (renal failure and proteinuria). Cardiac involvement was present in 11 (55%) cases (myocardial infarction, cardiac failure and silent valve lesions). Cerebral

Table 1
Demographic and clinical features of patients with catastrophic APS treated with rituximab.

	No. (%)
Sex (F/M)	13/7 (65/35)
Age at diagnosis of catastrophic APS (years)	38.7 ± 17.3
Previous diagnosis	
Primary APS	11 (55)
Systemic lupus erythematosus	6 (30)
Lymphoproliferative syndrome	2 (10)
Other	1 (5)
Precipitating factor*	
None	11 (55)
Infection	6 (30)
Non-AC compliance or AC withdrawn	3 (15)
Surgery	1 (5)
Clinical manifestations	
Kidney	14 (70)
Heart	11 (55)
Brain	10 (50)
Lung	9 (45)
Liver	7 (35)
Peripheral venous thrombosis	6 (30)
Spleen	4 (20)
Skin	4 (20)
Peripheral artery thrombosis	3 (15)
Bowel	3 (15)
Pancreas	3 (15)
Adrenal glands	2 (10)
Eye	1 (5)
Laboratory features	
Thrombocytopenia (<150,000/mm^3)	13 (65)
Lupus anticoagulant	14/16 (88)
IgG aCL	15/17 (88)
IgM aCL	5/11 (45)
Rituximab regimens†	
1000 mg fortnightly × 2	8 (40)
375 mg/m^2 weekly × 4	6 (30)
500 mg weekly × 2	1 (5)
1000 mg monthly × 2	1 (5)
1000 mg × 3 (spread out over two weeks)	1 (5)

AC: anticoagulation; APS: antiphospholipid syndrome.
* One patient presented infection and surgery as precipitating factors of catastrophic APS.
† In 3 patients specific dose of rituximab was not reported.