European Journal of Internal Medicine 26 (2015) 659–665

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Review Article

Rituximab in autoimmune thrombotic thrombocytopenic purpura: A success story

Antoine Froissart [a,b], Agnès Veyradier [b,c,d], Miguel Hié [e], Ygal Benhamou [b,f], Paul Coppo [b,g,h,*], French Reference Center for Thrombotic Microangiopathies

[a] Service de médecine interne, CHI, Créteil, France
[b] Centre de Référence des Microangiopathies Thrombotiques, AP-HP, Paris, France
[c] Service d'hématologie biologique, Hôpital Lariboisière, Paris, France
[d] Université Paris Diderot, Sorbonne Paris Cité, Paris, France
[e] Service de Médecine Interne, Hôpital la Pitié-Salpétrière, Paris, France
[f] Service de médecine interne, CHU Charles Nicolle, Rouen, France
[g] Service d'hématologie, Hôpital Saint Antoine, Paris, France
[h] Inserm U1009, Institut Gustave Roussy, Villejuif, France

ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form 30 July 2015
Accepted 31 July 2015
Available online 17 August 2015

Keywords:
Thrombotic thrombocytopenic purpura
ADAMTS13
Rituximab
Immunotherapy

ABSTRACT

Despite a significant improvement of thrombotic thrombocytopenic purpura (TTP) prognosis since the use of plasma exchange, morbidity and mortality remained significant because of poor response to standard treatment or exacerbations and relapses. Rituximab, a chimeric monoclonal antibody directed against the B-lymphocyte CD20 antigen, has shown a particular interest in this indication. Recent studies also reported strong evidence for its efficiency in the prevention of relapses. This review addresses these recent progresses and still opened questions in this topic: should rituximab be proposed in all patients at the acute phase? Should all patients benefit from a preemptive treatment? Is the infectious risk acceptable in this context?

1. Introduction

Acquired, autoimmune thrombotic thrombocytopenic purpura (TTP) is a severe form of thrombotic microangiopathy (TMA) characterized by the association of a microangiopathic hemolytic anemia with a peripheral thrombocytopenia, organ failure of variable severity due to thrombi in microvasculature, and an antibody-mediated severe deficiency (<10% of normal activity) in the von Willebrand-factor (VWF) cleaving protease ADAMTS13 (A Disintegrin And Metalloproteinase with Thrombospondine type 1 repeats, 13rd member) [1,2]. The standard treatment consists mainly in daily therapeutic plasma exchange (TPE), which allows supplying ADAMTS13 deficiency and to a lesser extend removing serum anti-ADAMTS13 antibodies and possibly proaggregant substances. TPE transformed the historically fatal prognosis of TTP, allowing current overall survival rates of 80–85% [3]. These last years, further significant changes occurred in the management of autoimmune TTP. The identification of a central role for anti-ADAMTS13 antibodies in acquired TTP pathophysiology, which is now considered as an autoimmune disease, led to a wider use of immunosuppressive treatments. In this context, the introduction of rituximab has probably been the second major breakthrough in the management of this disease. However, current knowledge about the use of rituximab in this indication is based on few studies with a limited number of patients and moderate levels of proof. Moreover, these studies raised many questions that remain unsolved so far: should rituximab be introduced frontline in all patients or in patients with a suboptimal response to TPE? Which schedules of rituximab administration can be proposed? Should rituximab be systematically proposed as a preemptive therapy? Which strategy one can propose when rituximab fails to improve ADAMTS13 activity? These topical points are addressed in this review.

2. Methodology

We conducted a literature review reporting the use of rituximab in autoimmune TTP. We searched via PubMed articles published until March 2015 using the terms thrombotic thrombocytopenic purpura [MesH] AND rituximab. We selected English-written articles reporting patients who received ≥1 rituximab infusion. We retained case reports and clinical studies, either retrospective or prospective as well as clinical trials. Studies reporting patients with an associated condition (an HIV infection, a neoplastic disease, drug intake, or transplantation) were subsequently

* Corresponding author at: Centre de Référence des Microangiopathies Thrombotiques, Service d'Hématologie, Hôpital Saint Antoine, Université Pierre et Marie Curie, 184 rue du Faubourg Saint Antoine, Assistance Publique – Hôpitaux de Paris, 75012 Paris, France. Tel.: +33 1 49 28 26 21; fax: +33 1 49 28 33 75.
E-mail address: paul.coppo@aphp.fr (P. Coppo).

http://dx.doi.org/10.1016/j.ejim.2015.07.021
0953-6205/

excluded. We considered studies that included patients with a severe ADAMTS13 deficiency or at least a decreased enzyme activity. Studies where ADAMTS13 activity was normal or not specified were not included in this review.

3. Rationale for the use of rituximab in autoimmune TTP

TTP results from an excessive systemic platelet aggregation caused by the accumulation of ultralarge multimers of VWF in plasma [4,5]. A failure to degrade these endothelium-derived hyper-reactive ultralarge multimers of VWF into smaller, less adhesive forms is related to a severe deficiency in ADAMTS13. In the acquired, autoimmune form of the disease, this deficiency is due to the presence of autoantibodies directed against the enzyme [2,6–8]. In most cases, anti-ADAMTS13 antibodies are of IgG type (rarely, IgM and/or IgA isotypes are associated) [9–12]. Several subtypes may be associated in the same patient. IgG_4 seems to be the most prevalent IgG subclass of anti-ADAMTS13 antibodies in acquired TTP (90%), followed by IgG_1 (52%), IgG_2 (50%), and finally, IgG_3 (33%) [12]. Anti-ADAMTS13 antibodies decrease ADAMTS13 activity by directly inhibiting the catalytic activity of the enzyme or by decreasing its plasma concentrations through opsonization (i.e., an accelerated clearance of the enzyme by the formation of immune complexes) [9,11,13]. The major involvement of ADAMTS13 in the occurrence of autoimmune TTP and the central role of anti-ADAMTS13 antibodies in the pathophysiology of the disease have been well demonstrated in an experimental primate model [14], which provides additional insights to consider acquired TTP as an autoimmune disease, and a strong rationale for the use of immunomodulators in this indication.

Patients with autoimmune TTP can present a single episode; in 40% of cases, however, they experience one or multiple relapses [9,15–17] where episodes of TTP are separated by free intervals of variable duration, ranging from months to years [16]. Repeated relapses result from the persistence of a severe ADAMTS13 deficiency, due to the persistence or the recurrence of anti-ADAMTS13 antibodies [9]. It is therefore likely that the typical sequence of a TTP episode is the following: (re)occurrence of anti-ADAMTS13 antibodies in a patient with predisposing genetic factors [18,19], a severe ADAMTS13 deficiency, thrombocytopenia and hemolytic anemia, and finally, clinical manifestations with organ(s) failure. These observations provided a rationale to evaluate the efficacy of rituximab in autoimmune TTP at the acute phase of the disease, and as a preemptive therapy in patients in clinical remission but with a persistent severe acquired ADAMTS13 deficiency.

4. Rituximab: mode of action

Rituximab is a human/murine chimeric monoclonal IgG1 antibody that specifically targets the transmembrane protein CD20 of B cells. With the exception of plasma cells, the CD20 molecule is present on all B cells after the pro-B cell state (before IgM expression) [20,21]. Rituximab causes a rapid (24–72 hours) and significant depletion of peripheral B cells [22] which frequently lasts for more than 6 months. The effector mechanisms leading to B cell depletion are multiple, non-exclusive, and include antibody-dependant cellular cytotoxicity (ADCC) [23,24], phagocytosis by the reticulo-endothelial system of rituximab-coated B cells [25], complement dependent cytotoxicity (CDC) [24,26], and B cells direct apoptosis by CD20 crosslinking [27].

The precise mechanisms of action of rituximab in autoimmune diseases are multiple [28] and only partially known to date and probably differ from one autoimmune disease to another. In autoimmune TTP, the striking parallelism between the rapid peripheral B cell depletion, anti-ADAMTS13 antibodies decrease, ADAMTS13 recovery, and disease remission [16,29–31] strongly suggests that the depletion of B cells at the origin of short-lived plasmocytes secreting anti-ADAMTS13 autoantibodies is the main mechanism of action of rituximab. Whether other immunoregulatory mechanisms as those reported in other autoimmune diseases [28,32–34] also have a role in the control of the disease still remains to be established.

The pharmacokinetics of rituximab has been studied in patients treated for lymphoid malignancies and in autoimmune diseases, especially rheumatoid arthritis (1000 mg on days 1 and 15) [35,36]. In this latter case, rituximab had a mean terminal half-life of 19–22 days after the second infusion; systemic clearance of rituximab with monotherapy was slow (242 mL/d), and the volume of distribution at steady state was low (4.28–4.74 L) and similar to normal plasma volume. The half-life of rituximab varies with the dosage, interval between infusions, diffusion velocity, and kinetics of elimination [37]. It may be possible to extrapolate data from patients treated for lymphomas or autoimmune diseases to patients receiving preemptive treatment for TTP [38]. On the opposite, in TTP at the acute phase, rituximab is performed in association with intensive (i.e., daily) TPE, which leads to the removal of part of the drug (up to 65%), particularly when performed less than 3 days after the infusion [39]. However, the remaining circulating rituximab is enough to provide an efficient and rapid peripheral B cell leading to a recovery of ADAMTS13 activity in most cases [29,38]. Despite daily TPE, profound peripheral B cell depletion occurs rapidly, within 3–7 days after the first rituximab infusion, and peripheral B cell recovery variably occurs between 6 and 12 months [38]. Naive B cells ($IgD^+/CD27^-$) recovery following treatment with rituximab and TPE predominates, whereas pre-switch ($IgD^+/CD27^+$) and post-switch ($IgD^-/CD27^+$) memory B cells remain low. During follow-up, there is a gradual decrease of naive B cells with a progressive increase of $CD27^+$ memory B cells. Although peripheral B cell depletion with rituximab is very efficient, B cells located in lymphoid organs have different sensitivities to the drug [40,41]. Particularly, B cells in the spleen seem to be less sensitive to the treatment [42], probably because of a low diffusion of anti-CD20 antibodies in extravascular areas. Moreover, it is likely that tissue microenvironment provides pro-survival signals (including signals from the B cell-activating factor of the TNF family/BAFF-BlyS [B lymphocyte signal] survival factor and integrin-regulated homeostasis) counteracting the proapoptotic signals of rituximab [40]. In this regard, median BAFF levels at presentation of idiopathic TTP are higher than in normal controls; moreover, these levels increase significantly after rituximab administration perhaps partly due to BAFF receptor loss as B cell numbers fell, whereas they decrease again at B cell recovery [43,44]. Also, some non-circulating B cells binding rituximab may not be depleted; this may result from microenvironment factors, cellular competition, or differential expression of inhibitory proteins, that could contribute to a decreased sensitivity of B cells to the proapoptotic effect of the drug [40,45,46]. The development of human antichimeric antibodies (HACA) could, in addition to being involved in the occurrence of serum sickness, reduce the efficacy of rituximab [47]. To date, however, they have not been reported in patients with TTP.

5. Rituximab at the acute phase

In patients with autoimmune TTP, rituximab was first introduced at the acute phase, in the more severe cases [30,48], and in patients with an insufficient (or suboptimal) response to conventional, TPE-based, treatment. Many single cases [49–67] and small series [48,68–84], most often from patients with a refractory disease or experiencing multiple relapses, reported encouraging results (Table 1). TPE were continued daily and rituximab was administered immediately after a TPE (except in one study [71], in which TPE were suspended). These studies were not randomized, non-controlled, usually retrospective, and displayed many confounding factors. Moreover, an accurate evaluation of the therapeutical response to rituximab was initially rendered challenging given the variability in the indications and in the schedules of drug administration, and the lack of consensual definitions in treatment responses. Moreover, rituximab was usually associated with other salvage therapies, making accountability uncertain. However, they