International Immunopharmacology 54 (2018) 131–138

Contents lists available at ScienceDirect

International Immunopharmacology

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

Review

Sixteen-year history of rituximab therapy for 1085 pemphigus vulgaris patients: A systematic review

Soheil Tavakolpour[a,b,*], HamidReza Mahmoudi[b], Kamran Balighi[b], Robabeh Abedini[b], Maryam Daneshpazhooh[b]

[a] Genomic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

Keywords:
Pemphigus vulgaris
Rituximab
Autoimmunity

ABSTRACT

Pemphigus vulgaris (PV) is a rare autoimmune disease due to the production of pathogenic autoantibodies directed against desmoglein 1 and 3, usually affecting both skin and mucous membranes. Recently, rituximab, a chimeric IgG1 monoclonal antibody which targets the CD20 molecules have been regarded as a promising treatment for PV. In this study, a systematic review was conducted to conclude on how and which PV patients could benefit from rituximab infusion. Search in PubMed results in 114 relevant studies, which met the criteria. Total of 1085 PV patients with different conditions, including unresponsive childhood/juvenile or adult PV patients, women of childbearing age, those with chronic infections with the risk of reactivation have been evaluated. Although the majority of these patients well responded to rituximab, some of them did not respond, and the paucity of patients experienced exacerbation of disease. In addition to the rituximab monotherapy or its combination with conventional therapies, different novel combination therapies of rituximab with immunoadsorption and/or IVIg have shown promising results. Moreover, using rituximab as the first-line treatment has emerged recently. Pneumocystis carinii pneumonia and septicemia were found as the two fatal and serious adverse events associated with rituximab. Moreover, development or reactivation of herpes simplex and herpes zoster and cytomegalovirus should be warned. Similar to the adults, those with childhood and juvenile PV could be successfully treated with rituximab. Although rituximab seems to trigger reactivation of chronic infections, such as viral hepatitis and HIV infection, no related report was found. Administration of rituximab in approximately ten months before conception also was found safe and effective for a successful pregnancy. In conclusion, rituximab is very effective in adult and childhood/juvenile PV. However, there is a risk of not responding, exacerbation of disease and development of fatal infections. Moreover, it seems to be a promising first-line treatment for refractory PV.

1. Introduction

Pemphigus vulgaris is a rare autoimmune, intraepithelial, blistering disease affecting both skin and mucous membrane. The various types of pemphigus include pemphigus vulgaris (PV), pemphigus foliaceus (PF), IgA pemphigus, and paraneoplastic pemphigus (PNP). Among these, PV is the most common form, and its incidence is increasing [1,2]. It is mediated by circulating desmoglein-reactive autoantibodies, including desmoglein (Dsg) 1 and Dsg3 directed against keratinocyte cell surface. Similar to most of the autoimmune conditions, there no cure for PV. However, the primary objective of the therapeutic management of PV is to control and heal the bullous skin and/or mucous lesions as well as attempting to minimize adverse effects associated with treatments procedure. According to the guideline by the European Dermatology Forum in cooperation with the European Academy of Dermatology and Venereology, systemic corticosteroid therapy was recommended as the first-line treatment option for PV patients [3]. Additionally, adjuvants could be employed for their steroid-sparing effects, but there is no grantee for resulting in steroid-free remission. Despite the several adverse effects of systemic corticosteroid, it has remained the first-line treatment for many years.

Recently, the treatments of autoimmune diseases are shifting from conventional therapies (e.g., corticosteroid) to more targeted therapies. Monoclonal antibodies and also other biologic drugs have allowed for targeted drug therapy in managing various autoimmune diseases [4]. Rituximab is a chimeric anti-human CD20 monoclonal antibody, which acts by depletion of CD20 positive cells. This drug was first approved for treatment of non-Hodgkin's lymphoma in adults and then for

* Corresponding author at: Genomic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail address: soheil.tavakolpour@gmail.com (S. Tavakolpour).

https://doi.org/10.1016/j.intimp.2017.11.005
Received 10 September 2017; Received in revised form 12 October 2017; Accepted 5 November 2017

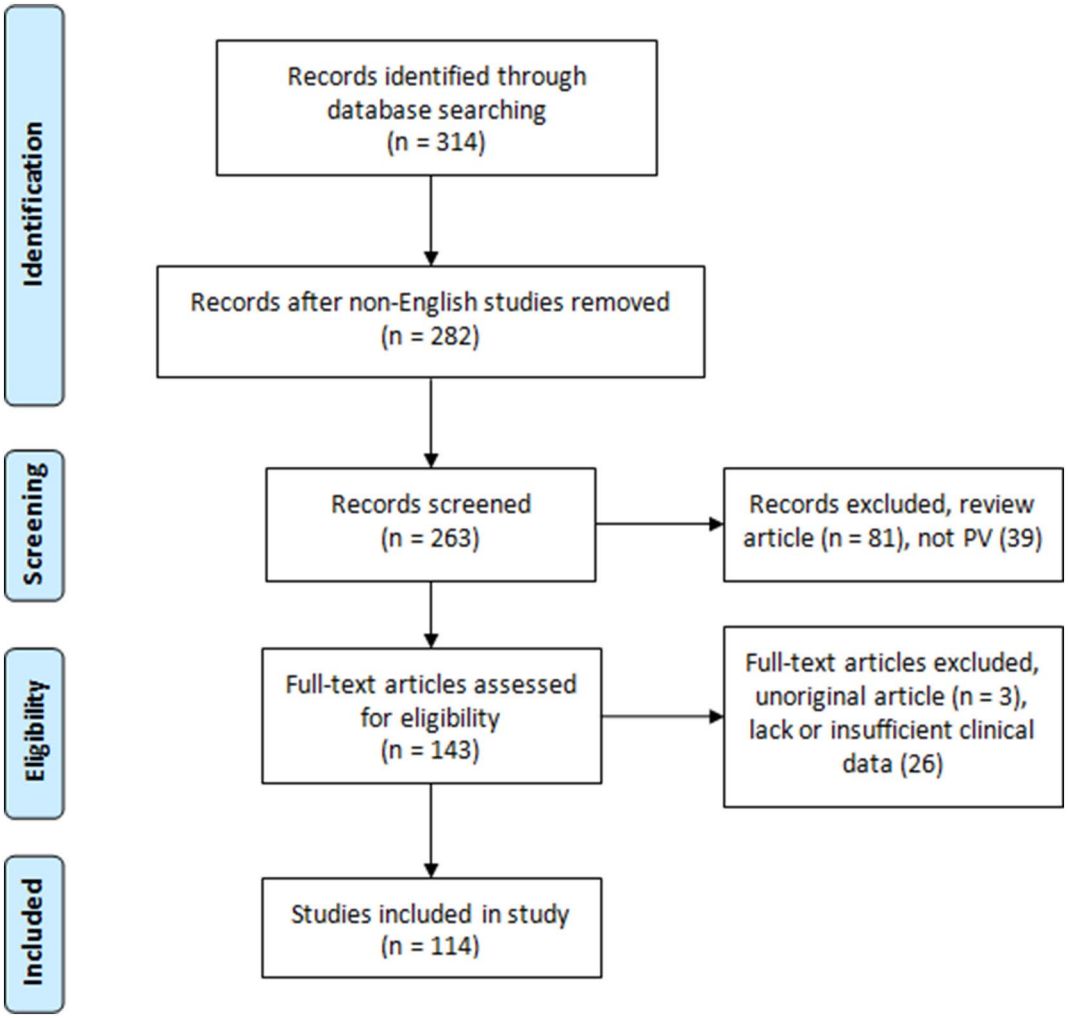

Fig. 1. Flowchart of identifying potential studies to include.

rheumatoid arthritis (RA) patients who do not respond adequately to disease-modifying antirheumatic drugs [5,6]. However, off-label application for pemphigus has emerged in recent decades [7]. Inspired from these two diseases, two protocols for treatment of PV patients with rituximab are common. Lymphoma protocol (LP), in which patients receive four weekly infusions of rituximab at the dose of 375 mg/m^2 and rheumatoid arthritis protocol (RAP), involving two 1000 mg intravenous infusions in two-week intervals.

Literature review reveals that unresponsive and refractory pemphigus could be treated with rituximab with remission in a reasonable time. However, there is some uncertainty associated with this magic bullet for pemphigus. Considerable numbers of reported patients had experienced a relatively long-lasting remission with a risk of relapse. Indeed, because rituximab does not target stem cells and pro-B cells, relapse of disease after reconstitution of B cell population could be expected. However, the paucity of patients did not respond and even had exacerbated symptoms following rituximab infusion [8–12]. Majority of published studies associated with rituximab only contain limited cases, which don't allow the reader to make some conclusions. Hence, it is essential to consider all the contradictory results, including not responding to rituximab, exacerbation of disease following rituximab infusions, and some unexpected adverse events to reach to a comprehensive conclusion. Moreover, there is no consensus associated with the most effective protocol, doses and number of rituximab courses with minimal adverse events. In contrast to the available guidelines, some authors have suggested that rituximab could be used as the first-line treatment in refractory pemphigus, which needs more discussion [13,14]. The safety of rituximab during the pregnancy and chronic infections is another issue that should be discussed. In this study, it was attempted to discuss all these uncertainties to reach a reasonable conclusion.

2. Methods

A PubMed search was conducted using the keywords “Rituximab” or “Anti-CD20” and “Pemphigus”. All the results were considered for the next step, with no date limitation.

Inclusion criteria were:

1- Articles published in the English language.
2- Initial diagnosis of pemphigus vulgaris with confirmation of histology and direct immunofluorescence.
3- Presentation or confirmation of a unique/novel clinical outcome(s), recommendation, the protocol of treatment, etc.

Treatment protocol (LP, RAP, or modified protocols) and response rate were not considered as the inclusion criteria. Of note, only patients diagnosed with PV (not PF, IgA, or PNP) are included in this study.

The eligible studies were carefully read to extract any learned lessons, which are beneficial for the treatment of PV patients with rituximab. In the studies on patients with a combination of different diseases or different variants of pemphigus, only data for PV patients were