

## REVIEW ARTICLE

# Rituximab as the treatment of pemphigus vulgaris in the COVID-19 pandemic era: A narrative review

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**Abstract**

Pemphigus vulgaris (PV), an autoimmune blistering disease is treated with immunosuppressive medications. As the immunosuppressive effect of rituximab, the first-line therapy of PV, lasts more than 6 months, many concerns have raised due to the ongoing novel coronavirus disease (COVID-19) pandemic. With this background, our objective was to review the currently available literature as well as important websites for the evidence related to rituximab, PV and COVID-19, adverse effects associated with drugs, and relevant guidelines. “PubMed” and “Google Scholar” database were systematically searched for retrieving all articles related to anti-CD20 therapy in pemphigus vulgaris and COVID-19 published up to 14 July 2020. A total of seven clinical studies are performed with anti-CD20 therapy in COVID-19, three of which are performed on pemphigus patients, and have shown concerns employing rituximab in patients with COVID-19. Evidence for treating PV patients with rituximab in COVID-19 pandemic is limited. Until sufficient evidence or guideline for pemphigus and COVID-19 treatment is available, we advocate caution commencing rituximab in patients with pemphigus, due to the reported adverse outcomes.

**KEYWORDS**

anti-CD20, COVID-19, pemphigus vulgaris, rituximab

## 1 | INTRODUCTION

Pemphigus, an autoimmune disease with yearly incidence of one to seven cases every million in European and American population has subtypes, that is, pemphigus vulgaris (PV) and pemphigus foliaceus with contribution of 75% and 20% patients, respectively.<sup>1</sup>

PV is potentially fatal disease with blisters involving mucocutaneous surfaces such as skin and oral cavity. Intraepidermal vesicles with acantholysis and intact basal layer are the characteristics of PV lesions.<sup>2</sup> Autoantibodies are targeted against desmosomal cadherins desmoglein-1 and desmoglein-3 antigens, which play role as adhesive factors between nearby keratinocytes. The result is loss of adhesion between cells and development of blisters.<sup>1,3,4</sup> Studies have shown that blood serum level of anti-

desmoglein IgG is associated with disease activity in PV patients.<sup>1,4</sup>

Mortality rate in patients with pemphigus has decreased from 75% to 30%, by treating with corticosteroids. About 30%-50% of patients experience complete remission by long-term systemic corticosteroids administered in the high-dose (prednisolone in the dose of 1.0 mg or more per kg every day).<sup>5</sup>

Current PV treatment includes corticosteroids given in high doses and immunosuppressive drugs.<sup>6</sup> Consequences of such combination therapy can include long standing suppression of immunity, and outcomes associated with this condition are the most common cause of mortality in PV.<sup>7</sup>

Patients not responding to the mentioned combination therapy, or who present with severe side effects, are given intravenous

immune globulin (IVIG). This is a successful method, and its monotherapy can be associated with long-term remission.<sup>8,9</sup>

Removing the autoantibodies from blood circulation can be considered as a therapeutic approach, due to their pathogenic role in pemphigus. A trial reported significant reduction in the anti-desmoglein antibodies in serum with single cycle of high-dose intravenous immunoglobulin (2 g/kg) and resulted in satisfying clinical outcome.<sup>10</sup>

Rituximab, a mouse/human monoclonal antibody (IgG<sub>1</sub>-κ) targets the CD20 antigens presenting on B lymphocytes surface. It clears the blood circulation out of CD20 expressing B lymphocytes by binding to CD20 antigens. Most patients taking rituximab experience lymphopenia, which lasts about 6 months. Complete recovery of B lymphocytes in peripheral blood circulation is usually observed nine to 12 months after the treatment course, when no CD20 antigen is expressed on hematopoietic stem cells.<sup>1,11</sup>

For the first time in 2007, thousands of PV and pemphigus foliaceus patients were treated with rituximab worldwide. In 2015, the European Academy of Dermatology and Venereology guideline suggested rituximab as a third-line treatment.<sup>1,12,13</sup>

Rituximab decreases blood serum level of anti-desmoglein autoantibodies rapidly, which results healing of pemphigus lesions after few weeks of infusion, and complete remission is achieved after 3-6 months.<sup>1,14</sup>

Experimental studies have shown that anti-CD20 therapy is the most important advance method for treating patients with pemphigus, after the advent of corticosteroids.<sup>1</sup>

Old age and comorbidities (eg, hypertension, diabetes, obesity, smoking, and cardiovascular and lung disease) are considered as risk factors for the novel coronavirus disease (COVID-19).<sup>15</sup> Immunocompromised patients, for example, those with PV receiving immunosuppressive disease-modifying therapies can also have increased risk of severe infection with coronavirus. As a result, any physicians and patients are concerned about the ongoing situation, particularly patients taking immunosuppressive drugs, as well as pemphigus patients.

In this article, we reviewed the literature focusing on the treatment, management, and subsequent consequences of rituximab as a treatment for PV in the present COVID-19 pandemic era.

## 1.1 | Evidence acquisition

We performed a computer-assisted search of "PubMed" and "Google Scholar" databases up to 14 July 2020 using the keywords "anti-CD20 therapy," "pemphigus vulgaris," and "COVID-19." We also searched other related keywords such as coronavirus, rituximab, immunocompromised, immunosuppressive drugs, pathogenesis, clinical presentations, treatment, and outcome.

## 2 | RESULTS

Experimental studies have proven that rituximab, monoclonal antibody has capability of binding to CD20 antigen and removing B

lymphocytes expressing CD20 from blood. According to the literature, it is considered as the first-line treatment for patients with PV based on the efficacy and safety profile.<sup>16</sup>

Due to the immunosuppressive role of rituximab, which could last at least 6 months, some cautions needs to be exercised when employing rituximab for treating patients with PV, especially during ongoing COVID-19 era.

Patients with autoimmune bullous diseases (AIBDs) must never drop out their immunomodulating therapy. Unjustified withdrawal can result in uncontrolled disease activity and lead to increased risk of morbidity and mortality. Risk of opportunistic infections (including viral infections) is much more in patients with AIBDs receiving immunosuppressive therapies, than the healthy population. Infections can activate the bullous activity. It is important to note that pemphigus as well as pemphigoid are associated with amplified risk of mortality due to pneumonia.<sup>17,18</sup> Although some studies may have reported that risk of infections is not different between AIBD patients treated with rituximab or high dose corticosteroids,<sup>16</sup> more complicated COVID-19 infection has been reported in AIBD patients who have taken rituximab during last 1 year, compared with healthy population. Hence, patients with PV having confirmed COVID-19 infection should be subjected to risk-benefit assessment in terms of chosen therapeutic regimen, and we should keep in mind that initiation of rituximab in AIBDs must be compared against the use of other traditional immunomodulatory agents, in the COVID-19 pandemic era.<sup>19</sup>

Rituximab, as the first-line therapy for moderate to severe PV, irreversibly affects humoral immunity. B-cell immunity reconstitution takes several months, which can make severe problems for patients who contract COVID-19. Due to the fact, we should temporarily postpone prescribing rituximab infusions, to reduce the level of immunosuppression of patients during the peak of COVID-19 incidence and prevent adverse outcomes. Besides rituximab, glucocorticoids are considered as the other mainstay of PV treatment, due to the high efficacy, quick therapeutic response, and low cost. However, they can also increase the risk of infections dose-dependently. Given that, all glucocorticoids and steroid-sparing immunosuppressive drugs like azathioprine and mycophenolate mofetil must be tapered to the minimum possible necessary dose. In an active COVID-19 infection, immunosuppressive steroid-sparing medications should be discontinued, if possible. The mentioned approaches above can be used as a novel therapeutic principle for patients with PV during the ongoing pandemic era.<sup>20</sup>

Coronavirus can target the central nervous system (CNS), which is protected by humoral immunity.<sup>21,22</sup> Although a theory proposed the expression of ACE 2 (receptor for corona virus on the surface of host cell) in the brain, the exact mechanism of CNS involvement in COVID-19 is still unknown.<sup>22</sup> According to the mentioned significant role of humoral immunity in corona virus infection, treating PV patients with rituximab is potentially risky. Given the fact, patients with PV who are treated with rituximab should be monitored closely, concurrent corticosteroids regimen should be tapered, and risk of taking rituximab must be weighed precisely, to minimize the risk of infections.<sup>16,23</sup>

Analysis of outcome of patients with known autoimmune and auto-inflammatory diseases and having COVID-19 showed that outcomes may differ because of the immunomodulatory therapeutic regimen. It suggested that patients treated with hydroxychloroquine, TNF $\alpha$  antagonists,<sup>24</sup> anakinra,<sup>25</sup> or tocilizumab,<sup>26</sup> may develop a mild infection and the mentioned medications can decrease the severity of COVID-19 infection. On the other hand, the patients taking rituximab<sup>27</sup> or secukinumab seems to have the worst outcomes, according to the rate of intensive care unit (ICU) admissions.<sup>28</sup> High amount of IL-6, a strong factor related to mortality in COVID-19 patients, is seen in patients given rituximab and secukinumab, that can be due to the failure of rituximab and secukinumab to modulate IL-6.<sup>28,29</sup>

According to a report of patients with granulomatosis and polyangiitis presenting with severe COVID-19 infection, shortly after taking rituximab, suggested the drug may not be as safe as usually considered.<sup>30</sup> Monti et al proposed that rituximab should be considered with caution during the COVID-19 pandemic.<sup>31</sup>

Also, Guilpain et al reported three systemic sclerosis (SSc) patients treating with rituximab, which resulted to late clinical worsening to severe pneumonia due to the COVID-19 infection.<sup>32</sup>

While searching data about anti-CD 20 treatments in COVID-19 pandemic era, we found some studies regarding the efficacy and harmlessness of anti-CD20 drugs for treating multiple sclerosis (MS) patients during COVID-19. Although prevalence of infections in MS patients treated with ocrelizuma, were slightly more common than the comparator arms,<sup>33,34</sup> but the data indicates that anti-CD20 therapies are may be safe to initiate and re-dose in MS patients during the COVID-19 period.<sup>15</sup>

### 3 | DISCUSSION

Rituximab is a monoclonal antibody which irreversibly affect CD20-expressing B lymphocytes and remove them from blood circulation. It is the only US-FDA approved agent for moderate to severe pemphigus. Although it is a the first-line treatment for PV patients,<sup>16</sup> some concerns have been made due to the immunosuppression in the ongoing COVID-19 pandemic.

Infectious events (IE) after treatment by rituximab can be extremely severe, particularly in patients immunocompromised by several drugs.<sup>35</sup> On the other hand, therapeutic regimen of pemphigus patients almost contains corticosteroid dose with other immunosuppressives (such as anti-CD20 agents).<sup>6</sup>

Besides, CNS is almost only protected by humoral immunity. There are evidences showing that CNS can be involved by coronavirus.<sup>23</sup>

Based on the available literature, we believe that reconsideration must be applied for therapeutic principles of treatment of patients with pemphigus receiving rituximab, during the present pandemic.

We propose that it is better to taper corticosteroids, and temporarily discontinue rituximab from the therapeutic regimen of patients with pemphigus, or reduction in the doses can be considered.

We can consider intravenous immunoglobulin as a replacement for rituximab, which is beneficial for both pemphigus<sup>36</sup> and COVID-19.<sup>37</sup> Also we can use hydroxychloroquine instead of rituximab, which is used to treat elderly or pregnant pemphigus patients.<sup>38</sup> Although anecdotal evidence in pemphigus and COVID-19, plasmapheresis could also be considered. Efficacy convalescent plasma in pemphigus is unknown.<sup>20</sup>

Overall, care should be taken while starting immunomodulatory drugs associated with a definitive risk of severe infection especially rituximab or some other nonbiologics such as TNF-alpha inhibitors.<sup>39</sup>

Emerging selective agents for example, a new oral bruton tyrosine kinase inhibitor which works via reversible covalent binding may offer some advantages for pemphigus. Immunomodulatory effect of this agent is self-limited. Access to this agent can be very useful, particularly in the present extraordinary circumstances.<sup>20</sup>

Additionally, ofatumumab a human monoclonal CD20 antibody has short duration of action than rituximab. Despite early promise in pemphigus treatment, a phase 3 clinical trial was prematurely stopped because of changing priorities of the sponsor. Tocilizumab, an anti-interleukin 6 humanized monoclonal antibody, proposed for treatment in inflammatory phase of COVID-19 has anecdotally reported to be of use in pemphigus.<sup>20</sup>

Another approach is extended-interval dosing of rituximab, in cases we can-not cut off rituximab. Anti-CD20 therapies used to treat pemphigus patients, including rituximab, are typically given every 4 weeks. The B-cell depletion effect usually lasts much beyond 6 months (the scheduled dosing interval).<sup>40,41</sup> In the ongoing COVID-19 pandemic, dosing at longer interval should be considered, particularly in B cell depleted patients at the time of the next scheduled dose or those with reduced level of serum IgG.

The mentioned approaches reduce hospital visits of patients, which has a great effect on reducing the exposure of patients to coronavirus.

Although, all of the above is suggested as a novel beneficial therapeutic principle for pemphigus patients in the COVID-19 pandemic, the final decision should be made by the relating physician, taking into account the severity of the disease, side effects of the drugs, risk of continuing the previous treatments and the consequences of changing the patient's treatment regimen.

### 4 | CONCLUSION

Although evidence for treating PV patients with rituximab in COVID-19 pandemic is limited, and outcomes of MS patients taking rituximab was controversial, until sufficient evidence as a guideline for pemphigus and COVID-19 treatment is available, we advocate caution commencing rituximab for pemphigus patients and adherence to basic principles of infection control and decreasing drug induced immunosuppression as possible.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

**AUTHOR CONTRIBUTION**

A.M.B. conceived and designed the study, wrote the draft; G.R.R. collected the data and wrote the draft. A.P. wrote and revised the draft; M.G. supervised the findings of this work, wrote and revised the draft.

**DATA AVAILABILITY STATEMENT**

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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