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NEW DIRECTIONS IN THE TREATMENT OF PEMPHIGUS VULGARIS? SAFETY AND EFFICACY OF RITUXIMAB AND DUPILUMAB – REVIEW OF LITERATURE

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ABSTRACT

Background. Recent years have demonstrated a considerable development of biological treatment of various autoimmune diseases. Lack of response and adverse effects of standard treatment have been pushing research to find new therapeutic agents with good efficacy and safety profile.
Aim. This study reviews the current knowledge about the potential use of rituximab and dupilumab, two biological drugs, in the treatment of pemphigus vulgaris (PV), a debilitating skin disease.
Material and methods. The article is based on research of clinical trials and case studies published on the PubMed and Cochrane databases using the following keywords: pemphigus vulgaris, rituximab, dupilumab.
Results. The existing trials show that rituximab offers faster achievement of complete remission when compared to standard prednisone or mycophenolate mofetil treatment. It also reduces the cumulative prednisone dose followed by alleviation of steroid-related adverse events. Its effect is even visible on the molecular level, being the depletion of T-helper cells that play a crucial role in activation of anti-desmoglein antibody producing B-memory cells. The use of dupilumab in PV has only been documented in a few case studies, which still show that most patients with refractory PV benefited from dupilumab treatment by finally achieving and maintaining remission.
Conclusions. Despite limited randomized studies and small patient groups, the results of the existing research suggest a promising role of biological agents in the future treatment of patients with pemphigus vulgaris.

KEYWORDS

Pemphigus Vulgaris, Biological Treatment, Rituximab, Dupilumab

CITATION

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Rituximab and dupilumab – mode of action

Rituximab is a chimeric monoclonal antibody targeting the CD20 antigen present on the surface of B lymphocytes. After binding of the monoclonal antibody's Fragment antigen-binding (Fab) region to the large extracellular loop of CD20, effector functions are triggered through the interaction of rituximab's Fragment crystallizable (Fc) region with the FcγR receptors found on immune cells (Du et al., 2007). This leads to the activation of these cells and consequently the destruction of CD20+ target cells via three main mechanisms: antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP)(Kamen et al., 2019; Taylor, 2007). The mechanism of rituximab's action is illustrated in Figure 1.

In ADCC, natural killer (NK) cells play a primary role. Upon engagement of their CD16 (FCγRIII) receptors with the Fc fragment of the antibody, they release cytolytic substances, leading to DNA degradation and apoptosis of target cells. In ADCP, B cells opsonized with anti-CD20 antibodies bind to FcγR receptors on phagocytes, initiating intracellular signaling cascades that ultimately result in internalization and degradation of B cells. Finally, CDC involves the classical complement activation pathway, wherein the Fc portion of monoclonal antibodies binds to the C1q protein, forming a membrane attack complex (MAC) and inducing B-cell lysis (Diebolder et al., 2014; Fishelson & Kirschfink, 2019; Mortensen et al., 2017).

Rituximab leads to B-cell depletion, indirectly reducing antibody production that contributes to autoimmune disease development. It was the first monoclonal antibody approved for use in oncology in 1997, improving outcomes in non-Hodgkin lymphoma therapy (Pierpont et al., 2018). Recognizing its potential in reducing autoantibody production, researchers investigated its use in autoimmune diseases, leading to its registration for treating rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris (PV).

Six rituximab-containing formulations are registered in Europe: MabThera (EMA 1998), Riximyo (EMA 2017), Rixathon (EMA 2017), Blitzima (EMA 2017), Truxima (EMA 2017), and Ruxience (EMA 2020). In Poland, available preparations include MabThera (intravenous infusion concentrate and subcutaneous injection solution), Riximyo, and Ruxience (both as infusion concentrates).

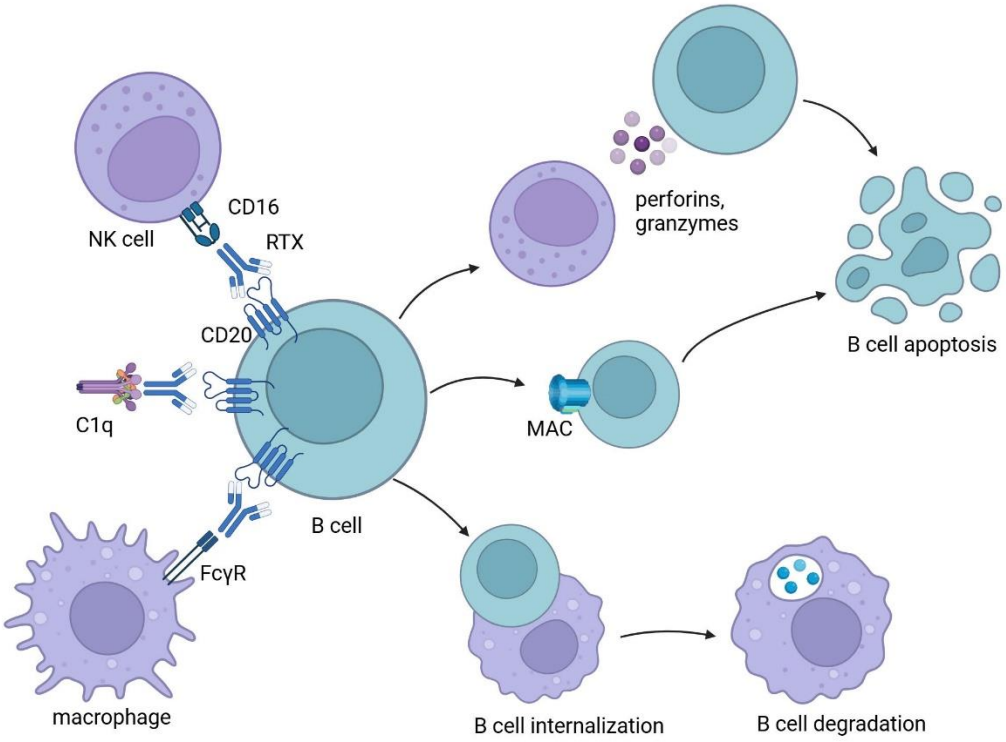

Fig. 1. *Mechanism of rituximab action. Abbreviations: RTX – rituximab, MAC – membrane attacking complex, NK cell – natural killer cell. Illustration created using Biorender.com*

Dupilumab is a human IgG4 monoclonal antibody that binds to the shared IL4-subunit alpha of IL-4 and IL-13 receptors, thus inhibiting the signaling pathway of IL-4 and IL-13, interleukins known as mediators typical for excessive type 2 inflammation.(McCann et al., 2024) Currently, there is only one dupilumab formulation registered in Europe, i.e. Dupixent (EMA 2027) and its indications include the treatment of atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis and prurigo nodularis. Even though pemphigus vulgaris is not on that list, some researchers have decided to use it off label in patients with refractory or poorly controlled disease. The reason behind the choice of this biologic agent was because Th2 cells, which are mainly involved in type 2 inflammation, are also driving the production of IgG1, IgG4 and IgE autoantibodies against desmoglein, and the levels of these classes of autoantibodies strongly correlate with the clinical activity of pemphigus vulgaris.(Daneshpazhooh et al., 2007; Fang et al., 2020; Zhong et al., 2011)

This paper aims to highlight the potential of rituximab and dupilumab as safe and effective alternatives or adjuncts to standard therapy in specific groups of patients with pemphigus vulgaris.

Methodology

An electronic literature search was conducted using PubMed up to August 2025. Keywords included'pemphigus vulgaris', 'rituximab' and'dupilumab'. Studies were selected based on relevance to the role of rituximab and dupilumab on the treatment of pemphigus vulgaris. Included were randomized clinical trials published in English, focusing on healthy adults, healthy elderly and patients suffering from psychiatric disorders. Studies on children and adolescents, animal studies, studies without an available DOI and non-full-text articles were excluded. The information on the study design concerning studies on dupilumab was summarized in tables, while the study design of studies on rituximab as well as the results from all the included studies were synthesized narratively.

Rituximab in the treatment of pemphigus vulgaris – the Ritux 3 RCT

Pemphigus vulgaris (PV) is an autoimmune blistering dermatosis marked by fragile blisters that easily rupture, forming painful erosions on the skin and mucous membranes. IgG autoantibodies targeting desmogleins disrupt the adhesive junctions between keratinocytes, resulting in fluid accumulation and blister formation. This severely impairs patients' quality of life and may become life-threatening due to bacterial infections and fluid loss.(Porro et al., 2019)

Systemic steroid therapy significantly reduced PV mortality from 99% to 5–15% and remains the first-line treatment.(Bystryn & Steinman, 1996) However, it carries notable side effects such as osteoporosis, diabetes, glaucoma, and myopathy.(Liu et al., 2013) Additionally, steroids may be ineffective or lose efficacy in some patients. Hence, alternative therapies that allow steroid dose reduction or replacement are being explored — rituximab being one such candidate.(Robinson et al., 2018)

In the randomized *Ritux 3* study, the addition of rituximab to first-line treatment was evaluated for its impact on remission rates and steroid-related side effects.(Joly et al., 2017) Patients (n=74) aged 18–80 with newly diagnosed moderate to severe PV were randomized into two groups: one receiving oral prednisone alone (n=36; 1 or 1.5 mg/kg/day tapered between months 12–18; later called'P group') and the other receiving rituximab plus prednisone (n=38; 1000 mg intavenous rituximab on days 0 and 14, 500 mg at months 12 and 18, with short-term oral prednisone: 0.5 or 1 mg/kg/day tapered between months 3–6, later called PRTX group). Follow-up lasted 3 years.

The primary endpoint was complete remission—defined as no need for corticosteroids for ≥2 months at month 24 (Chen et al., 2020), and was achieved by 27.7% of participants in the P group and by 89.5% of participants in the PRTX group. Furthermore, the addition of rituximab allowed for a significant reduction of the cumulative prednisone dose (5 800 mg in PRTX group versus 20 520 mg in P group) and, concomitantly, the ratio of steroid-related adverse events (38.2% in PRTX group versus 66.7% in P group). Notably, 22.2% percent of patients in the P group decided to withdraw from the study due to grade ¾ steroid adverse events, which further highlights the importance of novel treatment strategies.

Cytomolecular post-hoc analyses of Ritux 3

Several post-hoc analyses were conducted on the *Ritux 3* data. One focused on gene expression related to inflammatory cytokines before and after rituximab treatment. Surprisingly, memory DSG-specific B cells were found even in patients in complete remission. Auto-reactive B cells showed an increased expression of IL-1β, IL-23p19, IL-12p35, and IRF5. After rituximab therapy, B cells showed decreased IL-1β and CD27 expression only. Prednisone-treated B cells exhibited reduced IL-1β and IL-23p19 expression.(Hébert et al., 2019) This suggests distinct gene expression profiles, and that remission is achievable despite continued expression of some proinflammatory cytokine genes.

Another analysis revealed that while rituximab significantly reduced DSG-specific memory cells, antibody-secreting cells targeting DSG were undetectable in rituximab-remission patients. In contrast, the prednisone group retained DSG-specific memory cells and detectable antibody-secreting cells even among those in remission. Rituximab also significantly reduced T follicular helper cells—key players in B-cell memory activation—suggesting their depletion contributed to eliminating anti-DSG antibody-producing B cells and thus achieving remission.(Maho-Vaillant et al., 2021) Notably, the low reduction in anti-DSG antibody levels after the first rituximab dose was a risk factor for relapses, highlighting the potential benefit of a maintenance dose at month six.(Mignard et al., 2020)

The presence of anti-rituximab antibodies (ARA) was also examined. No significant difference in remission rates was observed between ARA+ and ARA– groups, though ARA+ patients had higher anti-DSG antibody levels. Two ARA+ patients who relapsed after 12 months showed no detectable rituximab in serum, incomplete B-cell depletion, and elevated anti-DSG antibody levels compared to other ARA+ patients in remission.(Lemieux et al., 2022)

Economic aspects of rituximab therapy

Ritux 3 was also analyzed from a cost perspective. Hebert et al. estimated costs over three years, including medication, consultations, hospitalizations, relapses, and adverse events. Initial costs were higher in the rituximab group due to the drug price, but costs from relapses and steroid side effects were higher in the prednisone group. The average cost per patient was €13, 997 for prednisone and €14, 818 for rituximab, making rituximab therapy 6% more expensive overall (Hébert et al., 2020).

Another study by Singh et al., independent of *Ritux 3*, compared cost-effectiveness between high-dose (RA protocol) and low-dose rituximab. Twenty patients were randomized: Group A received 1000 mg ×2 doses two weeks apart; Group B received 500 mg ×2 doses. Both groups received short-term oral steroids and were monitored quarterly. In case of B-cell repopulation, Group A received 500 mg and Group B 200 mg rituximab as a preventive measure.

Despite a 90% repopulation rate in Group B, additional rituximab effectively prevented clinical relapses. The low-dose regimen was 37.4% cheaper and showed comparable remission rates and steroid doses, indicating it may be a viable, cost-effective alternative (Singh et al., 2022).

Rituximab compared to other second-line agents

There are limited RCTs comparing rituximab directly with first-line corticosteroids, and even fewer comparing rituximab to second-line therapies. One such study, PEMPHIX, compared rituximab to mycophenolate mofetil (MMF), both combined with identical prednisone protocols (Werth et al., 2021). Rituximab was administered on days 1, 15, 168, and 182; MMF was given orally at 2g/day.

The primary endpoint was complete remission at week 52 (lesion clearance for ≥16 weeks without steroids), achieved in 40% of the rituximab group vs. 10% in the MMF group. Secondary endpoints included cumulative steroid dose, disease flares, DLQI score change, and serious adverse events. Table 1 compares selected results with *Ritux 3* data.

Table 1. Comparison of the results of Ritux 3 and PEMPHIX studies. Abbreviations: CROT: complete remission off therapy, RTX - rituximab, MMF - mycophenolate mofetil

Study name	Treatment group	Complete Remission (CROT)	Cumulative Steroid Dose (mg)	Clinical Relapse (%)
Ritux 3	Steroids	10 (27.7%)	20,520	70
	RTX+Steroids	34 (89.5%)	5,800	26
PEMPHIX	Rituximab	25 (40%)	3,545	5
	MMF	6 (10%)	5,140	46

Almost all secondary endpoints favored rituximab, except for serious adverse events: 22% in the rituximab group vs. 15% in the MMF group. Still, other studies using the same protocol would be necessary to assess whether those results are replicable and thus, to evaluate the safety profile of rituximab with more accuracy.

Dupilumab in the treatment of pemphigus vulgaris

Randomized clinical trials concerning the efficacy of dupilumab in patients with PV are still lacking. Nevertheless, there are a few case studies regarding that subject. Jiang et al. examined the efficacy and safety of dupilumab in three patients (age range: 47-80-year-old) who experienced no response with standard treatment. They all received slightly different, customized treatment protocols, but all included a stable dupilumab dose of 300 mg subcutaneously every two weeks. Two of them achieved complete remission and remained lesion-free at maintenance dose of dupilumab. They did have a mild to moderate disease flare after dupilumab introduction, yet it was most probably caused by prednisone cessation. The third patient had to discontinue the treatment due to the appearance of new blisters 4 weeks after dupilumab administration.(Jiang et al., 2023) The potential of dupilumab in recalcitrant PV has also been demonstrated in a case report by Moore et al., where a 41-year-old male with lesions lasting for 4 months and no response to systemic nor topical steroids has been administered dupilumab in a regimen like that in the study by Jiang et al. He achieved remission and maintained it at a slightly higher dose of 300 mg subcutaneously per week.(Moore & Hurley, 2023)

There is another interesting case of a patient with refractory PV that did not respond to standard treatment and had concomitant pulmonary tuberculosis (TB), which initially postponed his treatment. However, the patient was readmitted after 2 months due to progressively worsened lesions. He was first treated with methylprednisolone at a dose of 40 mg per day, but the disease progressed. Since rituximab causes a long-term B cell depletion, its use in a patient with TB was contraindicated. Thus, the patient received a combined therapy of dupilumab (at a protocol like that in the two studies) with methylprednisolone, anti-TB regimen, antibiotics and low dose intravenous immunoglobulins (IVIGs). After one and a half months an improvement was noted, and the patient was discharged on low dose methylprednisolone and dupilumab.(Chen et al., 2022)

A more detailed comparison of patients' characteristics is included in Table 2.

Table 2. Comparison of patients' characteristics in case studies using dupilumab to treat refractory PV. Previous PV treatment refers to the failed regimens before the initiation of dupilumab, whereas additional treatment includes drugs used in combination with dupilumab regimen. Maintenance treatment refers to dupilumab doses administered after achieving complete remission. Abbreviations: Pt - patients, PV - pemphigus vulgaris, CR - complete remission, F - female, M - male, AZA - azathioprine, MMF - mycophenolate mofetil, IVIGs - intravenous immunoglobulins, anti-TB regimen - anti-tuberculosis regimen, AEs – adverse effects.

Case study	Age and sex	Previous PV treatment	Dupilumab regimen	Additional treatment	Time until CR	Maintenance treatment
Jiang et al. (Pt 1)	55 F	systemic and topical steroids	loading dose: 600 mg; maintenance dose: 300 mg every 2 weeks	topical steroid	60 weeks	dupilumab 300 mg every 8 weeks
Jiang et al (Pt 2)	47 M	RTX, prednisone tapers, MMF, topical tacrolimus	dupilumab 300 mg every 2 weeks	none	63 weeks	dupilumab 300 mg every 6 weeks
Jiang et al (Pt 3)	80 F	oral prednisone, AZA, topical fluocinonide	dupilumab 300 mg every 2 weeks	prednisone taper, AZA, topical tacrolimus, topical steroids	not applicable	none – discontinuation due to AEs
Moore et al.	41 F	systemic and topical steroids	loading dose: 600 mg; 300 mg at weeks: 2,4,5	none	6 weeks	dupilumab 300 mg every week
Chen et al.	35 M	methylprednisolone 40 mg per day	loading dose: 600 mg, 300 mg every 2 weeks	methylprednisolone, anti-TB regimen, antibiotics, low dose IVIGs	6 weeks	dupilumab plus low dose methylprednisolone*

Notes: *Doses of dupilumab and methylprednisolone were unspecified.

Position of rituximab and dupilumab in PV Therapy – discussion and conclusion

Rituximab has marked a breakthrough in PV treatment, as evidenced by the *Ritux 3* study and others. It enables accelerated remission, avoids steroid-related side effects, and serves as an alternative for treatment-

resistant cases. However, it is not without limitations: most patients require at least two rituximab pulses, some even up to seven—significantly affecting treatment costs.(Miše et al., 2022)

In Poland, rituximab is included in a therapeutic program for severe PV resistant to immunosuppressants. Notably, moderate cases are excluded despite clinical indications. Some researchers advocate for rituximab as a first-line monotherapy to increase the likelihood of remission after a single dose, although literature is inconclusive on this approach.(Joly et al., 2020) A review by Amber et al. found no correlation between previous therapies and rituximab treatment outcomes.(Amber & Hertl, 2015; Shimanovich et al., 2020)

As for dupilumab, the currently available data comes from case studies with an extremely small number of participants and no uniform dupilumab dosage regimen. The existing studies show considerable safety and achievement of remission in patients who were unresponsive to standard treatment. One of the patients had an unsuccessful treatment with rituximab yet responded to dupilumab, which highlights the need to diversify the range of biological agents used in the treatment of PV. Another important aspect to consider is the route of administration – rituximab is an intravenous drug that requires hospitalization, while dupilumab is administered subcutaneously, allowing for ambulatory care and decreasing the overall cost of treatment.

More randomized clinical trials are required to accurately assess the efficacy and safety profile of the use of dupilumab in PV treatment. Nevertheless, these cases offer an interesting perspective on the potential role of dupilumab in patients with no response to rituximab or in patients with other concomitances who cannot receive rituximab due to its B-cell depleting effect.

Undoubtedly, this study reviews a limited number of clinical trials and case studies. Although there are many studies on rituximab use in pemphigus, their protocols were often inconsistent and included patients with not only pemphigus vulgaris, but also pemphigus foliaceus and paraneoplastic pemphigus. Therefore, rigorous exclusion criteria lead to a substantial reduction of studies eligible for this review.

In conclusion, pemphigus is indeed a rare skin condition, yet the patients affected by it often face great challenges when completing daily life tasks or getting involved in occupations. Therefore, the low incidence of PV should not inhibit undertaking large scale studies investigating the efficacy and safety profiles of existing and new biologics, which could lead to the registration of those drugs in the treatment of PV and allow for establishment of nationwide treatment programs.

Disclosure

Authors' contributions:

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Software: n/a
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Formal analysis: Kacper Jankowski
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Supervision: Jan Kamiński, Katarzyna Krupa
Project administration: Alicja Bury

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