Evidence Gap Analysis of the Burden of Illness and Treatment of Pemphigus Vulgaris and Foliaceus

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Background

- Pemphigus is a group of life-threatening, chronic, autoimmune blistering diseases (AIBDs) characterized by the formation of splits within the epidermis and surface-close epithelia, accompanied by acantholysis.[1] Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the 2 major variants.[1]
- PV is clinically characterized by flaccid blisters or erosions on the mucous membranes and the skin. Symptoms can include dysphagia, vocal hoarseness, vaginal irritation, and painful sexual intercourse.[2] As a result of these blisters and erosions, patients are at a higher risk of infections and hospitalization.[3-5]
- Unlike PV, PF affects only the skin, and mucosal lesions do not usually occur. Serious infection is a risk for patients with PF due to the presence of skin erosions.[4]
- Current treatments, including systemic corticosteroids and immunosuppressants, have significant adverse effects and contribute to disease morbidity and mortality in patients with pemphigus. Such medications increase the risk of infection, cardiovascular disease, and metabolic disorders, which complicate disease management and create a significant unmet need for more specific treatments that control the disease with reduced adverse effects.[6]

Objective

- To identify evidence gaps in the literature of the burden of illness and treatment of PV and PF to support the launch of efgartigimod to treat these rare diseases.

Methods

- A targeted literature review was conducted from 1 July 2011 to 26 October 2021 in PubMed, Embase, and the Cochrane Library using a predefined search strategy.
  - Articles on disease description, epidemiology, humanistic and economic burden, treatment guidelines, and treatment patterns were included.

Results

Diagnosis and Clinical Burden

- Pemphigus is correlated with increased mortality and multiple comorbid health conditions.

Key findings	Evidence gap
Diagnosis • Diagnosis of PV and PF is based on a combination of the clinical presentation, histopathology, and detection of autoantibodies by direct immunofluorescence and in the serum by indirect immunofluorescence or ELISA.[7,8] • The onset of lesions in PV involves the oral cavity, which is not often recognized in the early stages, where other oral ulcerative disorders are often suspected.[9] • Dermatological lesions usually occur 2-6 months after the appearance of oral mucosal hemorrhagic lesions in PV.[10] • Owing to the apparent absence of blisters and unimpacted oral mucosa, PF is often misdiagnosed as eczema, seborrheic dermatitis, actinic keratoses, or psoriasis.[11]	**• Late occurrence of dermatological lesions can lead to misdiagnosis, delayed diagnosis, and inappropriate treatment of a potentially fatal disorder.[10]** **• There are few epidemiological data concerning how skin color affects diagnosis.** **• The lack of images and evidence about PV in patients with dark skin tones can lead to a delay in diagnosis.**
Risk for autoimmune disease, infection, and hospitalization • Patients have 2:1 odds of developing at least 1 autoimmune disease, with eosinophilic esophagitis and vitiligo being most common.[5] • Serious infection remains a significant risk for patients with PV and PF due to the presence of skin erosions.[4]	**• Lack of studies that address the association between development of autoimmune disorders and pemphigus as well as opportunistic infections in these patients.** **• Effect of treatment to prevent serious complications, hospitalization, and death has not been studied.**

Epidemiology

- PV is the most common variant; PV has an estimated worldwide prevalence of 0.5-3.2 cases per 100,000 population.[12,13]
- The prevalence of PV ranges from 2.01 cases per 100,000 population in Romania to 9.48 cases per 100,000 in Germany.[14,15]
- Compared with the rest of the world, higher incidences are documented throughout the Mediterranean region.[15,17]
- PF is the dominant pemphigus variant in South America and North Africa, where it is commonly referred to as endemic PF.[16]
- The mortality rate for pemphigus is approximately 2.4 times higher than for the general population.[17]

Evidence gap
• Because of pemphigus' rarity, epidemiology data are available from a limited number of countries and regions, and the true incidence and prevalence of pemphigus variants are not completely known worldwide. **• Unlike *International Classification of Diseases, Ninth Revision* (ICD-9) codes, ICD-10 codes are specific to PV and PF subtypes, but only a few epidemiology studies have used ICD-10 codes to date.** **• No specific data are available on the prevalence or incidence of PV in people with dark skin tones or among racial minorities.**

Cost Data

Data on significant inpatient burden in US
Mean length of stay, diagnosis of pemphigus (type unknown) • Primary diagnosis: 7.2 days • Secondary diagnosis: 7.3 days • No pemphigus: 4.6 days[3]
Admission cost (mean), pediatric patients with AIBD in the US • Primary admission: US $13,388 • Secondary admission: US $27,064[18]
Excess annual costs of hospital care attributed to autoimmune disorders • Inpatients with pemphigus: US $2,286,588[19]

- 1 study each reported cost estimation with rituximab initiation (Canada) and first-line treatment costs between rituximab and corticosteroids (France).
- The comparison of disease-associated costs of PV with those of PF and cost of illness from a societal perspective is based on a single study from Hungary.
  - Total cost of illness of pemphigus per patient: €3,995 (€2,761-€5,434)
  - Cost associated with PV: €4,942; Cost associated with PF: €1,270.[20]

Evidence gap
• Data are limited both on the direct and indirect economic burden of PV and PF as only 6 studies were identified. **• The predominantly United States (US)–centric data in the literature had 3 studies reporting costs for pemphigus, but they did not cover indirect costs or adopt a societal perspective** **• No cost-effectiveness (CE) analyses were found, including CE models that supported health technology assessment decisions.**

Humanistic Burden

- Few studies estimating the HRQOL impact of PV and PF are available in the literature other than validation studies.

Key findings	Evidence gap
HRQOL instruments *Autoimmune blistering disease–specific instruments:* • Autoimmune Bullous Disease Quality of Life (ABQOL)[21-25] • Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL)[21-25] *Other dermatology-specific QOL measurements:* • Dermatology Life Quality Index (DLQI), Dermatology Life Quality Index–Relevant (DLQI-R)[21-25] • Family Dermatology Life Quality Index (FDLQI)[21-25] • Skindex-29[21-25]	**• Limited HRQOL data were found for PV and PF in studies that used AIBD-specific instruments such as ABQOL and TABQOL.** **• Most of the available HRQOL data were assessed by generic dermatology-specific QOL measurement tools, which have been used to assess general HRQOL not limited to dermatology, mental status, and subjective well-being.**
Patient HRQOL • The disease had a significant effect on QOL for most patients with PV (DLQI score showed a high impact in 39.7% and very high impact in 7.7% patients).[26] • The DLQI score was higher for patients with the mucocutaneous phenotype than patients with the mucosal phenotype; QOL was significantly affected by disease severity.[22] • All patients with PV experienced a negative effect on their DLQI scores compared with controls, and patients with PV recorded the worst QOL index score.[27]	**• Few studies estimating the HRQOL impact of PV and PF are available in the literature other than validation studies.** **• PV population predominates in the published studies over patients with PF, who constitute a small portion of the study population.**
Caregiver HRQOL • PV significantly affects the scores of caregivers and family when using the FDLQI.	**• The number of studies on caregiver HRQOL is limited in the literature.** **• Only 2 studies reported the impact of PV/PF on caregiver QOL (emotional, physical, and with daily activities).**

QOL = quality of life.

Current Treatments

- There is significant unmet need for more specific treatments that control the disease with reduced adverse effects.[6]

Treatment	Key available data	Evidence gap
Corticosteroids	• The cornerstone of therapy; effective • Have dramatically improved the prognosis of patients	**• Optimum dosing schedule not known**
Nonsteroidal immunosuppressive therapy	• Came into use in PV treatment in the 1960s and 1970s	**• No objective data to support the steroid-sparing effects of adjuvant therapies**
IVIG	• Rapid action reported in some cases • No increased risk of opportunistic infection • Mainly applied in severe and recalcitrant pemphigus	**• Only 1 RCT of a single cycle of high-dose IVIG (specific product was not specified) for pemphigus**
Rituximab	• FDA approved RTX for moderate-to-severe PV in 2018 • Most patients achieve complete remission on or off corticosteroid therapy, and on and off therapy with repeated rituximab infusions	**• Need to develop an optimal protocol for rituximab treatment and find suitable markers to predict relapse to improve disease management** **• Results lacking on treatment outcomes of patients who received maintenance therapy**

FDA = Food and Drug Administration; IVIG = intravenous immunoglobulin; RCT = randomized controlled trial.

Conclusions

- There are many gaps in the literature to support the launch of a new product in pemphigus, including the epidemiological data for budget-impact models, humanistic and economic burden studies, CE models, and treatment-pattern studies.

Disclosures

Arvin-Berod C, Phillips G, Verheesen P, Heyerick A, and Stoykov I are employees of argenx. Copley-Merriman C and D'Souza V are employees of RTI Health Solutions.

Funding

argenx provided funding to RTI Health Solutions to conduct this study and was involved in reviewing this poster.

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Presented at ISPOR Europe 2022; 6-9 November 2022; Vienna, Austria