KabaFusion
Patient-Focused Infusion Therapy

July 23, 2020

Pemphigus Vulgaris (PV) Treatment Strategies

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Introduction

Pemphigus vulgaris (PV) is an *autoimmune mucocutaneous blistering disease* (AMBD). AMBDs are a group of frequently fatal diseases, clinically characterized by erosions and/or blisters on the skin and mucous membranes (Van Beek 2018). PV is a chronic disease which usually takes years to evolve (Almugairen 2013). Death usually occurs due to septicemia with *Streptococcus aureus*, and the skin is usually the source of infection (Ahmed 1982). These dermatoses are histologically characterized by autoantibodies directed against structural proteins in the cadherins, called *desmogleins* (e.g., *desmoglein-1*, *desmoglein-3*), which the autoantibodies conceive as antigens, in the skin and mucous membranes (Schmidt 2013). AMBDs are divided into groups according to the structural proteins against which the autoantibodies are directed. *Pemphigoid diseases* (PD) are a group with subepidermal split formation and autoantibody binding to structural components of the dermal-epidermal junction (DEJ), whereas *pemphigus* autoantibodies are directed against desmosomal proteins that connect neighboring keratinocytes (Kasperkiewicz 2017, Schmidt 2013). Another special type of AMBD is *dermatitis herpetiformis*, in which autoantibodies are directed against the tissue and epidermal *transglutaminase* (Witte 2018). Of all the AMBDs, *bullous pemphigoid* (BP) and *pemphigus vulgaris* (PV) are the most common.

Pemphigus Vulgaris (PV) Overview

PV is a potentially fatal AMBD that affects the skin, mucosal surfaces, and oral cavity (Figure 1). The term pemphigus was first used by Hippocrates in 460-370 B.C. (Lever 1942). However, the differentiation between pemphigus and bullous pemphigoid based on lesional histopathological appearances was first made by Walter Lever in 1953 (Lever 1953). Pemphigus vulgaris is the most common form of pemphigus (Ruocco 2013). The incidence of PV globally ranges from 0.7 to 5 new cases per million per year. Although the disease can affect anyone, the incidence in Ashkenazi Jews can reach up to 16 to 32 cases per million per year (Joly 2001). The mean age of onset is 30 to 60 years of age, although many cases have been described in the elderly population and young children. The male to female ratio is 1:1 (Kershenovich 2014, International Pemphigus and Pemphigoid Foundation 2020). There is an estimated prevalence of 30,000 to 40,000 cases in the U.S. (International Pemphigus and Pemphigoid Foundation 2020).

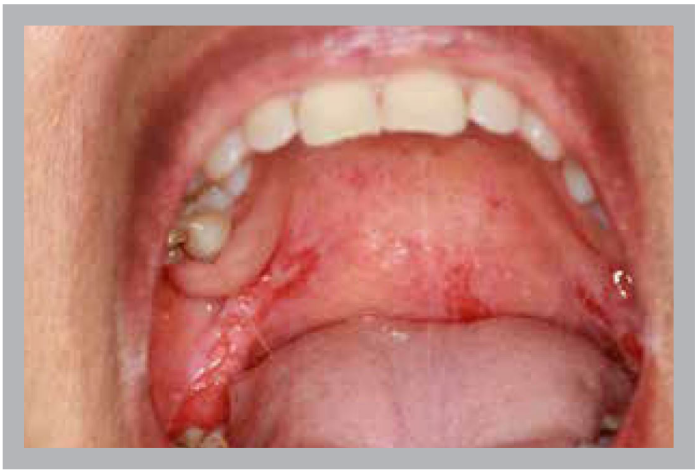

Figure 1. PV erosions extending into the hard and soft palates (Temilola 2018).

The skin lesions in PV are characterized by intraepidermal vesicles with *acantholysis* (disruption of normal cell-to-cell adhesion) being a histopathologic hallmark; the basal layer remains intact (Ahmed 1980). Patients produce an IgG antibody directed against *desmoglein-3* present in the intercellular substance

of the epidermis. Serum samples from patients with PV contain antibodies against *desmoglein-1* and *desmoglein-3*, which have been shown to be pathogenic (Table 1) (Bhol 1994, Bhol 1995, Hacker 2002).

Pemphigus Vulgaris (PV) Treatment Options

Conventional Treatment and Advent of Systemic Corticosteroids

The goal in pemphigus treatment is to maintain complete remission, which is defined as the absence of new or established lesions (Murrell 2020). The availability and usefulness of unconventional treatment options for serious dermatological conditions have undergone an evolution curve. Conventional treatment options like oral antibiotics, nicotinamide, dapsone, and anti-fungal agents were replaced with corticosteroid therapy in the early 1950s when findings of treatment with systemic corticosteroids were extensively researched and presented at the First ACTH conference in 1950 (Moore 1950). In one study in the early 1950s (Farber 1952), two of the 50 patients had pemphigus. Systemic corticosteroids (SCs) induced a dramatic response six months after therapy in a 54-year-old man seriously ill with acute fulminating pemphigus, who became free of lesions after several follow-up visits following systemic corticosteroid treatment (Figure 2).

Before the introduction of SCs in the management of PV, the prognosis was almost fatal, with mortality reported within 2 years following initial presentation (Hertl 2015). Presently, SCs are considered the gold standard of PV treatment (Bystryn 1984). SCs used alone or together with immunosuppressive agents (ISA), like methotrexate, mycophenolate mofetil, or azathioprine, at the onset of treatment substantially reduce the mortality associated with PV (Bystryn 1996). A major drawback of combination treatment with SCs and ISAs is long-term immunosuppression, the consequences of which are now the most common cause of mortality in patients with PV (Yeh 2005). Some of the undesirable effects of long-term SC use are osteoporosis, avascular bone necrosis, proximal myopathy, growth retardation, posterior subcapsular cataract, glaucoma, hyperglycemia, hyperlipidemia,

Table 1. Classification of the major pemphigus and pemphigoid variants

Disease		*Clinical Manifestations*	*Histology*	*DIF*	*IIF*	*Autoantigens*
Pemphigus	**Pemphigus vulgaris**	▪ Flaccid blisters[a] ▪ Painful erosions[a,b] ▪ Positive Nikolsky's sign	▪ Intraepidermal blisters ▪ Suprabasilar acantholysis	Intercellular IgG with or without C3	▪ Intercellular IgG ▪ Monkey esophagus	▪ DSG 3 ▪ DSG 1
	Pemphigus foliaceus	▪ Small flaccid blisters ▪ Crusted erosions ▪ No mucosal involvement ▪ Positive Nikolsky's sign	▪ Superficial intraepidermal blisters ▪ Granular layer acantholysis	Intercellular IgG with or without C3	▪ Intercellular IgG ▪ Guinea pig esophagus	▪ DSG 1
	Paraneoplastic pemphigus	▪ Extremely painful stomatitis ▪ Flaccid or tense blisters ▪ Lichenoid lesions ▪ Erythema multi-forme-like lesions ▪ TEN-like lesions	▪ Intraepidermal acantholysis ▪ Suprabasilar acantholysis ▪ Interface and lichenoid dermatitis	IgG intercellularly and at the dermo-epidermal junction	▪ Intercellular IgG ▪ Rat bladder	▪ DSG 3 ▪ DSG 1 ▪ Plakin proteins[c]
Pemphigoid	**Bullous pemphigoid**	▪ Polymorphic and non-specific eruption[d] ▪ Tense blisters[e]	▪ Eosinophilic infiltration in both the epidermis and dermis ▪ Subepidermal separation	Linear IgG and C3 at the dermo-epidermal junction	▪ Deposition of IgG at the dermo-epidermal junction ▪ Monkey esophagus	▪ BP180 ▪ BP230

Adapted from Kershenovich 2014.
Abbreviations: DIF, direct immunofluorescence; IIF, indirect immunofluorescence; DSG, desmoglein; TEN, toxic-epidermal necrosis.
[a] Mucocutaneous pemphigus vulgaris
[b] Mucosal dominant pemphigus vulgaris
[c] Plectin, Desmoplakin I, Desmoplakin II, BP230, Envoplakin, Periplakin, A2ML1
[d] Non-bullous phase bullous pemphigoid
[e] Bullous phase bullous pemphigoid

peptic ulcers, and weight gain.

These adverse events are driven largely by prolonged SC exposure, leading to cumulative effects, especially since high dosages are required to induce PV remission (Kridin 2018). In instances of adverse events leading to discontinuation, or contraindications to SCs or ISAs, treatment is often reverted to conventional therapies (e.g., oral antibiotics, nicotinamide, dapsone, and anti-fungal agents), which yield minimal or no improvement.

practice. The main disadvantage with this technology is difficulty producing large quantities of stable human mAbs due to the absence of suitable myeloma cell lines, which was overcome by genetic engineering and subsequently paved the way towards recombinant antibody technology. The first generation of humanized mAbs, the chimeric antibodies, was facilitated by genetic engineering. These antibodies consisted of variable regions of a murine monoclonal antibody linked to the constant regions of a human IgG molecule. A second generation of humanized antibodies soon

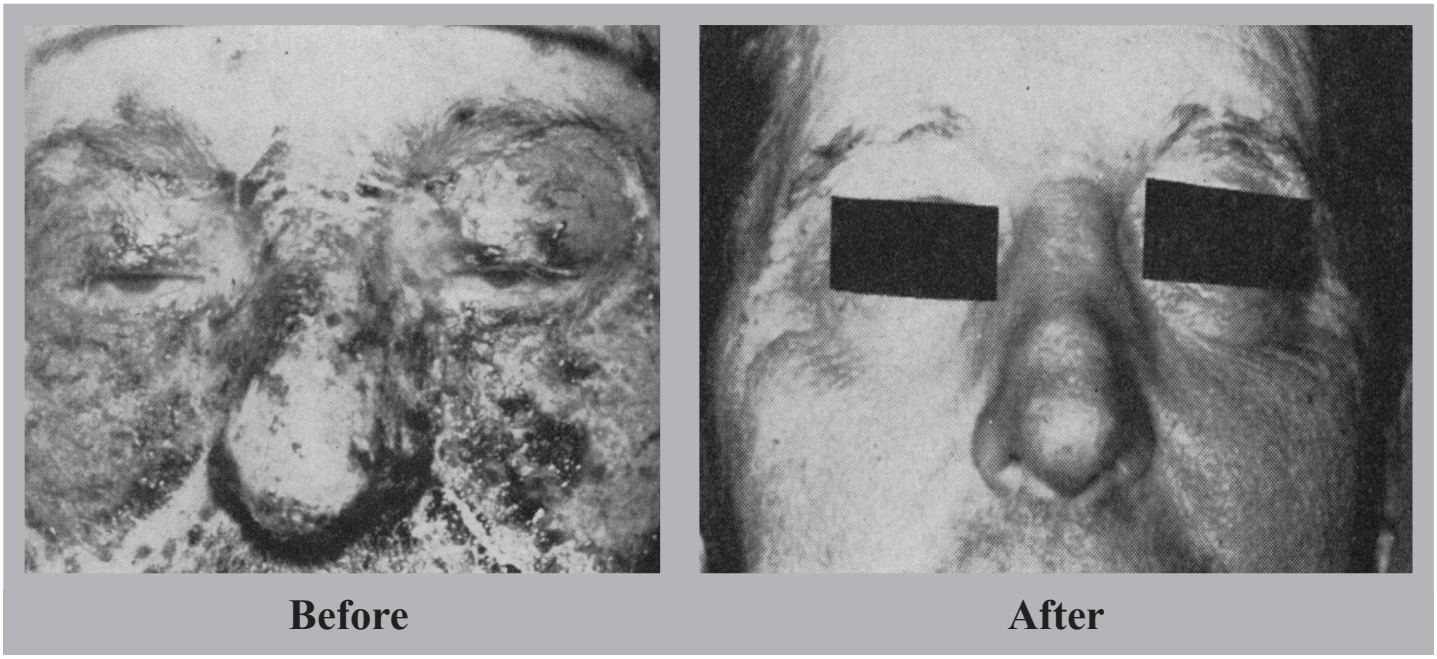

Figure 2. Effect of systemic corticosteroids in the treatment of acute fulminating pemphigus (Farber 1952).

Monoclonal Antibodies (mAbs)

After SCs and ISAs came the era of treating PV patients with monoclonal antibodies (mAbs). One of the pioneers in this area is Patrick Kung, who produced the now widely used series of mouse mAbs against T cell differentiation antigens, the OKT (Ortho, Kung, T cell) antibodies (Kung 1979). The most important contribution and influx of knowledge in this domain was the discovery of the hybridoma technique of producing mAbs (Köhler 1975). Hybridoma technology has facilitated the production of large amounts of rodent-derived, homogeneous, antigen-specific antibodies for use as diagnostic and therapeutic agents in medical

followed, in which the antigen-binding loops (CDRs) of the murine mAbs were successfully grafted onto a human IgG molecule (Stapleton 2004). The currently used monoclonal chimeric or humanized antibodies in PV are rituximab and infliximab. Although mAbs have benefited patients with PV and other blistering diseases who do not respond to combination treatment (e.g., SCs and ISAs), or who experience significant adverse events from these regimens, intravenous immunoglobulin (IVIg) use, in recent years, has become more prominent in the management of severe dermatological conditions refractory to all other non-IVIg treatments.

Rituximab

Rituximab is a monoclonal humanized antibody directed against the B-cell-specific cell surface antigen CD20. Rituximab binds to these CD20-expressing B lymphocytes including the immature B cells in bone marrow, autoantigen-activated follicular B cells, autoantigen-activated marginal zone B cells, and memory B cells; plasma cells are not targeted (Kridin 2018). Rituximab acts by binding to cell-surface receptors, and the principle mechanisms by which it acts includes antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cytotoxicity (CMC), and direct apoptosis. The removal of mature CD20-positive B lymphocytes, which differentiate into autoantibody-producing plasma cells, is considered the source of therapeutic effect from rituximab and makes its use particularly attractive in autoimmune diseases where pathological autoantibodies are the cause of the disease such as in pemphigus (Meurer 2012). Mild to moderate infusion-related reactions like fever, chills/rigors, nausea, pruritus, angioedema, hypotension, bronchospasm, throat irritation, rhinitis, urticaria, vomiting, myalgia, headache, dizziness, and hypertension have been reported in most patients during the first rituximab infusion. These reactions typically manifest 30 to 120 minutes after the beginning of the first infusion and subside with the slowing or interruption of the rituximab infusion and with symptomatic treatment (Kim 2015).

Infliximab

Infliximab is a genetically-engineered chimeric monoclonal antibody (mAb) that has variable regions derived from mouse antibodies fused with a constant region derived from human antibodies. It is a tumor necrosis factor (TNF) blocker and targets the CD20 molecule B cells but spares the CD20 molecule on plasma cells (Feldmann 2001). In human diseases, TNF is a key mediator of inflammatory tissue damage (Gottlieb 2005), and TNF-blocking therapy with antibodies like infliximab is highly efficient in the treatment of several inflammatory autoimmune diseases, as it binds to the soluble bioactive TNF-α and neutralizes its proinflammatory effects (Siegel 1995, Knight 1993). Transmembrane TNF-α has an important role in direct cell-to-cell interactions (Van Deventer 1997); hence, in inflamed tissues such as PV lesions, TNF blockade down-regulates cytokine expression and other pro-inflammatory molecules such as IL-8 and MCP-1 (Gottlieb 2005). Several other mechanisms of action have been proposed regarding the ability of infliximab to reduce mucosal inflammation. In vitro, infliximab binds membrane-bound TNF-α, facilitating destruction of those cells which have an enhanced cytokine response by antibody-dependent cellular toxicity or complement-dependent cytotoxicity mechanisms (Scallon 1995).

A multi-centered, randomized trial for the treatment of PV with infliximab and corticosteroids compared with corticosteroids alone was performed in 2015 (Hall 2015). This study revealed that there were no significant differences between study arms in the proportion of patients with severe or greater in severity treatment-related adverse events and that infliximab was not shown to be effective for the treatment of patients with PV, although infliximab treatment was seen to be associated with a decrease in anti-desmoglein-1 and anti-desmoglein-3. A single case study (Pardo 2005) describes that a patient improved dramatically after five infusions of infliximab, achieving total clearance of active lesions by week 22. This case study represents an isolated case of dramatic improvement and has not been generalized in larger sample sizes of PV patients.

The risk profile of mAbs include acute and delayed hypersensitivity reactions (seen in 10% of people) along with lowering one's ability to fight serious and opportunistic infections caused by viruses, fungi, or bacteria that have spread throughout the body, including tuberculosis (TB) and histoplasmosis. Reactivation of old latent TB as well as unusual cancers and liver disorders have also been reported.

Recently, International Pemphigus and Pemphigoid Foundation (IPPF) endorsed the treatment of PV with infliximab as a monotherapy. MAbs as monotherapy treatment is often insufficient, while combination therapy of mAbs (e.g., ritixumab or infliximab) with IVIg yields favorable outcomes in PV patients (Ahmed 2004).

Plasmapheresis and Immunoadsorption

Plasmapheresis and immunoadsorption are extracorporeal procedures of purification or filtration

of blood. During plasmapheresis, plasma proteins are non-selectively removed from blood circulation (Tavakolpour 2017). Blood is continuously removed from the patient and separated into cellular components and plasma, and the cellular component is returned whereas the plasma is replaced with albumin or fresh-frozen plasma (Gregoriou 2015). The procedure results in elimination of pathogenic autoantibodies from circulation, and the rationale of this treatment is based on the correlation observed between the titers of circulating anti-desmoglein-3 autoantibodies and disease severity (Turner 2000). Although rebound increase in autoantibodies occurs 2 weeks after the procedure, plasmapheresis is known to have resulted in lower long-term pemphigus antibody levels (Tan-Lim 1990). Adverse events reported during and after plasmapheresis include thrombocytopenia, hypogammaglobulinemia, fluid overload leading to hypertension and pulmonary edema in patients with underlying congestive heart failure, hypoproteinemia, anemia, leukopenia, disturbances in homeostasis, and hypocalcemia (Yeh 2005).

During the process of immunoadsorption, rapid removal of circulating autoantibodies against desmoglein-1 and desmoglein-3 takes place. In plasmapheresis, clotting factors, albumin, and hormones are inadvertently removed, which require replacement, whereas the process of immunoadsorption is more specific, where only immunoglobulins and immune complexes are attracted to the adsorber and removed from circulation (Kim 2015), and is therefore considered more efficient and safer than plasmapheresis (Braun 1998). Usually highly tolerable, limited adverse events, including hypotension, anaphylaxis, bradycardia, infarction, deep venous thrombosis, and herpes zoster infection, have been reported during and after immunoadsorption (Tavakolpour 2017).

Intravenous Immunoglobulin (IVIg)

Intravenous immunoglobulin (IVIg) is a polyclonal antibody and has been used as a component of adjuvant therapy for severe pemphigus since 1989 (Kim 2015). It is an immunomodulating agent obtained from sterile, purified IgG products manufactured from pooled human plasma. It contains 95% unmodified IgG, which has intact Fc-dependent effector functions and only trace amounts of IgA or IgM (Kim 2015). IVIg is usually administered in intractable disease or in case of contraindications to immunosuppressive adjuvants and is recommended as a second-line adjuvant by the European Dermatology Forum (EDF) guidelines (Hertl 2015) and as a third-line therapy by the British Association of Dermatologists (BAD) guidelines (Harman 2017). Some consider IVIg a steroid-sparing adjuvant to conventional pemphigus therapy, while others consider it a disease-modifying agent that can be used as monotherapy (Jolles 2002).

IVIg has been used to treat several conditions for many years and, over the course of time, has been found to be a relatively safe treatment compared with other therapies, such as SCs or ISAs (Carson 1996). Not only does IVIg recognize a multitude of bacterial, viral, and other infectious antigens, it also exhibits anti-

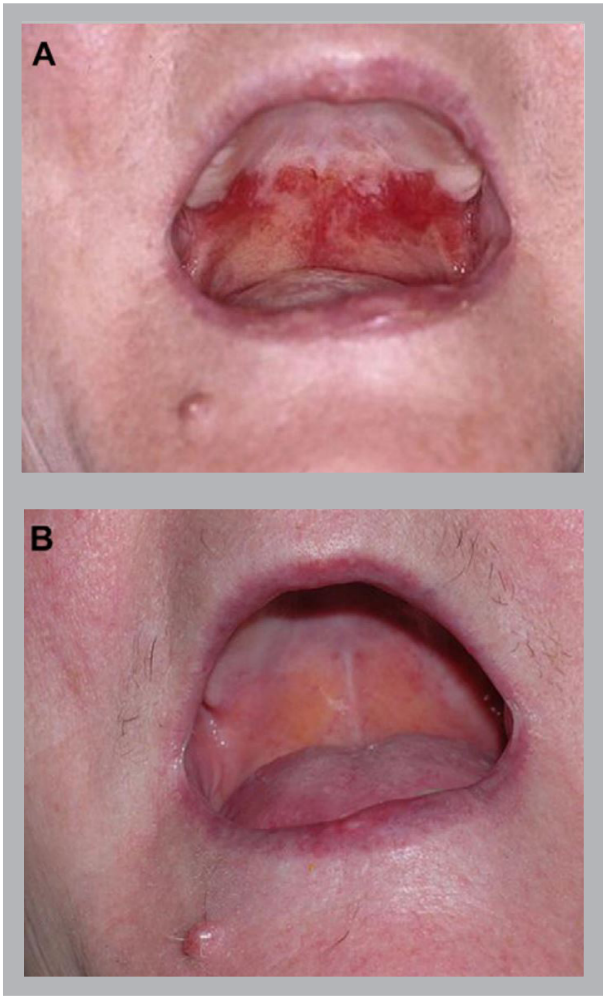

Figure 3. PV lesions before and after IVIg treatment (Segura 2007).

idiotypic specificity (Krause 2002). For this reason, in the last decade, IVIg has been increasingly used as an immunomodulatory agent in the treatment of patients with autoimmune and systemic inflammatory diseases (Lever 1979), with relatively few adverse events and drug interactions reported (Aberer 1987).

IVIg treatment has been found to be successful for the bullous autoimmune diseases, such as pemphigus and bullous pemphigoid. IVIg functionally blocks Fc receptors by saturation, leading to decreased cellular destruction because of Fc-mediated phagocytosis of antibody-coated cells (Dwyer 1992), auto-antibody neutralization and inhibition of its production via binding to autoreactive B lymphocytes (Sultan 1984), complement inhibition, modulation of cytokine and cytokine antagonist production, and decreased formation of the membrane attack complex (MAC) (Basta 1994, Andersson 1996). There is evidence in literature that patients with PV have been successfully treated with IVIg and, in addition to presenting with a favorable clinical outcome, have demonstrated that IVIg has a steroid-sparing effect (Figure 3). In addition to inducing remission, IVIg maintained remission over the long term (Yeh 2005).

Table 2. PV Treatment Strategies.

	First-Line Treatment	*Second-Line Treatment*	*Third-Line Treatment*
Treatment Options	1. Systemic corticosteroids (as monotherapy or as an adjunct to immunosuppressive agents)	1. Monoclonal antibodies (as monotherapy or as an adjunct to SCs) ▪ Infliximab ▪ Rituximab	1. IVIg (as monotherapy)
	2. Immunosuppressive agents (as an adjunct to SCs) ▪ Azathioprine ▪ Mycophenolate mofetil ▪ Cyclophosphamide ▪ Dapsone ▪ Methotrexate	2. IVIg (as an adjunct to conventional treatments)	
	3. Plasmapheresis or Immunoadsorption (as an adjunct to SCs/mAbs or IVIg)		

Adapted from Gregoriou 2015, Hertl 2015, and Kridin 2018.

Table 3. PV Treatment Strategies by Patient Type.

		First-Line Treatment*	*Second-Line* Treatment*	*Third-Line* Treatment*
Patient Type	SCs and immunosuppressive-naïve patients	✓		✓
	Patients with refractory disease or in case of contraindications to SCs	✓	✓	✓
	Patients with refractory disease or in case of contraindications to immunosuppressants			✓

Adapted from Hertl 2015.

*Please refer to first-line, second-line, and third-line treatment options referenced in Table 2.

An advantage of high-dose IVIg versus other commonly used immunomodulating therapeutic strategies is the excellent safety profile (Ruetter 2004). In sharp contrast to conventional immunosuppressive therapy, where patients are required to be hospitalized, IVIg can be easily administered as a home-based infusion (Abolhassani 2012). IVIg infusions may cause mild adverse events like mild headache, nausea, and vomiting that disappear shortly (Amber 2018). Due to its relatively high cost, IVIg use has been limited to a select group of patients to optimize the cost-benefit ratio (Colonna 1998).

Conclusion

IVIg is now increasingly being used as immunomodulatory agents in the treatment of patients with autoimmune and systemic inflammatory diseases, including PV, and is the best available treatment for patients with PV who are non-responsive to or adversely effected by conventional treatments. Not only does IVIg recognize many bacterial, viral, and other infectious antigens, it also exhibits excellent anti-idiotypic specificity which is greatly effective in the treatment or prevention of pemphigus vulgaris. Furthermore, IVIg is a useful agent in the prevention of blister formation in PV experimental model in-vivo. MAbs are useful and effective but have lower efficacy and success rates in achieving complete remission in patients suffering from PV.

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