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Restoring immune tolerance in pemphigus vulgaris

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Intravenous immunoglobulin (IVIg), a preparation of polyclonal serum IgG pooled from numerous blood donors, has been used for nearly three decades and is proving to be an efficient treatment for many autoimmune blistering diseases, including pemphigus vulgaris (PV). Despite its widespread use and therapeutic success, its mechanisms of action are not completely understood. Some of its anti-inflammatory and immunomodulatory actions have been studied. In this study, the authors present a twenty-year follow-up of 21 patients with clinical and immunopathological confirmed PV, treated with IVIg as monotherapy, according to an established published protocol. IVIg therapy produced long-term sustained, clinical, serological, and immunopathological remission. For 20 y, these patients received no drugs and experienced no disease. This observation suggests that there was the establishment of immune balance or restoration of immune regulation in these PV patients. Twelve (57%) patients experienced no relapse during follow-up. Six (29%) patients experienced a relapse due to acute stress or post-coronavirus infection and/or vaccination. Reinstitution of IVIg resulted in prompt sustained recovery. Three (14.2%) patients, in clinical and serological remission, died due to unrelated causes. No severe adverse effects from IVIg were documented in all 21 patients. The simultaneous or sequential anti-inflammatory and immunomodulatory effects of IVIg may have influenced the long-term clinical remission observed. This study provides a human prototype to examine the pathophysiology of autoimmunity and a model to study immune regulation and mechanisms that can facilitate restoring immune tolerance.

pemphigus vulgaris | intravenous immunoglobulin | twenty-year follow-up | long-term remission | immune tolerance

Significance

This research demonstrated a 20-y clinical and serological remission in patients with recalcitrant pemphigus vulgaris (PV), a potentially fatal mucocutaneous autoimmune disease. Conventional immunosuppressive therapy was unsuccessful. Consequently, as a treatment of last resort, they were treated with intravenous immunoglobulin (IVIg) as monotherapy by a defined protocol, requiring multiple infusions at defined intervals. The 20-y remission was post-IVIg therapy. This would suggest restoration of immune tolerance. IVIg has anti-inflammatory and immunomodulatory effects in the microenvironment. While its long-term benefits have not been completely investigated, such studies provide the opportunity. This long-term analytical study provides a human model to study autoimmunity and design disease-specific protocols that facilitate the mechanisms to restore immune tolerance in other autoimmune diseases.

Pemphigus vulgaris (PV) is a potentially fatal autoimmune blistering disease, involving the mucous membranes and the skin (1). It is a chronic disease with high morbidity, protein and fluid loss, and systemic infections contributing to mortality (2, 3). It is characterized by autoantibodies to desmosomal proteins. In addition, autoantibodies against keratinocyte muscarinic and nicotinic acetylcholine receptors, pemphaxin, an annexin-like molecule that binds to acetylcholine, have been described to play a role in the pathogenesis of PV (4). Histology demonstrates intraepidermal vesicles with acantholysis (3). Majority of the patients initially present with oral disease (2).

The use of systemic corticosteroids (CS) in the 1950s reduced the mortality rate (5). Their serious side effects warranted the use of immunosuppressive agents (ISAs) for their alleged steroid-sparing effect (6–10). The resultant prolonged immunosuppression eventually contributed to opportunistic infections, morbidity, and mortality, hence, the need for new modalities for safer treatments with fewer, limited, manageable side effects.

In 2001, 21 PV patients with extensive, widespread severe disease, with multiple relapses and recurrences, who had serious side effects from CS and multiple ISAs, frequent systemic infections, multiple hospitalizations, and were considered recalcitrant to available treatments, were reported (11). These patients received intravenous immunoglobulin (IVIg) as a treatment of last resort (11).

The purpose of this report was to provide a clinical and serological post-IVIg follow-up of 20 y or more on the same 21 PV patients.

Results

Details of clinical profiles, age at last follow-up, duration of conventional therapies prior to IVIg, length of clinical remission, and follow-up since the 2001 publication on the 21 PV patients are presented in Tables 1–3. Eighteen (85.7%) are alive and in clinical remission. Three (14.2%) patients died from unrelated causes but were in clinical remission at time of death.

The total mean duration of clinical remission and follow-up since the 2001 publication in the 21 patients was 17.5 y (range 5.1 to 30.5). The follow-up is presented in categories based on clinical outcomes as follows:

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Table 1. Pemphigus vulgaris (PV) patients with uneventful follow-up

Patient No.	Age (y) at onset/Sex	Duration of conventional tx prior to IVIg (mo)	Duration of remission & f/u since 2001 publication (y)	Age at last f/u (y)	Current Clinical Profile
1	71/M	50	16.9	92	Currently living in elderly housing facility
2	71/F	60	16.0	92	Currently living in elderly housing facility
3	76/F	32	18.4	97	Currently living in elderly housing facility
4	65/M	20.8	30.3	97	Currently living in elderly housing facility
5	59/F	32	19.4	81	Currently living in assisted living facility
6	58/M	15	20.75	80	Currently living in assisted living facility
7	57/F	28	19.6	79	Currently living at home with daughter
8	55/M	24	20.0	77	Currently living at home
9	49/F	18	20.5	71	Currently living at home—independent
10	42/F	22	20.1	64	Currently living at home, full-time employment
11	41/F	12	21.0	63	Currently living at home, full-time employment
12	69/M	25	10.0	Unknown	Followed for 10 y. after last IVIg infusion. Not reachable. Single man- No family.

y, years; *mo*, months; *tx*; treatment, f*/u*, follow-up.

Pemphigus vulgaris (PV) Patients with Uneventful Follow-up. Among the 21 patients, twelve (57%) patients had an uneventful follow-up (Table 1). The mean duration of conventional therapy prior to IVIg was 28.2 mo (range 12 to 60). The mean length of clinical remission and follow-up since the 2001 publication was 19.4 y (range 10.0 to 30.3), without recurrences or relapses. After 10 y of follow-up, while in clinical and serological remission, one patient was lost to follow-up.

Patient Deaths during Follow-up. Three (14.2%) patients in clinical and serological remission died due to unrelated causes (Table 2). The mean length of clinical remission and follow-up was 6.9 y (range 5.1 to 9.1).

Patients with Relapse Secondary to Acute Severe Stress. Four (19%) patients experienced a relapse of pemphigus due to acute, severe stress during follow-up. Prior to relapse, the patients were in clinical remission for a mean of 10.4 y (range 5.6 to 17). The detailed causes of relapses are in Table 3*A*. The diagnosis of relapse was confirmed by histology, direct immunofluorescence (DIF), and serology. All four patients received a short-term course, mean of 11 wk (range 9 to 18), of low-dose oral prednisone (0.5 to 1.0 mg/kg/day), and a mean of 11 cycles (range 9 to 13) of IVIg that resulted in clinical and serological remission and currently remain in remission for a mean of 14 y (range 10 to 18.5).

Patients with SARS-CoV-2-Related Relapse. Two (9.5%) patients relapsed due to the SARS-CoV2 virus or vaccine during follow-up and are presented in Table 3*B*. The first patient was in remission after initial IVIg for 15 y. This patient was hospitalized for PCR-confirmed SARS-CoV2 infection and had a relapse of PV 5 wk later. Treated with low-dose oral prednisone (0.5 to 1.0 mg/kg/d) and 9 cycles of IVIg. This patient was treated with low-dose prednisone (0.5 to 1.0 mg/kg/d) and 9 cycles of IVIg.

The second patient was in clinical remission after initial IVIg therapy for 14 y and had a clinical relapse of PV, 3 to 4 wk after COVID-19 vaccination. Relapse confirmed by biopsy, DIF, and serology. Treated with low-dose oral prednisone and 12 cycles of IVIg, resulted in clinical and serological remission that has lasted for 2 y.

Adverse Effects of IVIg. During this 20-y follow-up, no patient experienced any serious side effects or complications from previous IVIg therapy. No malignancies or other autoimmune diseases were reported.

Discussion

The cumulative evidence obtained from several studies suggests that IVIg is an effective alternative treatment for severe or recalcitrant pemphigus vulgaris (PV) (12). In this study, the authors followed 21 PV patients from a previous 2001 publication for a period of 20 y or more (11). Three (14.2%) patients died and 18 (85.8%) patients are alive and in remission. The indications for IVIg were recalcitrant disease, non-responsiveness to conventional immunosuppressive therapy (CIST), with severe side effects, and inability to obtain a prolonged, sustained clinical remission, off-therapy. Once CIST was discontinued, IVIg was used as monotherapy. In the majority of these patients, remission was maintained for a mean of 17.5 y, off-therapy. This was accompanied with the absence of pathogenic autoantibodies from the sera and sites of binding in the skin and mucosal tissue. The rationale for this successful outcome could be that IVIg helped in correcting the dysregulated humoral and cellular compartments that are characteristic of the immunopathogenesis of PV and, in turn, restored a long-term physiological immune equilibrium or immune tolerance.

The use of IVIg therapy produced long-term sustained clinical and serological remission in the 21 PV patients studied. Twelve (57%) patients experienced no relapses or recurrences, three (14.2%) patients died with cause of death unattributed to IVIg usage, and six (29%) patients experienced a relapse during follow-up. Four of these relapses (19%) were directly associated with severe and traumatic stress in the lives of the patients. There is significant evidence that acute emotional stress can trigger pemphigus relapse, especially in individuals with a previous history of it (13–16). Stress has also been demonstrated as a trigger in other autoimmune diseases (17, 18).

Since the emergence of the new coronavirus (COVID-19), there have been numerous reports on the incidence of exacerbations of PV, which occurred shortly after the infection or the vaccination (19). Two (9.5%) patients, who were in clinical and

Table 2. Patient deaths during follow-up

Patient No.	Age (y) at onset/ Sex	Duration of conventional tx prior to IVIg (mo)	Duration of remission & f/u since 2001 publication (y)	Age at last f/u (y)	Clinical Profile
13	62/M	84	6.5	75.5	Bladder + Prostate Ca in remission prior to PV. Tumor in remission for 6 y. post-IVIg Sudden tumor recurrence, mets & death in 9 mo. PV in remission at time of death
14	80/F	22	9.1	91	Died in sleep No autopsy PV in remission at time of death
15	83/F	17	5.1	89.6	Ruptured aortic aneurysm PV in remission at time of death

y, years; *mo*, months; *tx*; treatment, f/*u*, follow-up; *Ca*, Cancer; *PV*, Pemphigus vulgaris; *mets,* metastasis.

serological remission for many years, experienced a relapse during follow-up after COVID-19 infection or vaccination. At that time, IVIg preparations did not contain antibodies to SARS-CoV2 from donors who were either exposed to the virus or vaccinated. Reinstitution of IVIg, with a short initial course of prednisone, resulted in a prompt recovery and sustained clinical remission off-therapy.

There are several rare but serious adverse effects associated with the use of IVIg (20), however, none were documented throughout the follow-up period.

In the 2001 publication, IVIg therapy was used according to an established protocol, developed by an International Consensus Building Committee of Experts on Autoimmune Blistering Diseases, on the use of IVIg therapy for their treatment (21). Twenty years later, since these 21 PV patients were still in clinical, serological, and immunopathologic remission, these data suggest that the protocol is effective and may play a vital role in the restoration of physiological immune homeostasis or immune tolerance. Many other autoimmune diseases that use IVIg as a treatment option do not use a defined protocol. Consequently, long-term remissions are not reported and multiple reinfusions are necessary as in chronic inflammatory demyelinating polyneuropathy or multifocal motor neuropathy (22, 23). While the authors attribute successful outcome to the published protocol (21), they do not advocate its use in other autoimmune diseases affecting other organ systems. A novel protocol should be created for every autoimmune disease, that can benefit from IVIg, through consensus building.

In a cohort of 123 PV patients, long-term remissions were reported when IVIg was used in conjunction with immunosuppressive cytotoxic drugs, such as mycophenolate mofetil, azathioprine, and cyclophosphamide, alongside with mitochondrion-protecting drugs (doxycycline and nicotinamide) (24).

Recently rituximab (RTX) has been recommended as an effective first-line treatment of PV (25). Studies have demonstrated RTX's steroid-sparing effect (26). However, the rate of relapse on RTX increases with length of clinical follow-up, ranging from 40 to 81%, with long-term rates of clinical remission off-therapy observed in only 39 to 45% (27). In addition, complete B cell depletion, caused by RTX, predisposes to infection, which has been observed in 37% of patients (28). Furthermore, mortality has been reported in 10.2% of patients with PV (29). The most common cause of mortality reported was infection (30). Consequently, the addition of IVIg with RTX would allow immune prophylaxis. In a prospective study of RTX and IVIg combination protocol, 11 patients achieved clinical remission off-therapy, without infection in a 15-y follow-up (31). Other investigators have recommended that when PV patients are treated with a multi-drug protocol, including RTX and prednisone, addition of IVIg may lead to a long-term stable remission (32).

Inflammation is the hallmark of autoimmune conditions. The pathogenic immune response directed against the self-components leads to a dysregulated inflammatory reaction. IVIg exerts its beneficial role by its anti-inflammatory effect and by promoting a physiological immune status. This, in part, may explain the clinical benefits observed by its use in multiple autoimmune diseases. IVIg suppresses inflammation by resetting the threshold for innate immune effector cell activation and inhibition (33). These mechanisms include modulation of FcγR expression; inhibition of pro-inflammatory cytokines (IL-1β, IFN-γR2, IL-17, and TNF-α); production of anti-inflammatory cytokines (IL-1RA and IL-10); neutralization of activated complement components, blockade of macrophage activation and dendritic cell maturation, and upregulation of NK-cell functions (34). IVIg may also exert its effect, at least in part, by inducing apoptosis of immune cells via Fas-specific or neutrophil-specific antibodies present in the IVIg preparation (35, 36).

Interestingly, studies by Viard et al. demonstrated that IVIg has a beneficial effect in toxic epidermal necrolysis (TEN), or Lyell's syndrome, wherein they showed that IVIg interferes with the binding of Fas and its natural ligand (Fas L), thereby inhibiting the excessive apoptosis of keratinocytes (37). It is therefore reasonable to consider that both pro- and antiapoptotic antibodies may be found in IVIg and that the overall result could depend on the amount of antibodies and their affinity and avidity for their target molecule, Fas.

IVIg also plays a vital role in adaptive immunity, by influencing naive and mature B cells, plasma cells, and T cells, particularly the T_{regs} (34, 38). Positive clinical response to IVIg correlates with an increased number of CD138+ plasma cells, which produce normal or physiologic antibodies that compete with pathogenic antibodies in the diseased microenvironment (34). Expansion of antigen-specific T_{regs} further decreases inflammation (34, 38). The cumulative evidence demonstrates that IVIg possesses anti-inflammatory properties, in addition to immunomodulation, without the harmful adverse events frequently associated with conventional immunosuppressive therapy (CIST).

Several mechanisms implicating the anti-inflammatory and immunomodulatory effects of IVIg may explain its short-term beneficial influence in autoimmune diseases. However, effects that help produce long-term remissions, as in this cohort, need to be investigated. One of the important components of IVIg is the high content of natural antibodies (NAbs) (39), that are capable of interacting with a wide range of self- and non-self-antigens, in a physiological configuration. NAbs bind to pathogens, implicated in natural host defense against infectious pathogens, and remove

Table 3. Patients with relapse during follow-up

Patient No.	Age (y) at onset/ Sex	Duration of conventional tx prior to IVIg (mo)	Duration of remission & f/u since 2001 publication (y)	Age at last f/u (y)	Clinical Profile	Duration of relapse (mo)	Treatment of relapse & f/u
(A) Relapse secondary to acute severe stress							
16	60/M	30	17.5	80	Was in clinical remission for 7 y. Recurrence 4 wk. after spousal death. Autoantibody + Bx & DIF +	3	Prednisone 40 mg + taper x4 mo, IVIg 9 cycles Psych tx. needed Currently in remission for 10 y.
17	67/M	34	17.1	87	Was in clinical remission for 5.6 y. Recurrence 5 wk. after house completely destroyed by fire. Autoantibody + Bx & DIF +	5	Prednisone 40 mg + taper, IVIg 13 cycles Psych tx. needed Currently in remission for 11.5 y.
18	35/M	40	18.6	57	Was in clinical remission for 17 y. Recurrence 6 wk. after total bankruptcy & house auctioning. Autoantibody + Bx & DIF +	3	Prednisone 60 mg + taper IVIg 10 cycles Psych tx. needed Currently in remission for 16 y.
19	34/F	30	30.5	67	Was in clinical remission for 12 y. Recurrence 4 wk. after death of only son in Afghanistan. She is a single mother. Autoantibody + Bx & DIF +	4	Prednisone 40 mg + taper IVIg 12 cycles Psych tx. needed Currently in remission for 18.5 y.
(B) SARS-CoV-2-related relapses							
20	23/F	96	15	46	12 y. in remission Contracted severe COVID-19 infection Hospitalized- Not on ventilator PV relapse occurred 3 wk. later Skin only, no mucosal involvement Autoantibody + Bx & DIF +	3.5	Prednisone 40 mg + taper IVIg 9 cycles Currently in remission for 3 y.
21	27/F	67	16.4	49	14.4 y. in remission Received COVID-19 vaccine PV relapse occurred 4 wk. later Sx in oral cavity & skin Autoantibody + Bx & DIF +	4.3	Prednisone 60 mg + taper IVIg 12 cycles Currently in remission for 2 y.

y, years; *mo*, months; *wk,* weeks; *tx*; treatment; *f/u*, follow-up; *Sx,* symptoms; *Bx*, biopsy; *DIF*, Direct immunofluorescence; +, positive.

senescent cells, debris, and transformed malignant cells. NAbs modulate antigen processing and their subsequent presentation to T cells. Of significant importance for the understanding of the long-term effects of IVIg in antibody-mediated autoimmune diseases is the role of NAbs in the maintenance of T and B cell homeostasis, which may help restore immune homeostasis, as in this cohort (40).

NAbs prevent the expansion of specific autoreactive clones and are able to regulate self-reactivity of circulating antibodies through idiotypic interactions. The interaction of IVIg with idiotypes of

pathogenic autoantibodies accounts for the neutralization of circulating autoantibodies in patients with autoantibody-mediated autoimmune conditions and modulation of antibody synthesis by B cells expressing the relevant idiotype (39). Antibodies to variable region determinants of the T cell receptor (TCR) are also present in IVIg and these anti-TCR antibodies may be of relevance for the regulation of T cell function in patients with autoimmune disorders. Therefore, an overall impact of IVIg in restoring the immune homeostasis in autoimmune conditions is critical for the long-term effects of IVIg that were observed in this cohort (40).

More targeted recombinant approaches impacting humoral immunity in a selective fashion, functioning via FcRn and FcγRs, are currently being investigated (41). IVIg affects the neonatal Fc receptors (FcRn). The IgG in IVIg pharmaceutical preparations binds and saturates this receptor, resulting in enhanced clearance of pathogenic autoantibodies (42). FcRn regulates serum IgG levels by binding and rescuing it from degradation in lysosomes (41). FcRn is expressed in the endosomal compartment of intestinal epithelium, vascular endothelium, monocytes, and macrophages (43).

From a recent investigation, IVIg seems to have a pleiotropic effect, implicating a cooperative participation of several target pathways. The impact of each target in beneficial clinical outcomes could be different for each disease. Thus, the broad range of activity of IVIg could be critical to its beneficial effect in different diseases (44).

The current study has several limitations. This includes the lack of a control group of PV patients with identical recalcitrant disease. Reproducing this study will be difficult because a twenty-year follow-up will be a significant challenge. In 2001, Rituximab was not available to conduct a comparative study for efficacy in PV.

Conclusion

Despite limitations, certain important conclusions can be drawn from this data on the use of IVIg in PV. Long-term clinical and serological remission was achieved with IVIg, using a defined published protocol of 2 g/kg/cycle, which is gradually tapered after a clinical response, demonstrating the efficacy of the protocol. The data suggest that the beneficial effects of IVIg could be due to its anti-inflammatory influences to the microenvironment. IVIg, in part, provides the basis for the reestablishment of an immune equilibrium and the potential to eliminate clinical autoimmunity in PV and restore immune tolerance. Therefore, physicians treating PV should strongly consider IVIg as a therapeutic modality.

Materials and Methods

2001 Publication. In the 2001 publication, patient demographics, diagnostic and inclusion criteria, previous therapies and their side effects, and frequency of recurrence and relapses were described (11).

The salient and some relevant features of the 21 patients published in 2001 are presented as follows:

All patients were Caucasian. The mean age at disease onset was 56 y (range 23 to 83).

Five patients had only mucosal, and 16 had mucocutaneous disease.

All patients had positive direct immunofluorescence (DIF) of perilesional skin and histology, consistent with PV.

Prior to IVIg therapy, the mean dose of prednisone was 77 mg/d (range 50 to 120). The cumulative mean dose was 35,202 mg (range 14,750 to 89,500), for a mean duration of 36.4 mo (range 12 to 96 mo).

Recurrences, defined as appearance of new lesions while on systemic therapy, had a reported frequency with a mean of 5.6 (range 2 to 12).

Relapses, defined as new disease while off-therapy, had a reported frequency with a mean of 7.9 (range 0 to 18).

The indications for IVIg were recalcitrant disease, non-responsiveness to conventional immunosuppressive therapy (CIST), which produced catastrophic and consequential side effects, and inability to obtain a prolonged, sustained clinical remission off-therapy.

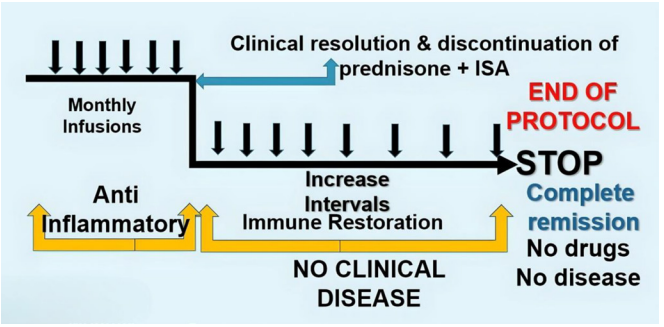

Fig. 1. IVIg treatment protocol. Diagrammatic representation of the protocol for using intravenous immunoglobulin (IVIg). Initially, there were monthly infusions of IVIg (anti-inflammatory phase) as systemic corticosteroids (CS) and immunosuppressive agents (ISA) were gradually discontinued. Upon clinical recovery and 3 mo after discontinuation of CS and ISA, the intervals between IVIg cycles were increased to 6, 8, 10, 12, and 14 wk. Last infusion was at a 16-wk interval. During this phase, immune restoration occurs. This was the end of the protocol. Patients were disease and drug-free and in complete clinical remission.

The Treatment Protocol. Thirty-eight international experts in an in-person Consensus Development Conference discussed and published a protocol for the use of IVIg in autoimmune mucocutaneous blistering diseases (21) (Fig. 1).

CISTs during IVIg Therapy. Clinical control was achieved in a mean of 4.5 mo (range 2.6 to 6.5). Tapering of IVIg required a mean of 22.7 mo (range 19.8 to 28.0).

After initiation of IVIg, oral prednisone was used for a mean of 4.8 mo (range 2.6 to 7.5). The cumulative dose of prednisone was a mean of 1,850 mg (range 1,180 to 3,200). ISAs were used for a mean of 2.9 mo (range 0 to 6).

Once CIST was gradually discontinued, IVIg was used as monotherapy.

Statistical Difference of Clinical Outcome Parameters. When comparing the following parameters of pre-IVIg and post-IVIg therapy, a high statistically significant difference was reported (11). These included total dose and duration of prednisone, duration of ISAs, side effects, number of hospital admissions, days of hospitalization, and number of recurrences and relapses (11).

The titers of pemphigus autoantibodies steadily decreased and were nondetectable at the time of publication (11, 45).

At the time of publication in 2001, patients were observed for a mean of 20.4 mo (range 13 to 73), post-IVIg therapy.

Post-2001 Publication Follow-up. For the first 3 y after the last IVIg cycle, all 21 patients were seen at 6-mo intervals for 3 y, then at 9-mo intervals, later, at yearly intervals. At each visit, they were clinically examined and serologically tested. A biopsy for DIF was performed, preferably from the same site as diagnosis. For patients who were unable to travel to the Center, their information was obtained from the primary care provider or referring physician.

While the motivations for participating in follow-up differed, the following were present in all the 21 patients.

(1) Patient Characteristics: All patients had recalcitrant disease and were desperate and frustrated, had a poor quality of life, and were aware that they could have a potentially fatal outcome.
(2) Cost of Treatment: IVIg therapy was authorized and provided by the individual's insurance companies, at no cost to the patient.
(3) Site of Infusion: The patients were treated in an ambulatory setting and not hospitalized. Since they were immunocompromised, concerns for infection were somewhat reduced. The presence of other patients in the infusion suite provided a powerful, positive psychological effect, which created a support group environment.
(4) A conscientious non-binding, non-legal agreement was made between the patients, their families, primary care physicians, and referring dermatologists. The patients agreed to a long-term follow-up, to determine whether IVIg could produce prolonged, sustained clinical remission. They realized that this information would benefit future patients and their treating physicians.

(5) In part, the patients' cooperation was based on their sense of gratitude for their recovery from a potential fatal outcome and the restoration of a high-quality life that IVIg facilitated.
(6) Majority of the patients were in the healthcare professions. They clearly understood the need and the benefits of such long-term follow-up.

IRB Approval. This study was approved by New England IRB-Study Number 1278568 in 2023. This is a retrospective study of patient medical records. This study did not include any active treatment protocol. The initial consent form for IVIg infusions and treatment was approved by the New England Baptist Hospital IRB in 1997.

Data, Materials, and Software Availability. All study data are included in the main text.

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