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IVIg TREATMENT OF PEMPHIGUS: How it Works & How to Use it

Jean-Claude Bystryn, M.D. and Jennifer L. Rudolph, M.D.
Ronald O. Perelman Department of Dermatology
New York University School of Medicine
New York, NY

Introduction

The treatment of pemphigus is one of the miracles of modern medicine. A disease that was once almost invariably fatal [1] has been transformed into one whose mortality is now only 5% to 10%. The mainstay of current therapy is the administration of systemic steroids in doses high enough to suppress the manifestations of the disease [2]. In addition, immunosuppressive (azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate), or immunomodulatory (dapsone, gold, antibiotics) drugs are often used as adjuvants as they may reduce the need for, and side effects of, systemic steroids. However, the effectiveness of these adjuvants has not been established objectively in a randomized trial.

Pemphigus is caused by autoantibodies (pemphigus antibodies) directed against adhesion molecules on the surface of keratinocytes [3,4]. In pemphigus vulgaris the antibodies are directed against desmoglein-3 and in about 50% of patients are also directed against desmoglein-1. In pemphigus foliaceus, the antibodies are all directed against desmoglein-1. It is possible that other autoantibodies may be involved. The involvement of pemphigus antibodies in the pathogenesis of the disease is evidenced by their selective presence in patients with pemphigus, the relation between their titer and disease activity [3], the rapid improvement in disease activity when antibodies are physically removed by plasmapheresis [5], and most convincingly by the ability of the antibodies to induce pemphigus when given to mice [6].

The need for better treatments for pemphigus

Despite the impressive progress treating pemphigus, better therapies are required. 1) No current treatment addresses the basic pathology of the disease, i.e. that pemphigus is caused by one or a few abnormal antibodies in the blood. Rather than selectively removing only the abnormal antibodies, current treatments non-specifically affect all antibodies – the good with the bad, which results in undesirable toxicities. 2) Pemphigus cannot be controlled in some cases even with very high doses of steroids. In other cases, treatment cannot be tapered without a flare in disease activity, or patients cannot tolerate side effects of the treatment. 3) Lastly, there is a need for adjuvant therapies that will more reliably minimize the use and side effects of steroids – which currently are the major cause of death in pemphigus. IVIg appears to provide a partial solution to these challenges.

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What is IVIg?

Intravenous immunoglobulin, or IVIg, refers to the intravenous administration of immunoglobulin. The immunoglobulin is prepared from plasma pooled from thousands of donors. It consists mostly of intact IgG molecules, with traces of IgA and of some cytokines and other immunomodulators found in serum. It contains the broad range of normal antibodies present in healthy individuals. Seven different formulations of IVIg were licensed in the US in 2002, each prepared somewhat differently. Their properties are summarized in Table I. As the composition of these preparations differ depending on the manufacturer [7], so does their effects, particularly their potential side effects. Clinically, the most relevant differences in composition are IgA, salt and sugar content, volume and osmolarity [7]. Preparations low in IgA are best for patients who are IgA - deficient and who may have anti-IgA antibodies (to minimize the risk of anaphylaxis). Low levels of sodium are best for patients with hypertension, cardiac and/or renal disease or those who are on a low salt diet. Low glucose preparations are best for diabetics, while those containing sucrose have been associated with adverse renal events. Preparations given in high concentration are best to minimize fluid overload in patients with impaired cardiac or renal function. Osmolarity, which is mostly related to salt, sugar and amino acid content, can cause fluid shifts and infusion-related adverse events [7]. Finally, various procedures are used to inactivate or remove virus from the plasma, and these differ in their effectiveness. Ig is expensive, costing approximately $10,000 for a single cycle of treatment, and multiple cycles of therapy are normally required.

How is IVIg used?

Important variables in using IVIg are dose, rate of infusion, the number of days over which it is given (a cycle), and the frequency with which cycles are repeated. The dose is usually 2 gm of Ig/kg per cycle, administered over 2 to 5 days. For example, 400 mg/kg can be given daily for 5 days or 500 mg/kg daily for 4 days. The faster the IVIg is given (by increasing the rate of administration and shortening the number of days over which it is given) the more convenient for the patient and the less the expense but the greater the chances for complications. Each daily infusion is normally given over 4-5 hours. Complications increase as the speed of administration increases. The optimal frequency with which cycles should be repeated or the number of cycles administered to treat pemphigus is not known. IVIg has been used frequently (every 2 weeks) for a limited number of cycles [3-5] to rapidly control active disease [8]; or monthly and then at increasingly longer intervals for prolonged periods (several years) to manage chronic disease [9]. As the treatment is expensive, what and how it is done is influenced by the reimbursement policies of insurance companies, which are not consistent. The treatment is usually given in an infusion center, an appropriately equipped physician's office, or in-hospital if the potential for complications is high. Commercial services will provide treatment at home, which is very convenient for the patient; however, precautions must be taken to handle any potential complications.

Mechanism of action of IVIg in pemphigus

The mechanism of action of IVIg in most autoimmune diseases remains uncertain [10]. In pemphigus however, it seems to work by rapidly, dramatically, and selectively lowering serum levels of pemphigus antibodies.

We have found that one week after a single cycle of IVIg, the average level of pemphigus antibodies decreased by an average of 70% [8]. The results in a representative patient are illustrated in **Fig 1**. The rate of decrease in pemphigus antibodies is as rapid as that induced when pemphigus antibodies are removed physically by plasmapheresis, and much more rapid than with conventional treatment with high doses of steroids and cytotoxic drugs where antibody levels decrease by only 16% after 3 weeks [11]. The magnitude of the decrease in antibody levels varies among patients – it is dramatic in some, minimal in others. We believe this diversity reflects in part variations in the ability of different individuals to synthesize pemphigus antibodies, with a few individuals being able to do so as rapidly as it is depleted.

FIGURE 1

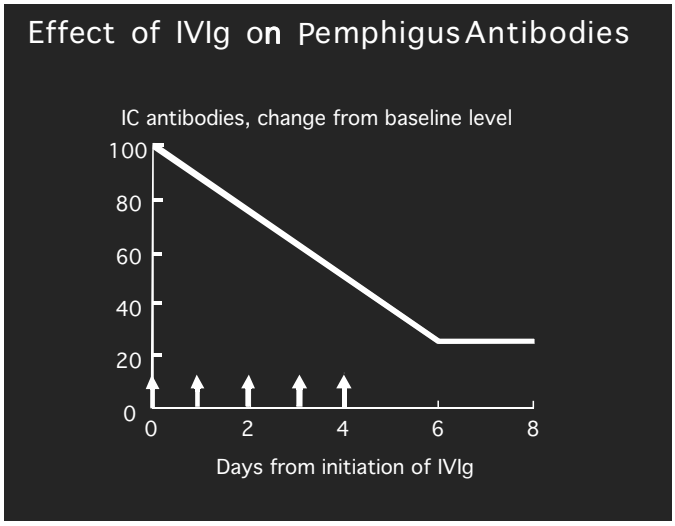

Fig 1. Effect of IVIg treatment on serum levels of pemphigus antibodies in a representative patient. Pemphigus antibodies were measured by indirect immunofluorescence at baseline immediately prior to administration of IVIg and following 5 daily IV infusions of Ig at a dose of 400 mg/kg/day. Note that one week following initiation of the treatment, pemphigus antibody levels were 70% lower than the pre-treatment level.

The decrease in pemphigus antibodies associated with IVIg treatment is highly selective. There is no decrease in the levels of unrelated antibodies, as

illustrated in **Fig 2**. Thus, IVIg can achieve the gold standard sought in the treatment of autoimmune diseases – suppressing the presence of abnormal antibodies but not that of normal antibodies.

FIGURE 2

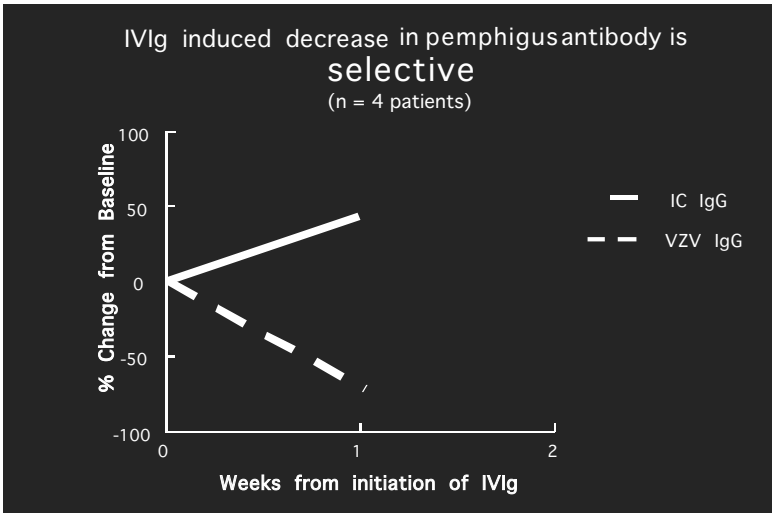

Fig 2. Effect of IVIg on serum levels of pemphigus and of a normal (VHZ = varicella-herpes zoster) antibodies in 4 patients. All patients had both types of antibodies in their serum prior to IVIg treatment. One week following initiation of therapy with a single cycle of IVIg, serum levels of pemphigus antibodies decreased by an average of 66% , while those of VHZ antibodies actually increased.

How does IVIg rapidly and selectively decrease serum levels of only pemphigus antibodies? Three possibilities could account for the decrease in pemphigus antibodies associated with IVIg therapy. Of these, the last is the most likely. The possibilities include: 1) IVIg blocks the synthesis of pathogenic antoantibodies. However, this is unlikely to be the full explanation as it cannot account for the very rapid decrease in pemphigus antibody levels that actually occur. The half-life of IgG in the circulation is approximately 3 weeks. Even if IVIg immediately and completely blocked all IgG synthesis, the level of pemphigus antibodies would decrease maximally by 50% in 3 weeks, far slower than the 50% or more in 1 week that actually occurs. 2) The presence of blocking factors in the IVIg preparation (such as anti-id antibodies) that inactivate or block the reactivity of pemphigus antibodies. This possibility is excluded by experiments in which we incubated the IVIg preparation used to treat patients with pre-treatment pemphigus antibodies obtained from several patients. There was no decrease in the level of pemphigus antibodies as measured by indirect immunofluorescence, 3) Increased catabolism. By exclusion, this appears to be the most viable explanation and as described below also explains how the decrease will be selective.

Our hypothesis is that IVIg stimulates a very rapid increase in the catabolism of all serum antibodies, and that this results in a decrease of only abnormal antibodies (pemphigus antibodies) as the normal antibodies which are also catabolized are replaced by those present in the Ig preparation.

Supporting this hypothesis: 1) There exists a physiological feedback mechanism which maintains constant total serum level of Ig. Increases in serum IgG accelerates the catabolism of all IgG molecules so reduce their serum levels back to normal. This is believed to occur as a result of the saturation of FcRn receptors that normally protect IgG molecules from degradation inside cells [12]. 2) This mechanism should be activated by IVIg treatment, which increases serum levels of Ig by approximately 50%. 3) The rate at which serum Ig level returns to normal (an indication of catabolic rate) once IVIg therapy is discontinued is similar to the rate at which serum level of pemphigus antibodies decreases [8]. 4) Serum levels of pemphigus antibodies decrease most rapidly when total serum Ig levels are highest, and no longer change once total Ig levels return to normal [8]. As discussed subsequently, this mechanism of action suggests a way to improve the effectiveness of IVIg treatment.

The mechanism of action of IVIg is very similar to that of plasmapheresis. Both procedures rapidly remove circulating pemphigus antibodies from the circulation and do so at about equal rates. However, IVIg has the major advantages over plasmapheresis that the pemphigus antibodies are removed selectively, whereas plasmapheresis as usually performed removes all circulating immunoglobulins, the good with the bad. Furthermore, IVIg appears to be safer.

Results of IVIg in the treatment of pemphigus

Individual case reports [see 13 for review] and several larger studies [8,9,14,15] indicate that IVIg can be an effective treatment for both pemphigus vulgaris and foliaceus. It is used in two distinct manners – as a short - term treatment to control active disease unresponsive to conventional therapy and as a long - term treatment for the management of chronic disease.

Active pemphigus unresponsive to high doses of prednisone (60-280 mg/day), given together with an immunosuppressive drug in half the cases, has been treated with one to 3 cycles of IVIg given every 2 to 3 weeks in 6 patients [8]. The disease was controlled in most patients within 2 weeks, and prednisone doses could be reduced within 3 weeks by an average of 40% from baseline level immediately pre-infusion. Similar results were observed when the study was extended to a total of 12 patients. Others have reported similar rapid response of extensive and rapidly progressive pemphigus to IVIg treatment [14]. However, not all patients respond equally well to treatment. In some, one cycle of IVIg is sufficient to clear most skin lesions within two weeks; in others, even several cycle of IVIg has little impact on the extent of disease. In part this variation

appears to be related to the ability of the treatment to lower serum levels of pemphigus antibodies, which in turn is probably related to the class and/or the pathogenicity of the pemphigus antibodies that are affected by the IVIg procedure, the rate at which new antibody is synthesized, by the frequency of the IVIg procedures and as discussed later by the use of cytotoxic agents to minimize new antibody synthesis.

In chronic, long standing pemphigus, two trials have been conducted, one in pemphigus vulgaris (n=21) [9], the other in pemphigus foliaceus (n=11) [15]. In both trials, a heterogeneous population of patients with either an unsatisfactory response to therapy or significant side effects was treated. IVIg was given monthly until all lesions were healed, and then at increasingly longer intervals until patients were disease-free for 16 weeks. In both studies, patients became lesion-free after a mean of 4.5 to 5.3 months. Eventually systemic therapy could be terminated in all patients. Patients required an average of 18-19 cycles of IVIg given over an average of 27-30 months. The ability to induce a remission in all of these patients is impressive. However, this positive result must be weighed against the expense and potential risk of repeated administrations of IVIg, given over several years.

Procedures to improve the effectiveness of IVIg treatment:

The mechanism of action of IVIg described above suggests two approaches to improve its clinical effectiveness.

1) IVIg is believed to work by lowing serum levels of pemphigus antibodies. Thus, one simple way to improve effectiveness is simply to increase the frequency of treatment, i.e. by administering it every 2 weeks rather than once a month. One cycle of IVIg will lower serum levels of pemphigus antibodies by approximately 50-60% under optimal conditions. Frequent monitoring of serum levels of pemphigus antibodies during IVIg therapy will help monitor the effectiveness of the treatment and how long it should be continued.

2) The effectiveness of IVIg treatment can also be improved, we believe, by co-administering a cytotoxic drug such as cyclophosphamide or azathioprine, in order to minimize the "rebound" in pemphigus antibody levels that may otherwise occur.

A physiological regulatory feedback mechanism maintains constant the level of individual antibodies in serum, and triggers new synthesis of any antibody whose level is lowered [16]. The feedback causes a rapid rebound in the serum level of any antibody that is depleted, which can exceed that present prior to the depletion *(as illustrated in Fig 3)*. This feedback mechanism will limit the effectiveness of any treatment that reduces serum levels of individual autoantibodies.

We have previously shown that the rebound can be reduced in animals [16] and in humans [17] by using cytotoxic drugs which inhibit antibody synthesis. The result of using cyclophosphamide to suppress the rebound in serum levels of a single antibody that follows its abrupt depletion by exchange plasmapheresis in animals is illustrated in **Fig 3**. The use of cytotoxic agents is now commonly accepted to improve the effectiveness of plasmapheresis treatment of pemphigus [18], by minimizing the rebound in pemphigus antibodies that would otherwise occur. We believe the same approach should improve the effectiveness of IVIg treatment, which like plasmapheresis, causes a rapid and profound decline in serum levels of pemphigus antibodies. Support for this suggestion comes from: a) case reports of IVIg therapy of pemphigus describe the procedure as clinically effective when a cytotoxic agent is given concurrently [19-21] and as ineffective when such an agent is not used [22,23]; b) our own studies where IVIg more rapidly controlled disease activity and lowered serum pemphigus antibody levels when given with an effective dose of cyclophosphamide or azathioprine than without; and c) reports that months are required for IVIg to lower serum levels of pemphigus antibodies when administered without a cytotoxic agent, while the decrease occurs in days to weeks if a cytotoxic drug is used.

FIGURE 3

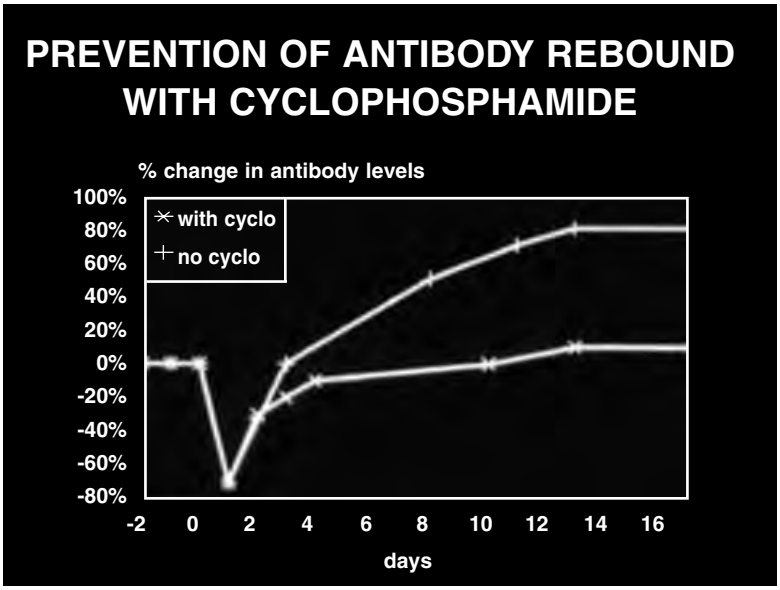

Fig 3. The "rebound" in antibody level that follows depletion in the serum level of that antibody, and suppression of the rebound by cyclophosphamide. Exchange transfusion was used to abruptly lower serum levels of a single antibody (anti-KLH) in a group of 15 mice. Half the mice were then treated with cyclophosphamide. There was a rapid rebound in serum in anti-KLH antibody levels in the mice not treated with cyclophosphamide (upper curve), so that 2 weeks later the average serum levels of that antibody were almost twice the baseline levels. By contrast, the rebound in mice treated with cyclophosphamide was markedly suppressed (lower curve).

Precautions and side effects

IVIg has the potential to cause serious side effects and thus should only be used in situations where its potential risk/benefit ratio outweighs that of alternate therapies. Patients who are IgA deficient, who have cardiac or renal disease or migraines are at particular risk of developing serious complications.

Screening studies done prior to initiation of therapy include serum Ig level (to look for IgA deficiency which is associated with increased chance of anaphylaxis), hepatic and renal function tests and urinalysis (to look for renal dysfunction), blood pressure (to look for cardiac disease), and serum immune complexes. Pemphigus antibodies should be obtained at baseline and periodically during therapy to monitor changes in their levels.

Pretreatment with non-steroidal anti-inflammatory agents (acetaminophen 650 mg) and antihistamines (diphenhydramine 50 mg) can minimize infusion-related headaches, rigors and other adverse events [15].

Mild side effects, usually infusion related, occur in approximately 5% to 15% of patients. These include fever, headache, muscle pains, low back pain, chills nausea, vomiting, and fatigue, changes in blood pressure, difficulty breathing, chest tightness, flushing, and infusion site reactions. These effects usually occur within 30 min. of initiating the infusion. They can be relieved by reducing the infusion rate or temporarily stopping it [24]. Acute aseptic meningitis, which may occur within 2 to 3 days after the infusion, can be minimized by anti-inflammatory drugs, and normally resolves spontaneously [10].

More serious side effects are unusual. They include anaphylaxis (most common with pre-existing IgA deficiency), thrombosis and strokes, renal dysfunction including acute renal failure (more common in patients treated with Ig preparations prepared from powder or those containing sucrose), infection, hemolysis, worsening of pre-existing congestive heart failure, and severe headache (particularly common in patients with a history of migraine). Because the Ig is prepared from large batches of pooled human plasma, there is a potential risk of transmitting infectious agents. To the best of our knowledge, no case of IVIg transmitted HIV or Creutzfeldt-Jakob disease has been reported. There were several outbreaks of hepatitis C linked to IVIg in the past, but this risk has been reduced by advances in the manufacturing process.

Indications for IVIg

There is general agreement that IVIg is indicated for the control of pemphigus unresponsive to conventional therapy, or when a serious complication to standard therapy occurs. Other suggested indications include inability to withdraw steroids without a flare in disease activity, absolute or relative contraindications to the use of systemic steroids, and progressive disease despite appropriate but safe conventional therapy [25]. An important element in the decision are the policies of Medicare or of he insurance plan that will pay for the treatment. The indications vary with each plan, and Medicare's indication vary from region to region in the US. A helpful guide to the regulatory and reimbursement issues involved in treating patients with IVIg is provided in reference 26.

A major advance in assuring reimbursement for the IVIg treatment of pemphigus was Medicare's issue of a National Coverage Decision in 2002 providing for coverage of IVIg treatment of biopsy proven pemphigus and other autoimmune blistering diseases, provided the patient met at least one of the following criteria: 1) Failed conventional therapy; 2) conventional therapy is otherwise contraindicated; or 3) rapidly progressive disease in whom a clinical response cannot be affected quickly enough using conventional therapy [27]. However, the exact definition of these criteria what left to the discretion of individual contractors. A detailed definition of these terms was provided by the Medicare contractor for the Northeast (MN, MS, NH, and VT) in October 2004. Failure of conventional control was defined as failure to control disease after prednisone 60 mg/d for 6 weeks with or without a concurrent immunosuppressive agent for 10-12 weeks. Contraindications to conventional therapy with systemic steroids was defined the presence of diabetes, significant osteoporosis, fractures, GI bleeding, subscapular cataracts, pseudotumor cerebri, bone marrow suppression, aplastic anemia, significant psychological changes, steroid myopathy, or glaucoma. Contraindications to conventional therapy with immunosuppressive agents was defined as persistent anemia; clinically significant neutropenia, abnormal hepatic function, or impaired renal function; hemorrhagic cystitis; bone marrow suppression or history of malignancy. It also added as an additional indication for IVIg treatment the presence of significant adverse effects of conventional therapy. These were defined as events which are potentially life-threatening, cause significant morbidity or inability to cope with activities of daily living, or require the intervention of a physician or drug therapy. Of note, is that patients may be taking these drugs to maintain control of disease, and thus do not need to have active disease at the time of initiation of the IVIg. Other Medicare contractor or insurance companies may have different definitions, and often limit the amount of Ig that can be given and the frequency of the treatment. Consequently, it is critical to contact and obtain authorization from the patient's own insurance carrier before initiating IVIg treatment.

Conclusions

IVIg is an important advance in the treatment of pemphigus. It achieves the most sought after therapeutic goal in the treatment of autoimmune diseases - the selective removal of pathogenic antibodies without altering that of normal antibodies.

IVIg seems particularly effective in the control of active disease unresponsive to conventional therapy. It is also useful as an adjunct to manage patients who have developed serious complications to standard therapy, or cannot be tapered off conventional therapy without a flare in disease activity. The effectiveness of IVIg treatment may be enhanced by repeating the procedure frequently to speed the removal of pemphigus antibodies and we believe by concurrently administering a cytotoxic agent to prevent new synthesis of these antibodies. That suggestion needs to be confirmed by appropriate clinical trials.

References

1. Bystryn JC. Adjuvant therapy of pemphigus. Arch Derm 120:941-951, 1984.
2. Bystryn JC, Steinman NM. The adjuvant therapy of pemphigus: an update. Arch Dermatol 1996; 132:203-12.
3. Sams W, Jordon RE, Correlation of pemphigoid and pemphigus antibody titers with activity of disease. Br J Dermatol. 1971;84:7-13.
4. Udey MC, Stanley JR. Pemphigus diseases of anti-desmosomal autoimmunity. JAMA. 1999; 282: 572-576.
5. Bystryn JC. Plasmapheresis therapy of pemphigus. Arch Dermatol 1988;124:1702-04.
6. Anhalt GJ, Labib RS, Voorhees JJ, Beals TF, Diaz LA. Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. N Engl J Med. 1982;306:1189-96.
7. Lemm G. Composition and properties of IVIg preparation that affect tolerability and therapeutic efficacy. Neurology 2002; 59:528-532.
8. Jiao, D., Natow S., Bystryn, JC. Treatment of pemphigus with IVIg. J Am Acad Dermatol Sep, 47:358-63, 2002.
9. Ahmed AR. Intravenous immunoglobulin therapy in the treatment of patient with pemphigus vulgaris unresponsive to conventional immunosuppressive treatment. J Am. Acad. Dermatology. 2001 Nov; 45(5):679-90.
10. Kazatchkine, MD, Kaveri, SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. NEJM. 2001 345(10):747-755
11. Rosario TL, Bystryn JC. Effect of plasmapheresis therapy on circulating levels of pemphigus antibodies. J Am Acad Dermatol. 1990;22:35-40.
12. Yu Z, Lennon VA. Mechanism of intravenous immune globulin thereapy in antibody-mediated autoimmune diseases. NEJM.Volume 340(3) 227-228.
13. Jolles S. A review of high-dose intravenous immunoglobulin (hdIVIg) in the reatment of autoimmune blistering blistering disorders. Clinical & Experimental Dermatology, 2001;26(2)127.
14. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. British Journal of Dermatology, 1999; 140: 865.
15. Ahmed AR, Sami N. Intravenous immunoglobulin therapy for patients with pemphigus foliaceus unresponsive to conventional therapy. J Am Acad Dermatol. 2002 46: 42-49.
16. Bystryn JC, Schenkein I, Uhr JW. A model for the regulation of antibody synthesis by serum antibody. Progress in Immunology, Vol. 1, Academic Press, New York, 1971, pg. 627.
17. Bystryn JC. Plasmapheresis therapy of pemphigus. Arch Dermatol 1988; 124:1702-04.
18. Stanley JR. Pemphigus. In: Freedberg IM, Eisen AZ, Wolff K, et al, eds. Dermatology in General Medicine. New York, NY: McGraw-Hill. 1999; 654-666.
19. Beckers RC, Brand A, Vermeer BJ, Boom BW. Adjuvant high dose intravenous gammaglobulin in the treatment of pemphigus and bullous pemphigoid: experience in six patients. Br J Dermatol. 1995;133:289-93.
20. Bewley AP, Keefe M. Successful treatment of pemphigus vulgaris by pulsed intravenous immunoglobulin therapy. Br J Dermatol. 1996;135:128-29.
21. Wever S, Zillikens D, Brocker EB. Successful treatment of refractory mucosal lesions of pemphigus vulgaris using intravenous gammaglobulin as adjuvant therapy. Br J Dermatol. 1996;135:862-63.
22. Tappeiner G, Steiner A. High-dosage intravenous gamma globulin: Therapeutic failure in pemphigus and pemphigoid. J Am Acad Dermatol 1989;20: 684-85.
23. Messer G, Sizmann N, Feucht J, Meurer M. High dose intravenous immunoglobulins for immediate control of severe pemphigus vulgaris. Br J Dermatol. 1995; 33:1014-16.
24. Misbah S.A.., Chapel H.M., Adverse effects of intravenous immunoglobulin. Drug Safety 1993; 9: 254-62.
25. Ahmed, A.R., MD, DSc; Dahl, M.V., MD et. Al. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mococutaneous blistering disease. Arch Dermatol. 2003;139:1051-1059.
26. Donofrio, P. D. MD, N.A. Busis, MD Regulatory and reimbursement issues in treating patients with immune-mediated neuropathies. Neurology 2002; 59:s41-s45.
27. Bholkc, N. S., Ahmed, A.R. Influence of IVIg therapy on autoantibody titers to desmoglein 1 in patients with pemphigus foliaceus. Clinical Immunology, 2002 105:192-198.