

The role of intravenous immunoglobulin in treatment of mucous membrane pemphigoid: A review of literature

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Background: Mucous membrane pemphigoid (MMP) is considered an autoimmune blistering disease that predominantly affects mucous membranes. Various treatments are available for controlling the diseases, but not all of them may respond. **Materials and Methods:** PubMed and Google Scholar were searched for all the associated studies until 2015, using the keywords such as “cicatricial pemphigoid” or “ocular pemphigoid” or “mucous membrane pemphigoid” or “MMP” and “intravenous immunoglobulin” or “IVIg” to find all the relevant studies. The last search update was for September 2, 2015. Among the searched items, only English studies were included in the review. **Results:** After excluding nonrelevant studies, 13 studies with a total number of seventy patients with MMP who were under treatment with IVIg were analyzed. The 65 patients responded completely, one did not respond, two had partially responded, and the remaining two patients stopped IVIg therapy, which resulted in ocular cicatricial pemphigoid progression. Majority of the studies reported mild adverse effects while two of them did not report any unwanted side effect. The most common side effect was headache, followed by nausea. Most of the patients who had a cessation of IVIg therapy before achieving clinical remission experienced the disease progression. **Conclusion:** Overall, it can be concluded that IVIg therapy was very helpful in treatment of MMP patients who did not respond to conventional therapy or stopped using them for various side effects. Adverse effects associated with IVIg therapy were considerably lower than conventional therapy that can lead toward treatment with this agent in patients who suffer from severe side effects.

Key words: Cicatricial pemphigoid, intravenous immunoglobulin, mucous membrane pemphigoid

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INTRODUCTION

There are four major groups of autoimmune blistering diseases, including pemphigus (pemphigus vulgaris pemphigus foliaceus [PF], pemphigus erythematous, paraneoplastic pemphigus, immunoglobulin A [IgA] pemphigus), pemphigoids (bullous pemphigoid [BP], pemphigoid gestationis, mucous membrane pemphigoid [MMP], linear IgA disease), epidermolysis bullosa acquisita (EBA), and dermatitis herpetiformis.^[1] Within the autoimmune blistering diseases, autoantibodies play a critical role in destruction of skin in different ways,

including loss of cell–cell adhesion, dermo-epithelial dysadhesion, or mixed form of them. Various types of autoantibodies are involved in blistering diseases. Autoantibody against desmoglein 1 (Dsg1), Dsg3, BP180, and BP230 is the most important player in the majority of autoimmune blistering diseases.^[1] In the MMP, BP180, laminin-332, and $\alpha 6\beta 4$ integrin are considered the most important known autoantigens.

MMP, which also known as cicatricial pemphigoid (CP), is characterized by subepithelial bullae, less commonly on the skin, and more associated with mucous membranes. This disease is predominant in females, and it usually occurs in individuals with older age, between

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60 and 80 years old.^[2] However, various studies reported childhood MMP.^[3,4] Different subclasses of IgG and IgA autoantibodies, especially IgG1 and IgG4 subclasses, are mainly responsible for MMP development.^[5,6]

There is no certain clinical manifestation of MMP. In fact, it depends strongly on site of involvement.^[7] In this disease, different parts of mucosal membranes including oral, nasal, ocular, laryngeal, esophageal, and anogenital could be damaged. Between patients with MMP, the oral mucosa is the most common, which is followed by the conjunctiva.^[8] Scarring of the MMP is also common among patients, which may result in severe life-threatening sequelae. Progressive scarring may potentially lead to serious complications affecting the eyes and throat. When the cornea of the eye is affected, repeated scarring may result in blindness.

Similar to other autoimmune diseases, MMP severity is mainly controlled with corticosteroids and different immunosuppressant agents. Recently, using of biological agents has been discussed by different authors. In this study, it was tried to analyze the efficiency and the safety of intravenous Ig (IVIg) in patients with MMP. The major adverse effects associated with IVIg therapy in MMP patients were also considered.

MATERIALS AND METHODS

A systematic literature searching for all the published articles associated with the use of IVIg and MMP which was conducted by databases of PubMed and Google Scholar was performed. All the associated studies until September 2015 were considered, using the keywords such as "cicatricial pemphigoid" or "ocular pemphigoid" or "mucous membrane pemphigoid" or "MMP" and "intravenous immunoglobulin" or "IVIg" to find all the relevant studies. Among the searched items, only English studies were included. It is worthy of note that although the combination therapy rituximab with IVIg was included in the study, it was not considered as the study associated with the role of IVIg in the treatment of MMP.

Essential data were extracted by the author from each article. All the extracted data including year of publishing, number of patients, their age and sex, the dose of administrated IVIg, response time, outcome, and IVIg-related side effects were categorized and then entered into a database. In addition, all the data were rechecked after preparing the database.

Conventional therapy for mucous membrane pemphigoid

Various therapeutic strategies are available for treatment of patients with MMP, but not all the patients respond to those treatments. Choice of appropriate treatment depends on several factors including site involved, severity of disease,

and its progression.^[9] Topical and systemic treatments are usually used for mild and severe MMP, respectively. In patients with more severe and progressive diseases, a combination of both topical and systemic treatment may be required to control disease progression.^[10] Overall, systemic corticosteroids, adjuvant immunosuppressive therapy, antibiotics, biologic agents such as rituximab and tumor necrosis factor- α (TNF- α) inhibitors, and immunomodulatory procedures such as IVIg are the main therapeutic agents used in treating of MMP.

Excellent oral care has been emphasized as being an important part of the treatment of MMP. Management of MMP is not limited to oral care. It also needs careful ocular care in cases with ocular MMP.^[10] Systemic corticosteroids which are the first-line treatment in severe MMP (ocular MMP, esophageal, laryngeal, severe gingival, and/or severe anogenital) usually response rapidly once treatment is initiated. However, several adverse effects are associated to this type of treatment. In more severe cases, using of immunosuppressive adjuvant therapies including azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CTX), and methotrexate (MTX) could help to better control of disease. In addition, a combination of these therapies may be effective for induction of remission of the disease.^[10] Antibiotics also could help in management of patients with MMP.^[9] In rare cases, surgical treatment is necessary if scarring narrows the airway and breathing becomes difficult or in some cases with ocular CP (OCP). In patients with OCP, eye surgery must be undertaken with care because it may lead to the disease reactivation.

Mild MMP that is limited to oral cavity could be controlled by topical treatments alone. However, in those with severe MMP, the systemic therapies may be essential. Corticosteroids are usually used in severe form of MMP. Prednisone is the most common first-line treatment which usually is given at a dose of 1–1.5 mg/kg/day while this treatment is the major source of side effects.^[9] CTX is another treatment in MMP, which could be used in more severe cases or those with rapid progression.^[11] It is an alkylating agent that suppresses B-lymphocytes (B-cells) function greater than T-lymphocytes (T-cells) function, which could result in several side effects.^[9] In cases with mild MMP and without rapid progression, dapsone usually is used to control the disease.^[9] AZA is considered another treatment which could be effective in the management of disease.^[12] Dosage ranges from 1 to 4 mg/kg/day, whereas it is recommended to be used at the dose of 1–2 mg/kg/day that could be increased to 5 mg/kg/day.^[13] Furthermore, different studies introduced MMF as an effective treatment in patients with MMP.^[14,15] MTX is another used therapy for patients with MMP, which was reported in few studies.^[16,17] In addition, there is much evidence that a combination of these treatments may be helpful.^[18,19]

Emerging treatments

In addition to conventional treatments, some biologic agents including rituximab,^[20,21] etanercept,^[22-24] infliximab,^[25] and immunomodulatory agents, such as IVIg, have been reported to be effective in the treatment MMP.

Several studies were reported a high level of TNF- α in patients with MMP. This caused the emergence the idea to inhibit this cytokine with different agents (etanercept, infliximab). Anti-TNF therapy is a common treatment in rheumatoid arthritis (RA) which is considered an autoimmune disorder. Rituximab is a chimeric, monoclonal antibody that binds to the molecule CD20 expressed on the cell surface of B-cells.^[26] First, it was approved by the US food and drug administration (FDA) for the treatment of non-Hodgkin's lymphoma in 1997.^[27] Subsequently, its usage was extended to treatment of various off-label diseases. During recent years, rituximab is increasingly used in autoimmune blister diseases.^[28]

IVIg therapy considered as another option for management of MMP patients with rapidly disease progression or those who did not respond to previous treatments. It is not the first-line therapy but could be used as the adjuvant therapy in patients with mentioned conditions. Over the last decade, there has been increased use of IVIg in the treatment of autoimmune diseases.

Intravenous immunoglobulin treatment

IVIg is a biologic immune modulatory agent, composed of polyclonal antibodies, derived from the plasma of a large pool of healthy donors. It was approved by the FDA for use in immune thrombocytopenic purpura, primary immunodeficiency, secondary immunodeficiency, pediatric human immunodeficiency virus (HIV) infection, Kawasaki disease, prevention of graft versus host disease, and infection in bone marrow transplant recipients. In addition to these approved conditions, it is increasingly used for various off-label autoimmune disorders including pemphigus, pemphigoid, systemic lupus erythematosus (SLE), RA, and multiple sclerosis (MS). In autoimmune diseases, IVIg is not the first-line treatment. However, it is generally accepted that IVIg therapy should be limited to patients who fail conventional therapy, demonstrate serious side effects, contraindications to conventional therapy, or patients with rapidly progressive disease. Despite the several case reports and case series in efficiency of IVIg therapy for treatment of autoimmune diseases, it remained a controversial topic. Immunosuppressive drugs are considered as the common therapy for patients with autoimmune diseases. This type of therapy may increase the risk of infection due to suppression of immune system. For instance, in hepatitis B virus or hepatitis C virus carriers who are at risk of reactivation of infection during or after immunosuppressant, adding IVIg

to treatment protocol may be effective in both controlling autoimmune disease and reduction of reactivation risk. Considering that the IVIg is not immunosuppressive and has a favorable side effect profile in compression to immunosuppressive therapy, it could be an appropriate treatment choice for patients who are at risk of infections or viral reactivation.

Sometimes, IVIg is used at a replacement dose of 200–400 mg/kg body weight. However, high-dose IVIg (hdIVIg) is most frequently at 2 g/kg, which is given monthly for major autoimmune and inflammatory disorders. The precise mechanism by which IVIg functions as an anti-inflammatory agent remains unclear. It provides the large amounts of immunoregulatory substances which have the capacity to regulate the immune system in different ways. Multiple different theories have been proposed to explain the mechanisms of action of IVIg.^[29] IVIg can act by potential actions including, anti-idiotypic antibody production, competitive inhibition of binding to activating Fc-receptors (FcRs), upregulation of inhibitory FcRs, increase clearance of autoantibodies by reticuloendothelial system, decreased half-life of autoantibodies due to competitive binding to FcRs, interference with the activation of complement and the cytokine network, and T-cell modulation.

In overall, IVIg therapy is considered as a safe treatment. However, there are several reports of IVIg adverse effects which vary in a wide range. Different factors including age, type of disease, dose of IVIg, and rate of the infusion play role in severity of adverse effects due to IVIg therapy.^[30] Some of them could be appeared during or immediately after infusion. In contrast, some others arise with a delay.^[31] The first group of adverse effects includes headache, flushing of the face, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnea, back pain, nausea, vomiting, diarrhea, change in blood pressure, and tachycardia.^[30] The major delayed adverse effect of IVIg therapy is an acute renal failure.^[30] It was reported that delayed adverse events to IVIg infusions are common in children.^[31]

The most common adverse reaction related to IVIg therapy is an infusion reaction, and symptoms may include flushing, headache, chills, nausea, tachycardia, hypotension, and wheezing. Headache was considered the most common adverse effect in cases with IVIg infusion.^[31]

Intravenous immunoglobulin as a treatment in mucous membrane pemphigoid

IVIg is used in various patients with MMP for different reasons. In 1997, Urcelay *et al.*^[32] reported two cases who had successful treatment with IVIg therapy. In the first case, a 50-year-old woman was diagnosed at MMP in

1992; betamethasone and cyclosporine did not control the disease completely. In addition, dapsone and AZA were not tolerated. Moreover, tetracycline and nicotinamide were unhelpful. Thus, IVIg was initiated at a dose of 2 g/kg/cycle in 1995. It caused an improvement, and the patient was lesion-free after six cycles. As the second patient on the same study, a 40-year-old man was diagnosed at MMP in 1995. After treatment with dapsone and betamethasone, IVIg was started with dosage of 2 g/kg/cycle. Interestingly, after four cycles, all the lesions had healed. However, it was stopped due to development of urticarial in the seventh infusion. In 1999, Foster and Ahmed^[33] reported ten cases that all of them were more than 50 years old. Duration of systemic therapy before initiation of IVIg varied from 3 to 14 years, with a mean of 8.3 years. Various treatments were used, but all of them were gradually stopped due to different reasons including side effects, ineffectiveness, and lack of response. Thereby, IVIg was initiated at the dosage of 2–3 g/kg/cycle, which led to fully control of the disease, during a minimum of 4 months. Reduction of immunoglobulin dose resulted in relapse of the disease. Furthermore, no side effect was reported. The next successful IVIg therapy in MMP patients was reported by Ahmed and Colón,^[34] who have analyzed the clinical outcomes as well as the disease progression in those with oral pemphigoid in a retrospective study in 2001. On that study, the patients were divided into two groups. In the first one, eight patients (containing six females and two males aged 43–67 years) who compared to 12 patients treated without using IVIg therapy were contributed on IVIg therapy. The dose of IVIg for patients in the first group was varied between 1 and 2 g/kg per cycle, which was divided into three doses for infusion during three consecutive days. Pemphigoid disease in all the patients, in both groups, was limited to oral cavity at the time of enrolling in the study. Average duration of treatment in the first group was considerably shorter than second (32.9 vs. 41.8 months). In addition, it resulted in lower average number of side effects (0.4 vs. 3.2), significantly lower number of relapse rate (0.1 vs. 2.1), higher remission rate (1 vs. 0.4), and considerable higher quality of live (lower than the poor index vs. higher than tolerant of reasonable index). Interestingly, among the patients in the first group, no one developed oral pemphigoid in any other mucous membrane. In contrast, more than half of patients in the second group were developed oral pemphigoid at extraoral sites. In issue of adverse effect, IVIg group did not demonstrate serious adverse effects. However, in the conventional therapy group, all the 12 patients experienced various side effects. Leverkus *et al.*^[35] reported a successful disease control in a 74-year-old female patient who was newly diagnosed with pemphigoid. On that patient, dapsone therapy was discontinued because of intolerable side effects. Moreover, she did not respond to MMF and high-doses of corticosteroids reasonably. Indeed, despite the reduction in disease severity, lesions persisted.

In addition, she experienced widespread erosions on the gingiva, marked conjunctivitis, and rapid scarring of the left eye after 6 months. This led to initiation of IVIg (1 g/kg/cycle) to control disease activity. A total of six cycles each 4 weeks were administrated which resulted in remission of disease for more than 12 months. Sami *et al.*^[36] presented the IVIg therapy in 15 patients with severe MMP who were nonresponsive to the conventional treatments or developed multiple side effects. The mean age was 62.1 and 14 of them had previous therapy. All 15 study patients were treated with an IVIg dose of 1–2 g/kg/cycle which was divided into three equal doses. All other conventional agents were also discontinued, and IVIg was eventually used as the monotherapy. In the absence of any treatments, all patients experienced remission for a period ranging from 12 to 72 months (mean, 23.9). There was significant statistical difference between before and after starting initiating of IVIg. Average month with side effects decreased considerably (5.8 vs. 0.6); relapse rate average decreased (7.33 vs. 1.47), and remission rate was increased (0 vs. 1) after initiation of IVIg. Furthermore, quality of life increased markedly (near unsatisfactory vs. almost high quality).

With reports that confirmed effectiveness of IVIg therapy in MMP patients, more patients were treated with this immunomodulatory agent. In 2004, Letko *et al.*^[37] compared the clinical outcomes of IVIg therapy to conventional immunosuppressive therapy in patients with MMP, whose disease progressed to involve the eye. Each group contains eight patients, who was age and sex matched. The male to female ratio was 1:3 in each group. IVIg and conventional therapy groups were clinically remitted within 4 and 8.5 months, respectively. No recurrence of ocular inflammation was recorded in IVIg-treated group. However, the recurrence of the disease was observed in five patients in the other group. Half of patients in IVIg group suffered from related side effects. Thus, it led to a decreasing in the rate of infusions which resulted in the resolution of those side effects. However, all the patients in the conventional therapy group demonstrated side effects. As the final outcome, all the patients who were treated with IVIg had been controlled completely. Conversely, in the other group, only three patients were completely controlled; three were partially controlled, and two remained uncontrolled. In the same year, a case series included ten patients with a diagnosis of OCP, reported successfully using of IVIg in patients with MMP.^[38] In eight patients who completed treatment, a sustained clinical remission was observed. In contrast, other two patients were excluded from the treatment protocol, which resulted in progression of OCP. On that study, the total number of cycles and duration of IVIg therapy reported ranged from 20 to 42 (mean, 32) and from 25 to 43 months (mean, 35), respectively.

The next report was published by Segura *et al.*,^[39] which contains four cases with MMP (three females and one male). One of them did not respond to IVIg therapy while another one had a complete response. The two remained patients achieved a partial remission. The IVIg therapy was stopped due to toxicity on patients with partial remission. However, other two patients did not experience any adverse effect. In 2008, Mignogna *et al.*^[40] reported a total of six patients with severe MMP, containing three males and three females aged 58–80 years (mean, 69.5). In all of them, gingival, buccal, and palate lesions were the initial signs of MMP, followed by chronic conjunctivitis and later extended to conjunctival shrinkage. Within the average of 9.1 months, an actual clinical remission (healing of previous oral lesions and resolution of ocular scarring without development new lesion) was achieved. Patients remained on systemic steroids and immunosuppressants that were gradually reduced by 50% in the first 3 months of IVIg therapy and further 20% during the last cycles of maintenance therapy.

A case report of treatment refractory OCP with IVIg was published in 2008.^[41] On that study, a 65-year-old man clinically diagnosed as having cryptogenic organizing pneumonia. Initial treatment included methylprednisolone, prednisone, and AZA that were unable to control disease progression. Thus, immunosuppressive treatment with CTX was initiated while inflammation could not be brought under control. To control disease progression, IVIg was planned to be administered at a total dose of 3 g/kg/cycle which was repeated every 2 weeks. After initiation IVIg, a rapid improvement was reported, which led to controlling of inflammation in both eyes after seven cycles. Despite the hdIVIg and relatively short time of repetition, no side effect was observed. According to those results, it was suggested that IVIg therapy could be more effective than conventional immunosuppression treatment for controlling inflammation and avoiding disease progression.

In 2009, a study of ten patients with autoimmune mucocutaneous blistering diseases, including seven pemphigus vulgaris (PV) and three MMP patients (two females and one male aged 42–76 [mean, 66]), confirmed the efficiency of IVIg therapy at the dose of 2 g/kg in controlling of MMP patients.^[42] Subsequently, Foster *et al.*^[43] analyzed the efficiency of combination of rituximab with IVIg compared to conventional therapy. Twelve patients with OCP were enrolled in that study. Each group contained six patients who were followed up for more than 4 years. All the patients in the first group who were treated using conventional therapy were blind in one eye. Four in the second group who were treated with the combination of rituximab and IVIg therapy were also blind in one of their eyes. Completion of the treatment protocol in the second group ranged from 3 to 19 months (mean, 11). As the result

of that study, patients in the first group became blind in both eyes due to disease progression. In contrast, no one in the second group experienced new blindness, in addition to stopping disease progression. No adverse effect was reported for any patient.

Barbosa Ldo *et al.*^[44] reported a 75-year-old female with MMP who went into remission following IVIg infusion at the dose of 1.5 g/kg. Recently, a case with oral MMP was reported.^[45] Despite the starting oral prednisolone and keeping for 6 months, no improvement was observed. After revealing that dapsone cannot help, IVIg was administered at a dose of 2 g/kg/cycle which caused complete remission. With maintaining IVIg therapy for 6 months, no recurrence was seen after 3 years. The categorized data of these studies were demonstrated in Table 1.

DISCUSSION

In addition to conventional therapies, some other treatments are used to treat various autoimmune diseases. Some of them act through the relatively clear signaling pathways, such as several biological agents. Conversely, the mechanisms of action in some other treatments are not well understood. For example, targeting a certain cytokine, molecule, or cell could be categorized in the first group. Recently, Tavakolpour^[47] suggested that targeting the interleukin (IL)-4 could be a possible treatment in pemphigus. Thereby, dupilumab, an anti-IL-4 receptor alpha monoclonal antibody, was introduced as an effective drug to treat those with pemphigus.^[48] In contrast to these types of treatments, IVIg does not block or induce a certain signaling pathway. Indeed, it acts through different known and unknown mechanisms.

IVIg is used at replacement dose to treat patients with primary antibody deficiencies while hdIVIg is used as an immunomodulatory agent in a wide range of autoimmune diseases. It also used for inflammatory disorders and bacterial and viral infections that could not be controlled by conventional therapy.^[49] There are several reports of using successfully IVIg therapy in different autoimmune diseases or diseases that caused by vigorous and uncontrolled immune responses, including MS, SLE, RA, autoimmune hemolytic anemia, asthma, PV, PF, EBA, BP, and MMP. In contrast, some other reports are available that did not confirm effectiveness of IVIg therapy in various autoimmune diseases. Table 2 summarizes the reported outcomes of IVIg therapy in some inflammatory and autoimmune diseases.

IVIg therapy can cause prevention or even treating of infection. The use of IVIg in children with HIV infection and low peripheral CD4 T-cell count was approved by the FDA early in the 1990s.^[96] In addition, a study demonstrated the

Table 1: The effectiveness, safety, and associated factors of intravenous immunoglobulin treatment in mucous membrane pemphigoid, based on reviewed studies

Author (years)	Sex (n) Age (mean)	Treatment prior to IVIg	IVIg dose and frequency	IVIg therapy duration (mean)	Response time	Outcome	Side effect	Reference
Urcelay <i>et al.</i> (1997)	Female (1); male (1) 50, 40	Betamethasone, cyclosporine, dapsone, betamethasone	2 g/kg/cycle during 3 days, repeat every 4 weeks	NM	6 infusions, 4 infusions	Clinical remission in all	Urticarial	[32]
Foster and Ahmed (1999)	Female (5); male (5) 50-77 (65.3)	Dapsone (10), prednisone (6), prograf (4), cytosine arabinoside (6), Imuran, cyclophosphamide (4), methotrexate (5), azathioprine (2)	2-3 mg/kg/cycle during 3 days, repeat every 2-6 weeks	16-23 months (19.3)	4-12 cycles	Remission in all	No untoward side effect	[33]
Ahmed and Colón (2001)	Female (6); male (2) 43-67 (58)	Dapsone	1-2 g/kg/cycle during 3 days, repeat every 4 weeks (when patient healed can increase to 6, 8, 10, 12, and 14 weeks)	26-42 months (32.9)	11-18 months (mean, 14.1)	Remission in all	Mild headache (2) Mild nausea (1)	[34]
Sami <i>et al.</i> (2002)	Female (8); male (7) 48-78 (62.1)	Prednisone (14), no previous therapy (1)	1-2 g/kg/cycle during 3 days, repeat every 4 weeks (in clinical remission increased to 6, 8, 10, 12, 14, and 16 weeks)	13-39 months (25.2)	2.7-6.4 (mean, 4.8)	Sustained clinical remission in all	Headache (4) Nausea (2) Palpitations (1) Vomiting (1)	[36]
Leverkus <i>et al.</i> (2002)	Female (1) 74	Prednisolone, dapsone, mycophenolate mofetil	1 g/kg/cycle during 2 days, repeat every 4 weeks	6 months	6 months	Remission in all	Transient, arthralgia, nausea	[35]
Letko <i>et al.</i> (2004)	Female (6); male (2) 52-70 (62.7)	Dapsone (8), cyclophosphamide (3), prednisone (7), azathioprine (2), cyclosporine (1), methotrexate (1), FK506 (1)	2 g/kg/cycle during 3 days, repeat every 2-4 weeks	16-30 months (24)	Mean 4 months	Clinical remission in all	In 4 patients Headache (2) Nausea (2)	[37]
Sami <i>et al.</i> (2004)	Female (5); male (5) 50-77 (65.3)	Aggressive systemic therapy	2-3 g/kg/cycle during 3 days, repeat every 2 weeks (in clinical remission increased to 8, 10, 12, 14, and 16 weeks)	25-43 months (35)	24-48 months (mean, 35)	Clinical remission (8) OCP progression (2)	Headache, nausea	[38]
Segura <i>et al.</i> (2007)	Female (3); male (1) 65-80 (70.8)	Prednisone (3), cyclophosphamide (2), dapsone (3), azathioprine (2)	2 g/kg per during 4 or 5 consecutive days, repeat every 4 weeks	3-9 cycles (6.25)	NM	Completely response (1) Do not response (1) Partial response (2)	In 2 patients Headache (1) Fever (1) Nausea (1) Vomiting (1) Diarrhea (1) Cephalgia (1) Hypertension (1) Epistaxis (1)	[39]
Mignogna <i>et al.</i> (2008)	Female (3); male (3) 58-80 (69.5)	Conventional therapy	Base on protocol ^[46]	8-20 months 10-20 cycles (16.8)	5-12 months (mean, 9.1)	Clinical remission in all	Headaches, nausea, chills, flushing, myalgia, and fever	[40]

Contd...

Table 1: Contd...

Author (years)	Sex (n) Age (mean)	Treatment prior to IVIg	IVIg dose and frequency	IVIg therapy duration (mean)	Response time	Outcome	Side effect	Reference
Galdos and Etxebarria (2008)	Male (1) 65	Methylprednisolone, minocycline, prednisone, azathioprine, cyclophosphamide	3 g/kg/cycle during 3 days, repeat every 2 weeks (after 9 th cycle increased to 4, 6, 8, and 10 weeks)	13 cycles	7 cycles	Clinical remission	No	[41]
Mignogna et al. (2009)	Female (2); male (1) 42-76 (66)	NM	2 g/kg/cycles during 3 days, repeat every 3-4 weeks (in clinical remission increased to 6, 8, 10, 12, 14 and 16 weeks)	10-15 cycles (11.6)	NM	Clinical remission in all	NM	[42]
Barbosa Ldo et al. (2011)	Female (1) 75	Methylprednisolone, prednisone	1.5 g/kg during 3 days, repeat every one week	3 days	Days after infusion	Improvement	NM	[44]
Laureano and Cardoso (2015)	Male (1) 57	Prednisolone, dapsone	2 g/kg/cycle, repeat every 3 weeks	6 months	3 cycles	Remission for 3 years	NM	[45]

NM = Not mentioned; n = Number of patients; IVIg = Intravenous immunoglobulin; OCP = Ocular cicatricial pemphigoid

Table 2: The effectiveness of intravenous immunoglobulin treatment in selected inflammatory and autoimmune diseases

Diseases	Beneficial	Not beneficial	Relatively beneficial
Multiple sclerosis	[50-54]	[55,56]	[57]
Systemic lupus erythematosus	[58-61]		[62,63]
Rheumatoid arthritis/JRA	[64,65]	[66,67]	[68-70]
Autoimmune hemolytic anemia	[71]	[72]	[73-75]
Asthma	[76-79]	[80,81]	
Pemphigus vulgaris	[82-86]		[39]
Pemphigus foliaceus	[87-89]		[39]
Epidermolysis bullosa acquisita	[90-93]		[39]
Bullous pemphigoid	[94,95]		
Mucous membrane pemphigoid	[32,33,35-37, 40-42,44,45]		[39]

JRA = Juvenile rheumatoid arthritis

possible role of hdIVIg therapy in adults with HIV infection.^[97] IVIg reduced the incidence of cytomegalovirus infection and interstitial pneumonia in allogeneic bone marrow transplant recipients in the era before ganciclovir.^[98] Furthermore, there are several proofs that it can be helpful in patients with some other infections such as respiratory syncytial virus.^[99,100] Thus, it may be suitable treatment in a patient with those infections who need to immunosuppressant for discussed autoimmune diseases. IVIg may help to suppress high viral replication due to immunosuppressant, in addition to controlling the autoimmune disease in several pathways. In addition, there is some evidence of passive transfer of hepatitis B antibodies from IVIg.^[101]

In patients with MMP, IVIg can be considered an effective treatment with minimum adverse effect compared to the conventional treatments. In this review, 13 studies with a

total of seventy patients who were diagnosed at MMP and were considered for IVIg therapy were analyzed. Sixty-five patients who continued therapy were treated successfully with IVIg while two patients in the study of Sami *et al.*^[36] did not completely treated and experienced OCP progression. Segura *et al.*^[39] reported four cases with MMP under IVIg therapy, in which only one of them demonstrated a complete response. One unsuccessful treatment, who completed therapy, and two patients who showed a partial response by IVIg therapy were also reported. In both cases with partial response, IVIg therapy was discontinued because of the IVIg-related adverse effects. With analyzing published studies, it can be concluded that IVIg is a relatively safe and fast response treatment compared to conventional treatments of MMP. Majority of patients included in this review did not demonstrate serious adverse effects. In those studies that compared two groups of conventional and IVIg therapy, a faster clinical response was recorded in IVIg group. This review revealed that IVIg therapy is a promising treatment for patients with MMP, who did not respond to conventional therapy or experienced adverse effects due to conventional therapy. Another lesson that can be learned is related to cessation of IVIg therapy before complete remission. It was shown that decreasing IVIg dose or cessation of that may result in relapse of the disease. All the included studies were used moderate IVIg and hdIVIg, varied between 1 and 3 g/kg/cycle. Response time was strongly variable in analyzed studies, but it seems that it is considerably lower than conventional therapy in MMP.

CONCLUSION

Considering the relatively low number of patients who were treated with IVIg, finding a reasonable association between

dose of IVIg and other involved factors in response to IVIg, including age, sex, and prior treatments among those with MMP is not possible. However, further studies are needed to clarify these factors and even the optimal dose of IVIg.

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Conflicts of interest

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AUTHOR'S CONTRIBUTION

ST carried out all the related issues to this manuscript.

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