Efficacy and Safety of intravenous immunoglobulin therapy in refractory uveitis

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Abstract

Purpose: To assess the efficacy and safety of intravenous immunoglobulin (IVIg) therapy in patients with uveitis unresponsive to conventional immunomodulatory agents.

Methods: Review of clinical charts at Massachusetts Eye Research and Surgery Institution was conducted to document response and clinical outcomes to IVIg treatment in five patients with treatment-refractory uveitis. All patients had severe and recalcitrant uveitis of diverse etiologies. Main outcome measures were control of intraocular inflammation, inducing durable remission, visual acuity, and side effects.

Results: Treatment was effective in controlling intraocular inflammation in four of five patients, one of these patients required two additional immunomodulatory agents to achieve remission. The average duration of treatment was 31 months (range of 8 months-4 years). Durable remission was achieved in three of five patients, with successful tapering of IVIg in all three cases, now still in remission for an average duration of 13 months (range of 6 months-2 years). Visual acuity was maintained in four of five patients. Side effects were migraine headache in one patient, malaise and shortness of breath in one other patient.

Conclusions: Intravenous immunoglobulin therapy was an effective therapeutic modality in the treatment of refractory uveitis in four of five patients, one of these patients required an additional immunomodulatory agent to achieve remission, IVIg was tapered and stopped in three of four patients and they are still in remission.

Keywords: Intravenous immunoglobulin; uveitis; refractory.

Abbreviations: Biologic response modifiers (BRM); Electroretinography (ERG); Fluorescein angiography (FA); Indocyanine green angiography (ICG); Intravenous Immunoglobulin (IVIg); Immunomodulatory Therapy (IMT); Optical coherence tomography (OCT); right eye (OD); Left eye (OS); Both eyes (OU); Systemic lupus erythematosus (SLE).

Introduction:

Uveitis is an important cause of visual loss in the United States, with an incidence of 50 cases per 100,000 person-years and a prevalence of 115.3 per 100,000 persons. [1] Most cases of uveitis in the United States are associated with a noninfectious autoimmune etiology. [2] Some cases of noninfectious uveitis may be unresponsive or only partially responsive to conventional immunomodulatory agents as well as to biologic response modifiers (BRM). In addition, conventional immunomodulatory agents used to treat noninfectious uveitis are associated with potential toxic side effects, including bone marrow suppression, increased risk of infection, liver and kidney toxicity, gonadal dysfunction, and increased risk of subsequent development of malignancy. [3]

Intravenous immunoglobulin (IVIg) has been reported to control intraocular inflammation in many previous studies. In an effort to control intraocular inflammation and hence preserve the sight in some of our patients who were unresponsive and/or who experienced side effects that required either dose reduction or the discontinuation of these agents, we used IVIg. We report here the results of this retrospective observational uncontrolled study of the efficacy and safety of IVIg treatment of patients with severe or recalcitrant uveitis.

Materials and Methods

This study is a retrospective observational case series study. The medical records of patients with refractory uveitis treated with IVIg at Massachusetts Eye Research and Surgery Institute over the last 10 years (2005–2015) were reviewed. Previous history and subsequent follow-up data were obtained through communication with the referring physician in between visits when necessary. Approval for this study was obtained through the New England Institutional Review Board. This study was performed in accordance with the Declaration of Helsinki and was HIPAA-compliant.

Inclusion criteria were patients who experienced either intolerance to at least two systemic immunomodulatory agents or who had failed (no control of inflammation after 3 months of treatment) and had shown particularly sight-threatening intraocular inflammation. A detailed ocular examination was performed at each visit, including best-corrected visual acuity on a Snellen scale, slit-lamp biomicroscopy, tonometry, and ophthalmoscopy. Clinical presentation of the individual patient and a detailed questionnaire completed by the patient at the initial visit formed the basis of a targeted diagnostic approach. Laboratory investigations were performed whenever indicated by the clinical presentation and review of data.
systems. Ancillary testing including fluorescein angiography and optical coherence tomography (OCT) done at first visit and as a follow-up to patients with posterior involvement.

The treatment goals were to control the intraocular inflammation, achieve durable remission defined as two years of inactive uveitis on IVIg, maintain visual acuity, and achieve durable remission off IVIg. Quiescence was defined as the absence of any inflammatory cell in the anterior chamber. Absence of active inflammatory lesions, optic nerve edema, or vasculitis was also required for patients with posterior involvement. In cases with retinal vasculitis the degree of inflammation was always confirmed with fluorescein angiography. Absence of staining and/or leakage of fluorescein from retinal vessels were indicative of control of retinal vascular inflammation.

According to our IVIg treatment protocol, the levels of quantitative immunoglobulins were determined in each patient before therapy. If normal (especially immunoglobulin-A), therapy was started after informed consent was obtained. Patients received 2 g/kg/cycle of treatment divided over 3 days. Premedication was with 650 mg acetaminophen and 50 mg diphenhydramine given orally 30 minutes before starting each infusion. The rate of infusion was determined by the general health of the patient, heart rate, and blood pressure. A slow continuous infusion lasting 210 to 240 minutes in an ambulatory setting using a belt-worn infusion pump was usual. Tapering was done by stretching the dose from a monthly interval, to every 6 weeks, then to every 8 weeks, and then every 10 weeks then stopping it.

The data collected from this retrospective review of charts included age at the time of the initial visit, gender, type of uveitis, underlying cause or clinical syndrome, previous and concurrent use of immunomodulatory agent(s), response to treatment, visual acuity at the initiation of IVIg, visual acuity at most recent visit, complications, side effects, and follow-up period.

Results:

Five patients (9 eyes) 3 females and 2 males, with a mean age of 29, age range 18-64 at the time of starting IVIg form the basis of this report. All patients were diagnosed with non-infectious uveitis, had active disease despite using conventional immunomodulatory therapy. Different uveitis entities were included in this study, one case of each of the following: idiopathic panuveitis, systemic lupus erythematosus (SLE) associated retinal vasculitis, birdshot chorioretinopathy, pars planitis, and sclerouveitis (Table 1).

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Previous therapy</th>
<th>Treatment to achieve remission</th>
<th>Baseline VA</th>
<th>Final VA</th>
</tr>
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<tbody>
<tr>
<td>18</td>
<td>F</td>
<td>Idiopathic Panuveitis OD</td>
<td>methotrexate, mycophenolate fomofel, azathioprine and cyclosporine-A</td>
<td>IVIg 20/40 20/20</td>
<td>20/25</td>
<td>20/20</td>
</tr>
<tr>
<td>33</td>
<td>F</td>
<td>SLE associated retinal vasculitis</td>
<td>methotrexate and azathioprine (leukopenia)</td>
<td>IVIg 20/25 20/20</td>
<td>20/25</td>
<td>20/20</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>Birdshot Retinochoroidopathy</td>
<td>methotrexate, mycophenolate fomofel and cyclosporine</td>
<td>IVIg 20/20 20/20</td>
<td>20/20 20/20</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>F</td>
<td>Sclerouveitis (OU)</td>
<td>mycophenolate fomofel, methotrexate</td>
<td>Failed IVIg 20/00 20/00</td>
<td>20/00 20/50</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>Pars planitis (OU)</td>
<td>methotrexate, infliximab, IVIg</td>
<td>Methotrexate, infliximab, IVIg</td>
<td>No light perception 20/60</td>
<td>No light perception 20/60</td>
</tr>
</tbody>
</table>

Table 1: Patients characteristics, and diagnosis

Treatment was effective in controlling intraocular inflammation in four of five patients (Table 2). One of these patients required two additional immunomodulatory agents to achieve remission. Durable remission was achieved in three of five patients now still in remission off IVIg. Visual acuity was maintained in four of five patients. Side effects were migraine headache in one patient, malaise and shortness of breath in another patient. IVIg was tapered and stopped after 2 years of achieving remission by lengthening the frequency of IVIg by an additional 2 weeks until doses were 12 weeks apart, after which the medication was stopped.

Cases:

Case 1:

An 18 year old female with stubborn panuveitis in the right eye (OD) had previously failed several regimens of immunomodulatory therapy including methotrexate, mycophenolate fomofel, chlorambucil, azathioprine and CSA. She was started on IVIg at 2g/kg/month given over 3 days, after her first infusion she had severe migraine headache, her transfusion was split to every 2 weeks (given over 2 days). She still had mild headache at this regimen which has been eliminated with extending the infusion duration to 8-10 hours. Her eyes were quiet for 2 years on IVIg, then it was tapered and stopped.

Case 2:

A 33 year old female, diagnosed with SLE associated retinal vasculitis, was treated with methotrexate then azathioprine. Her vasculitis was still active on FA (fluorescein angiography) and she developed leukopenia on these medications. The patient was switched to IVIg 2g/kg every 4 weeks. Her vasculitis showed improvement on FA. On her 10th infusion she developed myalgia, malaise and shortness of breath that lasted for 3 days, her IVIg dosage was reduced to 1 mg/kg every 4 weeks because of that. Her vasculitis was quiet for 2 years on IVIg. IVIg was tapered and stopped and she is off IVIg for 6 months now, still stable with no recurrence of her vasculitis.

Case 3:

A 64 year old male diagnosed with birdshot retinochoroidopathy had previously failed methotrexate and was intolerant to mycophenolate fomofel (GI upset) and cyclosporine. After tapering these medications he was switched to IVIg 2g/kg every 4 weeks over 3 days/month. He had IVIg infusions for 2.5 years, then the medication was tapered. His birdshot retinochoroidopathy is stable on both FA/ICG (Indocyanine Green Angiography)and ERG (electroretinography) for 1 year now (off IVIg).

Case 4:

A 29 year old female with a history of stubborn sclerouveitis and retinal vasculitis secondary to psoriatic arthritis, had been intolerant of mycophenolate fomofel (recurrent tonsillitis) and had failed methotrexate. IVIg was started at 2g/kg every 4 weeks. After 5 months she had a uveitis flare up and (+1.5) cells (OD) the dose was increased to 2.5g/kg. After 3 months she developed scleritis of the left eye (OS) while on this dose. IVIg was discontinued.

Case 5:

A 15 year old male, presented with a history of bilateral vision-robbing pars planitis. Retinal detachment surgery with scleral buckle and silicone oil was previously done (OD). At first visit his vision was NLP (OD), 20/80 (OS) with CME (OS), he was on methotrexate but found to have active uveitis in his left eye, infliximab was added. His inflammation was controlled for 1 year on methotrexate+infliximab but he flared up again, IVIg (2g/kg) monthly was added. His inflammation has been quiet for...
4 years on methotrexate+infliximab+IVIg and the plan at his last visit was to start tapering his treatment. Because the patient is monocular, the tapering will occur slower than in the previously described cases and will occur subsequent to tapering infliximab therapy.

**Discussion:**

Intravenous immunoglobulin (IVIg) consists of human immunoglobulin G obtained from the plasma of healthy donors. It is mainly used for the treatment of primary or secondary immunodeficiencies [4–6], but it has also demonstrated efficacy in a growing number of systemic inflammatory diseases, including Kawasaki disease, immune thrombocytopenic purpura, Guillain–Barre’ syndrome, dermatomyositis, and myasthenia gravis [4–6].

In the field of ophthalmology, IVIg treatment has been used previously for the treatment of ocular cicatricial pemphigoid, alone or in combination with rituximab. Such treatment achieved stabilization of disease activity in cases of progressive ocular cicatricial pemphigoid unresponsive to conventional treatment [7–9], and other conditions such as optic neuritis in multiple sclerosis refractory to conventional treatment [10], and orbital myositis [11]. The disadvantages of such therapy are mainly the inconvenience of the administration (three consecutive days of infusions every month) and its cost. Unlike other therapies for autoimmune disease, IVIg is not associated with immunosuppression, so it does not enhance the likelihood of developing an opportunistic infection, and it can be used during pregnancy.

The proposed mechanism of action is complex [12-17] and is hypothesized to include blockage and modulation of the expression of receptors for IgG constant fragment (e.g., prevention of platelet destruction during immune thrombocytopenic purpura by blocking receptors [FcγR] of splenic macrophages), attenuation of complement-mediated damage (e.g., decrease in deposit of complex membrane attack in endosomal capillaries in steroid-resistant dermatomyositis), modulation of the production of cytokines and chemokines (e.g., reduction of IL-1 production in Kawasaki's disease), modulation of cell proliferation and apoptosis, neutralization of circulating autoantibodies (e.g., anti-idiotypic antibodies able to neutralize pathogenic auto-antibodies in lupus, myasthenia), selection of B and T lymphocytes (e.g., inhibition of B-cell differentiation and Ig production by interaction of Ag receptor present on the surface of lymphocytes and Ig variable regions perfused), modulation of the maturation and function of dendritic cells (e.g., via the FcγR receptors, causing a decrease in the production of IL-12), interaction with other molecules on the surface of lymphocytes and monocytes (e.g., CD4, CD5, CCR5, CD40, MHC class I) and IgG glycosylation (e.g., anti-inflammatory properties most important for IgG rich in sialic acid). IVIg can dose-dependently inhibit CD8-mediated HLA class I-restricted cellular cytotoxicity of T cells. IVIg has also been shown to down regulate or stimulate B-cell clones expressing surface IgG that is complementary (anti-idiotypic) to variable regions of antibodies present in IVIg -- a mechanism that accounts for the rapid decrease in titer of circulating auto-antibodies observed within hours after the infusion of IVIg.

There is no consensus on the optimal dose, frequency, and duration of administration of IVIg to be used for the treatment of uveitis. In this study a dose of 2 g/kg/month over 3 days repeated at monthly intervals was chosen because of our experience over the past 20 years informing us of the need for significantly higher doses for ocular disease than for other diseases.

In this study all cases had uveitis stubborn to conventional Immunomodulatory agents. All received at least two IMT before receiving IVIg. IVIg was not the first option in any mainly because of high cost and the infusion protocol.

Although our study included diverse uveitis entities, comprising different clinical courses and clinical features, the outcomes as reported here support that IVIg treatment enabled inflammatory control and prevented progression of the disease (assessed by visual acuity, visual fields, fluorescein angiography) in patients refractory to conventional treatment in 4 of 5 patients in this series.

In our previous case reports about the use of IVIg in refractory uveitis [18], IVIg was also found to be effective in controlling intraocular inflammation in 3 of 5 cases. The duration of treatment was 3 to 36 months (mean, 16.8 months). In another case report series by Garcia et al. [19] IVIg treatment resulted in stabilization and prevention of progression of the disease in three of four patients. The median duration of the IVIg therapy was 7 months (range: 3-14 months). IVIg was not tapered in any patient in the previous studies. In this case series the duration of treatment range was 8 months to 4 years and IVIg was tapered in 3 cases which achieved remission for more than 2 years and these cases are still in remission off IVIg for 6 months to 2 years.

From this case series we can conclude that IVIg is a viable option to treat uveitis refractory to other immunomodulatory therapy and as an alternative treatment for patients who develop multiple recurrent infections while on conventional IMT or in whom other types of therapy are contraindicated. Future studies should assess the efficacy of IVIg in treating uveitis compared to other types of IMTs.

**References**