

Safety of Intravenous Methylprednisolone in Refractory and Severe Pediatric Uveitis

Hashem H Ghoraba¹, Wataru Matsumiya^{1,2}, Hassan Khojasteh¹, Amir Akhavanrezayat¹, Irmak Karaca¹, Christopher Or¹, Negin Yavari¹, Sherin Lajevardi¹, Jaclyn Hwang¹, Cigdem Yasar¹, Diana Do¹, Quan Dong Nguyen¹

¹Spencer Center for Vision Research, Byers Eye Institute, Stanford University, Palo Alto, CA, USA; ²Department of Surgery, Division of Ophthalmology, Kobe University Graduate School of Medicine, Kobe, Japan

Correspondence: Quan Dong Nguyen, Spencer Center for Vision Research, Byers Eye Institute, Stanford University School of Medicine, 2370 Watson Court, Suite 200, Palo Alto, CA, USA, Tel +16507257245, Fax +1 6507368232, Email ndquan@stanford.edu

Purpose: To evaluate the safety of intravenous high-dose pulse methylprednisolone succinate (IVHDM) in the management of severe or refractory non-infectious pediatric uveitis.

Methods: We reviewed all uveitis patients who were ≤ 16 years of age and who received IVHDM with a dose of ≥ 500 mg per day (1–3 days a month) for at least 3 months during their management at a tertiary care eye hospital.

Results: Twenty pediatric patients with severe or refractory uveitis who received IVHDM were identified. Six patients received IVHDM either once, as a preoperative medication, or at a lower dose than 500 mg, and were excluded. The remaining 14 patients received IVHDM for at least 4 months. Age (mean \pm SD) was 11.9 \pm 2.4 years and 50% were female. Duration of treatment was 14.2 \pm 7.5 months. Thirteen patients received IVHDM in combination with other immunomodulatory therapy (IMT). Except for two outliers, IVHDM was given at a dose of 8–25 mg/kg per infusion. Three major adverse events (AEs) occurred in two patients: a single episode of bradycardia, compression fracture following minor trauma and adrenal insufficiency. The number of AEs (major and minor) strongly correlated with duration of treatment ($p=0.004$) and moderately correlated with the cumulative dose/weight ($p=0.051$). Weight gain was associated with the use of concomitant oral steroids and not with duration of treatment or cumulative dose.

Conclusion: IVHDM may be a valid therapeutic option for aggressive/refractory pediatric uveitis. The reported AEs in this series can also be attributed to the concurrent IMT or the underlying disease itself.

Keywords: pediatric uveitis, intravenous methylprednisolone, adverse events

Introduction

Pediatric uveitis is a rare disease, with an estimated incidence of around 3–7 per 100,000 children/year.^{1–3} Despite its relatively low incidence, it imposes a challenge on both ophthalmologists and patients and their family members as it comes with a particular set of problems. Complications including cataracts, glaucoma, macular edema and hypotony are common.⁴ Some reports have indicated that ocular complications occur in 75% of patients 1 year after diagnosis and increase to 86% after 3 years.⁵ Delayed diagnosis, with the initial presentation at an advanced and complicated stage, is not uncommon with pediatric uveitis. The problem of amblyopia and difficult examination also add to the complexity of management.

Corticosteroid hormones were first used as anti-inflammatory agents to treat rheumatoid arthritis in 1948 by Philip Hench and Edward Kendall.⁶ Since then, they have been and are still being used extensively as anti-inflammatory agents for different autoimmune and rheumatological diseases. Corticosteroid use as an initial therapy, along with other immunosuppressives, is recommended in many guidelines for treatment of different autoimmune diseases with moderate or high activity owing to their ability to rapidly control the inflammation and its symptoms.^{7–9} However, the same guidelines strongly recommend against long-term use of steroids because of their side-effect profile. Long-term systemic steroid use has been associated with weight gain, hyperglycemia, hypertension, osteoporosis, cataracts, psychiatric

symptoms, infections and other detrimental effects.^{10–17} In addition to these toxic effects, steroid use in pediatric patients was reported to be associated with growth retardation.¹⁸

Intravenous high-dose pulse methylprednisolone succinate (IVHDM) has been associated with a better safety profile and faster response than long-term high-dose oral steroids.^{19–22} It also allows using lower oral steroid doses and faster steroid weaning.^{21,23} It is widely used in adult inflammatory diseases, such as systemic lupus erythematosus, multiple sclerosis, optic neuritis and thyroid eye disease.^{21,22,24–26} Some authors advocated the use of IVHDM for the induction of remission in severe ocular inflammation. They found that it is effective, generally well-tolerated and relatively safe.^{27–30} Studies have reported that the major adverse events (AEs) of IVHDM are cardiovascular events, infections and liver damage.^{31–34}

A few studies evaluated the use of IVHDM in pediatric systemic inflammatory diseases, which included Kawasaki disease,³⁵ lupus nephritis^{36,37} and severe complications associated with juvenile idiopathic arthritis,^{38,39} among others. In those studies, the investigators also found that IVHDM is effective in controlling inflammation and well-tolerated. Schnabel et al reported the use of high-dose intravenous methylprednisolone in juvenile non-infectious uveitis, but did not include a significant amount of information on safety.⁴⁰

Given that pediatric uveitis is often a difficult disease to control, demonstration of the safety of pulse steroids in such cases will allow wider usage, which will help in controlling the disease and decreasing its associated morbidity. In addition, pulse steroids may help to decrease the dosage of long-term steroids and, hence, decrease its associated AEs. In our study, we evaluated the safety profile of pulsed intravenous methylprednisolone with or without other immunosuppressives in treating severe and/or resistant pediatric uveitis.

Methods

Setting of the Study and Subjects

We conducted a retrospective study of pediatric patients, who were aged less than 16 years and were treated with IVHDM for at least 3 months for refractory sight-threatening uveitis between June 2018 and October 2020 at a tertiary ophthalmic center. High-dose methylprednisolone was defined as ≥ 500 mg per infusion per day.

The study was conducted in compliance with the Declaration of Helsinki, the United States Code of Federal Regulations Title 21 and the Harmonized Tripartite Guidelines for Good Clinical Practice (1996). Stanford University institutional review board approved the study under the protocol number 41266, and written informed consent was obtained from the patients' parents or legal guardians for the case details to be published.

Data Collection and Outcomes

We collected demographic data, including age and sex, weight changes between the first and last visits, type and etiology of uveitides, dose and duration of IVHDM, and concomitant use of topical or oral steroids and other immunosuppressives, based on the clinical records.

Adverse Events Evaluation

AEs included any abnormal laboratory or clinical findings that occurred during the treatment period or 3 months after the last infusion. We also included patient-reported AEs, similar to those reported in previous research.⁴¹ We classified the reported AEs into minor, which were defined as manageable and transient, with no potential permanent effect on the patient; and major, which were defined as severe, life threatening or causing possible disability.

Statistical Analysis

Descriptive statistics were calculated for the variables of interest. Continuous variables were expressed as mean and standard deviation or median and range. Tests of normality, including Shapiro's test and histograms, were used to determine the normality of the data. Pearson's correlation and Spearman's correlation were used for data with normal and non-normal distributions, respectively. Multivariate regression analysis was used to establish independent relationships after controlling for different potential confounders.

Data analysis was performed using RStudio[®] software (Version 1.3.1093).

Results

Demographic and Baseline Criteria

Twenty pediatric patients who received IVHDM at a dose of 500 mg or higher per infusion were identified. Six patients received IVHDM either once, as a preoperative medication, or at a lower dose, and were excluded. The remaining 14 patients received IVHDM for at least 4 months. Baseline and concomitant treatment characteristics for the patients who were included in the study are shown in Table 1. Thirteen patients received monthly cycles of one to three consecutive infusions per month and one patient received IVHDM infusions every 2 weeks for 4 months, given the aggressive nature of the inflammation. The mean±SD age at initiation of therapy was 11.9±2.4 years and 50% were female.

The mean duration of treatment was 14.2±7.5 months. Except for two patients, who received higher doses (up to 32.5 mg/kg) and were considered to be outliers, IVHDM was given at an average dose of 8–25 mg/kg per infusion, with a minimum of 500 mg and a maximum of 1000 mg per infusion. The median (range) cumulative dose per patient was 16.4 g (3.5–55.25 g). The mean cumulative dose/duration was 1.38±0.52 g/month. The mean cumulative dose/weight at initiation of therapy was 461±342 mg/kg.

Indications for Immunomodulatory/Immunosuppressive Therapy

Indications for IVHDM, among other immunosuppressives/immunomodulatory therapy (IMT), were panuveitis with retinal vasculitis (n=6/14, 43%), autoimmune retinopathy (AIR) (n=2/14, 14%), juvenile idiopathic arthritis (JIA)-associated optic neuritis (n=1/14, 7%), JIA-associated retinal vasculitis (n=1/14, 7%), HLA-related vasculitis and optic neuritis (n=1/14, 7%), posterior uveitis and retinal vasculitis (n=1/14, 7%), intermediate uveitis-related retinal vasculitis (n=1/14, 7%) and isolated retinal vasculitis (n=1/14, 7%).

Other Immunosuppressives and Immunomodulatory Therapy

Thirteen patients received IVHDM in combination with other IMTs. Concomitant IMT was intravenous infliximab (54%), tocilizumab (38%), immunoglobulins (IVIG) (15%) and rituximab (7%). Other oral concomitant immunosuppressives, which were used in combination with intravenous IMT, included mycophenolate (30%) and methotrexate (23%).

Other Steroid Uses (Oral and Topical)

Eight patients (57%) received daily oral prednisone along with the other therapies and nine patients (64%) received topical steroids (either prednisolone acetate or difluprednate).

Side Effects: Major and Minor

Three major systemic AEs in two separate patients were noted. The first AE was asymptomatic sinus bradycardia during infusions in a patient who had been treated with IVHDM, IVIG and rituximab infusions for 12 months. The bradycardia was deemed benign after cardiology consultation and did not require follow-up. The second patient, who had been treated with IVHDM and tocilizumab infusions for 11 months, had a compression fracture following a minor trauma to the back. This patient was diagnosed with adrenal insufficiency around the same time and was also on low-dose long-term oral prednisone.

The most common minor AEs were mild derangements in blood count (10/14, 71%), mild increase in random blood glucose (10/14, 71%) and mild increase in liver enzymes (8/14, 57%), none of which required intervention. Other minor side effects included weight gain more than 10 kg (7/14, 50%), recognizing that the children were also growing as part of their aging process; painful events (5/14, 36%) such as headaches, joint pain, abdominal pain and back pain; cataract development and/or progression (4/14, 29%); minor infections (3/14, 21%), including gastroenteritis, bronchitis and urinary tract infection; hyperlipidemia (3/14, 21%); and miscellaneous events (each once, 7%) such as hypertension, generalized fatigue, mood changes and electrolyte disturbance.

Mean weight gain was 9.2 kg and mean weight gain/month was 0.87 kg/month. Seven patients (50%) gained more than (10 kg) over the duration of treatment; six of these patients were on oral prednisone. De novo cataracts developed in two

Table 1 Baseline and Treatment Criteria

Patient	Sex	Age (Years)	Diagnosis	Etiology	Initial Weight (kg)	Duration of Treatment (Months)	Cumulative Methylprednisolone Dose (kg)	Average Monthly Methylprednisolone (kg/month)	Concomitant Topical Steroids	Concomitant Oral Steroids	Concomitant Infusion Therapy	Concomitant Oral IMT
1	M	12	Panuveitis and vasculitis	Idiopathic	29	22	22.5	1.02	Yes	Yes	Infliximab	–
2	F	8	AIR	Idiopathic	23	14	17.25	1.23	No	No	IVIg	–
3	M	8	Panuveitis and vasculitis	Idiopathic	55	12	18	1.50	Yes	Yes	Infliximab	Mycophenolate
4	F	15	Optic neuritis	JIA	60	4	5	1.20	No	Yes	Tocilizumab	Mycophenolate
5	M	13	Vasculitis and optic neuritis	HLA-B27	85	20	15.5	0.78	Yes	Yes	Tocilizumab	Methotrexate
6	F	13	Vasculitis	Idiopathic	43	18	19.5	1.08	Yes	Yes	Infliximab	–
7	M	12	Posterior uveitis and vasculitis	Idiopathic	51	29	55.25	1.91	No	Yes	Infliximab/tocilizumab*	Methotrexate
8	M	12	Panuveitis	Behçet	29	16	12.95	0.81	Yes	Yes	Infliximab	Mycophenolate
9	F	12	Panuveitis and vasculitis	TINU	60	7	13.5	1.93	Yes	No	Infliximab	–
10	F	14	Vasculitis	JIA	84	6	11.5	1.92	Yes	No	Tocilizumab	–
11	M	13	AIR	Idiopathic	46	21	47.25	2.25	No	Yes	IVIg/rituximab**	–
12	F	14	Panuveitis and vasculitis	Idiopathic	56	6	9	1.50	Yes	No	–	Methotrexate
13	F	13	IU and retinal vasculitis	Idiopathic	44	17	29	1.71	No	No	Infliximab	Mycophenolate
14	M	7	Panuveitis and vasculitis	Idiopathic	24	7	3.5	0.50	Yes	No	Tocilizumab	–

Notes: *Sequentially, not concomitantly. **Concomitantly.

Abbreviations: IMT, immunomodulatory therapy; AIR, autoimmune retinopathy; IVIG, intravenous immunoglobulins; JIA, juvenile idiopathic arthritis; HLA, human leukocyte antigen; TINU, tubulointerstitial nephritis and uveitis; IU, intermediate uveitis.

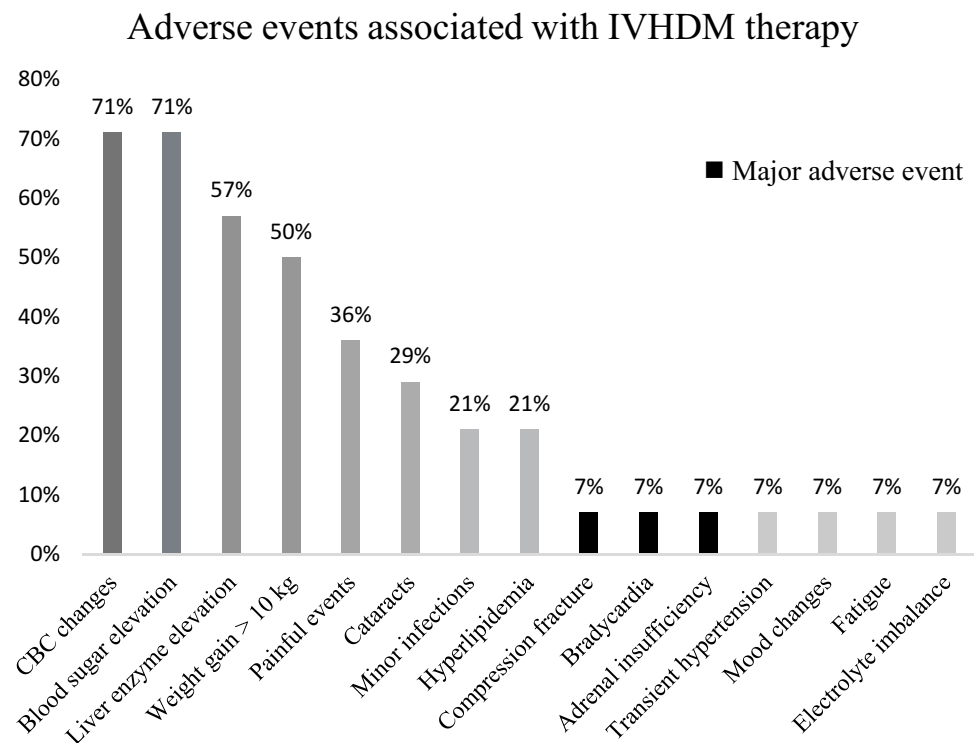


Figure 1 Frequency of different adverse events in pediatric patients treated with intravenous high-dose methylprednisolone (IVHDM). CBC: complete blood count.

patients and progressed in two patients. All four of these patients were on low-dose oral steroids and two of these four patients were on topical steroids, including the patient with the progressed cataract. None of these four patients had JIA.

Minor AEs are shown in [Figure 1](#).

Correlation Between Number of Side Effects and Different Parameters

The number of AEs strongly correlated only with the duration of IVHDM treatment ($Cor=0.72$; $p=0.004$) ([Figure 2](#)). Multivariate analysis showed that this relationship was independent after controlling for cumulative dose, cumulative

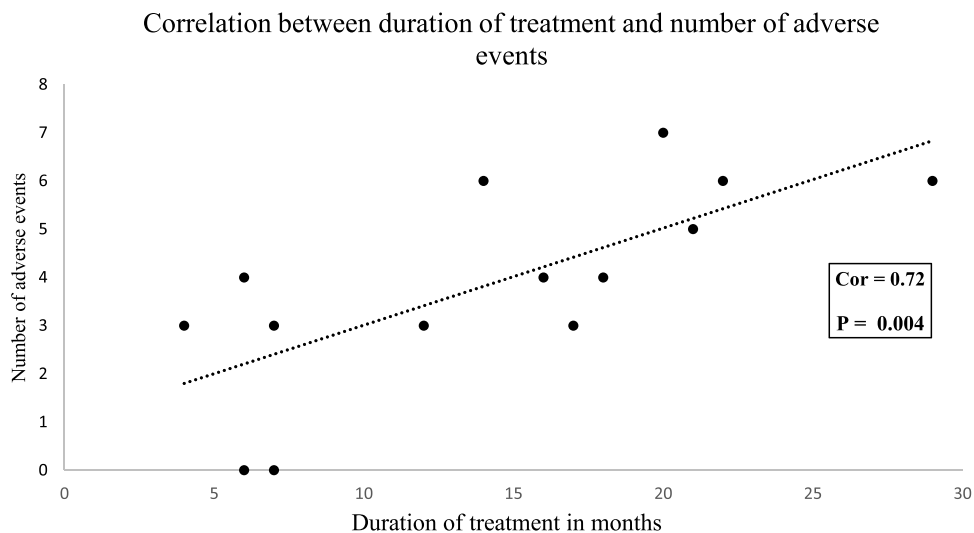


Figure 2 Strong linear relationship between duration of treatment with intravenous high-dose methylprednisolone and total number of adverse events.

dose/weight, concurrent oral steroids and other immunosuppressives [Coeff.: 0.29 (0.19–0.39); $p=0.023$]. The total number of complications also moderately correlated with the cumulative dose and the cumulative dose/initial weight, but the statistical significance was borderline for both (p values were 0.07 and 0.051, respectively). No statistically significant correlation was found with the age of patients or the initial weight at initiation of the infusions.

Neither total nor monthly weight gains were correlated with the duration of IVHDM treatment, cumulative dose or cumulative dose/duration. On the other hand, mean total and monthly weight gains were higher in patients who received concurrent oral steroids. For patients who received oral steroids, mean total and monthly weight gains were 12.9 and 1.1 kg/month, respectively. In the non-oral steroid group, mean total and monthly weight gains were 4.3 and 0.5 kg/month, respectively. The multivariate regression model showed that the use of oral steroids (along with IVHDM) was the only independent predictive factor for total and monthly weight gains ([Coeff.: 11.7 (7.5–15.9); $p=0.02$], [Coeff.: 1.7 (1.1–2.2); $p=0.01$], respectively), after controlling for duration of treatment, cumulative dose and cumulative dose/initial weight.

Case Reports

Case 1

A 12-year-old male presented to the uveitis clinic at Byers Eye Institute with bilateral active panuveitis. The patient had active anterior segment inflammation, vitreous cellular infiltration and significant retinal vasculitis, more in the left eye, which also had macular edema. The decision was taken to start treatment aggressively to prevent visual loss. After exclusion of infectious etiologies, the patient started infliximab infusions at 5 mg/kg monthly, methylprednisolone infusions at 750 mg for 3 consecutive days monthly (with one day receiving both infliximab and methylprednisolone) and oral prednisone at 30 mg daily. The patient was already on topical difluprednate, which was tapered gradually. After 6 months, the methylprednisolone frequency was reduced to once per month; after an additional 10 months, it was further reduced to 500 mg monthly; and it was discontinued after another 6 months. Oral steroids were tapered gradually to 1 mg daily over the period of 2 years.

The patient received 22 cycles of monthly intravenous methylprednisolone infusions. The cumulative dose of methylprednisolone was 22.5 g and the cumulative dose/initial weight was 775.9 mg/kg. AEs included repeated tiredness and weakness during infusions; hematological abnormalities, including immature granulocytosis, absolute leukopenia and minor changes in red blood cell indices; elevated liver enzymes, including aspartate transaminase and alkaline phosphatase; blood glucose elevations; and elevation of creatine kinase and lactate dehydrogenase levels. All of these AEs were transient and normalized shortly. Posterior subcapsular cataracts developed after 16 months of treatment but were visually insignificant, with visual acuity of 20/20 in both eyes. Over the 22 months of treatment, the patient gained 11 kg (weight at initiation of infusions was 30 kg). In general, the treatment was effective in markedly reducing the inflammation, even 4 months after stopping the infusions, but residual mild retinal vasculitis persisted during and after the period of treatment.

Case 2

A 13-year-old female presented with left idiopathic active panuveitis. She had active anterior segment inflammation, dense retroretinal cellular infiltration and active retinal vasculitis in the left eye, with the right eye showing no signs of inflammation. She had been treated with oral steroids, which failed to control the inflammation, and was on topical prednisolone. The decision was taken to start monotherapy with IVHDM owing to the failure of oral steroid treatment. She received six monthly cycles of IVHDM at 500 mg for 3 consecutive days every month. After five monthly cycles, oral methotrexate at the dose of 15 mg daily was started.

The patient received a cumulative dose of 9 g and a cumulative dose/initial weight of 160.7 mg/kg. No AEs were noted during the period of IVHDM therapy. Over the 6 month period, the patient lost 4 kg of weight. The retinal vasculitis has resolved.

Discussion

Methylprednisolone is a synthetic steroid with potent glucocorticoid activity and relatively moderate mineralocorticoid activity. With the very short half-life of methylprednisolone, most of the administered methylprednisolone is eliminated

from the circulation in one day.⁴² High-dose methylprednisolone pulse therapy appears to have more immunomodulatory than immunosuppressive effect, with the ability to reset the aberrant immune system.⁴³ Within the first day of pulse methylprednisolone therapy, circulatory monocytes and T lymphocytes decrease, with T-helper cells being more affected than T suppressors. This effect persists after the elimination of methylprednisolone from the circulation.⁴⁴

Two of the most common indications for IVHDM use in ophthalmology are optic neuritis and dysthyroid ophthalmopathy. Short courses of IVHDM have been shown to result in better visual acuity and fewer relapses than oral steroids in the treatment of optic neuritis associated with multiple sclerosis.⁴⁵ In addition, data support the rapid initiation of IVHDM in cases of neuromyelitis optica-associated optic neuritis in order to preserve the vision.⁴⁶ As for dysthyroid ophthalmopathy, evidence favors the use of IVHDM over oral steroids in managing moderate to severe cases; it has been shown to be more effective and safer than oral steroids.⁴⁷

Studies have shown that IVHDM is associated with fewer side effects than oral steroids in other diseases. Ruiz-Iratorza et al conducted a retrospective analysis on using IVHDM versus oral steroids in lupus nephritis and concluded that pulse steroids were associated with better responses and lower odds of inducing steroid-related AEs.²¹ In another study, Ruiz-Iratorza et al showed that pulse steroids allowed for lower doses of oral steroids while not affecting treatment outcomes of lupus nephritis. They also showed that the IVHDM group was associated with fewer AEs.²⁰ Other studies have shown that IVHDM was associated with worse clinical outcomes than continuous oral steroids.^{34,48}

The safety of methylprednisolone infusions in pediatric population has not been well studied. The insufficiency of information may be due to the infrequent use of methylprednisolone in pediatrics. Schnabel et al who evaluated high-dose methylprednisolone in 56 pediatric patients with non-infectious uveitis, reported that it was generally effective in the pediatric population. However, the investigators did not comment on the safety profile because of the relatively short follow-up period after finishing the infusions. Nonetheless, they did not report any serious AEs.⁴¹

In our case series, short- and intermediate-term use of IVHDM was associated with relatively mild adverse effects in most cases. Only two cases suffered from major side effects, in the form of cardiac arrhythmia, compression fracture following a minor trauma and adrenal insufficiency. The fracture occurred following back trauma, which resulted in a mild compression fracture of a dorsal vertebra. The fracture did not require any surgical intervention. This particular patient was also on oral steroids, although at a low dose, for nearly 2 years owing to medical necessity, before the fracture happened, which may have contributed to the fracture. Adrenal insufficiency was diagnosed in the setting of low-dose oral prednisone as well.

The relationship between daily steroid dose and the incidence of AEs is well established through multiple studies.^{19,49–53} Higher cumulative doses and longer durations were also associated with more AEs, even with lower daily doses. Curtis et al conducted a large population-based study that included 2446 patients with long-term steroid use, and found an independent strong relationship between eight specific AEs and the cumulative steroid dose.⁵⁴ In our current pediatric study, the number of AEs was strongly correlated with the duration of treatment ($p=0.004$), and this relationship was still significant after controlling for cumulative dose, cumulative dose/weight, concurrent oral steroids and other immunosuppressives. The number of AEs was also moderately correlated with the cumulative dose and cumulative dose/initial weight, although the significance was borderline for the last two variables (p values were 0.07 and 0.051, respectively). The stronger relationship between duration and side effects than that of the cumulative dose can be explained by the concurrent use of immunosuppressives and the cumulative AEs over the duration of administration. In addition, the borderline significance can be attributed to the relatively small number of patients.

Weight gain is a common side effect of steroids. Our data showed that total and monthly weight gains were greater in patients who received oral steroids, even after controlling for the duration of IVHDM treatment, cumulative dose and cumulative dose/initial weight. Monthly weight gain was more than the double in the oral steroid group. Such an observation implies that oral steroids cause more weight gain than IVHDM, which is consistent with similar previous studies. Lopate et al compared oral prednisone and high-dose IVHDM for the treatment of chronic inflammatory demyelinating polyneuropathy, and found that in the oral prednisone group, 58% of patients had weight gain versus 19% in the IVHDM group.⁵⁵ Similarly, Kapoor et al reported that 75.9% of patients who received oral prednisone suffered from weight gain versus only 16.1% of patients who received IVHDM for treatment of West syndrome.⁵⁶ The same observation was also confirmed by Dasgupta et al who compared oral prednisone and IVHDM for polymyalgia

rheumatica. However, they attributed this difference to the higher cumulative dose in their oral prednisone group.⁵⁷ On the contrary, our analysis showed no relationship between cumulative dose and weight gain.

Infections have been associated with cumulative doses of IVHDM higher than 5 g.⁵⁸ In our study, a low incidence of infections was reported despite the higher cumulative doses. Such an observation can be attributed to the generally stronger immune system in pediatric than in adult populations.

In a study by Zonana-Nacach et al where they analyzed the safety profile of IVHDM in systemic lupus, they found that the only AE which was statistically significant with pulse therapy was cognitive and psychiatric disturbances. For osteoporotic fractures, they failed to establish a significant risk with each pulse of IVHDM, although the *p*-value was 0.07.¹⁹ They also failed to demonstrate an increased risk of cataracts, diabetes mellitus, hypertension or avascular necrosis with each pulse of IVHDM administration. Similarly, in our study, we reported no cases of avascular necrosis. The four cases who had de novo or cataract progression and the only case with an osteoporotic fracture were all on oral steroids. This finding raises the possibility that these AEs were due to the chronic oral steroid use rather than the IVHDM.

Steroid-induced growth retardation in the pediatric population is a matter of a controversy. Some studies concluded that steroid use was associated with growth retardation in pediatric populations.^{18,59,60} However, several other reports did not find any relationship between steroid use and growth retardation, and attributed the observed decrease in growth velocity to the underlying disease rather than the steroid use.^{61–63} In our study, we did not evaluate the effect of steroids on growth owing to the relatively short period of follow up.

Our study has several limitations. It was retrospective, which may have allowed for different confounding factors that could not be detected. The AEs could not be solely attributed to the IVHDM, but also to the different medications as well as the underlying conditions. The small number of cases may have led to some of the potential AEs being missed, as well as yielding non-generalizable results. Bone densitometry was not performed within the study periods to document bone density changes, but has been arranged for subsequent visits. The relatively short-term follow-up did not allow for evaluation of the effect of steroids on growth retardation, which is of great concern in the pediatric population. The heterogeneity of the underlying conditions may have also contributed to the differences in reported AEs.

Conclusion

IVHDM can be a valid option for the treatment of resistant/severe cases of pediatric uveitis, with a relatively acceptable safety profile. The reported AEs in this series can also be attributed to the concurrent IMT or the underlying disease itself. Large prospective randomized studies are needed to establish the efficacy and safety profile of IVHDM in the pediatric population with severe uveitis.

Disclosure

Prof. Dr. Diana Do reports grants and personal fees from Regeneron, and personal fees from Genentech, outside the submitted work. Prof. Dr. Quan Dong Nguyen reports grants and personal fees from Genentech, personal fees from Bausch and Lomb, grants and personal fees from Regeneron, grants and personal fees from Novartis, and grants and personal fees from Santen, outside the submitted work. The authors report no conflict of interest in this work.

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