World Journal of Ophthalmology

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DOI: 10.5318/wjo.v5.i3.125

World J Ophthalmol 2015 February 12; 5(3): 125-132
ISSN 2218-6239 (online)

MINIREVIEWS

Intravitreal drug administration for treatment of noninfectious uveitis

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Author contributions: Both authors contributed to this manuscript.

Conflict-of-interest statement: None of the authors have conflict of interest.

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Received: February 25, 2015
Peer-review started: February 26, 2015
First decision: April 10, 2015
Revised: May 26, 2015
Accepted: June 15, 2015
Article in press: June 16, 2015
Published online: August 12, 2015

Abstract

Intravitreal treatment became popular with the discovery of the blood ocular barriers, which significantly limit drug penetration in systemic or topical administration. As the mainstay of treatment in noninfectious uveitis (NOIU) is still corticosteroids, triamcinolone acetonide (TA) was the first intravitreally used agent in this subset of patients. Although it was very effective in controlling inflammation and improving the inflammation related complications, TA was found to have a high rate of intraocular complications and a relatively short half-life necessitating frequent reinjections. Other systemically used therapeutic options such as methotrexate and anti-tumor necrosis factor-α agents were also tried intravitreally. Additionally anti-vascular endothelial growth factor agents that are widely used intravitreally in the management of diabetic retinopathy and age related macular degeneration have become an option to control the uveitis related complications like macular edema, retinal and choroidal neovascularizations. Advances in biotechnology led to the slow release biodegradable implant era. These implants have a longer duration of action, which may help in decreasing the number of reinjections. Today two forms of implants have been approved for use in NOIU, Retisert (0.59 mg flucinolone acetonide, surgical intervention) and Ozurdex (0.7 mg dexamethasone, office based intervention). Studies dealing with newer agents (cyclosporine, LFG31, sirolimus) in the management of chronic NOIU are on the way. The search for ideal effective, safe and biocompatible intravitreal agents in the management of NOIU has not ended yet.

Key words: Uveitis; Intravitreal; Steroid; Implant

Core tip: The limitations related to the systemic use of treatment options in noninfectious posterior uveitis yielded intravitreal route. The hallmark of intravitreal treatment triamcinolone acetonide has a short half-life with a high rate of intraocular complications, and this led to the development of implants as a treatment option with various agents in the market still under

investigation. In this review, we try to summarize the intravitreal therapeutic options that are being used in noninfectious uveitis.

Yazici A, Ozdal PC. Intravitreal drug administration for treatment of noninfectious uveitis. *World J Ophthalmol* 2015; 5(3): 125-132 Available from: URL: http://www.wjgnet.com/2218-6239/full/v5/i3/125.htm DOI: http://dx.doi.org/10.5318/wjo.v5.i3.125

INTRODUCTION

Ohm first described the use of intravitreal (IV) injections for therapeutic purposes in 1911 with injection of air in the repair of retinal detachment[1]. The therapeutic use of the IV route was not developed until the early 1970s, when investigations about the blood ocular barriers were started. The results of these investigations increased the use of the IV route which enables us to bypass anatomical barriers, for the administration of therapeutic agents[1]. From the middle of the 20th century, several agents such as antibiotics, antivirals, antifungals, steroids, anti-vascular endothelial growth factors (anti-VEGFs), immunomodulatory, anti-inflammatory, and antineoplastic agents have been used intravitreally[2-6]. Nowadays, as a method for providing higher therapeutic levels especially in the posterior segment of the eye, the IV route is widely used in many blinding diseases such as age related macular degeneration, diabetic retinopathy, vascular occlusions, macular edema, endophthalmitis, viral retinitis and ocular inflammatory disorders.

Noninfectious uveitis (NOIU) with posterior segment involvement is one of the ocular diseases in which IV injection is required. The mainstay of treatment in this subset of disease and its sight-threatening complications is still systemic corticosteroids. However, to overcome the blood ocular barrier effect, higher doses are needed causing higher risk of systemic side effects like hypertension, osteoporosis, diabetes mellitus, gastritis, skin thinning, hyperlipidemia and many fluid-electrolyte imbalances[7,8]. It is also important to note that children are more prone to side effects related to corticosteroids such as growth retardation, precocious puberty, immune and hypothalamic-pituitary-adrenal axis suppression[8]. Second line treatment, used for steroid sparing, consists of immunosuppressive and immunomodulatory agents, but these too have a serious systemic side effect profile. Thus, local therapy remains an attractive treatment of choice especially in uveitis that is not associated with systemic diseases, in unilateral presentation, and in patients with compliance problems for systemic drug use. It also offers an excellent adjunctive therapeutic opportunity in cases where adequate control of inflammation cannot be provided despite systemic treatment. As the blood ocular barriers do not permit topical treatment to achieve a sufficient therapeutic level in the posterior segment, local treatment by IV route serves as a good solution in posterior segment uveitis. IV triamcinolone acetonide (IVTA) has been the most widely preferred option but has a short half-life and limited duration of action. It also has important ocular side effects like cataract and glaucoma, which mostly require surgical intervention[9,10]. The evolution of IV injections has led to the development of IV implants which aim to increase the duration of action and decrease the number of injections.

In this paper we aim to perform a literature review of recent developments in IV treatment of NOIU.

CORTICOSTEROIDS

Triamcinolone acetonide

IVTA is effective in controlling vitritis, reducing macular edema and improving visual acuity with IV doses of 2 to 4 mg when applied in NOIU with posterior segment involvement[11-13]. Its method of action is *via* different pathways including the inhibition of phospholipase A synthesis, blocking the production of inflammatory cytokines, stabilizing the blood retinal barrier and reducing VEGF levels[5,14]. Kramer *et al*[15] found that IVTA was very effective in rapid clearing of the vitreous inflammation with improvement in the visual acuity when used either alone or in combination with systemic immunosuppressive therapy. Lasave *et al*[5] used a single IVTA injection in refractory uveitic cystoid macular edema and reported that both visual acuity and macular thickness measurements had improved successfully at the 6th month visit. They also found that there was a significantly better visual improvement in macular edema cases with duration of less than a year, and therefore suggested earlier use of IVTA in refractory cases. A similar efficiency was reported by Karacorlu *et al*[16] who also found that IVTA achieved an improvement in visual acuity at the end of 6-mo follow-up in 30% of cystoid macular edema cases due to Behcet's disease. Angunawela *et al*[17] published their long-term results of IVTA injections in uveitic macular edema refractory to systemic and orbital floor steroid injections and concluded that IVTA is effective. They stated that although retreatment is required, this can be maintained with orbital floor injections. In their series, 9 of the 12 eyes had increased visual acuity at the final control (mean 40.5-mo follow-up) while 3 of them were resistant.

One of the main limitations of the IVTA is the off-label use in Europe and many other countries and the preservative used which might be toxic to the retina. The second limitation is its relatively short duration of action lasting approximately 3-7 mo that necessitates frequent re-injections[18]. It is important to note that the vitreous half-life of IVTA in vitrectomized eyes is shorter since the clearance is quicker[10,19,20]. The third and most important limitation is the occurrence of ocular side effects such as cataract and intraocular pressure elevations. Approximately 1%-2% of cases require

Table 1 Summary of some intravitreal agents

	Application	Duration of action	Visual acuity	Glaucoma surgery	Cataract surgery
IVTA 4 mg (kenalog)	Injection	3-7 mo[17]	58.3% gained ⩾ 2 Snellen lines with a median 40.5-mo follow-up[16]	1%-2%[10]	15%-30%[10]
FA 0.59 mg (retisert)	Surgical implant	30 mo[21]	23% gained ⩾ 3 lines after 3 yr[21]	32%-40%[21,23,25]	Nearly 100%[21,23,25]
Dexamethasone 0.7 mg (ozurdex)	Non-surgical implant	4-6 mo[21]	38% gained ⩾ 3 lines at 6th month[29]	None[30]	1.3%[30]
MTX 400 μg	Injection	4 mo[21]	38% gained ⩾ 2 lines at 3rd month[21]	None[21]	None[21]

IVTA: Intravitreal triamcinolone acetonide; FA: Flucinolone acetonide.

glaucoma surgery, 15%-30% require cataract surgery, and the risk of the need for these procedures increases with the number of reinjections[11].

Both frequent reinjection necessity and a high risk of intraocular complications have driven researchers to investigate long-lasting implantable IV agents with different glucocorticoid agents. Nowadays, flucinolone acetonide (FA) (Retisert, surgically implanted) and dexamethasone (Ozurdex, non-surgically implanted) implants are being used in NOIU and considerable data with regards to their efficiency and side-effect profile have been collected.

FA

The beneficial effect of surgically introduced IV implant of ganciclovir for the treatment of cytomegalovirus retinitis is the hallmark in development of the posterior segment implants. This route seems to be a perfect solution for chronic NOIU with a probable improvement in the duration of action, which is the major limitation of IVTA. FA with its low water solubility is the first Food and Drug Administration (FDA) approved glucocorticoid implant (Retisert, Bausch and Lomb, Rochester, NY) to be used in NOIU[21]. The implant is surgically placed and contains 0.59 mg FA that is slowly released up to 30 mo allowing the opportunity of tapering systemic medications, avoidance of multiple IV injections and possible concurrent complications of injections. The comparison of eyes, one having implant and the other not, revealed that the FA implant reduced the recurrence rate significantly from 62% to 20% in the implanted eye whereas recurrence was 59% in non-implanted eye at the end of the 3-year follow-up[22,23]. In the Asian population, Sangwan *et al*[24] reported similar effectivity with a 0.59 mg dose to prevent recurrences with the rates declining from 43.6% to 17.1%. Studies have also found FA implant to be very successful in improving visual acuity and in reducing the need for adjunctive systemic or periocular steroid treatments[22,24,25]. Callanan *et al*[22] stated that the visual acuity increased ⩾ 3 lines in 23% of the 0.59 mg FA implanted eyes compared to 6% in non-implanted. The same rate was 31.1% *vs* 7.6% in Sangwan *et al*[24] study.

The major ocular side effects of the FA implant are cataracts and raised IOP. Nearly all of the patients required cataract surgery and 32%-40% required IOP lowering filtration surgery at the end of the 3-year follow-up[22,24,26]. Other ocular complications worthy of mention are retinal detachment (4.0%), endophthalmitis (1.0%), and hypotony which could occur at any time in 3-year follow-up (34.0%)[21]. Although 0.59 mg FA implant requires surgical implantation and further surgical interventions to treat ocular side effects like cataract and glaucoma, a recent review that compared systemic corticosteroid *vs* 0.59 mg FA implantation in terms of cost-effectivity has found the implant to be reasonably cost-effective in unilateral noninfectious intermediate, posterior and panuveitis cases[27].

Iluvien (Alimera Sciences Inc., Alpharetta, GA) is another FA implant approved to be used in diabetic macular edema. Its difference from Retisert is that Iluvien can be applied in the office setting without the need for surgical intervention. It also releases lower doses of medication and preliminary data suggest that the risk of a rise in IOP is lower compared to Retisert[28]. However, there are no data up to date for its use in uveitis.

Dexamethasone

Dexamethasone is approximately 3-5 times more potent compared to triamcinolone acetonide (TA) and 7.5-12.5 times more potent compared to FA. Its implant form is Ozurdex (Allergan Inc, Irvine Calif, United States) which is a bioerodible device composed of a mix of polylactic acid and polyglycolic acid polymers that releases 0.7 mg of dexamethasone for up to 6 mo. One of the major advantages over the former approved glucocorticoid implant Retisert is the office based application without any need for surgery[29]. The FDA approved its use in retinal vein occlusion, uveitis and diabetic macular edema[30]. The first data about the use of Ozurdex in uveitis were gathered from the results of HURON (Chronic uveitis evaluation of IV dexamethasone implant) trial[31]. The HURON study revealed that a single injection resulted in efficient control of inflammation and good visual outcomes for up to 6 mo in noninfectious intermediate or posterior uveitis. A recent multicenter study which evaluated Ozurdex implants in NOIU confirmed the success of the implant in controlling vitreous haze, cystoid macular edema and visual acuity[30]. Authors noted that the improvement in uveitis presentation can be observed as early as 2 to

4 wk after the injection. The percentage of eyes that gained ⩾ 3 lines in visual acuity were 38% at the end of the 6th month. The median time to reinjection was 10 mo and the time to uveitis relapse considering the changes in macular thickness, vitreous haze and visual acuity was 6 mo, which is comparable to the previously performed studies[32,33]. The main problems with the former glucocorticoid implant Retisert (high rate of a raised IOP and cataracts) were found to be significantly less with Ozurdex. The HURON study reported that only 23% of eyes required IOP lowering medications without any surgical intervention and 1.3% needed cataract extraction[31] (Table 1).

Zero point seven mg dexamethasone implant Ozurdex has many advantages, *i.e.*, 22G office based application and lower risk of IOP rise and cataract formation. However, considering the disease is mostly chronic and recurrent, reinjections are mostly needed.

Methotrexate

Methotrexate is an antimetabolite immunosuppressive that has been used in NOIU for many years as a steroid sparing agent[34,35]. It is also used in the treatment of intraocular lymphoma cases as IV injections at 400 μg doses[36,37]. In a retrospective study, Hardwig *et al*[38] reported that IV methotrexate preserved or improved visual acuity in seven of eight uveitis patients. Similarly, in a prospectively designed study Taylor *et al*[39] have announced that in 30 of 38 eyes, intraocular inflammation was successfully controlled with improved vision and without any ocular side effects. From 30 eyes that responded well, only 8 have relapsed and 7 of them responded to the reinjection. They also emphasized that 57% of the patients were able to reduce systemic treatments. IV methotrexate might serve as a preferable option in noninfectious posterior uveitis with high efficacy, nearly no side effect and an extended duration of action (Table 1).

Anti-tumor necrosis factor-α

Anti-tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that is involved in regulation of immune cells, tumor suppression and inhibition of viral replication[40,41]. It is also mentioned in the pathophysiology of ocular inflammatory conditions related to autoimmune diseases and ocular diseases that have an inflammatory component such as diabetic macular edema and neovascular age related macular degeneration[42-45]. There is a significant amount of data on systemic use of anti-TNF-α agents in uveitis especially in Behcet's disease, juvenile idiopathic arthritis and ankylosing spondylitis. However, the systemic side effects like fatal blood disorders, secondary infections, reactivation of latent infections, and demyelinating nerve system disorders limit its use[46]. As in the case of glucocorticoids, IV route was tried to avoid systemic side effects. For all TNF-α agents, the optimal IV dose was decided after the animal studies were completed. The results of the studies that will be discussed in this paper are mostly case series and the literature lacks standardized well-designed prospective works.

Etanercept was studied in a pilot study involving seven patients with resistant diabetic macular edema. At the end of 3 mo, no significant improvement or side effects were seen with a safe dose of 2.5 mg IV injection that was repeated at 2 weekly intervals[47]. It was then abandoned and no further studies were conducted afterwards. Thus, there are no available data on its use in uveitis.

Infliximab, a murine-based monoclonal antibody, was investigated in animal studies and IV doses below 2 mg were reported to be well-tolerated[48]. The Pan-American Collaborative Retina Study Group, the largest series that was conducted about the IV use of infliximab in diabetic macular edema and exudative age related macular disease, has concluded that IV infliximab did not result in any anatomic or functional benefit whereas 37.5%-42% of the injected eyes developed severe uveitis[49,50]. Its use in noninfectious posterior uveitis and Behcet's disease was found to improve vision initially but failed to stabilize the vision in the long-term[51,52]. In short, studies demonstrated that IV infliximab might be useful in uveitis but not in diabetic macular edema or exudative macular disease.

Adalimumab is also one of the preferred anti-TNF-α options that is successfully used in the treatment of NOIU[53]. Hamam *et al*[54] recently published the only study of IV adalimumab use in human. They performed an IV adalimumab injection of 0.03 mL (1.5 mg) at 0, 2 and then every 4 wk for a total 26-wk duration in 7 patients (13 eyes). Only 1 patient had worsened ocular inflammation and was removed from the study and switched to systemic and local corticosteroid treatment. Visual acuity improved in 7 of 12 eyes with ⩾ 2 ETDRS lines, whereas the other 5 eyes remained stable or improved 1 line. In 8 eyes with macular edema, 5 achieved complete resolution. No ocular or systemic side effects were reported. Authors had noticed that 4 patients had Behcet's disease, which might affect the results since anti-TNF-α has favorable results in this particular disease. More numerous studies are required to reach a conclusion about the IV use of adalimumab.

Anti-VEGF agents

IV anti-VEGF agents are widely used for age related macular degeneration related choroidal neovascularizations, and macular edema related to diabetic retinopathy and retinal vascular occlusions[55,56]. Their use in uveitis is mostly related to the management of secondary complications of uveitis such as macular edema and choroidal neovascularizations[57,58]. In a study comparing IV anti-VEGF agents and IVTA, Lasave *et al*[5] reported that a single injection of IVTA is superior to IV bevacizumab in chronic resistant uveitic macular edema cases with regards to improvement in visual acuity and macular thickness. A prospective non-comparative

therapeutic trial has been published recently evaluating the effect of ranibizumab on macular edema in clinically well-controlled 5 eyes of 5 uveitis patients. They performed 4.6 injections on average in the first 6 mo and 1.8 injections in the second 6-mo period according to the criteria they put forth at the beginning of their study. The 12th month follow-up visit for the same study revealed that there was a statistically significant 12.2 letter increase in visual acuity and 45.4% decrease in macular thickness. Another interesting study about the effect of anti-VEGF agents in uveitis was the retrospective study performed by Al-Dhibi *et al*[59] that evaluated the effect of bevacizumab in infectious uveitis and NOIU. Similarly, they reported improvement in visual acuity and macular thickness. The latest finding is that bevacizumab is effective and safe without any immunosuppressive effect against infectious agents.

In summary, they are not superior to IVTA and have short half-life necessitating reinjections. Therefore, they do not seem to be ideal agents for uveitis, which is mostly chronic and recurrent. The major advantage of these agents might be the relatively low incidence of ocular complications like cataract and IOP rise when compared to glucocorticoids. This might be very helpful especially in steroid responder cases. Additionally, they might be of use in uveitis induced choroidal or retinal neovascularizations.

Future intraocular devices and agents for the treatment of NOIU

I-vation is a screw shaped implant, which is twisted through the pars plana from a 0.5 mm sclerotomy. It contains 0.925 mcg TA that is reported to have 1-year duration of release. The 1-year results demonstrated that it was effective in diabetic macular edema with decrement in macular thickness and increment in visual acuity[60]. The phase 2 results have not been published yet. There are no data for uveitis patients as of yet.

Sirolimus, a macrolide antibiotic (rapamycin), was originally developed as an antifungal agent. After the immunosuppressive and antineoplastic effects were discovered, it is now being investigated for the treatment of different ocular diseases including uveitis. It suppresses T and B cell proliferation and inhibits interleukins-2, -4 and -5[61]. Sirolimus as Therapeutic Approach to Uveitis study has announced its 6-mo results, which reported equal success in improving vitreous haze with subconjunctival or IV administration[62]. The ongoing phases 2 and 3 studies will help clinicians to reach a better conclusion about the effectiveness and safety profile of local sirolimus treatment in NOIU.

LFG316 is a monoclonal antibody that inhibits activation of complement protein 5 and a phase 1 single ascending dose study of IV injections was performed in advanced AMD patients[63]. The IV use in multifocal choroiditis and panuveitis is currently under investigation.

Cyclosporine is a well-known second-line immunosuppressive agent, which is used especially in chronic NOIU patients. The IV implant form of cyclosporine was tested in 2 experimental uveitis models in rabbits and found to be effective and safe[64,65].

CONCLUSION

Uveitis is still one of the most challenging issues of ophthalmology from diagnosis to treatment. For a long time, corticosteroids served as the only treatment option in NOIU and are still the mainstay of treatment although many new agents have emerged. The IV route is a great option for clinicians to reach therapeutic levels in the posterior segment of the eye, since the blood ocular barriers significantly limit the efficacy of topical and systemic administrations. It also allows for a reduction in systemic treatment doses of therapeutic agents and thus a decrease in side effects related to higher doses. IV treatment is an excellent treatment of choice especially in cases with unilateral involvement, in uveitis not associated with systemic disease and in patients who have problems with systemic drug use. It is also a good adjunctive treatment in patients with active ocular inflammation despite optimal systemic therapy. The high rate of cataract, IOP rise and relatively short half-life, which requires frequent reinjections with conventional IVTA, has evoked the innovations of implant technology. Today, Retisert and Ozurdex are the most commonly preferred glucocorticoid options in uveitis management with some advantages and disadvantages. The systemic agents that are being successfully used in NOIU management (methotrexate, anti-TNF-α agents) are also being tested for IV administration. IV anti-VEGF agents might be an option for uveitic macular edema especially in steroid responder cases. However, studies performed for evaluation of IV drug administration in uveitis are mostly non-standardized (length of follow-up, doses, patient selection, criteria for effectiveness) and retrospective case series with small samples, which limit the clinicians' ability to reach a conclusion. It seems that the search for safe, cost-effective and long acting agents in uveitis management has not reached to an end yet.

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