Mini Review

Ophthalmic Research

Ophthalmic Res 2013;49:59–65
DOI: 10.1159/000345477

Received: August 13, 2012
Accepted after revision: October 27, 2012
Published online: December 15, 2012

Think Global – Act Local: Intravitreal Drug Delivery Systems in Chronic Noninfectious Uveitis

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Key Words
Chronic noninfectious uveitis · Corticosteroids · Intravitreal drug delivery

Abstract
The eye is probably the most attractive site of the body for treatment using locally delivered therapeutic agents. An ideal indication for such an approach is noninfectious posterior uveitis. Since intraocular structures of the posterior segment are difficult to reach and are otherwise accessible only by systemic treatment, current interest is focused on the pros and cons of intravitreal drug delivery. Because of its chronic and recurrent nature, the long-term release of anti-inflammatory agents is a major treatment goal. Intravitreal injections, intravitreal implants and biodegradable devices are the most commonly used and approved approaches to deliver various agents to the vitreous. Because of their broad and potent effects, corticosteroids (CS) have been the first-line candidates for intraocular delivery. An increasing spectrum of CS preparations including nondegradable and biodegradable devices is currently available. Since repeated and long-term applications bear the risk of steroid-related complications such as increased intraocular pressure and cataract, alternative agents are currently being tested. Intravitreal injection of methotrexate, anti-VEGF (vascular endothelial growth factor), anti-TNFα (tumor necrosis factor α) and sirolimus have also been applied in patients with conflicting results. Intravitreal treatment has significantly reduced the incidence of adverse effects compared to systemic application, but due to greater ocular side effects there are still some limitations.

Introduction

Treatment of chronic noninfectious posterior uveitis (CNIU) remains a challenge. Even when CNIU comprises a large spectrum of disorders (often considered as individual entities), initial treatment is predominantly based on corticosteroids (CS). It has been proposed that up to two thirds of patients with posterior uveitis can be controlled on CS alone. However, long-term applied systemic CS cause serious adverse effects to develop in many patients, and immune modulatory treatment is commonly suggested as a CS-sparing approach. While immune modulatory agents can be very effective, they may have serious and potentially life-threatening adverse effects, including renal and hepatic failure and bone marrow suppression. The intravitreal administration of anti-inflammatory medications is, therefore, an attempt to decrease the risks associated with systemic application and to increase the availability of drugs to the posterior segment

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Table 1. Pharmacokinetics and features of intravitreal CS

	Kenalog® (triamcinolone acetonide)	Retisert® (fluocinolone acetonide)	Ozurdex® (dexamethasone)	Iluvien® (fluocinolone acetonide)
Water solubility, μg/ml	21	50	100	50
Half-life in human vitreous (solubilized)	18 days	2–3 h	3.5 h	2–3 h
Relative potency	1 ×	0.4 ×	3–5 ×	0.4 ×
Drug kinetics (elimination)	First order	Zero order	First order	Zero order
Delivery to the vitreous	Nonsurgical	Surgical	Nonsurgical	Nonsurgical
Off-label	Off-label	FDA-approved; not EMA approved	FDA/EMA-approved	EMA-approved (DME); not FDA-approved

EMA = European Medicines Agency; FDA = Food and Drug Administration. DME= Diabetic macular edema.

of the eye. However, a number of important considerations have to be taken into account.

- Can we expect that intravitreal therapy will control an immune-mediated disorder – when specific (circulating) immune cells are considered to be important [1]?
- How do we deal with uveitis patients affected by systemic disease, e.g. sarcoidosis, but predominantly suffering from uveitis?

Conversely:

- How can we balance and compare the well-known adverse effects of local CS such as increase in intraocular pressure (IOP) and cataract formation versus systemic side effects related to steroid and immunsuppressive therapy?
- Are we on the right track using 'old' agents (CS) at a time when 'biologics' and 'small molecules' are gaining in importance?

Important answers to these questions have recently derived from recent trials [2, 3]. Observations indicate that both approaches, intravitreal and systemic CS are successful in controlling inflammation in most patients. However, intravitreal CS more often take effect significantly faster. In addition, vision-related quality of life, an important issue in our mainly young patients, improved significantly within 6 months following intravitreal therapy. These positive features vanished over time, however, and at the 24-month follow-up, both groups had equally improved. More eyes that received long-term intravitreal CS had to undergo cataract and glaucoma surgeries [4]. Even when these adverse effects are related to the features of this particular CS implant, identification of predisposing risk factors, e.g. for developing glaucoma, remains important [5].

Interestingly, the Multicenter Uveitis Steroid Treatment trial also revealed that patients receiving aggressively CS-sparing therapy and prednisone doses of less than 10 mg/day had a low risk of systemic adverse events [2]. Therefore, the choice of treatment for each individual patient needs to be balanced on the advantages and disadvantages identified with each therapeutic option. Taking these considerations into account, a treatment algorithm might be suggested (fig. 1). In this 'mini-review', we intend not only to focus on the increasing spectrum of intravitreally delivered drugs in humans, but also briefly touch on the issue of balancing the risks and benefits of intravitreal compared to systemic treatment.

Corticosteroids

Notably, even when the addition of immunosuppressive agents is often effective as a CS-sparing approach, most patients do not achieve visual improvement [6]. Therefore, attempts to achieve effective CS levels in the vitreous and retina remain an important treatment goal. Intraocular CS have been used to treat posterior uveitis and inflammatory chronic cystoid macular edema (CME) [7]. Experimental and clinical data indicate that the direct administration of steroids such as triamcinolone into the vitreous cavity has a significant advantage of delivering medication to the posterior segment, i.e. significantly higher concentrations for the adequate treatment of posterior segment inflammation can be reached [8]. However, frequent injections are often needed to maintain drug concentrations within a therapeutic range. Additionally, pharmacokinetics and features differ according to the type of the intravitreal CS (table 1).

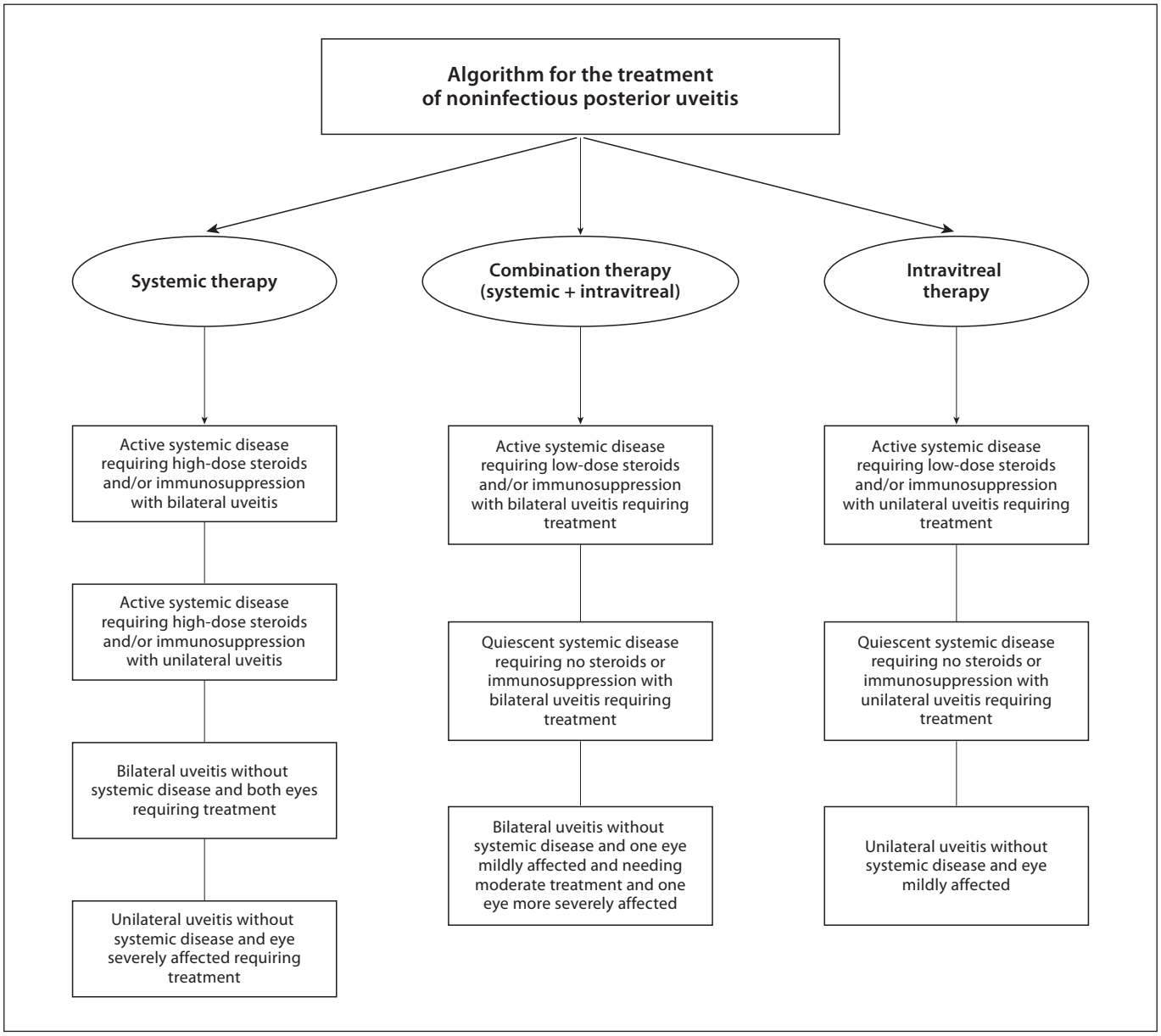

Fig. 1. Algorithm for the treatment of CNIU.

Intravitreal Triamcinolone Acetonide Injection

Intravitreal triamcinolone (IVTA) reduces CME and vitritis and improves vision, usually at a dose of 2–4 mg [9–11]. Behçet's disease, sarcoidosis ,Vogt-Koyanagi-Harada syndrome and sympathetic ophthalmia, are among others effectively treated with IVTA [11–14]. Even in such disorders, considered to be autoimmune-driven, a beneficial effect could be achieved. Cataract and glaucoma are frequent complications of IVTA (table 2) [9]. The risk of cataract formation and elevated IOP increases with repeat injections, and these are more pronounced in children [9, 15]. Furthermore, intravitreal injection of CS should not be used in infectious uveitis as serious consequences could result [16, 17].

Intravitreal Corticosteroid Implants

Repeated episodes of intraocular inflammation are known to result in cumulative damage to the retina [18,

Table 2. Comparison of intravitreal drug delivery systems used in CNIU

	Matrix	Duration of effect, months	Improvement in visual acuity	Tapered systemic medications	Glaucoma surgery	Cataract surgery
Kenalog® (4-mg triamcinolone acetonide intravitreal injection)	–	3–7	51% gained at least 2 Snellen lines by week 4	yes	1–2% (risk increases with repeat injections)	15–30% (risk increases with repeat injections)
Retisert® (0.59-mg fluocinolone acetonide implant)[a]	nonbiodegradable	24–36	21% gained at least 15 letters by week 34	yes	30.6% by month 24	93–100%
Ozurdex® (0.7-mg dexamethasone implant)[b]	biodegradable	4–6	38% gained at least 15 letters by week 26	yes	0–0.5%	0–4%
Iluvien® (0.019-mg fluocinolone acetonide implant)[b, c]	nonbiodegradable	24–36	20% gained at least 15 letters by month 12	data not available	0–5.9%	15–29%
Methotrexate (400 μg intravitreal injection)	–	4	87% gained at least 10 letters by month 3	yes	none	none
Sirolimus (intravitreal injection)	–	2	37%	yes	none	none
Biologicals (anti-TNFα, infliximab)	–	data not available	improved from 0.67 ± 0.56 to 1.37 ± 0.43 by week 4	data not available	none	none

[a] It is implanted through a sclerotomy incision made at the level of the pars plana and is secured with a suture to the sclera.
[b] It is directly administered via an injecting applicator through the pars plana similar to other intravitreal injections.
[c] As there is no published study involving uveitic patients, the data refer to patients with diabetic macular edema.

19]. Long-term control of intraocular inflammation without relapses may result in less retinal damage and reduce the risk of visual loss. Implantable devices in the vitreous can deliver a constant concentration of medication over prolonged periods of time (table 2). Whereas nonbiodegradable, long-term delivery systems seem preferable for chronic diseases, shorter-lasting biodegradable products are preferred for conditions that require short-term therapy, including CME. The profile of adverse effects following repeated applications still has to be evaluated [7].

Fluocinolone Acetonide Implants

Retisert® (Bausch & Lomb, 0.59 mg) is currently the only FDA-approved fluocinolone acetonide implant. It is applied in uveitis, diabetic macular edema (DME) and retinal vein occlusion [3, 4, 20, 21]. Several studies have demonstrated its efficacy in reducing recurrence, improving vision and reducing the need for systemic immunosuppressive medication in many types of posterior uveitis and panuveitis [3, 4]. However, the incidences of cataract and glaucoma are significantly high (table 3).

Iluvien® (Alimera Sciences Inc.) is another FA intravitreal implant, which is designed to deliver CS to the retina for up to 3 years as a treatment for DME [26]. It uses the same drug matrix as Retisert, but is thought to release a lower dose of medication (0.2 or 0.5 μg/day), and is injected through a proprietary 25-gauge injector system in an outpatient setting [26]. Phase III studies in DME have been completed with positive results. Preliminary data suggest that the risk of secondary IOP increase might be lower than with Retisert. Its use in CNIU is currently under clinical investigation.

Dexamethasone Implant

The commercial preparation of dexamethesone implant is Ozurdex® (Allergan, Inc., Irvine, Calif., USA; 0.7 mg). Published phase III trials were carried out to treat retinal vein occlusion, DME and uveitis [23, 27, 28]. Following a single intravitreal injection, a lower incidence of cataracts and rise in IOP was reported in the Huron trial than with Retisert (table 3) [23]. These observations were more recently confirmed by our own observations and are particularly important in our young patients affected by CNIU. The dexamethasone implant seems to be a useful alternative to control vitreous haze and CME, although repeated implants may be necessary to prevent recurrence [23, 29].

Table 3. Treatment effect of intravitreal drug delivery systems in studies with noninfectious uveitis

	Retisert (0.59-mg fluocinolone acetonide implant)		Ozurdex (0.7-mg dexamethasone implant)		Methotrexate (400-μg intravitreal injection)	
	Callanan et al. 2008 [4]	Pavesio et al. 2010 [3]	Williams et al. 2009 [22]	Lowder et al. 2011 [23]	Taylor et al. 2009 [24]	Bae and Lee 2012 [25]
Study design	multicenter, randomized, historically controlled trial	randomized, controlled, phase IIb/III, open-label, multicenter superiority trial	randomized, prospective, single-masked, controlled trial	randomized, prospective, multicenter, masked	prospective, consecutive, interventional case series	retrospective
Number of patients	110	66	41	77	15	7
Follow-up period	3 years	3 years	6 months	6 months	6 months	24.9 ± 8.2 weeks
Uveitis recurrence rates during 1-year period before treatment	62%	not mentioned	not mentioned	not mentioned	not mentioned	not mentioned
Uveitis recurrence rates after treatment	4% (1-year) 10% (2-year) 20% (3-year)	34.8% (2-year)	not mentioned	not mentioned	33.3%	28.6%
Decrease in macular thickness	not mentioned	not mentioned	not mentioned	99.4 μm (after 2 months)	150 μm	not mentioned
Improvement in fluorescein leakage	not mentioned	not mentioned	58%	not mentioned	not mentioned	57%
Improvement in visual acuity (at least 3 lines)	23%	17.2%	53.8%	40% (approximately)	87% (at least 2 lines)	85.7%
Reduction in the number of patients requiring systemic medications	80%	not mentioned	not mentioned	not mentioned	42.6%	42.9%
Cataract surgery	93%	87.8%	not mentioned[a]	1.3%	none	none
Glaucoma surgery	40% at 3-year	21.2%	none	none[b]	none	none

[a] Rate of cataract surgery cannot be detected appropriately as 18 patients were pseudophakic at the beginning of the study.
[b] The steroid responders are excluded from the study.

Intravitreal Methotrexate Injection

In an attempt to avoid the ocular side effects of intraocular CS, recent attention has been focused on alternative agents. One of these is methotrexate (MTX). The systemic use of MTX is standard care in conditions like in juvenile rheumatoid arthritis-associated uveitis because of its excellent safety record [30]. Intravitreal MTX was first administered as a therapy for intraocular lymphomas [31]. In addition, case series have shown the promising effects of intravitreal injection of 0.4 mg MTX for CNIU and uveitic CME without significant ocular complications (table 3) [24, 32]. Recently, a biodegradable microneedle MTX implant inserted into deep lamellar scleral pockets was tested without any intra- or postsurgical complications or toxic effects [33].

Anti-Vascular Endothelial Growth Factor Agents

Intravitreal anti-VEGF drugs are widely used to treat age-related choroidal neovascularization, DME and retinal vein occlusion edema [34–36]. They also successfully reduce choroidal neovascularization secondary to inflammation such as toxoplasmosis, punctate inner choroidopathy, serpiginous choroidopathy and multifocal choroiditis [37, 38]. They have ambiguous results in the treatment of uveitic macular edema [36, 39, 40].

Intravitreal bevacizumab and ranibizumab were reported to improve visual acuity and to reduce CME in optical coherence tomography and fluorescein angiography images [36, 39]. Both agents may be a supplementary off-label therapeutic option for persistent uveitic CME [25]. They hold little risk of increasing IOP, and thus seem to be a treatment option for patients known as CS re-

sponders. However, reinjection may be required because of their limited potency and short intravitreal half-life. When compared to IVTA injection, visual acuity and CME were more effectively treated with CS when compared to intravitreal bevacizumab in refractory CNIU at 6 months [40].

Anti-Tumor Necrosis Factor-α

Systemic anti-tumor necrosis factor α (TNFα) agents represent a significant advance in the treatment of many inflammatory diseases. The therapeutic effects of systemic anti-TNFα agents for various types of uveitis, particularly Behçet disease, has been repeatedly shown [41].

Intraocular injection of anti-TNFα agents was proposed to avoid the systemic side effects. Several experimental studies demonstrated the safety of intraocular infliximab [42]. There are a few case series reporting the effectiveness of infliximab in human eyes. Farvardin et al. [43] showed visual acuity improvement and macular thickness reduction in patients with CNIU. However, intravitreal infliximab causes immunogenic reactions and probably retinotoxicity which may limit its use [44].

Sirolimus

Sirolimus (rapamycin) has potent immunosuppressive, antiangiogenetic and antiproliferative properties. Oral sirolimus was reported to be effective in the treatment of CNIU. However, multiple gastrointestinal and dermatological side effects have been observed [45]. Subsequent experimental intravitreal applications of sirolimus were well tolerated and nontoxic to the retina [46]. Phase I/II studies using different dosages are currently underway and will highlight the effectiveness and safety of intravitreal sirolimus in CNIU [47].

Conclusion

Currently, we are facing a 'boost' of new options in the treatment of CNIU. Whereas for many years, a gap of approved treatments was a dilemma for clinicans, there is now a notable interest from the pharmaceutical industry. Significant efforts are focusing on both more selective interventions using targeted systemic immunomodulation and novel techniques for local sustained drug delivery. As so often in ophthalmology, more well-designed randomized studies are needed to provide the right answer with regard to how to act....more local?

Acknowledgement

D.H. received research funding from TUBITAK (The Scientific and Technological Research Council of Turkey).

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