ABSTRACT.

Intravitreal triamcinolone acetonide (IVTA) has increasingly been applied as treatment for various intraocular neovascular and oedematous diseases. Comparing the various diseases with respect to effect and side-effects of the treatment, the best response in terms of gain in visual acuity (VA) has been achieved for intraretinal oedematous diseases such as diffuse diabetic macular oedema, branch retinal vein occlusion, central retinal vein occlusion and pseudophakic cystoid macular oedema. In eyes with various types of non-infectious uveitis, including acute or chronic sympathetic ophthalmia and Adamantiadis–Behcet’s disease, VA increased and the degree of intraocular inflammation decreased. Some studies have suggested that intravitreal triamcinolone may be useful as angiostatic therapy in eyes with iris neovascularization and proliferative ischaemic retinopathies. Intravitreal triamcinolone may possibly be helpful as adjunct therapy for exudative age-related macular degeneration (AMD), particularly in combination with photodynamic therapy. In eyes with chronic, therapy-resistant ocular hypotony, intravitreal triamcinolone can induce an increase in intraocular pressure (IOP) and may stabilize the eye. The complications of intravitreal triamcinolone therapy include: secondary ocular hypertension in about 40% of the eyes injected; medically uncontrollable high IOP leading to antiglaucomatous surgery in about 1–2% of the eyes; posterior subcapsular cataract and nuclear cataract leading to cataract surgery in about 15–20% of elderly patients within 1 year of injection; postoperative infectious endophthalmitis occurring at a rate of about one per 1000; non-infectious endophthalmitis, perhaps due to a reaction to the solvent agent, and pseudo-endophthalmitis with triamcinolone acetonide crystals appearing in the anterior chamber. Intravitreal triamcinolone injection can be combined with other intraocular surgeries, including cataract surgery, particularly in eyes with iris neovascularization. Cataract surgery performed some months after the injection does not show a markedly elevated complication rate. The injection may be repeated if the resultant benefits decrease after the initial IVTA injection. In non-vitrectomized eyes, the duration of the effect and side-effects of a single intravitreal injection of triamcinolone is about 6–9 months for a dosage of about 20 mg, and about 2–4 months for a dosage of 4 mg. So far, it has remained unclear whether the solvent agent should be removed, and if so, how.

Key words: intravitreal triamcinolone acetonide – diabetic macular oedema – age-related macular degeneration – intraocular pressure – intraocular steroids

Introduction

The pathological proliferation of intraocular tissue, such as retinal pigment epithelium (RPE) cells in proliferative vitreoretinopathy and vascular cells in eyes with ischaemic retinopathies like proliferative diabetic retinopathy, has remained an important problem in clinical ophthalmology. The abnormal proliferation of intraocular cells is often accompanied and stimulated by intraocular inflammation. Besides the intraocular proliferation of cells, defects in the blood–retina barrier due to capillary leakage, with accumulation of fluid in the intraretinal and subretinal spaces of the macula, are other major causes for impaired vision. The reasons for such conditions are numerous, and include diabetic retinopathy, retinal vein occlusions, exudative AMD, perifoveal telangiectasias, pseudophakia, uveitis, ischaemic ophthalmopathy, and chronic pre-phthisical ocular hypotony, to mention only a few. Corticosteroids have been known to reduce intraocular inflammation and tighten the capillary walls, and, depending on the concentration, to suppress proliferation of cells. Consequently, steroids have been used in the treatment for many ocular diseases, applied topically as drops, given systemically or injected into the subconjunctival or sub-Tenon space. Often, however, the intraocular concentrations of steroids have not been high enough to achieve a therapeutic level, or the systemic side-effects have been too pronounced for a prolonged treatment.
In an attempt to overcome this limitation of ocular steroid therapy, various authors have suggested the intravitreal application of steroids to locally suppress intraocular inflammation and to reduce proliferation of cells, particularly in patients with aggressive proliferative vitreoretinopathy and infectious endophthalmitis (Graham & Peyman 1974; Machemer et al. 1979; Machemer et al. 1988; Tano et al. 1980a, b; McCuen et al. 1981; Schindler et al. 1982; Ishibashi et al. 1985; Hida et al. 1986; Chandler et al. 1987; Coats & Peyman 1992; Antoszyk et al. 1993; Machemer 1996). As soluble cortisone is washed out of the eye within approximately 24 hours of a single intravitreal injection (Schindler et al. 1982; Scholes et al. 1985), Machemer (1996) propagated the use of triamcinolone acetonide, which, as a crystalline steroid, has a considerably longer absorption time than an injection of soluble cortisone (Beer et al. 2003; Jonas 2002a; Jonas et al. 2002a; Jonas et al. 2004a, 2004b; Jonas et al. 2004c).

Recent studies have reported the increasing use of IVTA in the treatment of other intraocular proliferative, oedematous and neovascular diseases, such as proliferative vitreoretinopathy (Furino et al. 2003; Jonas et al. 2000, 2003a), proliferative diabetic retinopathy (Jonas et al. 2001a, 2003b), exudative AMD (Challa et al. 1998; Danis et al. 2000; Gillies et al. 2003, 2004; Jonas et al. 2002b, 2003c, 2004a, 2004c; Penfold et al. 1995; Penfold 2002a; Ranson et al. 2002; Spaiade et al. 2003; Wingate & Beaumont 1999), presumed ocular histoplasmosis syndrome (Rechtman et al. 2003), diffuse diabetic macular oedema (Jonas & Söcker 2001; Martidis et al. 2002; Jonas et al. 2003d; Audren et al. 2004; Ciardella et al. 2004; Degeneren et al. 2004; Karacorlu et al. 2004a; Lee et al. 2004; Massin et al. 2004; Micelli et al. 2004; Negi et al. 2004; Sutter et al. 2004), central retinal vein occlusion (Bynoe & Weiss 2003; Degeneren et al. 2003; Greenberg et al. 2002; Jonas et al. 2002a; Ip & Kumar 2002; Ip et al. 2003; Park et al. 2003), branch retinal vein occlusion (Chen et al. 2004a; Jonas et al. 2004d), neovascular glaucoma without or with cataract surgery (Jonas et al. 2001b, 2003e; Jonas & Söcker 2002), chronic pre-phthlial ocular hypotony (Jonas et al. 2001c; Rodriguez et al. 2003), chronic uveitis (Young et al. 2000; Antcliff et al. 2001; Benitez Del Castillo Sanchez & Garcia Sanchez 2001; Martidis et al. 2001; Degeneren & Jonas 2003; Sonoda et al. 2003), persistent pseudophakic cystoid macular oedema (Benhamou et al. 2003; Conway et al. 2003; Jonas et al. 2003f; Karacorlu et al. 2003; Jonas & Kampeter 2005a), perifoveal telangiectasia (Aldredge & Garretson 2003; Martinez 2003), sympathetic ophthalmia (Jonas 2004a), ischaemic ophthal- mopathy (Jonas et al. 2003g), immunologic corneal graft reaction (Jonas 2003i) extensive exudative retinal detachment (Jonas 2004b), radiation-induced macular oedema (Sutter & Gillies 2003a), and for other disorders (Navajas et al. 2003; Scott et al. 2003), such as cystoid macular oedema due to retinitis pigmentosa (Sarativa et al. 2003), endocrine orbitopathy (Rakic et al. 2003) and Vogt-Koyanagi-Harada syndrome (Andreade et al. 2004; Inoue et al. 2004). It has also been applied in combination with intraocular surgery to visualize the vitreous and for other purposes (Wilson et al. 1992; Sakamoto et al. 2002; Burk et al. 2003; Matsumoto et al. 2003; Kimura et al. 2004).

### Exudative age-related macular degeneration treated by intravitreal triamcinolone acetonide

Because exudative age-related macular degeneration is a neovascular and oedematous disease, and as studies have shown that triamcinolone acetonide may have an anti-angiogenetic and anti-oedematous effect, IVTA has been used in some studies for treatment of exudative AMD (Penfold et al. 1995; Challa et al. 1998; Wingate & Beaumont 1999; Danis et al. 2000; Jonas et al. 2002b, 2003c, 2004a, 2004c; 2005a, 2005b, 2005c; Jonas et al. 2005j; Spandau et al. 2005a), as well as clinical reports on the intravitreal use of triamcinolone acetonide for treatment of other causes for subretinal neovascularization, such as in Sorsby’s dystrophy (Peiretti et al. 2005).

Penfold et al. (1995) were the first to inject triamcinolone acetonide intravitreally in an effort to treat exudative AMD medically. Three years later, Challa et al. (1998) evaluated the safety and efficacy of intravitreal triamcinolone after a follow-up of 18 months in patients with exudative AMD considered unsuitable for laser photocoagulation. In the non-randomized clinical pilot study, 30 eyes of 28 patients were treated with an intravitreal injection of triamcinolone (4 mg). Of the 20 eyes with initial visual acuity of 0.10 or better, vision was stabilized in 11 eyes (55%), while six eyes (30%) suffered severe visual loss (six or more lines). Similar results were reported by Danis et al. (2000) in a randomized clinical trial on the effects of intravitreal triamcinolone for exudative AMD, and in other case series studies and non-randomized comparative investigations (Jonas et al. 2002b, 2003c, 2005a, 2005b). One of these studies looked for factors influencing VA after an intravitreal injection of triamcinolone acetonide for treatment of exudative AMD (Jonas et al. 2004c). A post-injection increase in VA was significantly (p < 0.001) and negatively correlated with preoperative VA, and it was significantly (p = 0.035) larger in eyes with RPE detachment than in eyes with minimally classic subfoveal neovascularization. The effect of IVTA on VA in patients with exudative AMD lasted about 6–8 months when a dose of about 20 mg was used. If after that time, VA decreased again, some patients were given a repeated injection of about 20 mg triamcinolone acetonide and achieved a re-increase in VA (Jonas et al. 2004a).

The results of these non-randomized studies partially contradict those of a double-masked, placebo-controlled, randomized clinical study by Gillies et al. (2003), who determined whether a single intravitreal injection of 4 mg of triamcinolone acetonide in patients with classic choroidal neovascularization (CNV) associated with AMD could safely reduce the risk of severe visual loss. They included 151 eyes of patients aged 60 years or older, who had CNV with any classic component, a duration of symptoms of less than
The study population was divided into a study group of 75 eyes, which received intravitreal triamcinolone acetonide, and a control group of 76 eyes, which did not have treatment. The development of severe loss of vision of 30 or more letters by survival analysis on an intention-to-treat basis was the main outcome measure. Gillies et al. (2003) did not find any significant difference between the two groups in terms of development of severe visual loss during the first year of the study. In both groups, the 12-month risk of severe visual loss was 35%. The change in size of the neovascular membranes, however, was significantly less in eyes receiving triamcinolone acetonide than in those receiving placebo 3 months after treatment, although no difference was noted after 12 months. Gillies et al. (2003) concluded that a single dose of 4 mg intravitreal triamcinolone had no effect on the risk of loss of VA during the first year of the study, despite a significant anti-angiogenic effect found 3 months after treatment. Although there were differences between the studies in the type of subfoveal neovascularization, the dosage of triamcinolone acetonide, and the timing of the follow-up examinations, the randomized controlled study by Gillies et al. (2003) may represent the landmark study that cautions against the use of triamcinolone acetonide as monotherapy for exudative AMD.

Spaide et al. (2003) were the first to report on the combination of IVTA and photodynamic therapy (PDT) in the treatment of exudative AMD. Their study included 26 eyes with exudative AMD with CNV. Thirteen eyes had already received PDT and experienced visual loss after the treatment. Thirteen additional eyes had not been treated with PDT prior to inclusion into the study. In the study, all patients were treated with PDT, immediately followed by an intravitreal injection of 4 mg of triamcinolone acetonide. The need for re-treatment was based on fluorescein angiographic evidence of leakage at 3-month follow-up intervals. Of the 13 patients who received the combination treatment as first procedure, the mean change in VA at 3 months follow-up was an improvement of 1.9 lines, and four eyes (30.8%) had an improvement of at least three lines. Two patients (15.4%) required re-treatment at 3 months. At the 6-month follow-up, available for 12 of the 13 patients, the mean change in VA from baseline was an improvement of 2.4 lines, four patients (33%) had an improvement of at least three lines and one patient required re-treatment. At both time-points, VA was significantly greater than at baseline (p = 0.023 and p = 0.007) at the 3-month and 6-month time-points. Among the 13 patients who had already undergone PDT treatment prior to inclusion in the study, the mean change in VA from baseline to the 3-month follow-up was 0.31 lines and one patient (7.7%) had an improvement of at least three lines. At the 6-month follow-up, available for 11 patients, the mean change in VA from baseline was 0.1 lines and one patient (9.1%) experienced an improvement of three or more lines. None of the patients required re-treatment at 3 or 6 months. At the 3-month and 6-month time-points, the VA did not significantly differ from baseline. The authors concluded that, although the number of patients in their pilot study was limited, the improvement in acuity and the lack of fluorescein leakage in these patients may suggest a viable combination therapy of photodynamic therapy with intravitreal triamcinolone acetonide, particularly when used as first-line therapy.

In a similar study by Rechtman et al. (2004), IVTA as an adjunctive treatment to PDT with verteporfin for new subfoveal CNV in AMD was evaluated in 14 patients who had received IVTA within 6 weeks of their first PDT treatment and who had follow-up periods of 1 year or longer. Eleven patients received one initial combined treatment and three received an additional combined treatment after 6 months. Median follow-up was 18 months (range 12–25 months). Overall, 7% of the patients gained by 30 or more letters, 50% of the patients maintained stable vision, 14% patients lost 15–29 letters, and 29% of the patients lost 30 or more letters. The mean greatest lesion diameter increased from 2580 ± 1088 μm to 3946 ± 1503 μm (p = 0.01). The mean number of PDT treatments during the first year was 2.57. The authors concluded that IVTA with PDT in patients with exudative AMD was found to be relatively safe and had reasonable results for lesions with some classic component. In a parallel manner, Roth et al. (2003) treated 43 eyes of 40 patients with subfoveal CNV associated with AMD by a combination of an intravitreal injection of 4 mg triamcinolone, given 1 week prior to PDT. Thirty eyes had received prior PDT with an incomplete response or significant residual subretinal fluid. Thirteen eyes had not received a therapy prior to inclusion in the study. Fluorescein angiography was repeated at 1 month, 3 months and 6 months during follow-up, and PDT was repeated if leakage persisted. During follow-up, none of the patients experienced severe visual loss. Median VA remained at 20/400 at the 6 month follow-up. Resolution of subretinal fluid was seen in 51% of eyes and a decrease in subretinal fluid was noted in an additional 42% of eyes. In a similar study performed by Al-Haddad et al. (2004), two series of 14 consecutive patients presenting with exudative AMD and a chororetinal anastomosis with a pigment epithelium detachment were, respectively, treated with PDT or with PDT 1–3 weeks after an intravitreal injection of 4 mg of triamcinolone acetonide. Minimum follow-up was 3 months, with 11 patients in each group followed for at least 6 months. Mean VA changes at 3 and 6 months were, respectively, a loss of 0.36 and 0.82 lines in eyes in group with only PDT, versus an improvement of 0.86 and 0.09 lines in eyes with the combination treatment. The authors inferred that intravitreal injection of triamcinolone acetonide followed by PDT may be a better therapeutic option than PDT alone in the management of exudative AMD associated with chororetinal anastomosis. A similar experience was presented by Degerring & Jonas (2005). The most extensive studies presented so far have been carried out by Augustin et al. (2005a, 2005b), who observed an improvement in VA after a combined treatment of IVTA with PDT. (Arevalo et al. 2005) performed an indocyanine green-mediated photothermolysis with IVTA for subfoveal CNV in AMD and concluded that combined indocyanine green-mediated photothermolysis with intravitreal TA may provide stability or improvement in VA and fundus findings in CNV.

The studies mentioned above were reason to initiate multicentre studies to evaluate the triamcinolone/photodynamic therapy combined treatment (the VISTA trial, led by Rick Spaide; the VERTACL trial, led by Karl Csaky at...
the National Eye Institute; and a third trial funded by a pharmaceutical company). Recent estimates suggest that about 70–90% of all verteporfin photodynamic treatments for exudative macular degeneration are combined with an intravitreal injection of triamcinolone acetonide.

Diffuse diabetic macular oedema and proliferative diabetic retinopathy treated by intravitreal triamcinolone acetonide

Recent studies have suggested that IVTA may be useful to temporarily increase VA in patients with diffuse diabetic macular oedema (Jonas & Söfler 2001; Martidis et al. 2002; Bandello et al. 2003; Jonas et al. 2003d; Jonas et al. 2005b; Jonas et al. 2005g; Kytö et al. 2005; Audren et al. 2004; Ciardella et al. 2004; Degenring et al. 2004; Islam et al. 2004; Karacorlu et al. 2004a; Lam et al. 2004a; Lee et al. 2004; Massin et al. 2004; Micelli et al. 2004; Negi et al. 2004; Ozkiris et al. 2004a; Sutter et al. 2004; Bakri & Beer 2004; Krepler et al. 2005a; Sorensen et al. 2005). Patients in study groups receiving IVTA compared with patients in control groups without intravitreal injections of triamcinolone acetonide showed a significant increase in VA during follow-up. The most convincing evidence for the effect of IVTA in the treatment of diabetic macular oedema comes from a recent randomized trial by Sutter et al. (2004). They performed a prospective, double-masked, placebo-controlled, randomized clinical trial on 69 eyes of 43 patients, with 34 eyes randomized to receive intravitreal triamcinolone acetonide (4 mg) and 35 eyes randomized to receive a placebo injection. Eighteen of 33 eyes (55%) treated with triamcinolone gained five or more letters in best corrected VA compared with five of 32 eyes (16%) treated with placebo (p = 0.002). Macular oedema was reduced by one or more grades as determined by masked semiquantitative contact lens examination in 25 of 33 treated eyes (75%) versus five of 32 untreated eyes (16%; p < 0.0001). Optical coherence tomography showed a mean reduction of central retinal thickness of 152 μm in the 21 treated eyes that were examined, compared with a reduction of 36 μm in the 20 placebo-treated eyes. Infectious endophthalmitis developed in one triamcinolone-treated eye that was treated adequately without loss of VA. The authors concluded that in the short-term, intravitreal triamcinolone is an effective and relatively safe treatment for eyes with diabetic macular oedema that have failed laser treatment.

A similar result was reported from a recent intravitreal injection treatment of patients with bilateral diabetic macular oedema who received a unilateral intravitreal injection of about 20 mg triamcinolone acetonide in the more severely affected eye (Jonas et al. 2004c). Compared with the contralateral non-treated eyes, VA in the injected eyes increased significantly (p < 0.001) by 3.0 ± 2.6 Snellen lines. In the contralateral eyes, differences between baseline VA and VA measured at any of the re-examinations during follow-up were not significant (p > 0.10). Correspondingly, gain in VA was significantly (p < 0.05) higher in the injected eyes for the measurements obtained up to 4 months after baseline. In the study group, from a peak in VA at about 2–6 months after the injection, VA decreased significantly (p = 0.001) towards the end of the follow-up, at which VA was still higher, although not significantly so (p = 0.18), than at baseline. In the control group, VA at the end of follow-up was lower, although not significantly so (p = 0.26), than at baseline. The study confirmed another recent investigation with a similar study design carried out by Massin et al. (2004). Their study included 15 patients with bilateral diabetic macular oedema unresponsive to laser photocoagulation. Performing a unilateral injection of 4 mg triamcinolone acetonide, Massin et al. (2004) found a significant reduction in macular thickness. Perhaps due to the smaller number of patients involved in their study, or to the smaller dosage of triamcinolone acetonide injected intravitreally, Massin et al. (2004) detected a slight, although not statistically significant, increase in VA in the injected eyes compared with the contralateral eyes without intravitreal injection.

Using a dosage of about 20 mg triamcinolone acetonide, the increase in VA was most marked during the first 3–6 months after the injection, and was observable for a period of about 6–9 months (Jonas et al. 2004b). Using a dosage of 4 mg triamcinolone acetonide, the duration of a reduction in the macular thickness as measured by optical coherence tomography (OCT) was less than 6 months (Massin et al. 2004). At the end of the follow-up, VA measurements returned to baseline values, with no significant difference between baseline values and the measurements obtained at the end of the follow-up. Another clinical investigation evaluated which factors influence change in VA after intravitreal injection of triamcinolone acetonide as treatment for diffuse diabetic macular oedema (Jonas et al. 2005d). A multiple linear regression analysis revealed that improvement in VA after the intravitreal injection of triamcinolone acetonide was significantly correlated with a lower degree of macular ischaemia (p < 0.001), higher preoperative VA (p = 0.002) and a higher degree of macular oedema. Change in VA after the intravitreal triamcinolone injection was statistically independent (p > 0.20) of age, gender, and pseudophakia.

In a retrospective, interventional, non-comparative case series study, Ciardella et al. (2004) performed an intravitreal injection of 4 mg of triamcinolone acetonide in 30 eyes of 22 consecutive patients with diabetic macular oedema refractory to laser treatment. Mean VA improved from 0.17 ± 0.12 at baseline to 0.34 ± 0.18, 0.36 ± 0.16 and 0.31 ± 0.17 at the 1, 3 and 6 months, respectively. Mean OCT macular thickness measurements decreased from 476 ± 98 μm at baseline to 277 ± 97 μm, 255 ± 96 μm and 331 ± 147 μm at 1, 3 and 6 months, respectively. Twelve eyes received two, seven eyes received three, and two eyes received four IVTA injections. The mean interval between the first and second IVTA injections was 5.7 ± 2.7 months and between the second and third was 5.7 ± 3.3 months. Hard exudates were present in the macula at baseline in all eyes. Progressive reduction in the number and size of the hard exudates was noted after IVTA in all patients. Intraocular pressure was raised above 21 mmHg in 12 (40%) of 30 eyes. Two eyes developed posterior subcapsular cataract and two developed vitreous haemorrhage. The authors concluded that IVTA is a promising treatment for patients with diabetic macular oedema refractory to laser treatment. Similar results were reported in studies performed by Micelli et al.
Within 2 weeks of the injection, vision improved from counting fingers at 1 metre to 20/50, and from counting fingers at 4 metres to 20/40. This improvement was accompanied by resolution of optic disc swelling and macular oedema. Vision remained stable in both eyes at 20/40 for 8 months of follow-up.

So far, it has remained unclear whether and how intensively triamcinolone acetonide crystals injected into the vitreous body may influence the vitreo-retinal interface. One may suspect that, due to their weight, the crystals may lead to a posterior vitreous detachment if the vitreous was not already detached prior to the injection. The disadvantage of a posterior vitreous detachment is the possibly increased risk of rhegmatogenous retinal detachment. So far, however, there have been no reports in the literature on a markedly elevated rate of retinal rhegmatogenous detachments as in the follow-up of patients who received an IVTA injection (Jonas et al. 2004f).

The advantage of a posterior vitreous detachment in patients with diabetic retinopathy may be a reduction of macular oedema, as suggested by studies on pars plana vitrectomy in patients with diffuse diabetic macular oedema, and a decreased risk of retinovitreal proliferations.

Interestingly, triamcinolone acetonide has not been found in clinically significant concentrations in the serum shortly after intravitreal injections of about 20 mg triamcinolone acetonide (Degenerg & Jonas 2004a). This agrees with clinical observations that the metabolic control of patients with diabetes mellitus is not markedly influenced by the intraocular application of the steroid.

As a possible alternative to the intravitreal application of triamcinolone acetonide, using the posterior sub-Tenon injection has been reported. Bakri & Kaiser (2005) included 63 eyes of 50 patients with persistent clinically significant diabetic macular oedema involving the centre of the fovea 3 or more months after one or more treatments of focal macular photocoagulation. Exclusion criteria were a history of corticosteroid-responsive IOP rise, intraocular surgery within 3 months, and any laser treatment within 1 month. All patients received a posterior sub-Tenon injection of 40 mg triamcinolone acetonide. Mean VA significantly improved from 20/80 to 20/50 at 1 month, then stabilized to 20/65 at 3 months, 20/68 at 6 months, and 20/63 at 12 months. Complications were rare, with a transient significant rise in IOP at the 3-month evaluation and ptosis in two patients. In view of the statistically significant improvement in VA at 1 month after the sub-Tenon injection, future studies should directly compare the intravitreal application with the sub-Tenon application for safety and efficacy. In a similar manner, sub-Tenon injections of triamcinolone acetonide were reported to be effective in the treatment of polypoidal choroidal vasculopathy (Okubo et al. 2005). Without doubt, the sub-Tenon method is less invasive and, therefore, may possess a higher level of safety compared with the intravitreal injection. A recent pharmacokinetic study showed that the intravitreal application of triamcinolone acetonide leads to significantly higher concentrations than the sub-Tenon application (Inoue et al. 2004).

Pars plana vitrectomy for proliferative diabetic vitreoretinopathy combined with intravitreal triamcinolone acetonide

Due to the anti-inflammatory and anti-angiogenic effects of triamcinolone acetonide, the latter was used in combination with pars plana vitrectomy in patients with proliferative diabetic retinopathy. A pilot case series study including 29 patients suggested that intravitreal injection of crystalline cortisone with most of the vehicle removed may be well tolerated (Jonas et al. 2001a). A subsequent non-randomized, comparative investigation consisted of a study group of 32 eyes undergoing pars plana vitrectomy with intravitreal triamcinolone acetonide, and a control group of 32 eyes, which was matched with the study group for preoperative and intraoperative parameters, and which underwent pars plana vitrectomy for proliferative diabetic retinopathy without intravitreal injection of triamcinolone acetonide (Jonas et al. 2003b). The study and control groups did not vary significantly in the rate of postoperative retinal detachment,
Pars plana vitrectomy for proliferate vitreoretinopathy combined with intravitreal triamcinolone acetonide

In a pilot study, intravitreal triamcinolone acetonide was applied in combination with pars plana vitrectomy for treatment of proliferative vitreoretinopathy (Jonas et al. 2000). During the follow-up (mean 1.64 months), intraocular inflammation and postoperative pain were significantly lower in the study group. The study suggested that IVTA with most of the vehicle removed may not be toxic to intraocular structures, and that it reduces postoperative intraocular inflammation. However, in a subsequent study, the re-detachment rate was about 30% (Jonas et al. 2003a), so that up to now, IVTA has not generally been shown to be markedly useful in combination with pars plana vitrectomy for proliferative vitreoretinopathy. Enaida et al. (2003) used triamcinolone acetonide in combination with pars plana vitrectomy. They found no significant differences in the frequency of improved vision after surgery, rate of IOP > 21 mmHg after the operation, and frequency of additional filtering surgery between the study group (with triamcinolone acetonide; n = 94 eyes) and the control group (without triamcinolone acetonide; n = 83 eyes). The study group had a slightly lower incidence of re-operations caused by preretinal fibrous membrane formation than the control group. If we summarize the available clinical reports, it remains unclear whether IVTA suppresses the proliferation of RPE cells in vivo.

In a previous experimental study, triamcinolone acetonide inhibited the proliferation of rabbit dermal and conjunctival fibroblasts in cell cultures at 150 mg triamcinolone acetonide/litre, but paradoxically increased the proliferation almost two-fold at concentrations of 1–30 mg triamcinolone acetonide/litre under identical culture conditions (Blumenkranz et al. 1984). In contrast, Chandler et al. (1987) observed a protective effect of intravitreal triamcinolone acetonide, when injected simultaneously with, or prior to, fibroblasts into the vitreous cavity of rabbit eyes, in reducing the rate of retinal detachment.

Pars plana vitrectomy combined with intravitreal triamcinolone acetonide to visualize membranes and vitreous body

In several studies, intraocular triamcinolone acetonide was used intraoperatively during pars plana vitrectomy to visualize the inner limiting membrane, epiretinal membranes and remnants of the vitreous base. Various authors have reported the use of triamcinolone acetonide in peeling of the internal limiting membrane (Kimura et al. 2004; Chen et al. 2005; Karacorlu et al. 2005; Spaide & Fisher 2005). Yamamoto et al. (2004a) used intravitreal triamcinolone acetonide in six eyes during vitrectomy in highly myopic eyes with retinal detachment due to a macular hole. After separation of the posterior hyaloid and removal of any visible epiretinal membrane, triamcinolone acetonide was injected over the posterior pole to detect any remaining epiretinal membranes. The authors concluded that using triamcinolone acetonide during vitrectomy may facilitate both removal of the epiretinal membrane around the macular hole and separation of the residual vitreous cortex from the retina in highly myopic eyes with retinal detachment. In a similar setting, the same authors used intravitreal triamcinolone acetonide and trypan blue for pars plana vitrectomy for macular holes (Yamamoto et al. 2004b). They found that double visualization of the posterior vitreous cortex and inner limiting membrane may facilitate the separation of the posterior vitreous cortex from the retina and removal of the inner limiting membrane around the macular hole in patients with idiopathic macular holes.

Cataract surgery in eyes with iris neovascularization combined with intravitreal triamcinolone acetonide to suppress neovascularization

In patients with dense cataract and iris neovascularization due to ischaemic retinopathies, the lens opacification prevents a transpupillary laser coagulation of the retina. An intraocular intervention such as cataract surgery will, however, lead to a marked postoperative inflammation, if iris neovascularization is additionally present. In that clinical situation, cataract surgery has been combined with an IVTA injection (Jonas & Söker 2002). In the postoperative period, VA increased, and, without additional retinal ablative treatments, iris neovascularization markedly regressed within the first 5 weeks after surgery. The study suggested that IVTA may be a useful adjunctive treatment tool in eyes with iris neovascularization undergoing cataract surgery, and that it may also have an anti-angiogenic effect.

Cataract surgery combined with intravitreal triamcinolone acetonide or after intravitreal triamcinolone acetonide

Cataract is one of the most common ophthalmological diseases in the elderly population. It is, therefore, not unusual for cataract to be present in eyes that also show other age-related disorders, such as diabetic retinopathy, exudative AMD and retinal vein occlusions. As these diseases may be treatable by intraocular injections of triamcinolone acetonide, and because intraocular triamcinolone acetonide by itself may further increase any pre-existing lens opacification, it may be...
useful to combine an IVTA injection with cataract surgery. In a recent clinical investigation, frequencies of postoperative infectious endophthalmitis, wound leakage or other corneal wound healing problems, persisting corneal endothelial decompensation, rhegmatogenous retinal detachment, marked postoperative pain, or a clinically significant decentration of the intraocular lens (IOL) did not vary between a study group of 60 eyes undergoing cataract surgery with implantation of a posterior chamber lens and additionally receiving an intravitreal injection of about 20 mg triamcinolone acetonide, and a control group of 290 eyes consecutively receiving IVTA without additional intraocular cataract surgery (Jonas et al. 2005c). It was concluded that for a mean follow-up of about 9 months, the frequency and amount of complications arising from IVTA injection, such as increased IOP, do not markedly differ whether or whether not the injection is combined with a standard cataract surgery. A similar conclusion was drawn in a study by Lam et al. (2004b) on 19 eyes of 15 consecutive diabetes patients with cataract and diabetic macular oedema, in which phacoemulsification with concurrent intravitreal injection of 4 mg triamcinolone acetonide appeared to be a safe option for managing diabetes patients with cataract and diabetic macular oedema. Yamakiri et al. (2004) used intracameral triamcinolone acetonide in six eyes to visualize the removal of vitreous from the anterior chamber in complicated cataract surgery. Because steroids applied in high dosages may lead to several changes, such as alterations in collagenous structures as well as in immunological status, intraocular surgery performed after an intravitreal application of triamcinolone acetonide may have an unusual spectrum of complications. One case series included 22 patients presenting with cataract which had progressed after a single or repeated intravitreal injection of about 20 mg of triamcinolone acetonide for treatment of exudative AMD or diffuse diabetic macular oedema (Jonas et al. 2004g). During routine phacoemulsification surgery, an intraoperative dialysis of the lens zonules with vitreous prolapse occurred in one (4.5%) eye. During the postoperative follow-up, an optically significant decentration of the IOL or infectious endophthalmitis were not encountered in any patient.

It was concluded that cataract surgery after single or repeated intravitreal injections of about 20 mg triamcinolone acetonide may not harbour a markedly elevated frequency or a markedly changed profile of the complications of standard cataract surgery.

### Pseudophakic cystoid macular oedema treated by intravitreal triamcinolone acetonide

Phacoemulsification with implantation of an IOL can be complicated by severe postoperative cystoid macular oedema. The latter has usually been treated by topical, peribulbar and systemic application of steroids or non-steroidal anti-inflammatory agents. Recently, IVTA has been used in the treatment of persisting pseudophakoid cystoid macular oedema (Benhamou et al. 2003; Conway et al. 2003; Jonas et al. 2003f; Karacorlu et al. 2003; Boscia et al. 2005; Sorensen et al. 2005). Patients who developed cystoid macular oedema after cataract surgery and who received an IVTA injection showed an increase in VA from 0.26 ± 0.13 to a mean best VA of 0.60 ± 0.19 (Jonas et al. 2003f). There was no clear tendency suggesting a decrease in VA towards the end of the follow-up period. The increase in VA was statistically independent of the time interval between cataract surgery and the intravitreal injection of triamcinolone acetonide.

### Retinal vein occlusions treated by intravitreal triamcinolone acetonide

Intravitreal triamcinolone acetonide has recently been applied in the treatment of retinal vein occlusions (Scott & Ip 2005).

#### Branch retinal vein occlusion

Due to the anti-oedematous and anti-angiogenic effects shown in experimental investigations and clinical studies, IVTA has also been used in pilot studies on branch retinal vein occlusions (Chen et al. 2004a; Jonas et al. 2004d; Ozkiris et al. 2005a; 2005b; Yerpremyan et al. 2005). A recent prospective, non-randomized clinical intervention study included 10 patients with branch retinal vein occlusion (two eyes with ischaemic-type branch retinal vein occlusion; eight eyes with non-ischaemic occlusion), who received an intravitreal injection of 20–25 mg of triamcinolone acetonide, and 18 patients in a control group without IVTA. The patients in the study group experienced a significant increase in VA, while the patients in the control group did not show a significant change in VA during the follow-up. Comparing the study and control groups with one another, the gain in VA was seen to be significantly more marked in the study group for the measurements obtained 1 and 2 months after baseline (Jonas et al. 2004d). This confirmed another study in which IVTA reduced macular oedema in eyes with branch central retinal vein occlusion (Jonas et al. 2004b). In a study by Yerpremyan et al. (2005), which included 12 eyes with severe cystoid macular oedema secondary to acute branch retinal vein occlusion, VA improved by three lines or more in 42% of patients at 1 week, 50% at 1 month, and 42% at last follow-up during a mean whole follow-up of 15.3 months. All eyes showed reduction of foveal thickness as measured by OCT. Eight eyes developed recurrent cystoid macular oedema at an average of 5.5 months after the initial IVTA injection. Ten eyes required additional intervention during the follow-up period. The authors concluded that early treatment of severe cystoid macular oedema due to branch retinal vein occlusion with IVTA is effective in reducing foveal thickness as measured by OCT and temporarily improving VA. Ozkiris et al. (2005b) evaluated the efficacy of the IVTA injection on persistent macular oedema in branch retinal vein occlusion that failed to respond to previous laser photocoagulation. During a mean follow-up period of 6.2 ± 1.0 months, the best corrected logMAR (logarithm of minimal angle of resolution) value for improved significantly (p < 0.001), from 1.01 ± 0.16 at baseline to 0.55 ± 0.22 at 1 month after the injection, to 0.56 ± 0.22 at 3 months after the injection, and to 0.62 ± 0.22 at the end of follow-up. The authors concluded that IVTA application may be helpful in patients with branch retinal vein occlusion that does not respond to laser photocoagulation.
Central retinal vein occlusion

Cystoid macular oedema is one of the major causes of decreased vision in patients with central retinal vein occlusion. With the exception of retinal laser coagulation in eyes with early iris neovascularization, other therapeutic options have not been proven effective in increasing VA after central retinal vein occlusion (Hayreh et al. 1990; Central Vein Occlusion Study Group 1995; Hayreh 2003). Recent studies on IVTA have also addressed macular oedema due to central retinal vein occlusion (Greenberg et al. 2002; Ip & Kumar 2002; Jonas et al. 2002a, 2005f; Bynoe & Weiss 2003; Degener et al. 2003; Ip et al. 2003, 2004; Park et al. 2003; Bashshur et al. 2004; Karacorlu et al. 2004c; Lahy et al. 2004). Bashshur et al. (2004) evaluated the efficacy of IVTA in the management of persistent macular oedema secondary to non-ischaemic central retinal vein occlusion. Twenty consecutive patients with a 3–4-month history of non-ischaemic central retinal vein occlusion received a single intravitreal injection of 4 mg of triamcinolone acetonide. The follow-up period ranged from 10 to 12 months. Treated patients were compared with a retrospectively matched group of patients managed with observation only. The study group showed a significantly better outcome than the control group. At the final follow-up, the treated group had a mean VA of 20/37, while the observation group had a mean VA of 20/110 (p = 0.001). A total of 60% of treated patients had a final VA of 20/40 or better versus only 20% in the observation group (p = 0.01); 40% of untreated patients had a final VA < 20/200, while none of the treated patients did (p < 0.001). At final follow-up, 75% of treated patients had complete resolution of macular oedema on clinical examination versus only 20% of the untreated patients (p < 0.001). Two of the treated patients had recurrence of macular oedema at 6 months, and three had elevated IOP. The authors concluded a treatment benefit from intravitreal triamcinolone in terms of VA and macular oedema for non-ischaemic central retinal vein occlusion.

In a similar study, Ip et al. (2004) found that eyes with non-ischaemic central retinal vein occlusion demonstrated a significant improvement in VA, whereas eyes with ischaemic central retinal vein occlusion showed a tendency towards a VA improvement. They inferred that IVTA appears to be a possibly effective treatment in some patients with macular oedema associated with central retinal vein occlusion, and that patients with non-ischaemic central retinal vein occlusion may respond more favourably than patients with ischaemic central retinal vein occlusion. In another prospective, comparative, non-randomized, clinical interventional study on 11 eyes with central retinal vein occlusion receiving an injection of IVTA, compared with six eyes of a control group without an IVTA injection, the gain in VA was significantly (p = 0.003) higher in the study group (own data). This confirms other reports on the beneficial effects of intravitreal triamcinolone acetonide on macular oedema and VA in patients with central retinal vein occlusion (Greenberg et al. 2002; Ip & Kumar 2002; Jonas et al. 2002a; Bynoe & Weiss 2003; Degener et al. 2003; Ip et al. 2003; Park et al. 2003; Krepler et al. 2005b). The results additionally suggested that the increase in VA after the injection of IVTA may not last permanently in eyes with central retinal vein occlusion. After a significant increase in VA in the first 4 months after the injection, VA showed a tendency to decline towards the end of follow-up. Correspondingly, final VA and preoperative VA did not vary significantly. In a recent study by Krepler et al. (2005c), the significant increase in VA after an intravitreal injection of 4 mg triamcinolone acetonide persisted for 6 months. In a similar manner, Williamson & O’Donnell (2005) found that IVTA in a dosage of 2 mg was very effective in reversing cystoid macular oedema and improving VA in recent-onset non-ischaemic central retinal vein occlusion in the first 6 months, but this was not sustained at 1 year. Another positive effect of IVTA in eyes with ischaemic central retinal vein occlusion may be a direct or indirect anti-angiogenic effect, possibly decreasing the risk of neovascularization (Folkman & Ingber 1987; Wilson et al. 1992; Danis et al. 1996; Penfold et al. 2000, 2001, 2002; Ciulla et al. 2001, 2003; Penn et al. 2001; Carroll et al. 2002; Wang et al. 2002; Gao et al. 2004).

Uveitis treated by intravitreal triamcinolone acetonide

Chronic intraocular inflammation such as chronic uveitis can lead to cystoid macular oedema, papillodema and vitreous opacities temporarily or permanently reducing VA. Chronic uveitis is usually treated by topical or systemic application of steroids. Topical treatment, however, has often not been sufficiently effective in suppressing intraocular inflammation and reducing cystoid macular oedema. Systemic treatment with steroids inevitably leads to secondary side-effects, such as systemic suppression of the whole immune system and Cushing’s syndrome. Based on the clinical experience gathered for the use of IVTA for other indications, triamcinolone acetonide has also been applied in eyes with chronic, therapy-resistant uveitis (Young et al. 2000; Antcliff et al. 2001; Andrade et al. 2004; Karacorlu et al. 2004d; Kramer et al. 2004; Larsson et al. 2005b; Marullo et al. 2004; Pathengay et al. 2004). These diseases include Adamantiadis–Behcet’s disease (Karacorlu et al. 2004d; Kramer et al. 2004). Three patients with acute severe exacerbations of non-infectious panuveitis and vitritis due to Adamantiadis–Behcet’s disease were reported by Kramer et al. (2004), who treated them with IVTA injections alone or as an adjunct to systemic immunosuppressive agents. They observed a rapid clearance of the vitreous inflammation with improvement in VA 1–2 weeks after the injection. The effect lasted 2–6 months, with the shortest duration taking place in a vitrectomized eye. Repeated injections were required in all patients. Karacorlu et al. (2004d) performed an intravitreal injection of triamcinolone acetonide (4 mg) in 10 eyes of 10 patients with cystoid macular oedema due to Behcet’s disease. At the 1-month, 3-month and 6-month follow-ups, foveal thickness was significantly reduced. None of the eyes had lost vision at 1 month, and eight eyes (80%) showed an improvement in VA. At the 3-month and 6-month follow-ups,
three eyes (30%) remained stable and the other eyes had maintained the improved acuity.

Other diseases for which IVTA has been used are Eales’ disease (Pathengay et al. 2004), Vogt-Koyanagi-Harada syndrome (Andrade et al. 2004), acute sympathetic ophthalmia (Ozdemir et al. 2005a), chronic sympathetic ophthalmia (Jonas 2004a), adult Coats’ disease (Jarin et al. 2005), and other reasons (Marullo et al. 2004).

Other conditions treated by intravitreal triamcinolone acetonide

Other indications for which the intravitreal use of triamcinolone acetonide has been reported are ocular ischaemic syndromes (Jonas et al. 2003g; Klais & Spaide 2004) and cystoid macular oedema due to retinitis pigmentosa (Sallum et al. 2003; Ozdemir et al. 2005b).

A recent report on a patient presenting with longstanding cystoid macular oedema after penetrating keratoplasty suggests that intravitreal triamcinolone acetonide, like phacoemulsification, may be an additional tool in the treatment of longstanding, therapy-resistant cystoid macular oedema after intracocular surgery (Jonas et al. 2005a). An additional advantage of intraocular steroids in the treatment of cystoid macular oedema after penetrating keratoplasty may be the suppression of an immunological graft reaction, as described recently (Reinhard & Sundmacher 2002; Jonas 2003).

Intravitreal injection of triamcinolone acetonide has also been applied as treatment for foveal telangiectasia. In two reports, IVTA increased VA, while in a third report only one of two patients experienced an increase in VA (Alldredge & Garretson 2003; Jonas & Kamppeter et al. 2005c; Martinez 2003). Smithen & Spaide (2004) reported a combined treatment of PDT with verteporfin and IVTA injection (4 mg) for subfoveal neovascularization secondary to bilateral idiopathic juxtapapillary telangiectasis. Leakage in the late phase of fluorescein angiography resolved, with attenuation of telangiectatic vessels and an improvement in VA from 20/200 to 20/50. At 9 months post-treatment, recurrent leakage was treated with repeated PDT and intravitreal triamcinolone. One year after initial presentation, VA was 20/60 with no leakage on fluorescein. The authors concluded that combined treatment with PDT and IVTA resulted in regression of a subfoveal neovascular membrane and improvement in VA during the course of follow-up.

In contrast to ocular hypertension, which can often successfully be cured by a whole array of antiglaucomatous medical and surgical methods, progressive ocular hypotony can be an untreatable condition, eventually leading to blindness and painful phthisis bulbi. In an attempt to use a side-effect of steroids as a desired effect, triamcinolone acetonide was injected intravitreall in three eyes with longstanding pre-phthihsical ocular hypotony (Jonas et al. 2001c; Rodriguez et al. 2003). In all three patients, IOP and VA increased after the injection associated with a stabilization of the eyes. It may suggest that in some eyes with longstanding pre-phthihsical ocular hypotony, an IVTA injection can help to increase IOP and stabilize the eye.

The possibly anti-angiogenic effect of triamcinolone acetonide, which has been postulated by experimental investigations as well as by clinical studies on patients receiving triamcinolone acetonide for treatment of exudative AMD, was observed in an investigation on 14 eyes with neovascular glaucoma due to proliferative diabetic retinopathy or ischaemic central retinal vein occlusion (Jonas et al. 2001a, 2003c; Jonas & Stöffer 2002). All patients received an intravitreal injection of about 20 mg acetonide as the only procedure (n = 4 eyes), or in combination with additional procedures such as goniosynchytosis (n = 1) and transcleral peripheral retinal cryocoagulation. Postoperatively, the degree of iris neovascularization decreased significantly (p = 0.02). In the four patients for whom the intracameral cortisone injection was the only procedure performed, mean IOP decreased from 26.5 ± 12.1 mmHg to 21.75 ± 11.3 mmHg.

Complications of intravitreal injections of triamcinolone acetonide

Secondary ocular hypertension, secondary steroid-induced, open-angle glaucoma

Clinical studies on IVTA have shown several side-effects of the therapy. One of the two most common side-effects of IVTA concerns the steroid-induced elevation of IOP (Wingate & Beaumont 1999; Bui Quoc et al. 2002; Bakri & Beer 2003; Jonas et al. 2003b, 2004h; Jonas et al. 2004i; Jonas et al. 2005i; Agrawal et al. 2004; Chan et al. 2004; Detry-Morel et al. 2004; Lee et al. 2004; Levy et al. 2004; Singh et al. 2004; Smithen et al. 2004; Ozkiris & Erklic 2005). A recent prospective, clinical, interventional, comparative, non-randomized study included 260 consecutive patients (293 eyes) receiving an intravitreal injection of 20–25 mg triamcinolone acetonide as treatment for diffuse diabetic macular oedema, exudative AMD, retinal vein occlusions, uveitis, and cystoid macular oedema (own data). Intraocular pressure readings > 21 mmHg, > 30 mmHg, > 35 mmHg and > 40 mmHg, respectively, were measured in 94 (36.2%) patients, 22 (8.5%) patients, 11 (4.2%) patients, and four (1.5%) patients, respectively. Triamcinolone-induced elevation of IOP could be treated by antiglaucomatous medication in all but three (1.0%) eyes, for which filtering surgery became necessary. About 40% of the patients developed a secondary ocular hypertension, starting about 1 week after the injection in a few eyes, and occurring in most eyes, which developed ocular hypertension, about 1–2 months after the intravitreal injection of 20–25 mg triamcinolone acetonide. At this dosage, the increase in IOP last about 7–9 months, after which the IOP measurements return to the normal range without any further antiglaucomatous medication. In a multiple regression analysis, younger age was a significant factor contributing to the triamcinolone acetonide-induced increase in IOP.

 Unexpectedly, the post-injection rise in IOP did not vary significantly between patients with a pre-injection diagnosis of chronic open-angle glaucoma and patients without a history of glaucoma. So far, the reason for this unexpected finding has remained unclear. Either the number of patients in the glaucoma group was too small to show a statistically significant difference between the two groups, or the pre-injection antiglaucomatous treatment in the glaucoma group prevented a higher increase in IOP, or the mega-dosage of 20–25 mg injected IVTA obscured the baseline differences between the glaucoma group and the
non-glaucomatous group. If further studies confirm the finding, one may infer that, depending on the clinical situation and the severity of the macular disease, diagnosis of chronic open-angle glaucoma may not be a major contraindication against the IVTA injection.

Diagnosis of diabetes mellitus or the presence of a clinically significant diffuse diabetic macular oedema did not influence the response of IOP to the injection. This may agree with previous randomized clinical trials, in which diabetes mellitus was not a major risk factor for glaucoma (Palmberg 2001). From a clinical point of view, diagnosis of diabetes mellitus may not be a contradiction against an intravitreal application of triamcinolone acetonide, as previous studies have also demonstrated (Jonas & Söfker 2001; Martidis et al. 2002; Jonas et al. 2003; Degenring et al. 2004; Massin et al. 2004).

Interestingly, increase in IOP was associated with an increase in VA. The multifactorial regression analysis revealed that the increase in IOP was significantly associated with a higher gain in VA during follow-up. This finding might be explained by the pathophysiology of leaking retinal capillaries. If the macular capillaries exhibit an increased permeability, the amount of leakage might depend on the transmural pressure gradient as the difference between the pressure in the vessel and the pressure in the space surrounding the vessel (i.e. intraocular pressure). If IOP is elevated, the pressure difference between the intraluminal space and the extraluminal space will be decreased, eventually leading to a smaller amount of fluid leaking through the wall of the vessel. This agrees with previous studies in which elevation of IOP was associated with a decrease in pseudophakic cystoid macular oedema (Civerchia & Balent 1984; Melberg & Olk 1993).

The rise in IOP started at about 1 week after the injection, and the measurements returned to baseline values after about 9 months. These figures are valid for a dosage of 25 mg triamcinolone acetonide. Although not systematically investigated in the present study, many eyes included in the investigation showed ophthalmoscopically visible triamcinolone acetonide crystals in the vitreous for a similar length of time as the increase in IOP lasted. This suggests that when the triamcinolone acetonide crystals have resolved, IOP may return to its baseline level, and that the triamcinolone-induced increase in IOP is reversible. It also concurs with previous studies on the reaction of IOP after topical application of corticosteroids (Becker et al. 1966).

Those patients who received a second injection of 20–25 mg triamcinolone acetonide showed a similar reaction in IOP as after the first injection (Jonas et al. 2004h). This suggests that, if after a first injection IOP remains in the normal range, it might also remain in the normal range after a second injection. Similarly, if IOP increases after the first injection, a similar rise in IOP might be expected after a second injection. So far, there are no reports on a permanent rise in IOP after an IVTA injection.

Comparing studies using different dosages of triamcinolone acetonide for intravitreal injection may suggest that the higher the dosage, the longer the duration of the steroid-induced ocular hypertension (Wingate & Beaumont 1999; Bui Quoc et al. 2002; Bakri & Beer 2003; Jonas et al. 2003h, 2003i, 2004b; Ozkiris et al. 2005b). The figures of the frequency of secondary ocular hypertension may not be directly correlated with the dosage injected. In the study performed by Smithen et al. (2004) on the intravitreal use of 4 mg triamcinolone acetonide, a pressure elevation defined as a pressure ≥ 24 mmHg during follow-up was found in 36 (40.4%) of 89 patients at a mean of 101 ± 83 days after the injection. Of the non-glaucomatous patients with baseline IOP ≥ 15 mmHg, 60.0% experienced an elevation in IOP, compared with only 22.7% of those with baseline pressures < 15 mmHg. Among the glaucoma patients, six of 12 (50%) experienced an elevation in IOP, and this elevation did not correlate with baseline pressure. A total of 32 patients (36.0%) received repeat injections; there was no difference in the incidence of IOP elevation in patients receiving multiple injections versus that in patients receiving a single injection. Pressure elevation was controlled with topical medications in all patients. Using a dosage of 8 mg triamcinolone acetonide, Ozkiris et al. (2005a) detected a transient elevation of IOP > 21 mmHg in 20.8% of eyes. Average IOP rose by 28.5%, 38.2%, 16.7% and 4.2% from baseline at 1, 3, 6 and 9 months, respectively. Kaushik et al. (2004) reported that seven of nine non-glaucomatous patients who received 4 mg intravitreal triamcinolone acetonide for central retinal vein occlusion had a post-injection rise in IOP. One of the patients developed intractable secondary glaucoma requiring removal of the depot corticosteroid by pars plana vitrectomy combined with trabeculectomy. Two patients were controlled only by maximal medical therapy.

If further studies confirm the assumption that the frequency of secondary ocular hypertension after an IVTA injection may not markedly depend on the dosage used, one may assume that relatively low triamcinolone acetonide dosages are already so high that all steroid receptors are occupied. One has to take into account the fact that the eye represents about 0.01% of the body volume. Assuming an equal distribution of triamcinolone acetonide throughout the body, an intravitreal injection of 4 mg is equal to an intralugal injection of 40 g, and an intravitreal injection of 25 mg triamcinolone acetonide is equal to 0.25 kg injected intraglategally.

**Post-injection infectious endophthalmitis**

In recent studies on patients receiving an IVTA injection, the frequency of post-injection infectious endophthalmitis ranged between 0/700 and 8/992 (0.87%) (Benz et al. 2003; Jonas et al. 2003j; Moshfeghi et al. 2003; Nelson et al. 2003; Parke 2003; Jonas & Bleyl 2004). The risk of an infectious endophthalmitis may partially depend on the setting of the injection itself. The studies suggest that if the injection is performed under sterile conditions, the risk may be less.

Histologically, eyes with intravitreal triamcinolone acetonide and infectious endophthalmitis show a marked destruction of the whole globe. The most striking finding can be that some areas show a massive infiltration by granulocytes, while other areas can be almost completely devoid of inflammatory cells (Jonas & Bleyl 2004). Between both areas, there is a sharp demarcation line. This represents a morphallaxia-like histology in which a dense infiltration of granulocytes is sharply demarcated by tissue areas in which inflammatory cells are almost completely missing. Such a histology,
normally characteristic of the demarcation and destruction of necrotic anaemic tissue such as the intruterine resorption of a dead fetus, may be explained by the intraocular presence of high concentrations of triamcinolone acetonide. As a steroid, it may have inhibited the immigration of granulocytes into those areas where the triamcinolone acetonide crystals are present. Morphallaxis-like histology is not commonly found in globes enucleated due to foudroyant infectious endophthalmitis, which is normally characterized by a marked destruction of all intraocular structures via the dense infiltration of all ocular structures by inflammatory cells. The morphallaxis-like morphology of infectious endophthalmitis in eyes with intravitreal triamcinolone acetonide may be paralleled by the clinical observation that patients with infectious endophthalmitis after an IVTA injection usually show almost no pain, which is rather uncommon for infectious endophthalmitis in eyes without intraocular steroids (Nelson et al. 2003). The lack of inflammatory cells migrating into the eye may be the histological correlate of the clinical observation (Benz et al. 2003; Jonas et al. 2003j; Moshfeghi et al. 2003; Nelson et al. 2003; Parke 2003; Jonas & Bleyl 2004).

With respect to susceptibility to infectious endophthalmitis, a recent experimental study showed that rabbit eyes with IVTA had a significantly higher rate of apparent intraocular infection than rabbits eyes without IVTA when both groups were inoculated with *Staphylococcus epidermidis* organisms (Bucher et al. 2005). Concerning the use of multiple-dose bottles containing triamcinolone acetonide, another investigation (Bucher & Johnson 2005) showed that even after 24 hours of exposure to the benzyl alcohol preservative, four of five challenge organisms demonstrated moderate growth in the bottle, so that the use of multiple-dose containers of triamcinolone for intravitreal injections was discouraged.

### Post-injection sterile endophthalmitis

A ‘sterile endophthalmitis’ has been reported to occur after an IVTA injection (Nelson et al. 2003; Parke 2003; Roth et al. 2003). One may speculate whether the solvent agent of triamcinolone acetonide, if not removed prior to the injection, may be the cause of sterile intraocular inflammation after the injection. The issue of whether the solvent agent should be removed before triamcinolone acetonide is injected has not been resolved so far. The disadvantage of removing the solvent agent is that the dosage then becomes inaccurate (Rodriguez-Coleman et al. 2004; Spandau et al. 2005b). Bakri et al. (2004) reported on the use of a commercially available, preservative-free solution of triamcinolone acetonide, and Hernaez-Ortega & Soto-Pedre (2004) described the use of density gradient centrifugation to remove the preservative.

### Post-injection pseudo-endophthalmitis

If triamcinolone acetonide crystals are washed from the vitreous cavity into the anterior chamber, they usually settle down in the inferior anterior chamber angle mimicking a hypopyon (Jonas et al. 2000; Sutter & Gillies 2003b; Chen et al. 2004b; Moshfeghi et al. 2004). The diagnostic problem is the differentiation between a painless hypopyon caused by a post-injection infectious endophthalmitis and a pseudo-hypopyon due to triamcinolone acetonide crystals. Using high magnification slit-lamp biomicroscopy usually reveals the crystalline structure of triamcinolone acetonide. Triamcinolone acetonide crystals in the anterior chamber usually disappear spontaneously and may not need to be removed. There have been no reports so far showing corneal endothelial damage or damage to the trabecular meshwork by the crystals. If the intravitreal injection is performed towards the centre of the vitreous cavity, a pseudo-hypopyon may only rarely occur. If, however, the injection touches the posterior chamber, the triamcinolone acetonide crystals may not be trapped by the vitreous body but may be partially washed into the anterior chamber.

### Rhegmatogenous retinal detachment

Because the triamcinolone acetonide injection is carried into the vitreous cavity, leading to a de-arrangement of the structure of the vitreous body, and because an abnormal vitreous may exert traction on the retina, this may result in a rhegmatogenous retinal detachment. In a recent study on 348 eyes receiving an intravitreal injection of about 20 mg triamcinolone acetonide as treatment for exudative AMD, diabetic macular oedema, retinal vein occlusions, persistent pseudophakic cystoid macular degeneration, and uveitis, none of the eyes developed a rhegmatogenous retinal detachment or retinal lesions (Jonas et al. 2004). This holds particularly true for the inferior midperipheral area of the fundus, where the triamcinolone acetonide crystals settle in the preretinal vitreal cortex; for the superior midperipheral and peripheral fundus, where vitreous traction might be induced by the weight of the triamcinolone acetonide crystals settled at 6 o’clock; and for the far periphery of the fundus, where retinal traction by vitreous if incarcerated into the injection site might occur (Macky et al. 2002; Gillies et al. 2004; Jaisse et al. 2004).

### Post-injection, steroid-induced cataract

In a recent study on 144 phakic eyes which consecutively received intravitreal injections of about 20 mg triamcinolone acetonide for diffuse diabetic macular oedema, exudative AMD and branch retinal vein occlusion, cataract surgery was performed in 20 (13.9%) eyes between 17.4 ± 9.1 months (median 12.7 months, range 8.0–35.5 months) after the intravitreal injection (Jonas et al. 2005e). Out of the 20 eyes undergoing cataract surgery, 19 (95%) eyes received one intravitreal injection and one (5%) eye received two previous injections. It was concluded that in the elderly population of patients with exudative AMD, diffuse diabetic macular oedema or branch retinal vein occlusion, high-dose IVTA injections led to clinically significant cataract, with eventual cataract surgery occurring in about 15% to 20% of eyes within about 1 year of the intravitreal injection.

In an analysis of longitudinal data from a randomized, double-masked, placebo-controlled trial of intravitreal triamcinolone for AMD, Gillies et al. (2005) compared 57 phakic eyes in the treatment group (with 4 mg triamcinolone acetonide) versus 54 phakic eyes in the control group. They found that progression of posterior subcapsular cataract by two or more grades in the
treatment group was significantly higher among the 16 subjects in whom they found an IOP response (51% after 2 years) than among the 37 non-responders (3%; \( p = 0.015 \)). The progression of cortical cataracts was also significantly higher among responders than non-responders (15% versus 3%; \( p = 0.3 \)). The authors concluded that although steroid-related cataracts are unlikely to develop in eyes that do not experience an elevation of IOP after intravitreal triamcinolone, those eyes in which IOP is increased have a very high risk of rapidly experiencing posterior subcapsular lens opacification. They postulated that the strong association suggests a similar mechanism responsible for the development of steroid-induced posterior subcapsular cataract and for the elevation of IOP.

Central serous chorioretinopathy
As steroids may be a risk factor for central serous chorioretinopathy (CSC) (Bouzas et al. 2002; Haimovici et al. 2004), the question arises as to whether IVTA may lead to an increased frequency of CSC. A previous case report described a patient who developed CSC after vitrectomy with IVTA for diabetic macular oedema (Imasawa et al. 2005). It is not clear whether the occurrence represented a non-causal coincidence or whether the intravitreal steroid led to the development of CSC. In another previous report on a patient who showed longstanding CSC that recurred continuously for six years, an IVTA injection did not result in a resolution of the subfoveal accumulation of fluid, suggesting that for this type of macular disorder, IVTA injections may not have a therapeutically positive effect (Jonas & Kampaeter 2005b).

Toxic effects
Direct toxic effects of triamcinolone acetonide on the retina and optic nerve have not yet been observed, independently of the dosage used. Correspondingly, recent safety and efficacy studies have not shown a toxic effect of intraocular steroids (Young et al. 2000; Gillies et al. 2004). The same was found by Hida et al. (1986) and Tokuda et al. (2004). It may be significant that triamcinolone acetonide is usually not found in the serum shortly after its intravitreal application, suggesting that major systemic side-effects may not be very probable (Degenring & Jonas 2004a).

However, a recent study performed by Yeung et al. (2004) reported on a possible cytotoxic effect of triamcinolone acetonide. The authors cultured an RPE cell line (ARPE19) and added corticosteroids (0.01–1 mg/ml) or vehicle (benzyl alcohol 0.025%), diluted in culture medium. Subsequently, the culture medium containing corticosteroid or vehicle was refreshed daily. After 1, 3 and 5 days, the proliferated amount of cells with and without corticosteroid treatment was determined. They found that triamcinolone acetonide caused a significant reduction in cell numbers throughout the whole range of concentrations when cells were exposed to it for more than 1 day. Compared with dexamethasone and hydrocortisone, triamcinolone acetonide showed the higher relative toxicity. The vehicle alone had no effect. In an earlier study, Yeung et al. (2003) compared the cytotoxic effect of triamcinolone acetonide on human RPE (cell line ARPE19) and human glial cells over a range of concentrations and durations of exposure. They found that triamcinolone acetonide caused a significant reduction in the RPE cell line ARPE19 that had been exposed to it for more than 1 day. Significant reductions in the number of glial cells were observed as early as day 1. The glial cells appeared to be more susceptible to triamcinolone acetonide. The vehicle of triamcinolone acetonide had no effect tested the hypothesis that the preservative in the commercial triamcinolone acetonide compound was toxic. Nine New Zealand rabbits were injected with either a control or the test article benzyl alcohol at elevating concentrations. The authors found that concentrations of benzyl alcohol only 3.3 times higher than that injected intravitreally in humans was toxic to the retina and that higher concentrations was extremely toxic. Changes occurred largely in the outer retina and included the loss and shortening of outer segments and photoreceptors. At higher concentrations exudative retinal detachment was seen. The authors concluded that benzyl alcohol at concentrations modestly higher than that present in commercial Kenalog (Bristol-Myers-Squibb-New York, NY, USA) is toxic to the eye. They suggested that if commercial preserved Kenalog is to be used clinically, decanting or another means of removing the benzyl alcohol should be considered.

Safety of intravitreal injections of triamcinolone acetonide including high-dose re-injections
In a recent prospective randomized study by Gillies et al. (2004), the safety of a single IVTA injection (4 mg) in patients with subfoveal CNV caused by AMD was evaluated. Out 75 eyes assigned to study treatment and 76 eyes assigned to placebo, no moderate or severe adverse events related to the surgical procedure occurred in either group. Triamcinolone-treated eyes had a significantly increased risk of developing mild or moderate elevation of IOP. Topical glaucoma medication reduced IOP to acceptable levels in all patients. There was significant progression of cataract in the triamcinolone-treated eyes. The authors concluded that, despite a significant adverse event profile, intravitreal triamcinolone is generally well tolerated by the human eye as long as patients are carefully followed up by their surgeon and treated appropriately, when necessary.

Another recent case series study included 46 patients who received at least two IVTA injections of about 20 mg for treatment of diffuse diabetic macular oedema, exudative AMD, secondary angle-closure glaucoma due to iris neovascularization, central retinal vein occlusion, branch retinal vein occlusion, non-infectious uveitis, Coats’ disease and exudative retinal detachment of unknown aetiology (own data). The second injection was carried out 6.7 ± 3.4 months after the first. Nine eyes received a third injection 8.0 ± 4.6 months after the second injection, two eyes received four injections 9.5 and 10.8 months after the third injection, respectively, and one eye received a total of six injections. No complications or side-effects other than those already known to occur
after a single IVTA injection were detected. After the first, second and third injections, IOP remained within the normal range in 24 (51%), 25 (53%), and five (56%) eyes, respectively. Those eyes without a rise in IOP > 21 mmHg after the first injection did not show an elevation in IOP after the repeated injections. Mean maximal IOP after the first, second and third injections, respectively, did not vary significantly (p > 0.50). The results suggest that intravitreal high-dose re-injections may be tolerated by eyes within a mean follow-up of about 21 months after the first injection or about 10 months after the last injection; that an increase in IOP may be not more marked after a repeat injection than after the first injection; and that side-effects or complications may not occur more frequently after re-injections of triamcinolone acetonide than after a primary high-dose IVTA injection.

Pharmacokinetics of intravitreal triamcinolone acetonide

Comparing the intravitreal application with a sub-Tenon injection, a recent investigation of vitreous samples collected from patients who required vitreous surgery (six patients with a sub-Tenon injection, six patients with an intravitreal injection) showed that considerably higher vitreous concentrations of triamcinolone acetonide were achieved after an intravitreal injection than after a sub-Tenon injection (Inoue et al. 2004). In another study, intravitreal concentrations of triamcinolone acetonide were detectable up to 2.75 months after a single 4 mg injection in non-vitrectomized eyes (Mason et al. 2004). In other studies, triamcinolone acetonide was found in aqueous humour and in silicone oil up to 1.5 years after the intravitreal injection (given in a dosage of about 20 mg) (Scholes et al. 1985; Jonas 2002a, 2002b; Beer et al. 2003). In vitrectomized eyes, the turnover rate of IVTA is considerably shorter than in non-vitrectomized eyes. It has also remained unclear so far, whether and how a silicone oil endotamponade influences the pharmacokinetics of intravascular triamcinolone acetonide (Jonas 2002a).

In conclusion, the intravitreal injection of triamcinolone acetonide may possibly open new avenues for the treatment of intraocular oedematous and neovascular diseases (Aiello et al. 2004). The use of IVTA for any new therapy, however, should be approached with extreme caution as longterm experience is not yet available. There are many open questions still unanswered. What might be the best dosage for which disease and for which clinical situation? Most studies on IVTA have used a dosage of 4 mg. A few studies have used a dosage of about 20 mg filtered triamcinolone acetonide. Comparing the studies with one another may suggest that the frequency and severity of side-effects may not differ markedly between the dosages used, and that the duration of the side-effects, particularly of secondary ocular hypertension, depends on the dosage. Other unanswered questions concern whether the proliferation of RPE cells is decreased in high concentrations of triamcinolone acetonide, and, paradoxically, increased in low concentrations (Blumenkranz et al. 1984). What is the best mode of application of triamcinolone acetonide? Is the sub-Tenon application, the subconjunctival application or the retrobulbar application better than the intravitreal injection (Moshfeghi et al. 2002; Coats et al. 2003; Gupta et al. 2003; Okada et al. 2003)? Are there complications other than those already described in clinical studies or after accidental injection of triamcinolone acetonide into the vitreous cavity (Ghopal et al. 1995; Modarres et al. 1998; Enaida et al. 2003; Takeuchi et al. 2003)? Is it necessary to remove the solvent agent prior to the intraocular injection, and if so, how should the solvent agent be removed (Nishimura et al. 2003). The most fascinating aspect may involve the point that the IVTA injection, together with previous clinical experiences in the use of intravitreal antibiotics and virustatic drugs, makes one understand that retinal diseases, particularly macular disorders, become locally treatable diseases. Unbelievably high intraocular concentrations of drugs become achievable and systemic side-effects may mostly be avoided. Future directions may include the combined applications of intravitreal triamcinolone acetonide with photodynamic therapy, possibly also combined with other intravitreal anti-angiogenic medications, for the treatment of exudative age-related macular degeneration; and the intraocular application of triamcinolone acetonide in slow-release devices, possibly with a trigger mechanism to release the drug if necessary.

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Correspondence:
Dr J. Jonas
Universitäts-Augenklinik
Theodor-Kutzer-Ufer 1–3
68167 Mannheim
Germany
Tel: + 49 621 383 2652
Fax: + 49 621 383 3803
Email: Jost.Jonas@augen.ma.uni-heidelberg.de