

Intravitreal triamcinolone acetonide for treatment of intraocular proliferative, exudative, and neovascular diseases

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Abstract

Within the last three years, triamcinolone acetonide has increasingly been applied intravitreally as treatment option for various intraocular neovascular edematous and proliferative disorders. The best response in terms of gain in visual acuity after the intravitreal injection of triamcinolone acetonide was found in eyes with intraretinal edematous diseases such as diffuse diabetic macular edema, branch retinal vein occlusion, central retinal vein occlusion, and pseudophakic cystoid macular edema. Visual acuity increased and degree of intraocular inflammation decreased in eyes with various types of non-infectious uveitis including acute or chronic sympathetic ophthalmia and Adamantiadis–Behcet's disease. Intravitreal triamcinolone may be useful as angiostatic therapy in eyes with iris neovascularization and proliferative ischemic retinopathies. Possibly, intravitreal triamcinolone may be helpful as adjunct therapy for exudative age-related macular degeneration, possibly in combination with photodynamic therapy. In eyes with chronic, therapy resistant, ocular hypotony, intravitreal triamcinolone can induce an increase in intraocular pressure and may stabilize the eye. The complications of intravitreal triamcinolone therapy include secondary ocular hypertension in about 40% of the eyes injected, cataractogenesis, postoperative infectious and non-infectious endophthalmitis, and pseudo-endophthalmitis. Intravitreal triamcinolone injection can be combined with other intraocular surgeries including cataract surgery. Cataract surgery performed some months after the injection does not show a markedly elevated rate of complications. If vision increases and eventually decreases again after an intravitreal triamcinolone acetonide injection, the injection can be repeated. The duration of the effect of a single intravitreal injection of triamcinolone depended on the dosage given. Given in a dosage of about 20 mg to non-vitrecomized eyes, the duration of the effect and of the side-effects was 6–9 months.

Intravitreal triamcinolone acetonide may offer a possibility for adjunctive treatment of intraocular edematous and neovascular disorders. One has to take into account the side-effects and the lack of long-term follow-up observations.

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1. Introduction

In the early days of intracapsular cataract surgery, the vitreous body was a “noli me tangere” if during surgery a vitreous prolapse occurred. Consequently, the introduction of pars plana vitrectomy into clinical ophthalmology by Machemer (1988) was a profound paradigm change opening avenues for treatment of ocular diseases, such as proliferative vitreoretinopathy, which up to that time had been incurable. It was again Robert Machemer, who together with Yasuo Tano, Gholam Peyman, Stephan Ryan, and other researchers further extended the role the vitreous, and particularly the vitreous cavity, may play in the treatment of intraocular diseases. Considering the vitreous cavity as a drug reservoir, Machemer and others started to inject triamcinolone acetonide intravitreally, so that intraocular diseases may become locally treatable, such as a skin scratch is treated by an ointment. These intraocular diseases include disorders associated with an abnormal proliferation of cells and diseases associated with intraretinal and subretinal edema.

The pathologic proliferation of intraocular tissue, such as retinal pigment epithelium cells in proliferative vitreoretinopathy and vascular cells in eyes with ischemic 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 space of the macula are other major causes for impaired vision. Reasons for such conditions are numerous, such as diabetic retinopathy, central retinal vein occlusion, branch retinal vein occlusion, exudative age-related macular degeneration, perifoveal telangiectasias, pseudophakia, uveitis, ischemic ophthalmopathy, and chronic pre-phthysical 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 for 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 were not high enough to achieve a therapeutic level, or the systemic side-effects were too pronounced for a prolonged treatment. In an attempt to overcome this limitation of ocular steroid therapy, Peyman, Machemer, Tano, Ryan, and others 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 (Antoszyk et al., 1993; Chandler et al., 1987; Coats and Peyman, 1992; Graham and Peyman, 1974; Hida et al., 1986; Ishibashi et al., 1985; Machemer et al., 1979; Machemer, 1996; McCuen et al., 1981; Schindler et al., 1982; Tano et al., 1980a,b). Since soluble cortisone is washed out of the eye within

approximately 24 h after a single intravitreal injection (Schindler et al., 1982; Scholes et al., 1985), Machemer 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,b; Jonas et al., 2002a,b, 2004a–i).

Following the pioneers in the intravitreal use of triamcinolone acetonide, intravitreal triamcinolone acetonide has increasingly been applied in recent studies for treatment of other intraocular proliferative, edematous, and neovascular diseases, such as proliferative vitreoretinopathy (Furino et al., 2003; Jonas et al., 2000, 2003a–j), proliferative diabetic retinopathy (Jonas et al., 2001a–c, 2003a–j), exudative age-related macular degeneration (Challa et al., 1998; Danis et al., 2000; Gillies et al., 2003, 2004; Jonas et al., 2002a, b, 2003a–j, 2004a–i; Penfold et al., 1995; Penfold, 2002a, b; Ranson et al., 2002; Spaide et al., 2003; Wingate and Beaumont, 1999), presumed ocular histoplasmosis syndrome (Rechtman et al., 2003), diffuse diabetic macular edema (Audren et al., 2004; Ciardella et al., 2004; Degenring et al., 2004a, b; Jonas and Söfker, 2001; Jonas et al., 2003a–j; Karacorlu et al., 2004a–d; Lee and Yang, 2004; Martidis et al., 2002; Massin et al., 2004; Micelli Ferrari et al., 2004; Negi et al., 2004; Sutter et al., 2004), central retinal vein occlusion (Bynoe and Weiss, 2003; Degenring et al., 2003; Greenberg et al., 2002; Ip and Kumar, 2002; Ip et al., 2003; Jonas et al., 2002a, b; Park et al., 2003), branch retinal vein occlusion (Chen et al., 2004a, b; Jonas et al., 2004a–i), neovascular glaucoma without or with cataract surgery (Jonas et al., 2001a–c, 2003a–j; Jonas and Söfker, 2002), chronic pre-phthical ocular hypotony (Jonas et al., 2001a–c; Rodriguez et al., 2003), chronic uveitis (Antcliff et al., 2001; Benitez Del Castillo Sanchez and Garcia Sanchez, 2001; Degenring and Jonas, 2003; Martidis et al., 2001; Sonoda et al., 2003; Young et al., 2001), persistent pseudophakic cystoid macular edema (Benhamou et al., 2003; Conway et al., 2003; Jonas et al., 2003a–j; Karacorlu et al., 2003), perifoveal telangiectasia (Alldredge and Garretson, 2003; Martinez, 2003), sympathetic ophthalmia (Jonas, 2004a–c), ischemic ophthalmopathy (Jonas et al., 2003a–j), immunologic corneal graft reaction (Jonas, 2003), extensive exudative retinal detachment (Jonas, 2004a–c), radiation induced macular edema (Sutter and Gillies, 2003a, b), and for other disorders (Navajas et al., 2003; Scott et al., 2003) such as cystoid macular edema due to retinitis pigmentosa (Saraiva et al., 2003), endocrine orbitopathy (Rakic et al., 2003), and Vogt–Koyanagi–Harada syndrome (Andrade et al., 2004; Inoue et al., 2004). It has also been applied in combination with intraocular surgery to visualize the vitreous and other purposes (Burk et al., 2003; Kimura et al., 2004; Matsumoto et al., 2003; Sakamoto et al., 2002; Wilson et al., 1992).

2. IVTA in combination with intraocular surgery

2.1. IVTA combined with pars plana vitrectomy as adjunctive treatment of proliferative vitreoretinopathy

In a pilot study, intravitreal triamcinolone acetonide was applied in combination with pars plana vitrectomy for treatment of proliferative vitreoretinopathy (Jonas et al., 2000). The study group included 16 patients who underwent pars plana vitrectomy for treatment of proliferative vitreoretinopathy and who received an intravitreal injection of about 20 mg triamcinolone acetonide at the end of surgery. A control group consisted of 144 patients undergoing pars plana vitrectomy for proliferative vitreoretinopathy without intravitreal triamcinolone acetonide. During the follow-up (mean, 1.64 months), intraocular inflammation and postoperative pain were significantly lower in the study group. The study suggested that intravitreal triamcinolone acetonide with most of the vehicle removed may not be toxic to intraocular structures, and that it reduces postoperative intraocular inflammation.

A second study included 33 patients undergoing pars plana vitrectomy with silicone oil endotamponade for complicated proliferative vitreoretinopathy due to preceding retinal detachment surgeries or due to traumatic retinal lesions (Jonas et al., 2003j). After a mean follow-up of 8.6 ± 6.6 months, retinal re-detachment was detected in 10 (30%) patients. In five of the 10 patients with retinal re-detachment, the detachment was observed within the first 3 months after surgery. In two patients, triamcinolone acetonide crystals settled on the macular region. Three months after surgery, the crystals had completely resolved. Upon ophthalmoscopy, no tissue damage in the region, where the triamcinolone acetonide crystals had settled, was detected. The recurrence rate of retinal detachments of about one-third was relatively high, which was unexpected in view of the presumed anti-inflammatory and anti-proliferative properties of steroids such as triamcinolone acetonide.

Enaida et al. (2003a, b) used triamcinolone acetonide in combination with pars plana vitrectomy and found between the study group with triamcinolone acetonide ($n = 94$ eyes) and the control group without triamcinolone acetonide ($n = 83$ eyes) no significant difference in frequency of improved vision after surgery, rate of an intraocular pressure higher than 21 mmHg after the operation, and frequency of an additional filtering surgery. The study group had a slightly lower incidence of re-operations caused by preretinal fibrous membrane formation than in the control group.

Summarizing the available clinical reports, it has remained unclear, whether indeed intravitreal triamcinolone acetonide suppresses the proliferation of retinal pigment epithelium 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 acetate/L, but paradoxically increased the proliferation almost two-fold at concentrations ranging from 1 to 30 mg triamcinolone acetate/L under identical culture conditions (Blumenkranz et al., 1984). In contrast, Chandler et al. (1987) observed a protective effect of intravitreal triamcinolone acetate, if it was injected simultaneously with, or prior to, fibroblasts into the vitreous cavity of rabbit eyes, in reducing the rate of retinal detachment. In a recent in vitro examination, triamcinolone acetate inhibited the proliferation of retinal pigment epithelium cells in a dosage-dependent manner in a follow-up of 8 days (own data). As long as the influence of low concentrations of steroids on the proliferation of retinal pigment epithelium cells remains unclear, intravitreal triamcinolone acetate may, therefore, cautiously be taken as adjunct treatment of proliferative vitreoretinopathy. It has also remained unclear so far, whether and how a silicone oil endotamponade influences the pharmacokinetics of intraocular triamcinolone acetate (Jonas, 2002a), and whether the locations of the retinal re-detachments in the inferior fundus were incidentally or causally in spatial relationship to the triamcinolone acetate crystals, which settled in the inferior fundus periphery.

2.2. IVTA in combination with pars plana vitrectomy for proliferate diabetic vitreoretinopathy

Due to the anti-inflammatory and anti-angiogenic effects of triamcinolone acetate, 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., 2001c). A non-randomized comparative investigation consisting of a study group of 32 eyes undergoing pars plana vitrectomy with intravitreal triamcinolone acetate, 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 acetate (Jonas et al., 2003e) followed. The study group and the control group did not vary significantly in the rate of postoperative retinal detachment, re-pars plana vitrectomy, postoperative enucleation, and phthisis bulbi, and in best postoperative visual acuity, visual acuity at the end of the study, and gain in visual acuity. It was concluded that intravitreal triamcinolone acetate did not show a higher than usual rate of postoperative complications, and that as a corollary, the adjunct use of intravitreal triamcinolone acetate combined with pars plana vitrectomy as treatment of proliferative diabetic retinopathy had not shown a marked therapeutic benefit.

2.3. IVTA in combination with pars plana vitrectomy to visualize membranes and vitreous body

In several studies, intraocular triamcinolone acetate was used intraoperatively during pars plana vitrectomy to visualize the inner limiting membrane, epiretinal membranes, and remnants of the vitreous base. Kimura et al. (2004) used triamcinolone acetate to peel off the internal limiting membrane. Yamamoto et al. (2004a) used intravitreal triamcinolone acetate 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 acetate was injected over the posterior pole to detect any remaining epiretinal membranes. The authors concluded that using triamcinolone acetate 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 acetate 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.

2.4. IVTA combined with cataract surgery in eyes with iris neovascularization

In patients with dense cataract and iris neovascularization due to ischemic 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 intravitreal injection of triamcinolone acetate (Jonas and Söfker, 2002). In the postoperative period, visual acuity increased, and without additional retinal ablative treatments, iris neovascularization markedly regressed within the first 5 weeks after surgery. The study suggested that intravitreal triamcinolone acetate may be a useful adjunctive treatment tool in eyes with iris neovascularization undergoing cataract surgery, and that intravitreal triamcinolone acetate may have an anti-angiogenic effect.

2.5. IVTA combined with cataract surgery in eyes without iris neovascularization

Cataract is one of the most common ophthalmologic diseases in the elderly population. It is, therefore, not

rare that cataract is present in eyes additionally showing other age-related disorders, such as diabetic retinopathy, exudative age-related macular degeneration, and retinal vein occlusions. Since these diseases may be treatable by intraocular injections of triamcinolone acetonide, and because intraocular triamcinolone acetonide by itself may further increase a pre-existing lens opacification, it may be useful to combine an intravitreal injection of triamcinolone acetonide with cataract surgery. Taking into account that just recently intravitreal injections of triamcinolone acetonide clinically have started to be evaluated, and in view of the already known complications and side-effects of intraocular triamcinolone acetonide, such as secondary ocular hypertension, secondary open-angle glaucoma, postoperative infectious endophthalmitis, and postoperative sterile endophthalmitis, any additional procedure may further increase the frequency and enlarge the spectrum of complications of the new therapy. In a recent clinical investigation, however, 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 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 intravitreal triamcinolone acetonide without additional intraocular cataract surgery (Jonas et al., 2005f). It was concluded that for a mean follow-up of about 9 months, the frequency and the amount of complications of an intravitreal injection of triamcinolone acetonide, such as increased intraocular pressure, do not markedly differ whether or not the injection is combined with a standard cataract surgery. A similar conclusion was drawn in a study by Lam et al. (2004) on 19 eyes of 15 consecutive diabetic patients with cataract and diabetic macular edema, in which phacoemulsification with a concurrent intravitreal injection of 4 mg triamcinolone acetonide appeared to be a safe option for managing diabetics with cataract and diabetic macular edema. Yamakiri et al. (2004) used intracameral triamcinolone acetonide in six eyes to visualize vitreous removal out of the anterior chamber in complicated cataract surgery.

2.6. Cataract surgery after IVTA

Since steroids applied in a high dosage may lead to several changes, such as alterations in collagenous structures as well as in the immunologic status, intraocular surgery performed after an intravitreal application of triamcinolone acetonide may have an unusual spectrum of complications. A recent case-series

study 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 age-related macular degeneration or diffuse diabetic macular edema (Jonas et al., 2004f). 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 intraocular lens or infectious endophthalmitis was 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 harbor a markedly elevated frequency or a markedly changed profile of complications of standard cataract surgery.

3. Intravitreal triamcinolone acetonide for exudative age-related macular degeneration

Age-related macular degeneration is one of the most common irreversible causes of severe loss of vision in the elderly population in Western countries (Bressler et al., 1988; Mitchell et al., 1995; Vingerling et al., 1995). Despite its high importance for quality of life of the individual patient and its marked socio-economic impact on the society, treatment of age-related macular degeneration has remained unclear for many patients with the exudative type of age-related macular degeneration. Since exudative age-related macular degeneration is a neovascular and edematous disease, and since studies have shown that triamcinolone acetonide may have an anti-angiogenic, anti-proliferate, and anti-edematous effect, intravitreal triamcinolone acetonide has increasingly been used as a treatment option for exudative age-related macular degeneration (Challa et al., 1998; Danis et al., 2000; Gillies et al., 2003, 2004; Haddad et al., 2004; Jonas et al., 2002a, b, 2003a–j, 2004a–i; Penfold et al., 1995; Penfold, 2002a, b; Ranson et al., 2002; Roth et al., 2004; Spaide et al., 2003; Wingate and Beaumont, 1999).

Penfold et al. (1995) started to inject triamcinolone acetonide intravitreally in an effort to treat exudative age-related macular degeneration medically. In 1998, Challa et al. (1998) evaluated safety and efficacy of intravitreal triamcinolone after a follow-up of 18 months in patients with exudative age-related macular degeneration 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 an 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). Visual acuity improved in three of 10 eyes with initial vision of

3/60 or worse. The authors concluded that a single intravitreal injection of 4 mg triamcinolone may be reasonably well tolerated and helpful in the treatment of exudative age-related macular degeneration. In a randomized clinical trial, [Danis et al. \(2000\)](#) examined the effects of an intravitreal injection of 4 mg triamcinolone acetonide on visual and the clinical course of exudative age-related macular degeneration in 27 patients who were compared with a non-treated control group. The authors found that visual acuity was significantly ($p < 0.005$) better in the treated group compared with control subjects at 3 and 6 months follow-up. Increase of intraocular pressure was present in 25% of treated patients, but was controlled with topical medication. Progression of cataract was more frequently detected in the treated group. The authors concluded that intravitreal triamcinolone acetonide may provide improvement in visual acuity in exudative age-related macular degeneration. These clinical studies were supported by experimental studies on the effect of intravitreal cortisone on experimental subretinal neovascularization and other types of intraocular proliferations ([Carroll et al., 2002](#); [Chen et al., 1992](#); [Ciulla et al., 2001, 2003](#); [Danis et al., 1996](#); [Folkman and Ingber, 1987](#); [Penfold et al., 2000, 2001, 2002](#); [Penn et al., 2001](#); [Spandau et al., 2005a](#); [Wang et al., 2002](#); [Wilson et al., 1992](#)). Another recent investigation including 71 eyes with exudative age-related macular degeneration demonstrated a significant increase in visual acuity after an intravitreal injection of 25 mg of triamcinolone acetonide ([Jonas et al., 2003a–j](#)) ([Fig. 1](#)). The improvement in visual acuity was significant at 1 month ($p = 0.04$) and 2 months ($p = 0.04$) after the injection. About 3–5 months after the injection, visual acuity had decreased so that the visual acuity at the end of the follow-up did not differ significantly ($p = 0.17$) from the baseline values. Altogether, 48 (66.2%) eyes gained in visual acuity during the follow-up ([Jonas et al., 2003a](#)). A recent report on a single patient who repeatedly received intravitreal injections of triamcinolone acetonide (about 20–25 mg) demonstrated after each injection a re-increase of visual acuity during a period of several months ([Jonas et al., 2002b](#)).

In another recent prospective comparative non-randomized clinical interventional study including 115 patients receiving an intravitreal injection of about 20 mg triamcinolone acetonide and a control group of 72 patients without treatment, visual acuity increased significantly ($p = 0.03$) in the study group, and decreased significantly ($p = 0.01$) in the control group, 1 and 3 months after the study started ([Jonas et al., 2004g](#)). Between the study group and then control group, the differences in change of visual acuity were significant ($p = 0.001$). In the study group, the number of patients with an increase in visual acuity of two or more Snellen lines was significantly ($p = 0.001$) larger

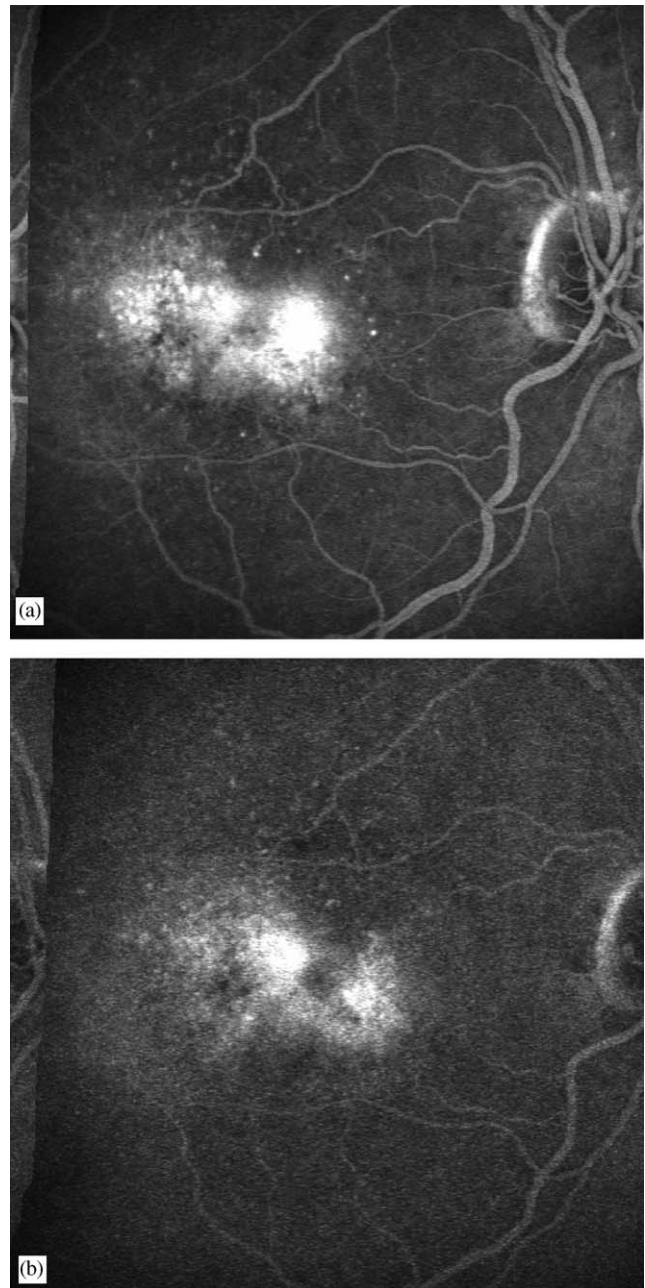


Fig. 1. Fluorescein angiogram of the macular region prior to (a), and 3.6 months after (b), the intravitreal injection of triamcinolone acetonide (about 20 mg) in a patient with exudative age-related macular degeneration (detachment of the retinal pigment epithelium).

than in the control group. Correspondingly, the number of patients with a decrease of two or more Snellen lines was significantly ($p = 0.007$) smaller in the study group. Forty-three (37.4%) patients of the study group increased in best visual acuity by two or more Snellen lines.

The results of these studies are partially in contrast to a recent 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 associated with age-related macular degeneration can safely reduce the risk of severe visual loss. They included 151 eyes of patients 60 years or older who had choroidal neovascularization with any classic component, a duration of symptoms of less than 1 year, and a visual acuity of 20/200 or better. The whole study population was divided into a study group of 75 eyes receiving intravitreal triamcinolone acetonide and a control group of 76 eyes without 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 and colleagues did not have a significant difference between the two groups for the 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 and colleagues concluded that a single dose of 4 mg intravitreal triamcinolone had no effect on the risk of loss of visual acuity during the first year of the study, despite a significant anti-angiogenic effect found 3 months after treatment. One of the reasons for the discrepancy between the investigation performed by Gillies and colleagues and the other studies may be the difference in the dosage of triamcinolone acetonide injected. Another reason may be that in the study by Gillies and colleagues, re-injections were not performed. It would fit with the observation that the peak in visual acuity occurred about 2–5 months after an injection of about 20 mg (own data). Interestingly, Gillies and coworkers found a statistically significant and therapeutically positive effect of intravitreal triamcinolone on the size of the subfoveal neovascularization 3 months after the injection. It is in agreement with experimental studies on an angiostatic effect of intravitreal cortisone on experimental subretinal neovascularization and other types of intraocular blood vessel proliferation as well as with investigations on the anti-phlogistic and anti-proliferative effect of intravitreal triamcinolone acetonide (Carroll et al., 2002; Chen et al., 1992; Ciulla et al., 2001, 2003; Danis et al., 1996; Folkman and Ingber, 1987; Penfold et al., 2000, 2001, 2002; Penn et al., 2001; Wang et al., 2002; Wilson et al., 1992). An additional reason for the discrepancy between the study by Gillies and colleagues and the other investigations may be that Gillies' investigation included patients with the classic type of subfoveal neovascularization, which is associated with a worse prognosis compared to the occult type of subfoveal neovascularization.

Another recent investigation looked for factors influencing visual acuity after an intravitreal injection of triamcinolone acetonide as treatment of exudative

age-related macular degeneration (Jonas et al., 2004e). A post-injection increase in visual acuity was significantly ($p < 0.001$) and negatively correlated with preoperative visual acuity, and was significantly ($p = 0.035$) larger in eyes with retinal pigment epithelium detachment than in eyes with minimal classic subfoveal neovascularization. Post-injection change in visual acuity was statistically independent of age, refractive error, gender, and duration of follow-up. The type of subfoveal neovascularization was another factor influencing gain in visual acuity after the intravitreal injection. Eyes with a detachment of the retinal pigment epithelium showed a significantly higher increase in visual acuity than eyes with a minimally classic subfoveal neovascularization in which visual acuity did not markedly change after the intravitreal injection. It may have clinical importance, since photodynamic therapy has not been shown to increase visual acuity in patients with retinal pigment epithelium detachment.

In another investigation, the duration of the effect of intravitreal triamcinolone acetonide on visual acuity in patients with exudative age-related macular degeneration was evaluated (own data). The prospective clinical interventional case-series study included 42 patients with exudative age-related macular degeneration, who had shown an increase in visual acuity by at least two Snellen lines after an intravitreal injection of about 20–25 mg triamcinolone acetonide. Within the first week after the injection, visual acuity started to increase significantly ($p = 0.008$) to reach a plateau-like maximum at 1–6 months after the injection. Visual acuity returned to baseline values 8–9 months after the injection. It may suggest that triamcinolone may be re-injected about 6–9 months after a primary successful injection.

In a consequent study, the effect of intravitreal re-injections of triamcinolone acetonide as treatment for exudative age-related macular degeneration was investigated (Jonas et al., 2004a). The study included 13 patients with progressive exudative age-related macular degeneration with occult, or predominantly occult, subfoveal neovascularization. All patients had shown an increase or stabilization in visual acuity after a first intravitreal injection of about 20 mg triamcinolone acetonide. They received a second intravitreal injection of about 20–25 mg triamcinolone acetonide 3.1–18 months after the first injection. Visual acuity increased significantly ($p = 0.005$ and 0.003 , respectively) after the first and after the second injection. Increase in visual acuity was found for 10 (77%) patients after the first and after the second injection. The peak of visual acuity, and in a chronologically parallel manner, the peak in intraocular pressure elevation, occurred 2–5 months after each injection. Interestingly, the peak of the increase in visual acuity occurred at about 2–5 months after the injections with no marked difference in the time of the peaks between the first injection and the

re-injection. It suggests that a re-injection of triamcinolone acetonide may be performed about 3–5 months or later after an initial injection if the first injection was associated with an increase in visual acuity. In a chronologically parallel manner, the peak of the elevation in intraocular pressure was about 2–5 months after the injection. It shows that patients after an intravitreal injection of triamcinolone acetonide must closely be followed up for several months to detect a steroid-induced increase in intraocular pressure. Besides the chronological correlation between an increase in visual acuity and an elevation of intraocular pressure, the post-injection increase in visual acuity was statistically independent of the elevation in intraocular pressure.

Spaide et al. (2003) were the first to report on the combination of intravitreal triamcinolone acetonide with photodynamic therapy as treatment of exudative age-related macular degeneration. Their study included 26 eyes with exudative age-related macular degeneration with choroidal neovascularization. Thirteen eyes had already received a photodynamic therapy and experienced visual loss after the treatment. Thirteen additional eyes had not been treated with photodynamic therapy prior to inclusion into the study. In the study, all patients were treated with photodynamic therapy 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, mean visual acuity change 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 visual acuity change 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, visual acuity was significantly greater than at baseline ($p = 0.023$ and 0.007) at the 3- and 6-month time points. Among the 13 patients who had already undergone photodynamic treatment prior to inclusion in the study, mean change in visual acuity from baseline at the 3-month follow-up was 0.31 lines, and one patient (7.7%) had an improvement of at least three lines. At 6-month follow-up, available for 11 patients, mean change from baseline visual acuity 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- and 6-month time points the visual acuity was not significantly different than the baseline acuity. The authors concluded that although the number of patients in their pilot study was limited, the improvement of acuity and the lack of fluorescein

leakage in these patients may suggest a combination therapy with photodynamic therapy with intravitreal triamcinolone acetonide, particularly when used as first-line therapy.

In a similar study by Rechtman et al. (2004), intravitreal triamcinolone acetonide as an adjunctive treatment to photodynamic therapy with verteporfin for new subfoveal choroidal neovascularization in age-related macular degeneration was evaluated in 14 patients who had received intravitreal triamcinolone acetonide within 6 weeks of their first photodynamic therapy and who had a follow-up 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 to $3946 \pm 1503 \mu\text{m}$ ($p = 0.01$). The mean number of photodynamic therapies during the first year was 2.57. The authors concluded that intravitreal triamcinolone acetonide with photodynamic therapy in patients with exudative age-related macular degeneration was found to be relatively safe and had reasonable results for lesions with some classic component.

In a parallel manner, Roth and colleagues treated 43 eyes of 40 patients with subfoveal choroidal neovascularization associated with age-related macular degeneration by a combination of an intravitreal injection of 4 mg triamcinolone, given 1 week prior to photodynamic therapy. Thirty eyes had received prior photodynamic therapy with an incomplete response or significant residual subretinal fluid. Thirteen eyes had not received a therapy prior to inclusion into the study. Fluorescein angiography was repeated at 1, 3, and 6 months during follow-up, and photodynamic therapy was repeated if leakage persisted. During follow-up, none of the patients experienced severe visual loss. Median visual acuity 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 Haddad et al., two series of 14 consecutive patients presenting with exudative age-related macular degeneration and a chorioretinal anastomosis associated with a pigment epithelium detachment were, respectively, treated with photodynamic therapy or with photodynamic therapy 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 visual acuity changes at 3 and 6 months were, respectively, a loss of 0.36 and 0.82 lines in eyes in the group with only photodynamic therapy,

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 photodynamic therapy may be a better therapeutic option than photodynamic therapy alone in the management of exudative age-related macular degeneration associated with chorioretinal anastomosis.

The studies mentioned above were reason to initiate multi-center studies that evaluate the triamcinolone/photodynamic therapy combined treatment (the VISTA trial, lead by Rick Spaide; the VERTACL trial lead by Karl Csaky at the NEI; and a third trial funded by a pharmaceutical company).

4. Regression of neovascular iris vessels by intravitreal triamcinolone acetonide

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 age-related macular degeneration, was observed in an investigation on 14 eyes with neovascular glaucoma due to proliferative diabetic retinopathy or ischemic central retinal vein occlusion (Jonas and Söfker, 2001, 2002; Jonas et al., 2003c). 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 goniosynchiolysis ($n = 1$) and transscleral peripheral retinal cryocoagulation. Postoperatively, degree of iris neovascularization decreased significantly ($p = 0.02$). Considering only the four patients for whom the intraocular cortisone injection was the only procedure performed, mean intraocular pressure decreased from 26.5 ± 2.1 to 21.75 ± 11.3 mmHg.

5. Intravitreal triamcinolone acetonide for diabetic macular edema

One of the main reasons for reduced vision in patients with diabetic retinopathy is macular edema. It can be divided into a focal type and a diffuse type (Bresnick, 1983; Early Treatment Diabetic Retinopathy Study Research Group, 1985; Early Treatment Diabetic Retinopathy Study Research Group, 1991). The study on the early treatment of diabetic retinopathy (ETDRS) has shown that focal laser coagulation of leaking circumscribed retinal areas in eyes with focal diabetic macular edema is therapeutically useful to improve visual outcome compared to no treatment. In eyes with diffuse macular edema, however, laser treatment cannot be focused on localized retinal leakage spots since the entire macula is involved. Diffuse diabetic macular

edema is, therefore, much less responsive to macular laser coagulation than focal diabetic macular edema (Lee and Olk, 1991; Olk, 1986). Recommendation for grid laser treatment covering the whole macular region with a fine net of small laser coagulation spots has been controversial since large randomized prospective studies proving the efficacy of this treatment have not been published so far (Degenring et al., 2004a,b; Lee and Olk, 1991; McDonald and Schatz, 1985; Olk, 1986).

Recent studies have suggested, that intravitreal triamcinolone acetonide may be useful to increase visual acuity in patients with diffuse diabetic macular edema (Audren et al., 2004; Ciardella et al., 2004; Degenring et al., 2004a,b; Jonas and Söfker, 2001; Jonas et al., 2003a–j; Karacorlu et al., 2004a–d; Lee and Yang, 2004; Martidis et al., 2002; Massin et al., 2004; Micelli Ferrari et al., 2004; Negi et al., 2004; Sutter et al., 2004) (Fig. 2). The patients of a study group receiving intravitreal triamcinolone acetonide compared with patients of control groups without intravitreal injections of triamcinolone acetonide showed a significant increase in visual acuity during the follow-up, expressed in Snellen lines as well as in log MAR units (Jonas et al., 2005c). A similar result was obtained in another comparative study including 25 consecutive patients (50 eyes) with bilateral diabetic macular edema who received a unilateral intravitreal injection of about 20 mg triamcinolone acetonide into the eye (study group) more severely affected by diabetic maculopathy (Jonas et al., 2004i). The contralateral eyes served as the control group. In the study group, visual acuity increased significantly ($p < 0.001$) by 3.0 ± 2.6 Snellen lines. An increase in best visual acuity was found in 23 (92%) eyes. In the control group, differences between baseline visual acuity and visual acuity measured at any of the re-examinations during follow-up were not significant ($p > 0.10$). In an intraindividual intereye comparison, gain in visual acuity 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 visual acuity at about 2–6 months after the injection, visual acuity decreased significantly ($p = 0.001$) toward the end of the follow-up, at which visual acuity was still higher, however, not significantly ($p = 0.18$) higher, than at the baseline. In the control group, visual acuity at the end of the follow-up was lower, however, not significantly lower ($p = 0.26$), than at the baseline. The study confirmed another recent investigation with a similar study design carried out by Massin et al. (2004). Massin's study included 15 patients with bilateral diabetic macular edema unresponsive to laser photocoagulation. Performing a unilateral injection of 4 mg triamcinolone acetonide, Massin and colleagues found a significant reduction in macular thickness. Perhaps due to the smaller number of patients involved in their study, or due to the smaller dosage of triamcinolone

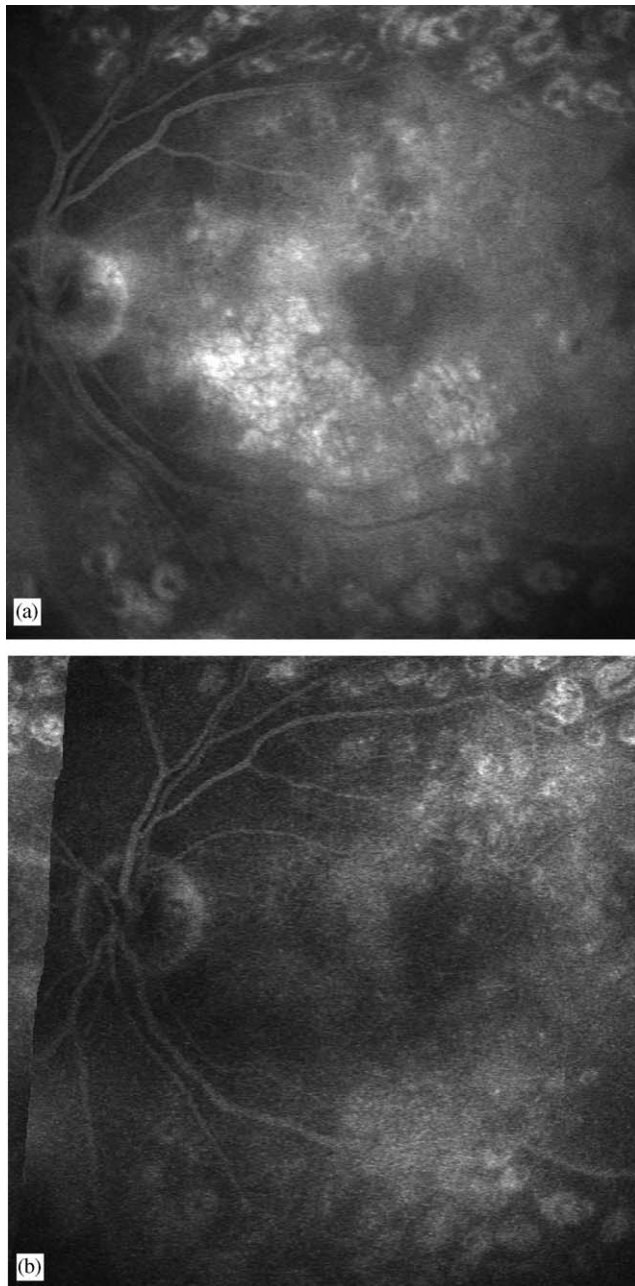


Fig. 2. Fluorescein angiogram of the macular region prior to (a), and 3 months after (b), the intravitreal injection of triamcinolone acetate (about 20 mg) in a patient with diffuse diabetic macular edema.

acetate injected intravitreally, Massin and coworkers detected a slight, however, not statistically significant, increase in visual acuity in the injected eyes compared with the contralateral eyes without intravitreal injection.

Using a dosage of about 20 mg triamcinolone acetate, the increase in visual acuity was most marked for 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 acetate, the duration of a reduction in the macular

thickness as measured by optical coherence tomography was less than 6 months (Massin et al., 2004). At the end of the follow-up, visual acuity measurements returned to the 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 visual acuity after intravitreal injection of triamcinolone acetate as treatment for diffuse diabetic macular edema (Jonas et al., 2005e). A multiple linear regression analysis revealed that improvement in visual acuity after the intravitreal injection of triamcinolone acetate significantly correlated with a lower degree of macular ischemia ($p < 0.001$), higher preoperative visual acuity ($p = 0.002$) and higher degree of macular edema. Change in visual acuity after the intravitreal triamcinolone injection was statistically independent ($p > 0.20$) of age, gender, and pseudophakia.

Similar results were obtained in other studies. Sutter et al. (2004) performed a prospective, double-masked, placebo-controlled, randomized clinical trial on 69 eyes of 43 patients, with 34 eyes randomized to receive intravitreal triamcinolone (4 mg) and 35 eyes randomized to receive a placebo injection. The main outcome measures were improvement of the best-corrected logarithm of the minimum angle of resolution visual acuity by five or more letters and incidence of moderate or severe adverse events. Eighteen of 33 eyes (55%) treated with triamcinolone gained five or more letters of best-corrected visual acuity compared with five of the 32 eyes (16%) treated with placebo ($p = 0.002$). Macular edema was reduced by one or more grades as determined by masked semiquantitative contact lens examination in 25 of the 33 treated eyes (75%) versus five of the 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 20 placebo-treated eyes. Infectious endophthalmitis developed in one triamcinolone-treated eye that was treated adequately without loss of visual acuity. The authors concluded that in the short term, intravitreal triamcinolone is an effective and relatively safe treatment for eyes with diabetic macular edema that have failed laser treatment.

In a retrospective, interventional, non-comparative case-series study, Ciardella et al. (2004) performed an intravitreal injection of 4 mg of triamcinolone acetate in 30 eyes of 22 consecutive patients with diabetic macular edema refractory to laser treatment. Mean visual acuity 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 follow-up, respectively. Mean optical coherent tomographic macular thickness measurement decreased from $476 \pm 98 \mu\text{m}$ at baseline to 277 ± 97 , 255 ± 96 , and $331 \pm 147 \mu\text{m}$ at the 1, 3, and 6 months follow-up period,

respectively. Twelve eyes received two, seven eyes received three, and two eyes received four intravitreal triamcinolone acetonide injections. The mean interval between the first and second IVTA injection 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 intravitreal triamcinolone acetonide in all patients. Intraocular pressure was raised above 21 mmHg in 12 (40%) of the 30 eyes. Two eyes developed posterior subcapsular cataract and two developed vitreous hemorrhage. The authors concluded the intravitreal triamcinolone acetonide is a promising treatment for patients with diabetic macular edema refractory to laser treatment. Similar results were reported in studies performed by Micelli Ferrari et al. (2004), Karacorlu et al. (2004a–d), Lee and Yang (2004), Gharbiya et al. (2004), and Negi et al. (2004).

It has remained unclear so far, whether and how intensively triamcinolone acetonide crystals injected into the vitreous body may influence the vitreoretinal interface. One may suspect that the crystals due to their weight may lead to a posterior vitreous detachment if the vitreous was not already detached prior to the injection. A posterior vitreous detachment may have as disadvantage a 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 complication in the follow-up of patients who received an intravitreal injection of triamcinolone acetonide (Jonas et al., 2004c). The advantage of a posterior vitreous detachment in patients with diabetic retinopathy may be a reduction of macular edema as suggested by studies on pars plana vitrectomy in patients with diffuse diabetic macular edema, and a decreased risk of retino-vitreous 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 (Degenring and Jonas, 2004a). It agrees with clinical observations that the metabolic control of patients with diabetes mellitus is not markedly influenced by the intraocular application of the steroid.

6. IVTA for proliferative diabetic retinopathy

Besides, for diabetic macular edema, intravitreal triamcinolone acetonide has been used for treatment for proliferate diabetic retinopathy without additional surgery.

Karacorlu et al. (2004b) reported on the clinical outcome of a patient with proliferative diabetic retinopathy and diabetic macular edema, which progressed despite grid laser photocoagulation in the macular

region. After a single intravitreal injection of 4 mg triamcinolone acetonide, visual acuity increased, macular edema decreased, and the optic nerve head neovascularization markedly regressed. Al-Haddad and colleagues presented a patient with a severe drop in vision in both eyes caused by diabetic papillopathy, which was treated with an intravitreal injection of triamcinolone acetonide. Within 2 weeks after the injection, vision improved from counting fingers at 1 m to 20/50 OS, and from counting fingers at 4 m to 20/40 OD. This improvement was accompanied by resolution of optic disk swelling and macular edema. Vision remained stable in both eyes at 20/40 for 8 months of follow-up. Bandello et al. demonstrated the clinical course of a young patient with florid proliferative diabetic retinopathy in whom a greater reduction of retinal thickening and fluorescein leakage from retinal new vessels was observed after the intravitreal injection of triamcinolone followed by scatter panretinal photocoagulation in the right compared with the left eye which was treated only by panretinal laser coagulation. The authors concluded that intravitreal triamcinolone acetonide may be a useful adjunct to scatter panretinal photocoagulation for florid proliferative retinopathy.

7. Intravitreal triamcinolone acetonide for pseudophakic cystoid macular edema

Phacoemulsification with implantation of an intraocular lens can be complicated by severe postoperative cystoid macular edema. The latter has usually been treated by topical, peribulbar, and systemic application of steroids or non-steroidal anti-inflammatory agents. Recently, intravitreal triamcinolone acetonide has been used for the treatment of persisting pseudophakic cystoid macular edema (Benhamou et al., 2003; Conway et al., 2003; Jonas et al., 2003a–j; Karacorlu et al., 2003). Patients who developed cystoid macular edema after cataract surgery and who received an intravitreal injection of triamcinolone acetonide showed an increase in visual acuity from 0.26 ± 0.13 to a mean best visual acuity of 0.60 ± 0.19 (Jonas et al., 2003a–j) (Fig. 3). There was no clear tendency suggesting a decrease in visual acuity toward the end of the follow-up period. The increase in visual acuity was statistically independent of the time interval between cataract surgery and the intravitreal injection of triamcinolone acetonide.

8. Branch retinal vein occlusion treated by intravitreal triamcinolone acetonide

Due to its anti-edematous and anti-angiogenic effects as shown in experimental investigations and clinical studies, intravitreal triamcinolone acetonide has also

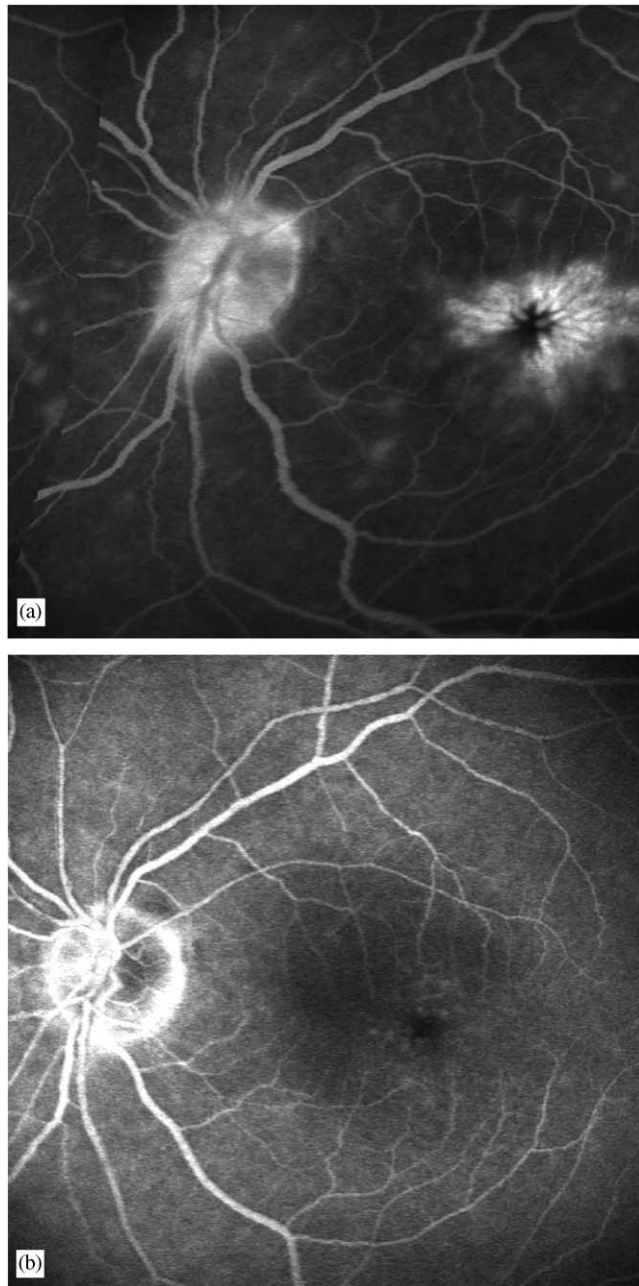


Fig. 3. Fluorescein angiogram of the macular region prior to (a), and 3.2 months after (b), the intravitreal injection of triamcinolone acetonide (about 20mg) in a patient with pseudophakic cystoid macular edema.

been used in pilot studies on branch retinal vein occlusions (Chen et al., 2004a,b; Jonas et al., 2004a–i). A recent prospective comparative non-randomized clinical interventional study included 10 patients with branch retinal vein occlusion (two with ischemic type of branch retinal vein occlusion; eight eyes with non-ischemic type), who received an intravitreal injection of 20–25 mg of triamcinolone acetonide, and 18 patients of a control group without an intravitreal injection of triamcinolone acetonide. The patients of the study

group experienced a significant increase in visual acuity, while the patients of the control group did not show a significant change in visual acuity during the follow-up. Comparing the study group and the control group with each other, gain in visual acuity was significantly more marked in the study group for the measurements obtained 1 and 2 months after baseline. It confirmed another study in which intravitreal triamcinolone acetonide reduced macular edema in eyes with branch central retinal vein occlusion (Jonas et al., 2004a–i).

9. Intravitreal triamcinolone acetonide for treatment of central retinal vein occlusion

Cystoid macular edema 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 to increase visual acuity after central retinal vein occlusion (Hayreh et al., 1990; Hayreh, 2003; The Central Vein Occlusion Study Group, 1995). Recent studies on intravitreal triamcinolone acetonide have also addressed macular edema due to central retinal vein occlusion (Bashshur et al., 2004; Bynoe and Weiss, 2003; Degenring et al., 2003; Greenberg et al., 2002; Ip and Kumar, 2002; Ip et al., 2003, 2004; Jonas et al., 2002a; Karacorlu et al., 2004c; Lahey et al., 2004; Park et al., 2003). Bashshur and colleagues evaluated the efficacy of intravitreal triamcinolone acetonide in the management of persistent macular edema secondary to non-ischemic central retinal vein occlusion. Twenty consecutive patients with a 3- to 4-month history of non-ischemic 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 who were 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 visual acuity of 20/37 while the observation group had a mean visual acuity of 20/110 ($p = 0.001$). Sixty percent of treated patients had a final visual acuity of 20/40 or better versus only 20% in the observation group ($p = 0.01$). Forty percent of the untreated patients had a final visual acuity worse than 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 edema on clinical examination versus only 20% of the untreated patients ($p < 0.001$). Two of the treated patients had recurrence of macular edema at 6 months, and three had elevated intraocular pressure. The authors concluded a treatment benefit from intravitreal triamcinolone in terms of visual acuity and macular edema for non-ischemic central retinal vein occlusion (Tables 1 and 2).

Table 1

Studies on intravitreal triamcinolone acetonide as treatment for exudative age-related macular degeneration

Author (year of publication)	Study design	n	Dosage	Procedure	Results	Complications
Penfold et al. (1995)	Case series	30	4 mg unfiltered	Intravitreal inj.	Visual acuity increase	
Challa et al. (1998)	Case series	30	4 mg unfiltered	Intravitreal inj.	Visual acuity increase	IOP increase/ cataract
Wingate and Beaumont (1999)	Case series	113	4 mg unfiltered	Intravitreal inj.	IOP increase in 30%	
Danis et al. (2000)	Randomized	27	4 mg unfiltered	Intravitreal inj.	Visual acuity increase	IOP increase in 25%
Jonas (2002b)	Case report	1	About 20 mg filtered	Repeated intravitreal inj.	Visual acuity increase after each injection	IOP increase
Ranson et al. (2002)	Case series	14	4 mg unfiltered	Intravitreal inj.	May be of benefit	
Jonas et al. (2003a)	Case series	72	About 20 mg filtered	Intravitreal inj.	Visual acuity increase	IOP increase
Gillies et al. (2003)	Randomized	73/75	4 mg unfiltered	Intravitreal inj.	No difference in visual acuity; neovasc. membrane smaller	IOP increase
Jonas et al. (2003a–j)	Case series	13	About 20 mg filtered	Repeated intravitreal inj.	Visual acuity increase after first and second inj.	IOP increase
Jonas et al. (2004e)	Case series	94	About 20 mg filtered	Intravitreal inj.	Predictive factors: RPE-detachment best	
Jonas et al. (2004g)	Non-randomized comparative	115/72	About 20 mg filtered	Intravitreal inj.	Visual acuity increase	IOP increase
Haddad et al. (2004)	Non-randomized comparative		4 mg unfiltered	Intravitreal inj. + photodyn. th.	Visual acuity increase	
Spaide et al. (2003)	Case series	26	4 mg unfiltered	Intravitreal inj. + photodyn. th.	May be of benefit	
Roth et al. (2004)	Case series	43	4 mg unfiltered	Intravitreal inj. + photodyn. th.	Suggestion of benefit	
Smithen et al. (2004)	Case report	1	4 mg unfiltered	Intravitreal inj. + photodyn. th.	Suggestion of benefit	

Note: The study by Gillies and coworkers showed the best study design as prospective randomized, double-masked, placebo-controlled clinical trial.

In a similar study, Ip and coworkers found that eyes with non-ischemic central retinal vein occlusion demonstrated a significant improvement in visual acuity, whereas eyes with ischemic central retinal vein occlusion showed a tendency toward a visual acuity improvement. They inferred that intravitreal triamcinolone acetonide appears to be a possibly effective treatment in some patients with macular edema associated with central retinal vein occlusion, and that patients with non-ischemic central retinal vein occlusion may respond more favorably than patients with ischemic central retinal vein occlusion. In another prospective comparative non-randomized clinical interventional study on 11 eyes with central retinal vein occlusion receiving an intravitreal injection of triamcinolone acetonide, compared with six eyes of a control group without intravitreal injection triamcinolone acetonide, gain in visual acuity was significantly ($p = 0.003$) higher in the study group (own data). It confirms other reports on the beneficial effect of intravitreal triamcinolone acetonide on macular edema and visual acuity in patients with central retinal vein occlusion (Bynoe and Weiss, 2003; Degenring et al., 2003; Greenberg et al., 2002; Ip and Kumar, 2002; Ip et al., 2003; Jonas et al., 2002a, b; Park

et al., 2003). The results additionally suggested that the increase in visual acuity after the intravitreal injection of triamcinolone acetonide may not last permanently in eyes with central retinal vein occlusion. After a significant increase in visual acuity in the first 3 months after the injection, visual acuity showed a tendency of decline toward the end of the follow-up. Correspondingly, final visual acuity and preoperative visual acuity did not vary significantly. Another positive effect of intravitreal triamcinolone acetonide in eyes with ischemic central retinal vein occlusion may be a direct or indirect anti-angiogenic effect possibly decreasing the risk of neovascularization (Carroll et al., 2002; Ciulla et al., 2001, 2003; Danis et al., 1996; Folkman and Ingber, 1987; Gao et al., 2004; Penfold et al., 2000, 2001, 2002; Penn et al., 2001; Wang et al., 2002; Wilson et al., 1992).

10. Intravitreal triamcinolone acetonide for cystoid macular edema after penetrating keratoplasty

A recent report on a patient presenting with long-standing cystoid macular edema after penetrating keratoplasty suggests that intravitreal triamcinolone

Table 2

Studies on intravitreal triamcinolone acetonide as treatment for diabetic retinopathy including diabetic macular edema

Author (year of publication)	Study design	n	Dosage	Procedure	Results	Complications
Jonas et al. (2001a)	Case report	1	About 20 mg filtered	Intravitreal inj.	Decrease in leakage	None
Jonas et al. (2001c)	Case series	29	About 20 mg filtered	Vitrectomy	Decrease in iris neovascularization	Pseudo-hypopyon
Martidis et al. (2002)	Case series	16	4 mg unfiltered	Intravitreal inj.	Decrease in macular thickness (OCT)	IOP increase in 5/16; cataract in 1/16
Jonas et al. (2003b)	Non-random. comparative	20	About 20 mg filtered	Intravitreal inj.	Visual acuity increase	IOP increase
Jonas et al. (2003e)	Non-random. comparative	30	About 20 mg filtered	Vitrectomy	Visual acuity increase	IOP increase
Massin et al. (2004)	Intereye comparison	15	4 mg unfiltered	Intravitreal inj.	Macular thickness reduced	IOP increase
Jonas et al. (2004b)	Case series	38	About 20 mg filtered	Intravitreal inj.	Duration: 6–9 months	
Sutter et al. (2004)	Randomized	34/35	4 mg unfiltered	Intravitreal inj.	Visual acuity increase macular thickness reduced	
Al-Haddad et al. (2004)	Case report	1	4 mg unfiltered	Intravitreal inj.	Visual acuity increase optic disk swelling reduced	
Karacorlu et al. (2004a)	Case series	12	4 mg unfiltered	Intravitreal inj.	Visual acuity increase macular thickness reduced	
Karacorlu et al. (2004b)	Case series	1	4 mg unfiltered	Intravitreal inj.	Visual acuity increase	
Jonas et al. (2004i)	Intereye comparison.	25	About 20 mg filtered	Intravitreal inj.	Visual acuity increase	IOP increase
Ciardella et al. (2004)	Case series	30	4 mg unfiltered	Intravitreal inj.	Visual acuity increase hard exudates reduced	IOP increase in 12/30 (40%)
Bandello et al. (2004)	Case report	1	4 mg unfiltered	Intravitreal inj.	Visual acuity increase	
Micelli Ferrari et al. (2004)	Case series	6	4 mg	Intravitreal inj.	Visual acuity increase	None macular thickness reduced
Jonas et al. (2005a)	Case series	4	About 20 mg filtered	Repeated intravitreal inj.	Visual acuity increase	IOP increase
Jonas et al. (2005c)	Non-random. comparative	97	About 20 mg filtered	Intravitreal inj.	Visual acuity increase	IOP increase
Jonas et al. (2005e)	Case series	38	About 20 mg filtered	Intravitreal inj.	Predictive factors: ischemia, edema	IOP increase

Note: The study by Sutter and colleagues showed the best study design as prospective randomized, double-masked, placebo-controlled clinical trial.

acetonide may be an additional tool in the treatment of long-standing therapy resistant cystoid macular edema after intraocular surgery besides phacoemulsification (own data). An additional advantage of intraocular steroids in the treatment of cystoid macular edema after penetrating keratoplasty may be the suppression of an immunologic graft reaction as described recently (Jonas, 2003; Reinhard and Sundmacher, 2002).

11. Intravitreal triamcinolone acetonide and central serous chorioretinopathy

In a previous report on a patient who showed long-standing central serous chorioretinopathy continuously recurring for 6 years, an intravitreal injection of triamcinolone acetonide did not result in a resolution

of the subfoveal accumulation of fluid suggesting that for this type of macular disorder, intravitreal injection of triamcinolone acetonide may not have a therapeutically positive effect (Jonas and Kampeter, 2005). It agrees with a recent study on patients with central serous chorioretinopathy for, which preceding steroid therapy has been detected to be a risk factor (Bouzas et al., 2002; Haimovici et al., 2004).

12. Intravitreal triamcinolone acetonide for foveal telangiectasia

Intravitreal injection of triamcinolone acetonide has also been applied as treatment for foveal telangiectasia. In two reports, intravitreal triamcinolone acetonide increased visual acuity, while in a third report only one out of two patients experienced an increase in visual

acuity (Alldredge and Garretson, 2003; Martinez, 2003). Smithen and Spaide (2004) reported a combined treatment of photodynamic therapy with verteporfin and intravitreal triamcinolone acetonide injection (4 mg) for subfoveal neovascularization secondary to bilateral idiopathic juxtafoveal telangiectasis. Leakage in the late phase of fluorescein angiography resolved with attenuation of telangiectatic vessels and improvement in visual acuity from 20/200 to 20/50. At 9 months post-treatment, recurrent leakage was treated with repeated photodynamic therapy and intravitreal triamcinolone. One year after initial presentation, visual acuity was 20/60 with no leakage on fluorescein. The authors concluded that combined treatment with photodynamic therapy and intravitreal triamcinolone acetonide resulted in regression of a subfoveal neovascular membrane and improvement in visual acuity during the course of follow-up.

13. Intravitreal triamcinolone acetonide for chronic pre-phthical ocular hypotony

In contrast to ocular hypertension, which can often successfully be cured by a whole array of anti-glaucomatous 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 desired effect, triamcinolone acetonide was injected intravitreally in three eyes with long-standing pre-phthical ocular hypotony (Jonas et al., 2001a–c; Rodriguez et al., 2003). In all three patients, intraocular pressure and visual acuity increased after the injection associated with a stabilization of the eyes. It may suggest that in some eyes with long-standing pre-phthical ocular hypotony, intravitreal injection of triamcinolone acetonide can be beneficial to increase intraocular pressure and stabilize the eye.

14. Intravitreal triamcinolone acetonide for uveitis

Chronic intraocular inflammation such as chronic uveitis can lead to cystoid macular edema, papilledema, and vitreous opacities temporarily or permanently reducing visual acuity. Chronic uveitis has usually been treated by topical or systemic application of steroids. Topical treatment, however, often has not been sufficiently effective to suppress intraocular inflammation and to reduce cystoid macular edema. 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 intravitreal triamcinolone acetonide for other indications, triamci-

nolone acetonide has also been applied in eyes with chronic therapy resistant uveitis (Andrade et al., 2004; Antcliff et al., 2001; Karacorlu et al., 2004a–d; Kramer et al., 2004; Pathengay et al., 2004; Young et al., 2001). These diseases include Adamantiadis–Behcet's disease (Karacorlu et al., 2004a–d; Kramer et al., 2004): Kramer and colleagues reported on three patients with acute severe exacerbations of non-infectious panuveitis and vitritis due to Adamantiadis–Behcet's disease who were treated with intravitreal triamcinolone acetonide injections alone or as an adjunct to systemic immunosuppressive agents. They observed a rapid clearance of the vitreous inflammation with improvement in visual acuity 1–2 weeks after injection. The effect lasted 2–6 months, with the shortest duration in a vitrectomized eye. Repeated injections were required in all patients. Karacorlu et al. (2004a–d) performed an intravitreal injection of triamcinolone acetonide (4 mg) in 10 eyes of 10 patients with cystoid macular edema due to Behcet's disease. At 1-, 3-, and 6-month follow-up, foveal thickness was significantly reduced. None of the eyes had lost vision at 1 month, and eight eyes (80%) showed improvement in visual acuity. At 3- and 6-month follow-up, three eyes (30%) remained stable and the other eyes maintained improved acuity.

Other diseases for which intravitreal triamcinolone acetonide has been used are Eales' disease (Pathengay et al., 2004) and Vogt–Koyanagi–Harada syndrome (Andrade et al., 2004).

15. Other indications for intravitreal triamcinolone acetonide

Other indications for which the intravitreal use of triamcinolone acetonide has been reported are ocular ischemic syndromes (Jonas et al., 2003i; Klais and Spaide, 2004) and cystoid macular edema due to retinitis pigmentosa (Sallum et al., 2003) as well as to visualize vitreous during surgery (Peyman et al., 2000).

16. Complications of intravitreal injections of triamcinolone acetonide

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

The clinical studies on intravitreal triamcinolone acetonide have shown several side-effects of the therapy. One of the two most common side-effects of intravitreal triamcinolone acetonide was the steroid-induced elevation of intraocular pressure (Agrawal et al., 2004; Bakri and Beer, 2003; Bui Quoc et al., 2002; Chan et al., 2004; Detry-Morel et al., 2004; Jonas et al., 2003a–j, 2004a–i; Singh et al., 2004; Smithen et al., 2004; Wingate and

Beaumont, 1999). 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 edema, exudative age-related macular degeneration, retinal vein occlusions, uveitis, and cystoid macular edema (Jonas et al., 2005d). Intraocular pressure readings higher than 21, 30, 35, 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 intraocular pressure could be treated by anti-glaucomatous 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 for few eyes, and occurring for most eyes, which develop an ocular hypertension, about 1–2 months after the intravitreal injection of 20–25 mg triamcinolone acetonide. Using this dosage, the increase in intraocular pressure lasted about 7–9 months after which the intraocular pressure measurements return to the normal range without any further anti-glaucomatous medication taken. In a multiple regression analysis, younger age was a significant factor contributing to the triamcinolone acetonide induced increase in intraocular pressure.

Unexpectedly, post-injection rise in intraocular pressure did not vary significantly between patients with a pre-injection diagnosis of chronic open-angle glaucoma and patients without a history of glaucoma. The reason for this unexpected finding has remained unclear so far. Either the number of patients in the glaucoma group was too small for a statistically significant difference between the two groups, or the pre-injection anti-glaucomatous treatment in the glaucoma group prevented a higher increase in intraocular pressure, or the megadosage of 20–25 mg of triamcinolone acetonide intravitreally injected made baseline differences between the glaucoma group and the non-glaucomatous group disappear. 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 intravitreal injection of triamcinolone acetonide.

Diagnosis of diabetes mellitus or presence of a clinically significant diffuse diabetic macular edema did not influence the reaction of intraocular pressure after the injection. It 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 (Degenring et al., 2004a,b; Jonas and

Söfker, 2001; Jonas et al., 2003a–j; Martidis et al., 2002; Massin et al., 2004).

Interestingly, increase in intraocular pressure was associated with an increase in visual acuity. The multifactorial regression analysis revealed that the increase in intraocular pressure was significantly associated with a higher gain in visual acuity 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 difference between the pressure in the vessel and the pressure in the space surrounding the vessel, i.e. intraocular pressure. If intraocular pressure 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. It agrees with previous studies in which elevation of intraocular pressure was associated with a decrease in pseudophakic cystoid macular edema (Civerchia and Balent, 1984; Melberg and Olk, 1993).

The rise in intraocular pressure started at about 1 week after the injection, and the measurements returned to the baseline values after about 9 months. These figures are valid for a dosage of 25 mg triamcinolone acetonide. Although not systemically investigated in the present study, many eyes included in the investigation showed ophthalmoscopically visible triamcinolone acetonide crystals in the vitreous for a similar period as the increase in intraocular pressure lasted. It suggests that when the triamcinolone acetonide crystals have resolved, intraocular pressure may return to its baseline level, and that the triamcinolone induced increase in intraocular pressure is reversible. It concurs with previous studies on reaction of intraocular pressure 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 of intraocular pressure as after the first injection (Jonas et al., 2004a–i). It suggests that if after a first injection, intraocular pressure remained in the normal range, intraocular pressure may also remain in the normal range after a second injection. In a similar manner, if intraocular pressure increased after the first injection, a similar rise in intraocular pressure may be expected after a second injection. So far, there are no reports on a permanent rise in intraocular pressure after an intravitreal injection of triamcinolone acetonide.

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 (Bakri and Beer, 2003; Bui Quoc et al., 2002; Jonas et al., 2003a–j, 2004a–i; Wingate and Beaumont, 1999). The figures of the frequency of secondary ocular hypertension may not

directly be correlated with the dosage injected. In the study performed by [Smithen et al. \(2004\)](#) with the intravitreal use of 4 mg triamcinolone acetonide, a pressure elevation defined as a pressure of 24 mmHg or higher during follow-up was found in 36 (40.4%) out of 89 patients at a mean of 101 ± 83 days after the injection. Of non-glaucomatous patients with a baseline intraocular pressure of 15 mmHg or above, 60.0% experienced a pressure elevation, compared with only 22.7% of those with baseline pressures below 15 mmHg. In glaucoma patients, six of the 12 (50%) experienced a pressure elevation, and this elevation was not correlated with baseline pressure. Thirty-two patients (36.0%) received repeat injections, and there was no difference in the incidence of procedure elevation in patients receiving multiple injections versus those receiving a single injection. Pressure elevation was controlled with topical medications in all patients. [Kaushik et al. \(2004\)](#) reported that seven of the nine non-glaucomatous patients who received 4 mg intravitreal triamcinolone acetonide for central retinal vein occlusion had a post-injection rise in intraocular pressures. 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 intravitreal injection of triamcinolone acetonide 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 that the eye makes out 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 intragluteal injection of 40 g, and an intravitreal injection of 25 mg triamcinolone acetonide is equal to a quarter of a kilogram injected intragluteally.

16.2. Post-injection infectious endophthalmitis

In recent studies on patients receiving an intravitreal injection of triamcinolone acetonide, the frequency of post-injection infectious endophthalmitis ranged between 0/700 and 8/992 (0.87%) ([Benz et al., 2003](#); [Jonas et al., 2003a–j](#); [Jonas and Bleyl, 2004](#); [Moshfeghi et al., 2003](#); [Nelson et al., 2003](#); [Parke, 2003](#)). 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 and Bleyl, 2004](#)). Between both areas, there is a sharp demarcation line. It is morphallaxia-like histology in which a dense infiltration of granulocytes is sharply demarcated by tissue areas in which inflammatory cells were almost completely missing. Such a histology, normally characteristic for demarcation and destruction of necrotic anemic tissue-like intrauterine 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 in which the triamcinolone acetonide crystals are present. Morphallaxia-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 with dense infiltration of all ocular structures by inflammatory cells. The morphallaxia-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 intravitreal injection of triamcinolone acetonide 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 migrated into the eye may be the histologic correlate of the clinical observation ([Benz et al., 2003](#); [Jonas et al., 2003a–j](#); [Jonas and Bleyl, 2004](#); [Moshfeghi et al., 2003](#); [Nelson et al., 2003](#); [Parke, 2003](#)).

16.3. Post-injection sterile endophthalmitis

A “sterile endophthalmitis” has been described to occur after an intravitreal injection of triamcinolone acetonide ([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 causative for the sterile intraocular inflammation after the injection. It has been inconclusive so far, whether the solvent agent should be removed before triamcinolone acetonide is injected. The disadvantage of removal of the solvent agent is that the dosage gets inaccurate ([Spandau et al., 2005b](#); [Rodriguez-Coleman et al., 2004](#)). [Bakri et al. \(2004\)](#) reported on the use of a commercially available preservative-free solution of triamcinolone acetonide, and [Hernaez-Ortega](#) described the use of density gradient centrifugation to remove the preservative.

16.4. 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 (Chen et al., 2004a,b; Jonas et al., 2000; Moshfeghi et al., 2004; Sutter and Gillies, 2003a,b). 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 a corneal endothelial damage or a damage to the trabecular meshwork by the crystals. If the intravitreal injection is performed in direction to the center of the vitreous cavity, a pseudo-hypopyon may only rarely occur. If, however, the injection touched the posterior chamber, the triamcinolone acetonide crystals may not be trapped by the vitreous body but may partially be washed into the anterior chamber.

16.5. Rhegmatogenous retinal detachment

Since the triamcinolone acetonide injection is carried out into the vitreous cavity leading to a de-arrangement of the structure of the vitreous body, and because an abnormal vitreous may exert a traction on the retina leading to a rhegmatogenous retinal detachment, a potential complication of the intravitreal injection may be a rhegmatogenous retinal detachment. In a recent study on 348 eyes receiving an intravitreal injection of about 20 mg triamcinolone acetonide as treatment of exudative age-related macular degeneration, diabetic macular edema, 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., 2004a–i, 2005b). It holds true particularly for the inferior midperipheral area of the fundus, where the triamcinolone acetonide crystals had settled in the preretinal vitreal cortex; for the superior midperipheral and peripheral fundus, where a vitreous traction might be induced by the weight of the triamcinolone acetonide crystals settled at six o'clock; and for the far periphery of the fundus, where retinal traction by vitreous if incarcerated into the injection site might have resulted (Gillies et al., 2004; Jaissle et al., 2004; Macky et al., 2002).

16.6. Post-injection, steroid-induced cataract

In a recent study on 144 phakic eyes which consecutively received an intravitreal injection of about 20 mg triamcinolone acetonide for diffuse diabetic macular edema, exudative age-related macular degeneration, and branch retinal vein occlusion, cataract

surgery was performed in 20 (13.9%) eyes 17.4 ± 9.1 months (median, 12.7 months; range, 8.0–35.5 months) after the intravitreal injection (own data). Out of the 20 eyes undergoing cataract surgery, 19 (95%) eyes had received one intravitreal injection, and one (5%) eye had received two previous injections. It was concluded that in the elderly population of patients with exudative age-related macular degeneration, diffuse diabetic macular edema or branch retinal vein occlusion, intravitreal high-dosage injection of triamcinolone acetonide leads to clinically significant cataract with eventual cataract surgery in about 15–20% of eyes within about 1 year after the intravitreal injection.

16.7. Toxic effects

Direct toxic effects of triamcinolone acetonide on the retina and optic nerve have not been observed yet, independent of the dosage used. Correspondingly, a recent safety and efficacy study of an intravitreal fluocinolone acetonide sustained delivery device as treatment for cystoid macular edema in patients with uveitis and other clinical and experimental studies have not shown a toxic effect of intraocular steroids (Gillies et al., 2004; Young et al., 2000). The same was found by Hida et al. (1986). It may be of importance 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 and Jonas, 2004b).

A recent study, however, performed by Yeung et al. (2004), reported on a possible cytotoxic effect of triamcinolone acetonide. Yeung and coworkers cultured a retinal pigment epithelium 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 a higher relative toxicity. The vehicle alone had no effect. In a similar study, Yeung et al. (2003) compared the cytotoxic effect of triamcinolone acetonide on human retinal pigment epithelium (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 retinal pigment epithelium 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. Morrison et al. (2004) tested the hypothesis that the preservative in the commercial compound of triamcinolone acetonide was toxic. Nine New Zealand rabbits were injected with either a control or the test article benzyl alcohol at elevating concentrations. They found that concentrations of benzyl alcohol only 3.3 times higher than what is injected intravitreally in humans was toxic to the retina and that higher concentrations were extremely toxic. Changes occurred largely in the outer retina and included 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 what is present in commercial Kenalog is toxic to the eye. They suggested that if commercial preserved Kenalog is to be used clinically, decanting or other means to remove the benzyl alcohol should be considered.

16.8. 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 intravitreal injection of triamcinolone acetonide (4 mg) in patients with subfoveal choroidal neovascularization caused by age-related macular degeneration was evaluated. Out of 75 eyes assigned to study treatment and 76 eyes assigned to placebo, there were no moderate or severe adverse events related to the surgical procedure in either group. Triamcinolone-treated eyes had a significantly increased risk of developing mild or moderate elevation of the intraocular pressure. Topical glaucoma medication reduced intraocular pressure 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.

In another recent case-series study included 46 patients who received at least two intravitreal injections of about 20 mg triamcinolone acetonide for treatment of diffuse diabetic macular edema, exudative age-related macular degeneration, 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 etiology (own data) were included. The second injection was carried out in 6.7 ± 3.4 months. 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, and one eye received altogether six injections. After the

re-injections, no complications or side-effects other than those already known to occur after a single intravitreal injection of triamcinolone acetonide were detected. After the first, second, and third injection, respectively, intraocular pressure remained within the normal range in 24 (51%), 25 (53%), and five (56%) eyes, respectively. Those eyes without a rise in intraocular pressure above 21 mmHg after the first injection did not show an elevation of intraocular pressure after a repeated injection. Mean maximal intraocular pressures after the first, second, and third injection did not vary significantly ($p > 0.50$). The results suggest that intravitreal high-dosage 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 intraocular pressure may not be more marked after a repeated 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 intravitreal high-dosage injection.

16.9. Dosages of intravitreal triamcinolone acetonide used so far

In most studies on intravitreal triamcinolone acetonide, a dosage of 4 mg has been used. Few centers have used a dosage of about 20 mg filtered triamcinolone acetonide. For the authors of the present report, reasons to use the high dosage were that: the same dosage was used from the beginning of the study series, the frequency and amount of side-effects appear not to be markedly different from the lower dosage, the duration of the effect of the higher dosage is longer, and possibly the effect may be more marked with higher dosage.

17. Future directions

The intravitreal injection of triamcinolone acetonide may possibly open new avenues for the treatment of intraocular edematous and neovascular diseases (Aiello et al., 2004). As for any new therapy, however, one has to be very careful since long-term experience has not been available yet. There are many open questions unanswered yet. What may be the best dosage for which disease and for which clinical situation? Is the proliferation of retinal pigment epithelium cells in high concentrations of triamcinolone acetonide decreased, and paradoxically, in low concentrations increased (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 (Coats et al., 2003; Gupta et al., 2003, 2004;

Moshfeghi et al., 2002; Okada et al., 2003)? Are there other complications than those already described in clinical studies or after accidental injection of triamcinolone acetonide into the vitreous cavity (Enaida et al., 2003a,b; Ghopal et al., 1995; Modarres et al., 1998; Takeuchi et al., 2003)? Is it necessary to remove the solvent agent prior to the intraocular injection, and how should the solvent agent be removed (Nishimura et al., 2003). The most fascinating point may be that the intravitreal injection of triamcinolone acetonide together with previous clinical experiences on the use of intravitreal antibiotics and virustatic drugs makes one understand that retinal diseases, particularly macular disorders, become locally treatable diseases since rather 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-angiogenics, 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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