Intravitreal Injection of Triamcinolone Acetonide

9

Jost B. Jonas[1]

Core Messages

- Intravitreal triamcinolone acetonide may offer a possible adjunctive treatment for intraocular edematous and neovascular disorders
- The best response after intravitreal triamcinolone acetonide injection in terms of gain in visual acuity was obtained for 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 sympathetic ophthalmia
- Intravitreal triamcinolone may be useful as angiostatic therapy in eyes with iris neovascularization and proliferative ischaemic retinopathies
- Intravitreal triamcinolone may possibly be helpful for exudative age-related macular degeneration, alone or 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
- 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 did not show a markedly elevated rate of complications
- If vision increases after the intravitreal triamcinolone injection, the injection may be repeated
- The duration of the effect of a single intravitreal injection of about 20 mg triamcinolone acetonide ranges between 2 and 9 months

9.1 Introduction

The introduction of pars plana vitrectomy in clinical ophthalmology by Robert Machemer and colleagues was a profound paradigm change which opened up new avenues for the treatment of ocular diseases, such as proliferative vitreoretinopathy, which up to that time had been incurable [79]. It was again Robert Machemer who together with Yasuo Tano, Gholam Peyman, Stephan Ryan and other researchers fur-

[1] The author has no proprietary interest in this chapter.

ther 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 became locally treatable, like a skin scratch being treated by ointment. In a first attempt, Peyman, Machemer and colleagues suggested the intravitreal application of steroids to reduce the proliferation of cells, particularly in patients with aggressive proliferative vitreoretinopathy and infectious endophthalmitis [4, 21, 33, 39, 80, 81, 87, 111, 112, 118, 119]. Crystalline triamcinolone acetonide instead of soluble steroids was taken, since soluble cortisone is washed out of the eye within approximately 24 h after a single intravitreal injection [111, 112].

Intravitreal triamcinolone acetonide has a considerably longer absorption time than intravitreal soluble cortisone [6, 42, 43, 45, 73, 80]. The intravitreal application of drugs allows extremely high concentrations of the drug at its site of acquired action, and simultaneously decreases or avoids systemic side effects [26]. Based on the studies by Machemer and others, the intraocular diseases for which intravitreal triamcinolone acetonide has been applied so far include disorders associated with an abnormal proliferation of cells and diseases associated with intraretinal and subretinal edema. Examples are proliferative diabetic retinopathy [54, 64], diabetic macular edema [50, 84, 65, 85], exudative age-related macular degeneration [15, 24, 31, 57, 66, 69, 71, 76, 95, 96, 102, 104, 115], presumed ocular histoplasmosis syndrome [38], central retinal vein occlusion [13, 34, 38, 56, 93], branch retinal vein occlusion [17, 72], neovascular glaucoma with or without cataract surgery [51, 55, 61], proliferative vitreoretinopathy [29, 52, 67], chronic pre-phthisical ocular hypotony [53, 106], chronic uveitis [3, 8, 11, 25, 83, 114, 123], persistent pseudophakic cystoid macular oedema [7, 22, 59, 77], perifoveal telangiectasias [1, 82], sympathetic ophthalmia [47], ischaemic ophthalmopathy [60], immunologic corneal graft reaction [44], extensive exudative retinal detachment [46], radiation induced macular oedema [116], and other disorders such as cystoid macular oedema due to retinitis pigmentosa [110], endocrine orbitopathy [101], Vogt-Koyanagi-Harada syndrome [2] and others [37, 90, 113]. It has also been applied in combination with intraocular surgery to visualize the vitreous and for other purposes [12, 86, 100, 109].

The effect of intravitreal triamcinolone acetonide may be differentiated into a mainly anti-edematous effect and a possibly antiangiogenic effect.

9.2 Anti-edematous Effect of Intravitreal Triamcinolone Acetonide

9.2.1 Diabetic Macular Edema

Recent studies have suggested that intravitreal triamcinolone acetonide may be useful to increase visual acuity in patients with diffuse diabetic macular edema [50, 64, 65, 84, 85]. 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. Using a dosage of about 20 mg triamcinolone acetonide, 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 [73]. Using a dosage of 4 mg triamcinolone acetonide, the duration of a reduction in the macular thickness as measured by opti-

cal coherence tomography was less than 6 months [85]. 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. In a multiple linear regression analysis, improvement in visual acuity after the intravitreal injection of triamcinolone acetonide was significantly correlated with a lower degree of macular ischaemia, a lower preoperative visual acuity, and a more marked macular edema. Change in visual acuity after the intravitreal triamcinolone injection was statistically independent of age and gender. It has remained unclear so far whether and how much 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 of a markedly elevated rate of retinal rhegmatogenous detachments as a complication in the follow-up of patients who received an intravitreal injection of triamcinolone acetonide [32, 70]. 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 retinovitreal proliferations.

9.3 Pars Plana Vitrectomy for Proliferate Diabetic Vitreoretinopathy Combined with Intravitreal Triamcinolone Acetonide

Due to the anti-inflammatory and antiangiogenic effects of triamcinolone acetonide, the latter has been used in combination with pars plana vitrectomy in patients with proliferative diabetic retinopathy [18, 19, 23, 28, 99, 120]. A pilot case series study including 29 patients suggested that intravitreal injection of triamcinolone with most of the vehicle removed may be well tolerated [54]. A following non-randomized comparative investigation consisted of a study group of 32 eyes undergoing pars plana vitrectomy with intravitreal triamcinolone acetonide, and a control group of 32 eyes which was matched with the study group for preoperative and intraoperative parameters, and which underwent pars plana vitrectomy for proliferative diabetic retinopathy without intravitreal injection of triamcinolone acetonide [64]. The study group and 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 acetonide did not show a higher than usual rate of postoperative complications, and that, as a corollary, the adjunct use of intravitreal triamcinolone acetonide combined with pars plana vitrectomy as treatment of proliferative diabetic retinopathy had not shown a marked therapeutic benefit.

9.4 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 in increasing visual acuity after central retinal vein occlusion. Recent studies on intravitreal triamcinolone acetonide have also addressed macular edema due to central retinal vein occlusion [13, 34, 38, 56, 93]. In a prospective comparative non-randomized clinical interventional study, gain in visual acuity was significantly higher in the study group, confirming other reports on the beneficial effect of intravitreal triamcinolone acetonide on macular edema and visual acuity in patients with central retinal vein occlusion. 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 to decline towards 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 ischaemic central retinal vein occlusion may be an antiangiogenic effect possibly decreasing the risk of neovascularization [18, 19, 23, 28, 49, 99].

9.5 Branch Retinal Vein Occlusion Treated by Intravitreal Triamcinolone Acetonide

Due to its anti-edematous and antiangiogenic effects as shown in experimental investigations and clinical studies, intravitreal triamcinolone acetonide has also been used in pilot studies on central retinal vein occlusions [17, 72]. In a recent prospective comparative non-randomized clinical interventional study with an intravitreal injection of 20–25 mg of triamcinolone acetonide in the study group, 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 [72]. Comparing study group and 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 [17].

9.6 Intravitreal Triamcinolone Acetonide for Pseudophakic Cystoid Macular Edema

Severe postoperative cystoid macular oedema can be a complication of phakoemulsification with implantation of an intraocular lens. It 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 treatment of persisting pseudophakic cystoid macular oedema [7, 22, 59]. 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 [59]. There was no clear tendency suggesting a decrease in visual acuity towards 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.

9.7 Intravitreal Triamcinolone Acetonide for Cystoid Macular Edema After Penetrating Keratoplasty

Long-standing cystoid macular edema can occur rarely after penetrating keratoplasty. A recent report suggests that intravitreal triamcinolone acetonide may be an additional tool in the treatment of this condition [49]. 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 [44, 105].

9.8 Intravitreal Triamcinolone Acetonide and Central Serous Chorioretinopathy

In a previous report on a patient who had long-standing central serous chorioretinopathy recurring continuously 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 (own data). It agrees with other recent studies on patients with central serous chorioretinopathy for which preceding steroid therapy has been detected to be a risk factor [35].

9.9 Foveal Telangiectasias

For foveal telangiectasias, intravitreal injection of triamcinolone acetonide has also been used. In two reports, intravitreal triamcinolone acetonide increased visual acuity, while in a third study only one out of two patients experienced an increase in visual acuity [1, 82].

9.10 Antiangiogenic Effect of Intravitreal Triamcinolone Acetonide

9.10.1 Regression of Neovascular Iris Vessels by Intravitreal Triamcinolone Acetonide

The possibly antiangiogenic effect of triamcinolone acetonide, which has been postulated by both experimental investigations and clinical studies on patients receiving triamcinolone acetonide for treatment of exudative age-related macular degeneration, was observed in an investigation of 14 eyes with neovascular glaucoma due to proliferative diabetic retinopathy or ischaemic central retinal vein occlusion [51, 55, 61]. 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 pa-

tients for whom the intraocular cortisone injection was the only procedure performed, mean intraocular pressure decreased from 26.5 ±12.1 mmHg to 21.75 ±11.3 mmHg.

9.10.2 Cataract Surgery Combined with Intravitreal Triamcinolone Acetonide in Eyes with Iris Neovascularization

In patients with dense cataract and iris neovascularization due to ischaemic retinopathies, the lens opacification prevents a transpupillary laser coagulation of the retina. An intraocular intervention such as cataract surgery will, however, lead to a marked postoperative inflammation if iris neovascularization is additionally present. In that clinical situation, cataract surgery has been combined with an intravitreal injection of triamcinolone acetonide [51]. 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 acetonide may be a useful adjunctive treatment tool in eyes with iris neovascularization undergoing cataract surgery, and that intravitreal triamcinolone acetonide may have an antiangiogenic effect.

9.11 Exudative 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 antiangiogenetic, antiproliferate and antiedematous effect, intravitreal triamcinolone acetonide has increasingly been used as a treatment option for exudative age-related macular degeneration [15, 24, 31, 57, 66, 69, 71, 76, 95, 96, 102, 104, 115].

In 1995, Penfold and colleagues started to inject triamcinolone acetonide intravitreally in an effort to treat exudative age-related macular degeneration medically [96]. In 1998, Challa and co-workers [15] 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 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 ten eyes with an 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 and colleagues examined the effects of intravitreal injection of 4 mg triamcinolone acetonide on the visual and clinical course of exudative age-related macular degeneration in 27 patients who were compared with a non-treated control group [24]. 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 in 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 an 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 proliferation of blood vessels [14, 18, 19, 23, 28, 30, 35, 97–99, 120, 121]. 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 [66]. 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 [66]. 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 [57]. 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, at 1 month and 3 months after study start [76]. Between the study group and 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 2 or more Snellen lines was significantly (p=0.001) larger than in the control group. Correspondingly, the number of patients with a decrease of 2 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 2 or more Snellen lines. The results of these studies are partially in contrast to a recent study by Gillies and colleagues, who found no effect of 4 mg of intravitreal triamcinolone acetonide on the development of severe visual loss over a follow-up period of 1 year [31]. 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, reinjections 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. Interestingly, Gillies and co-workers 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 antiphlogistic effect of intravitreal triamcinolone acetonide [14, 18, 19, 23, 28, 30, 35, 97–99, 120, 121]. 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 [69]. A postinjection increase in visual acuity was signif-

icantly ($p<0.001$) and negatively correlated with preoperative visual acuity, and it was significantly ($p=0.035$) larger in eyes with retinal pigment epithelium detachment than in eyes with minimally classic subfoveal neovascularization. Postinjection change in visual acuity was statistically independent of age, refractive error, gender, and duration of follow-up. The results suggested that for eyes with a preoperative visual acuity of less than 0.20, intravitreal injection of triamcinolone acetonide can result in an increase in visual acuity. Eyes with a preoperative visual acuity of higher than 0.20 may lose visual acuity after the injection. It does, however, not necessarily mean that the loss in visual acuity after the intravitreal injection was due to the intravitreal injection itself. It might have been that the eyes with loss in visual acuity after the injection would have lost more in visual acuity if the intravitreal injection had not been performed. 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 2 Snellen lines after an intravitreal injection of about 20–25 mg triamcinolone acetonide. Within the 1st 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 reinjected about 6–9 months after a primary successful injection.

In a consequent study, the effect of intravitreal reinjections of triamcinolone acetonide as treatment for exudative age-related macular degeneration was investigated [71]. 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 of 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 $p=0.003$, respectively) after the first and after the second injection, respectively. Increase in visual acuity was found for ten (77 %) patients after the first and after the second injection, respectively. 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 reinjection. It suggests that a reinjection 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 be followed up closely 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 postinjection increase in visual acuity was statistically independent of the elevation in intraocular pressure.

9.12 Intravitreal Triamcinolone Acetonide for Proliferative Vitreoretinopathy

In a pilot study, intravitreal triamcinolone acetonide was applied in combination with pars plana vitrectomy for treatment of proliferative vitreoretinopathy [52]. 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 [67]. After a mean follow-up of 8.6±6.6 months, retinal re-detachment was detected in ten (30 %) patients. In five of the ten patients with retinal re-detachment, the detachment was observed within the first 3 months after surgery. The shortest intervals between surgery and detection of re-detachment were 1 week and 3 weeks. 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 in that study. It was unexpected in view of the presumed anti-inflammatory and antiproliferative properties of steroids such as triamcinolone acetonide. It may be explained, however, by the results of a previous experimental study in which triamcinolone acetonide inhibited the proliferation of rabbit dermal and conjunctival fibroblasts in cell culture at 150 mg/l, but paradoxically increased proliferation almost twofold at concentrations ranging from 1 to 30 mg/l under identical culture conditions [10]. In contrast, Chandler and colleagues observed a protective effect of intravitreal triamcinolone acetonide if it was injected simultaneously with, or prior to, fibroblasts into the vitreous cavity of rabbit eyes, in reducing the rate of retinal detachment [16].

As long as the influence of low concentrations of steroids on the proliferation of retinal pigment epithelium cells has remained unclear, intravitreal triamcinolone acetonide 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 pharmakokinetics of intraocular triamcinolone acetonide [43], and whether the location of the retinal re-detachments in the inferior fundus were incidentally or causally in spatial

relationship to the triamcinolone acetonide crystals which also settled in the inferior fundus periphery.

Enaida and colleagues 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 [27]. The study group had a slightly lower incidence of reoperations caused by preretinal fibrous membrane formation than in the control group. In another study, Kimura and coworkers used triamcinolone acetonide as help in peeling of the internal limiting membrane [78].

9.13 Cataract Surgery After Intravitreal Triamcinolone Acetonide

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 who 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 oedema [68]. 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 harbour a markedly elevated frequency or a markedly changed profile of complications of standard cataract surgery, and that the cataractogenic effect of intravitreal triamcinolone acetonide is not a major contraindication to using triamcinolone acetonide intravitreally.

9.14 Chronic Pre-phthisical Ocular Hypotony

In contrast to ocular hypertension, which can often successfully be cured by a whole array of antiglaucomatous medical and surgical methods, progressive ocular hypotony can be an untreatable condition eventually leading to blindness and painful phthisis bulbi. In an attempt to use a side effect of steroids as desired effect, triamcinolone acetonide was injected intravitreally in three eyes with long-standing pre-phthisical ocular hypotony [53, 106]. In all three patients, intraocular pressure and visual acuity increased after the injection was associated with a stabilization of the eyes. It may suggest that in some eyes with long-standing pre-phthisical ocular hypotony, intravitreal injection of triamcinolone acetonide can be beneficial in increasing intraocular pressure and stabilizing the eye.

9.15 Uveitis

Intravitreal triamcinolone acetonide has additionally been used for treatment of therapy-resistant chronic uveitis [3, 8, 11, 25, 26, 83, 114, 123]. In these studies, a marked regression of intraocular inflammation, a reduction of cystoid macular oedema, and an increase in visual acuity was observed. An alternative to intravitreal triamcinolone acetonide has been the use of intraocular slow-release devices containing fluocinolone with a longer duration of action in the treatment of uveitis [40].

9.16 Future Studies

In view of the possible neuroprotective effect of steroids, intravitreal triamcinolone acetonide has been considered to be of use for the treatment of acute optic neuropathies such as non-arteritic anterior ischaemic optic neuropathy or arteritic anterior ischaemic optic neuropathy, and acute central or branch retinal artery occlusion.

9.17 Complications of Intravitreal Injections of Triamcinolone Acetonide

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 [5, 62, 63, 74, 122]. A recent prospective clinical interventional comparative non-randomized study included 253 consecutive patients (280 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 (own data). Intraocular pressure readings higher than 21 mmHg, 30 mmHg, 35 mmHg, and 40 mmHg, respectively, were measured in 94 (36.2 %) patients, 22 (8.5 %) patients, 11 (4.2 %) patients, and 4 (1.5 %) patients, respectively. Triamcinolone induced intraocular pressure elevation was treated by antiglaucomatous medication in all but three (1.0 %) eyes, for which filtering surgery was performed. About 40 % of the patients developed a secondary ocular hypertension with values above 21 mmHg, starting about 1 week after the injection for a few eyes, and occurring for most eyes, which developed an ocular hypertension, about 1–2 months after the intravitreal injection of 20–25 mg triamcinolone acetonide. Younger age and pre-baseline diagnosis of glaucoma were significantly associated with triamcinolone induced ocular hypertension. Intraocular pressure increase during follow-up was significantly correlated with higher gain in visual acuity. Triamcinolone responders and triamcinolone non-responders did not vary significantly in gender, refractive error, diabetes mellitus, and reason for treatment. If triamcinolone acetonide was reinjected, the change in intraocular pressure after the reinjection was similar to the change in intraocular pressure after the first injection.

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. This may agree with previous randomized clinical trials in which diabetes mellitus was not a major risk factor for glaucoma [92]. From a clinical point of view, diagnosis of diabetes mellitus may not be a contraindication against intravitreal application of triamcinolone acetonide

as previous studies have also demonstrated [50, 54, 64, 65, 84, 85].

Interestingly, an increase in intraocular pressure was associated with an increase in visual acuity. 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 the 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. This agrees with previous studies in which elevation of intraocular pressure was associated with a decrease in pseudophakic cystoid macular oedema [20, 88].

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 about 20–25 mg triamcinolone acetonide. Many eyes show ophthalmoscopically visible triamcinolone acetonide crystals in the vitreous for a similar period as the increase in intraocular pressure lasts. This 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. This concurs with previous studies on reaction of intraocular pressure after topical application of corticosteroids [63].

Those patients who received a second injection of 20–25 mg triamcinolone acetonide showed a similar reaction of intraocular pressure to after the first injection [71]. This suggests that if after a first injection, intraocular pressure remains in the normal range, intraocular pressure may also remain in the normal range after a second injection. In a similar manner, if intraocular pressure increases after the first injection, a similar rise in intraocular pressure may be expected after a second injection. So far, there have been no reports of 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 steroid-induced ocular hypertension [5, 62, 63, 122]. The figures of the frequency of secondary ocular hypertension may not be directly correlated with the dosage injected. If further studies confirm this assumption, it may be explained by the fact that already relatively low triamcinolone acetonide dosages are so high that all steroid receptors may be occupied by triamcinolone already at the relatively low dosages of 2 mg or 4 mg of triamcinolone acetonide. One has to take into account that the eye makes up 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.

9.17.1 Postinjection Infectious Endophthalmitis

In recent studies on patients receiving an intravitreal injection of triamcinolone acetonide, the frequency of postinjection infectious endophthalmitis ranged between 0/700 and 8/992 (0.87 %) [9, 48, 58, 89, 91, 94]. The risk of 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 [48]. Between both areas, there is a sharp demarcation line. There is a morphallaxia-like histology in which a dense infiltration of granulocytes is sharply demarcated by tissue areas where inflammatory cells are almost completely missing. Such a histology, normally characteristic of demarcation and destruction of necrotic anaemic 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. This histopathologic pattern 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 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 [91]. The lack of inflammatory cells migrating into the eye may be the histologic correlate of the clinical observation.

9.17.2 Postinjection Sterile Endophthalmitis

A "sterile endophthalmitis" has been described to occur after an intravitreal injection of triamcinolone acetonide [91, 94, 108]. 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 becomes inaccurate [107].

9.17.3 Postinjection 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 [52, 117]. The diagnostic problem is the differentiation between a painless hypopyon caused by a postinjection 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 of corneal endothelial damage or damage to the trabecular meshwork by the crystals. If the intravitreal injection is performed in the direction of the centre 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.

9.17.4 Rhegmatogenous Retinal Detachment

Since the triamcinolone acetonide injection is carried out into the vitreous cavity leading to a dearrangement 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 of 348 eyes receiving an intravitreal injection of about 20 mg triamcinolone acetonide as treatment of exudative age-related macular degeneration, diabetic macular oedema, retinal vein occlusions, persistent pseudophakic cystoid macular degeneration, and uveitis, none of the eyes developed a rhegmatogenous retinal detachment or retinal lesions [32, 70]. This holds true particularly for the inferior midperipheral area of the fundus, where the triamcinolone acetonide crystals have 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 6 o'clock; and for the far periphery of the fundus, where retinal traction by vitreous if incarcerated into the injection site might have resulted.

9.17.5 Postinjection, Steroid Induced Cataract

In a recent study of 144 phakic eyes which consecutively received an intravitreal injections of about 20 mg triamcinolone acetonide for diffuse diabetic macular oedema, 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 oedema 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.

9.18 Toxic Effects

Direct toxic effects of triamcinolone acetonide on the retina and optic nerve have not yet been observed, independently of the dosage used [18]. 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

has not shown a toxic effect of intraocular steroids [123]. The same result was found by Hida, Machemer and co-workers [36]. 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 [26].

9.19 Safety of Intravitreal Injections of Triamcinolone Acetonide Including High-Dose Reinjections

In a recent prospective randomized study by Gillies and colleagues, 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 [32]. Out 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.

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 oedema, 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 aetiology [75]. The second injection was carried out at 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 none of the reinjections were complications or side effects detected other than those already known to occur after a single intravitreal injection of triamcinolone acetonide. After the first, second and third injections, respectively, intraocular pressure remained within the normal range in 24 (51 %), 25 (53 %), and 5 (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 injections, respectively, did not vary significantly ($p>0.50$). The results suggest that intravitreal high-dosage reinjections 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 be not more marked after a repeated injection than after the first injection; and that side effects or complications may not occur more frequently after reinjections of triamcinolone acetonide than after a primary intravitreal high-dosage injection.

In summary, intravitreal triamcinolone acetonide has increasingly been applied as a treatment option for various intraocular neovascular and edematous 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 oedema, branch retinal vein occlusion, central retinal vein occlusion, and pseudophakic cystoid macular oedema. Visual acuity increased and degree of intraocular inflammation decreased in eyes with various types of non-infectious uveitis including sympathetic ophthalmia. Intravitreal triamcinolone may be useful as angiostatic therapy in eyes with iris neovascularization and proliferative ischaemic 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 ranged between 2 and 9 months, probably depending on the dosage used. Intravitreal triamcinolone acetonide may offer a possibility for adjunctive treatment of intraocular oedematous and neovascular disorders. One has to take into account the side effects and the lack of long-term follow-up observations.

As for any new therapy, however, one has to be very careful since long-term experience is not yet available. There are many open questions as yet unanswered. What is 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? What is the best mode of application of triamcinolone acetonide, is the subtenon application, the subconjunctival application or the retrobulbar application better than the intravitreal injection? Are there other complications than those already described in clinical studies or after accidental injection of triamcinolone acetonide into the vitreous cavity? Is it necessary to remove the solvent agent prior to the intraocular injection, and how should the solvent agent be removed? 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.

References

1. Alldredge CD, Garretson BR (2003) Intravitreal triamcinolone for the treatment of idiopathic juxtafoveal telangiectasias. Retina 23:113–116
2. Andrade RE, Muccioli C, Farah ME, Nussenblatt RB, Belfort R Jr (2004) Intravitreal triamcinolone in the treatment of serous retinal detachment in Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol 137:572–574
3. Antcliff RJ, Spalton DJ, Stanford MR, Graham EM, ffytche TJ, Marshall J (2001) Intravitreal triamcinolone for uveitic cystoid macular edema: an optical coherence tomography study. Ophthalmology 108:765–772

4. Antoszyk AN, Gottlieb JL, Machemer R, Hatchell DL (1993) The effects of intravitreal triamcinolone acetonide on experimental pre-retinal neovascularisation. Graefes Arch Clin Exp Ophthalmol 231:34–40
5. Bakri SJ, Beer PM (2003) The effect of intravitreal triamcinolone acetonide on intraocular pressure. Ophthalmic Surg Lasers Imaging 34:386–390
6. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB 3rd, Miller M (2003) Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. Ophthalmology 110:681–686
7. Benhamou N, Massin P, Haouchine B, Audren F, Tadayoni R, Gaudric A (2003) Intravitreal triamcinolone for refractory pseudophakic macular edema. Am J Ophthalmol 135:246–249
8. Benitez Del Castillo Sanchez JM, Garcia Sanchez J (2001) [Intravitreal injection of triamcinolone acetonide in non infectious uveitis]. Arch Soc Esp Oftalmol 76:661–664
9. Benz MS, Murray TG, Dubovy SR, Katz RS, Eifrig CW (2003) Endophthalmitis caused by *Mycobacterium chelonae* abscessus after intravitreal injection of triamcinolone. Arch Ophthalmol 121:271–273
10. Blumenkranz MS, Claflin A, Hajek AS (1984) Selection of therapeutic agents for intraocular proliferative disease. Cell culture evaluation. Arch Ophthalmol 102:598–604
11. Bui Quoc E, Bodaghi B, Adam R, Burtin T, Cassoux N, Dreifuss S, Fardeau C, Lehoang P (2002) [Intraocular pressure elevation after subtenon injection of triamcinolone acetonide during uveitis]. J Fr Ophtalmol 25:1048–1056
12. Burk SE, Da Mata AP, Snyder ME, Schneider S, Osher RH, Cionni RJ (2003) Visualizing vitreous using Kenalog suspension. J Cataract Refract Surg 29:645–651
13. Bynoe LA, Weiss JN (2003) Retinal endovascular surgery and intravitreal triamcinolone acetonide for central vein occlusion in young adults. Am J Ophthalmol 135:382–384
14. Carroll LA, Hanasono MM, Mikulec AA, Kita M, Koch RJ (2002) Triamcinolone stimulates bFGF production and inhibits TGF-beta1 production by human dermal fibroblasts. Dermatol Surg 28:704–709
15. Challa JK, Gillies MC, Penfold PL, Gyory JF, Hunyor AB, Billson FA (1998) Exudative macular degeneration and intravitreal triamcinolone: 18 month follow up. Aust N Z J Ophthalmol 26:277–281
16. Chandler DB, Hida T, Sheta S, Proia AD, Machemer R (1987) Improvement in efficacy of corticosteroid therapy in an animal model of proliferative vitreoretinopathy by pretreatment. Graefes Arch Clin Exp Ophthalmol 225: 259–265
17. Chen SD, Lochhead J, Patel CK, Frith P (2004) Intravitreal triamcinolone acetonide for ischaemic macular oedema caused by branch retinal vein occlusion. Br J Ophthalmol 88: 154–155
18. Ciulla TA, Criswell MH, Danis RP, Hill TE (2001) Intravitreal triamcinolone acetonide inhibits choroidal neovascularisation in a laser-treated rat model. Arch Ophthalmol 119: 399–404
19. Ciulla TA, Criswell MH, Danis RP, Fronheiser M, Yuan P, Cox TA, Csaky KG, Robinson MR (2003) Choroidal neovascular membrane inhibition in a laser treated rat model with intraocular sustained release triamcinolone acetonide microimplants. Br J Ophthalmol 87:1032–1037
20. Civerchia LL, Balent A (1984) Treatment of pseudophakic cystoid macular edema by elevation of intraocular pressure. Ann Ophthalmol 16:890–894
21. Coats ML, Peyman GA (1992) Intravitreal corticosteroids in the treatment of exogenous fungal endophthalmitis. Retina 12:46–51
22. Conway MD, Canakis C, Livir-Rallatos C, Peyman GA (2003) Intravitreal triamcinolone acetonide for refractory chronic pseudophakic cystoid macular edema. J Cataract Refract Surg 29:27–33
23. Danis RP, Bingaman DP, Yang Y, Ladd B (1996) Inhibition of preretinal and optic nerve head neovascularisation in pigs by intravitreal triamcinolone acetonide. Ophthalmology 103: 2099–2104
24. Danis RP, Ciulla TA, Pratt LM, Anliker W (2000) Intravitreal triamcinolone acetonide in exudative age-related macular degeneration. Retina 20:244–250
25. Degenring RF, Jonas JB (2003) Intravitreal injection of triamcinolone acetonide as treatment of chronic uveitis. Br J Ophthalmol 87:361
26. Degenring R, Jonas JB (2004) Serum levels of triamcinolone acetonide after intravitreal injection. Am J Ophthalmol 137:1142–1143
27. Enaida H, Hata Y, Ueno A, Nakamura T, Hisatomi T, Miyazaki M, Fujisawa K, Sakamoto T, Ishibashi T (2003) Possible benefits of triamcinolone-assisted pars plana vitrectomy for retinal diseases. Retina 23:764–770

28. Folkman J, Ingber DE (1987) Angiostatic steroids. Method of discovery and mechanism of action. Ann Surg 206:374–383
29. Furino C, Micelli Ferrari T, Boscia F, Cardascia N, Recchimurzo N, Sborgia C (2003) Triamcinolone-assisted pars plana vitrectomy for proliferative vitreoretinopathy. Retina 23:771–776
30. Gao H, Qiao X, Gao R, Mieler WF, McPherson AR, Holz ER (2004) Intravitreal triamcinolone does not alter basal vascular endothelial growth factor mRNA expression in rat retina. Vision Res 44:349–356
31. Gillies MC, Simpson JM, Luo W, Penfold P, Hunyor AB, Chua W, Mitchell P, Billson F (2003) A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration: one-year results. Arch Ophthalmol 121: 667–673
32. Gillies MC, Simpson JM, Billson FA, Luo W, Penfold P, Chua W, Mitchell P, Zhu M, Hunyor AB (2004) Safety of an intravitreal injection of triamcinolone: results from a randomized clinical trial. Arch Ophthalmol 122:336–340
33. Graham RO, Peyman GA (1974) Intravitreal injection of dexamethasone. Treatment of experimentally induced endophthalmitis. Arch Ophthalmol 92:149–154
34. Greenberg PB, Martidis A, Rogers AH, Duker JS, Reichel E (2002) Intravitreal triamcinolone acetonide for macular oedema due to central retinal vein occlusion. Br J Ophthalmol 86: 247–248
35. Haimovici R, Koh S, Gagnon DR, Lehrfeld T, Wellik S (2004) Central Serous Chorioretinopathy Case-Control Study Group. Risk factors for central serous chorioretinopathy: a case-control study. Ophthalmology 111:244–249
36. Hida T, Chandler D, Arena JE, Machemer R (1986) Experimental and clinical observations of the intraocular toxicity of commercial corticosteroid preparations. Am J Ophthalmol 101: 190–195
37. Inoue M, Nagai N, Shinoda H, Shinoda K, Kitamura S, Oguchi Y (2004) [Intravitreal injection of triamcinolone acetonide for cystoid macular edema resistant to vitreous surgery.] Nippon Ganka Gakkai Zasshi 108:92–97
38. Ip MS, Kumar KS (2002) Intravitreous triamcinolone acetonide as treatment for macular edema from central retinal vein occlusion. Arch Ophthalmol 120:1217–1219
39. Ishibashi T, Miki K, Sorgente N, Patterson R, Ryan SJ (1985) Effects of intravitreal administration of steroids on experimental subretinal neovascularisation in the subhuman primate. Arch Ophthalmol 103:708–711
40. Jaffe GJ, Ben-nun J, Guo H, Dunn JP, Ashton P (2000) Fluocinolone acetonide sustained drug delivery device to treat severe uveitis. Ophthalmology 107:2024–2033
41. Jaissle GB, Szurman P, Bartz-Schmidt KU (2004) Nebenwirkungen und Komplikationen der intravitrealen Triamcinolonacetonid-Therapie. Ophthalmologe 101:121–128
42. Jonas JB (2002) Concentration of intravitreally applicated triamcinolone acetonide in aqueous humour. Br J Ophthalmol 86:1066
43. Jonas JB (2002) Concentration of intravitreally injected triamcinolone acetonide in intraocular silicone oil. Br J Ophthalmol 86:1450–1451
44. Jonas JB (2003) Intravitreal triamcinolone acetonide as treatment of chronic focal immunologic corneal graft reaction. Graefes Arch Clin Exp Ophthalmol 241:779–780
45. Jonas JB (2004) Intraocular availability of triamcinolone acetonide after intravitreal injection. Am J Ophthalmol 137:560–562
46. Jonas JB (2004) Intravitreal triamcinolone acetonide as treatment for extensive exudative retinal detachment? Br J Ophthalmol (in press)
47. Jonas JB (2004) Intravitreal triamcinolone acetonide for treatment of sympathetic ophthalmia. J Ophthalmol 137:367–368
48. Jonas JB, Bleyl U (2004) Morphallaxia-like ocular histology after intravitreal triamcinolone acetonide. Br J Ophthalmol 88:839–849
49. Jonas JB, Kamppeter B (2004) Intravitreal triamcinolone acetonide for persisting cystoid macular edema after penetrating keratoplasty. Cornea (in press)
50. Jonas JB, Söfker A (2001) Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. Am J Ophthalmol 132:425–427
51. Jonas JB, Söfker A (2002) Intravitreal triamcinolone acetonide for cataract surgery with iris neovascularisation. J Cataract Refr Surg 28: 2040–2041
52. Jonas JB, Hayler JK, Panda-Jonas S (2000) Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative vitreoretinopathy. Br J Ophthalmol 84:1064–1067
53. Jonas JB, Hayler JK, Panda-Jonas S (2001) Intravitreal injection of crystalline cortisone as treatment of pre-phthisical ocular hypotony. Graefes Arch Clin Exp Ophthalmol 239:464–465

54. Jonas JB, Hayler JK, Söfker A, Panda-Jonas S (2001) Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative diabetic retinopathy. Am J Ophthalmol 131: 468–471
55. Jonas JB, Hayler JK, Söfker A, Panda-Jonas S (2001) Regression of neovascular iris vessels by intravitreal injection of crystalline cortisone. J Glaucoma 10:284–287
56. Jonas JB, Kreissig I, Degenring RF (2002) Intravitreal triamcinolone acetonide as treatment of macular edema in central retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol 240:782–783
57. Jonas JB, Kreissig I, Degenring RF (2002) Repeated intravitreal injections of triamcinolone acetonide as treatment of progressive exudative age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 240:873–874
58. Jonas JB, Kreissig I, Degenring RF (2003) Endophthalmitis after intravitreal injection of triamcinolone acetonide. Arch Ophthalmol 121:1663–1664
59. Jonas JB, Kreissig I, Degenring RF (2003) Intravitreal triamcinolone acetonide for pseudophakic cystoid macular edema. Am J Ophthalmol 136:384–386
60. Jonas JB, Kreissig I, Degenring RF (2003) Intravitreal triamcinolone as treatment for ischemic ophthalmopathy. Eur J Ophthalmol 13:575–576
61. Jonas JB, Kreissig I, Degenring RF (2003) Neovascular glaucoma treated by intravitreal triamcinolone acetonide. Acta Ophthalmol 81:540–541
62. Jonas JB, Kreissig I, Degenring RF (2003) Secondary chronic open-angle glaucoma after intravitreal triamcinolone acetonide. Arch Ophthalmol 121:729–730
63. Jonas JB, Kreissig I, Degenring R (2003) Intraocular pressure after intravitreal injection of triamcinolone acetonide. Br J Ophthalmol 87:24–27
64. Jonas JB, Söfker A, Degenring RF (2003) Intravitreal triamcinolone acetonide as additional tool in pars plana vitrectomy for proliferate diabetic retinopathy. Eur J Ophthalmol 13:468–473
65. Jonas JB, Kreissig I, Söfker A, Degenring RF (2003) Intravitreal injection of triamcinolone acetonide for diabetic macular edema. Arch Ophthalmol 121:57–61
66. Jonas JB, Kreissig I, Hugger P, Sauder G, Panda-Jonas S, Degenring R (2003) Intravitreal triamcinolone acetonide for exudative age-related macular degeneration. Br J Ophthalmol 87: 462–468
67. Jonas JB, Söfker A, Hayler J, Degenring RF (2003) Intravitreal crystalline triamcinolone acetonide as additional tool in pars plana vitrectomy for complicated proliferative vitreoretinopathy? Acta Ophthalmol 81:663–665
68. Jonas JB, Kreissig I, Degenring RF (2004) Cataract surgery after intravitreal injection of triamcinolone acetonide. Eye 18:361–364
69. Jonas JB, Kreissig I, Degenring RF (2004) Factors influencing visual acuity after intravitreal triamcinolone acetonide as treatment of exudative age-related macular degeneration. Br J Ophthalmol (in press)
70. Jonas JB, Kreissig I, Degenring RF (2004) Retinal complications of intravitreal injections of triamcinolone acetonide. Graefes Arch Clin Exp Ophthalmol 242:184–185
71. Jonas JB, Akkoyun I, Budde WM, Kreissig I, Degenring RF (2004) Intravitreal re-injection of triamcinolone for exudative age-related macular degeneration. Arch Ophthalmol 122:218–222
72. Jonas JB, Akkoyun I, Kamppeter B, Kreissig I, Degenring RF (2004) Intravitreal triamcinolone acetonide as treatment of branch retinal vein occlusion. Eye (in press)
73. Jonas JB, Degenring R, Kamppeter B, Kreissig I, Akkoyun I (2004) Duration of the effect of intravitreal triamcinolone acetonide as treatment of diffuse diabetic macular edema. Am J Ophthalmol (in press)
74. Jonas JB, Degenring RF, Kamppeter BA (2004) Filtering surgery after intravitreal triamcinolone acetonide injection. J Glaucoma 13:261
75. Jonas JB, Degenring RF, Kreissig I, Akkoyun I (2004) Safety of intravitreal high-dose reinjections of triamcinolone acetonide. Am J Ophthalmol (in press)
76. Jonas JB, Degenring RF, Kreissig I, Friedemann T, Akkoyun I (2004) Exudative age-related macular degeneration treated by intravitreal triamcinolone acetonide. A prospective comparative non-randomized study. Eye (in press)
77. Karacorlu M, Ozdemir H, Karacorlu S (2003) Intravitreal triamcinolone acetonide for the treatment of chronic pseudophakic cystoid macular oedema. Acta Ophthalmol Scand 81: 648–652

78. Kimura H, Kuroda S, Nagata M (2004) Triamcinolone acetonide-assisted peeling of the internal limiting membrane. Am J Ophthalmol 137:172–173
79. Machemer R (1988) Proliferative vitreoretinopathy, PVR. A personal account of its pathogenesis and treatment. Proctor lecture. Invest Ophthalmol Vis Sci 29:1771–1783
80. Machemer R (1996) Five cases in which a depot steroid (hydrocortisone acetate and methylprednisolone acetate) was injected into the eye. Retina 16:166–167
81. Machemer R, Sugita G, Tano Y (1979) Treatment of intraocular proliferations with intravitreal steroids. Trans Am Ophthalmol Soc 77:171–180
82. Martinez JA (2003) Intravitreal triamcinolone acetonide for bilateral acquired parafoveal telangiectasias. Arch Ophthalmol 121:1658–1659
83. Martidis A, Duker JS, Puliafito CA (2001) Intravitreal triamcinolone for refractory cystoid macular edema secondary to birdshot retinochoroidopathy. Arch Ophthalmol 119:1380–1383
84. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, Baumal C (2002) Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 109: 920–927
85. Massin P, Audren F, Haouchine B, Erginay A, Bergmann JF, Benosman R, Caulin C, Gaudric A (2004) Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. Ophthalmology 111:218–224; discussion 224–225
86. Matsumoto H, Enaida H, Hisatomi T, Ueno A, Nakamura T, Yamanaka I, Sakamoto T, Ishibashi T (2003) Retinal detachment in morning glory syndrome treated by triamcinolone acetonide-assisted pars plana vitrectomy. Retina 23:569–572
87. McCuen BW 2nd, Bessler M, Tano Y, Chandler D, Machemer R (1981) The lack of toxicity of intravitreally administered triamcinolone acetonide. Am J Ophthalmol 91:785–788
88. Melberg NS, Olk RJ (1993) Corticosteroid-induced ocular hypertension in the treatment of aphakic or pseudophakic cystoid macular edema. Ophthalmology 100:164–167
89. Moshfeghi DM, Kaiser PK, Scott IU, Sears JE, Benz M, Sinesterra JP, Kaiser RS, Bakri SJ, Maturi RK, Belmont J, Beer PM, Murray TG, Quiroz-Mercado H, Mieler WF (2003) Acute endophthalmitis following intravitreal triamcinolone acetonide injection. Am J Ophthalmol 136:791–796
90. Navajas EV, Costa RA, Farah ME, Cardillo JA, Bonomo PP (2003) Indocyanine green-mediated photothrombosis combined with intravitreal triamcinolone for the treatment of choroidal neovascularisation in serpiginous choroiditis. Eye 17:563–566
91. Nelson ML, Tennant MT, Sivalingam A, Regillo CD, Belmont JB, Martidis A (2003) Infectious and presumed noninfectious endophthalmitis after intravitreal triamcinolone acetonide injection. Retina 23:686–691
92. Palmberg P (2001) Risk factors for glaucoma progression: Where does intraocular pressure fit in? Arch Ophthalmol 119:897–898
93. Park CH, Jaffe GJ, Fekrat S (2003) Intravitreal triamcinolone acetonide in eyes with cystoid macular edema associated with central retinal vein occlusion. Am J Ophthalmol 136:419–425
94. Parke DW (2003) Intravitreal triamcinolone and endophthalmitis. Am J Ophthalmol 136: 918–919
95. Penfold PL (2002) Intravitreal triamcinolone in recurrence of choroidal neovascularisation. Br J Ophthalmol 86:600–601
96. Penfold PL, Gyory JF, Hunyor AB, Billson FA (1995) Exudative macular degeneration and intravitreal triamcinolone. A pilot study. Aust N Z J Ophthalmol 23:293–298
97. Penfold PL, Wen L, Madigan MC, King NJ, Provis JM (2002) Modulation of permeability and adhesion molecule expression by human choroidal endothelial cells. Invest Ophthalmol Vis Sci 43:3125–3130
98. Penfold PL, Wong JG, Gyory J, Billson FA (2001) Effects of triamcinolone acetonide on microglial morphology and quantitative expression of MHC-II in exudative age-related macular degeneration. Clin Exp Ophthalmol 29:188–192
99. Penn JS, Rajaratnam VS, Collier RJ, Clark AF (2001) The effect of an angiostatic steroid on neovascularisation in a rat model of retinopathy of prematurity. Invest Ophthalmol Vis Sci 42:283–290

100. Peyman GA, Cheema R, Conway MD, Fang T (2000) Triamcinolone acetonide as an aid to visualization of the vitreous and the posterior hyaloid during pars plana vitrectomy. Retina 20:554–555
101. Rakic JM, Zelinkova M, Comhaire-Poutchinian Y, Galand A, Duchateau E (2003) [Treatment of Graves macular edema with intravitreal injection of corticosteroids.] Bull Soc Belge Ophtalmol 288:43–48
102. Ranson NT, Danis RP, Ciulla TA, Pratt L (2002) Intravitreal triamcinolone in subfoveal recurrence of choroidal neovascularisation after laser treatment in macular degeneration. Br J Ophthalmol 86:527–529
103. Rechtman E, Allen VD, Danis RP, Pratt LM, Harris A, Speicher MA (2003) Intravitreal triamcinolone for choroidal neovascularisation in ocular histoplasmosis syndrome. Am J Ophthalmol 136:739–741
104. Rechtman E, Danis RP, Pratt LM, Harris A (2004) Intravitreal triamcinolone with photodynamic therapy for subfoveal choroidal neovascularisation in age related macular degeneration. Br J Ophthalmol 88:344–347
105. Reinhard T, Sundmacher R (2002) Adjunctive intracameral application of corticosteroids in patients with endothelial immune reactions after penetrating keratoplasty. A pilot study. Transpl Int 15:81–88
106. Rodriguez ML, Juarez CP, Luna JD (2003) Intraocular steroids as a treatment for blind painful red eyes. Eur J Ophthalmol 13:292–297
107. Rodriguez-Coleman H, Yuan P, Kim H, Gravlin L, Srivastava S, Csaky KG, Robinson MR (2003) Intravitreal injection of triamcinolone for diffuse diabetic macular edema (letter to the editor, concerning the article Jonas JB, Kreissig I, Söfker A, Degenring RF 2003 Intravitreal injection of triamcinolone acetonide for diabetic macular edema. Arch Ophthalmol 121:57–61). Arch Ophthalmol (2004) (in press)
108. Roth DB, Chieh J, Spirn MJ, Green SN, Yarian DL, Chaudhry NA (2003) Noninfectious endophthalmitis associated with intravitreal triamcinolone injection. Arch Ophthalmol 121: 1279–1282
109. Sakamoto T, Miyazaki M, Hisatomi T, Nakamura T, Ueno A, Itaya K, Ishibashi T (2002) Triamcinolone-assisted pars plana vitrectomy improves the surgical procedures and decreases the postoperative blood-ocular barrier breakdown. Graefes Arch Clin Exp Ophthalmol 240:423–429
110. Saraiva VS, Sallum JM, Farah ME (2003) Treatment of cystoid macular edema related to retinitis pigmentosa with intravitreal triamcinolone acetonide. Ophthalmic Surg Lasers Imaging 34:398–400
111. Schindler RH, Chandler DB, Thresher R, Machemer R (1982) The clearance of intravitreal triamcinolone acetonide. Am J Ophthalmol 93:415–417
112. Scholes GN, O'Brien WJ, Abrams GW, Kubicek MF (1985) Clearance of triamcinolone from vitreous. Arch Ophthalmol 103:1567–1569
113. Scott IU, Flynn HW Jr, Rosenfeld PJ (2003) Intravitreal triamcinolone acetonide for idiopathic cystoid macular edema. Am J Ophthalmol 136:737–739
114. Sonoda KH, Enaida H, Ueno A, Nakamura T, Kawano YI, Kubota T, Sakamoto T, Ishibashi T (2003) Pars plana vitrectomy assisted by triamcinolone acetonide for refractory uveitis: a case series study. Br J Ophthalmol 87:1010–1014
115. Spaide RF, Sorenson J, Maranan L (2003) Combined photodynamic therapy with verteporfin and intravitreal triamcinolone acetonide for choroidal neovascularisation. Ophthalmology 110:1517–1525
116. Sutter FK, Gillies MC (2003) Intravitreal triamcinolone for radiation-induced macular edema. Arch Ophthalmol 121:1491–1493
117. Sutter FK, Gillies MC (2003) Pseudo-endophthalmitis after intravitreal injection of triamcinolone. Br J Ophthalmol 87:972–974
118. Tano Y, Chandler D, Machemer R (1980) Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide. Am J Ophthalmol 90:810–816
119. Tano Y, Sugita G, Abrams G, Machemer R (1980) Inhibition of intraocular proliferation with intravitreal corticosteroid. Am J Ophthalmol 89:131–136

120. Wang YS, Friedrichs U, Eichler W, Hoffmann S, Wiedemann P (2002) Inhibitory effects of triamcinolone acetonide on bFGF-induced migration and tube formation in choroidal microvascular endothelial cells. Graefes Arch Clin Exp Ophthalmol 240:42–48
121. Wilson CA, Berkowitz BA, Sato Y, Ando N, Handa JT, de Juan E Jr (1992) Treatment with intravitreal steroid reduces blood-retinal barrier breakdown due to retinal photocoagulation. Arch Ophthalmol 110:1155–1159
122. Wingate RJ, Beaumont PE (1999) Intravitreal triamcinolone and elevated intraocular pressure. Aust N Z J Ophthalmol 27:431–432
123. Young S, Larkin G, Branley M, Lightman S (2001) Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis. Clin Exp Ophthalmol 29:2–6