Intravitreal Triamcinolone

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Key Words

Triamcinolone · Intraocular steroids · Diabetic retinopathy · Macular edema · Retinal vein occlusion · Ocular hypotony · Ocular hypertension, steroid induced

Abstract

Background: To provide an update on the intravitreal use of triamcinolone acetonide. **Methods:** Review of literature regarding triamcinolone-related research. **Results:** After the introduction of bevacizumab and ranibizumab into clinical practice, intravitreal triamcinolone has lost its leading position as the drug most often injected intravitreally. Due to its properties as a long-acting steroid, triamcinolone has still been used for various conditions such as diffuse diabetic macular edema, retinal vein occlusions, pseudophakic cystoid macular edema, chronic preperphthical ocular hypotony and uveitis, and in combination with bevacizumab or ranibizumab. The complications of intravitreal triamcinolone therapy include secondary ocular hypertension in about 40% of the eyes injected, cataract and postoperative infectious or noninfectious endophthalmitis. **Conclusions:** Due to its widespread biological effects as a steroid and due to a relatively large therapeutic window, intravitreal triamcinolone has remained in clinical use for a variety of intraocular disorders, and it may be a promising candidate for intravitreal medical combination therapies.

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Introduction

It was Robert Machemer among others who suggested to use the vitreous cavity as a reservoir for drugs to directly treat intraocular diseases [1–12]. Robert Machemer and colleagues in particular thought about intravitreal triamcinolone acetonide (IVTA) as a therapy of proliferative vitreoretinopathy [1, 3, 4, 9, 13–16]. As a consequence of Machemer's suggestion, IVTA has been used for the treatment of other intraocular proliferative, edematous and neovascular diseases such as proliferative diabetic retinopathy [17, 18], diffuse diabetic macular edema (DME) and diabetic retinopathy in general [18–79], branch retinal vein occlusion (BRVO) [80–92], central retinal vein occlusion (CRVO) [93–111], neovascular glaucoma without or with cataract surgery [112–115], exudative age-related macular degeneration (AMD) [116–152], myopic choroidal neovascularization [153, 154], presumed ocular histoplasmosis syndrome [155], chronic preperphthical ocular hypotony [156–158], chronic uveitis [159–168], persistent pseudophakic cystoid macular edema [169–174], sympathetic ophthalmia [175–177], radiation-induced macular edema [178, 179], immunologic corneal graft reaction [180], perifoveal telangiectasia [181–183], ischemic ophthalmopathy [184, 185], extensive exudative retinal detachment [186], and other disorders such as cystoid macular edema due to retinitis pigmentosa [187–189], endocrine orbitopathy [190], Vogt-Koy-

anagi-Harada syndrome [165] and others [191–206]. It has also been applied in combination with intraocular surgery to visualize the vitreous and for other reasons [207–221].

The reasons for using a steroid for the treatment of intraocular edematous and proliferative diseases were that the abnormal proliferation of intraocular cells is often accompanied and stimulated by intraocular inflammation, and that besides the intraocular proliferation of cells, defects in the blood-retina barrier due to capillary leakage, with accumulation of fluid in the intraretinal and subretinal spaces of the macula, are other major causes of impaired vision. The reason for injecting the steroid into the eye was that corticosteroids applied topically as drops, given systemically or injected into the subconjunctival or sub-Tenon space, often did not reach a sufficiently high intraocular concentration to achieve a therapeutic level, or that the systemic side effects were too pronounced for prolonged treatment. The reason for using triamcinolone acetonide (TA) was that soluble substances injected into the eye usually leave the globe within hours to a few days [6, 222]. In an attempt to achieve long-lasting concentrations of a drug, the drug may have to be used in a crystalline form or packed into a slow-release device [6, 36, 40, 222–225]. TA has been one of a few crystalline steroids available for clinical practice.

The Compound: Physicochemical Characteristics

TA is a synthetic steroid of the glucocorticoid family with a fluorine instead of a hydrogen atom in the ninth position [226]. The molecular weight of TA is 434.50 and its empirical formula is $C_{24}H_{31}FO_6$ [227]. It is commercially available as an ester, a white powder only minimally soluble in water but soluble in alcohol and chloroform [226, 228]. The current commercial preparations include Kenalog, Flutex, Kenacort-A, Kenaquart, Ledercort D, Oncilon-A, Respicort, Rineton, Solodelf, Tramacin, Triclinolon, Vetalog, Volonimat, and Aristocort acetonide [229].

The decreased water solubility accounts for its prolonged duration of action [228]. The elimination half-life of the commercial preparation of TA in vitreous humor of rat recently detected by Oishi et al. [230] was 6.08 days. In nonvitrectomized patient eyes, the mean elimination half-life was 18.6 days, while in 1 postvitrectomy patient eye, it decreased to 3.2 days [223]. After single intravitreal injection, peak aqueous humor concentrations ranged from 2.15 to 7.20 $\mu\text{g/ml}$ [223]. Inoue et al. [40]

found that the vitreous concentrations of TA after intravitreal injection were significantly higher than those after sub-Tenon injection (1.22 ± 0.24 vs. $<0.001 \mu\text{g/ml}$; $p = 0.003$).

Preclinical (Animal) Studies

IVTA has been applied in several preclinical studies [1, 3, 4, 8–10, 208, 210, 215, 216, 219]. Most animal studies did not show significant intraocular toxicity [5, 231–235]. As early as 1981, McCuen et al. [5] performed intravitreal injections of 1 mg of TA into 1 eye of each of 21 rabbits, whereas the other eye received an injection of an equal volume of saline solution as a control. The results of slit-lamp examinations, ophthalmoscopy, intraocular pressure, electroretinography and light electron microscopy all remained normal throughout the 3-month course of the experiment, demonstrating the lack of ocular toxicity of TA in the rabbit. Ruiz-Moreno et al. [233] demonstrated that up to 30 mg of intravitreal TA did not seem to have acute toxic effects on the function (electroretinogram) or structure (electron and light microscopy) of the retina of albino rabbits at 28 days after IVTA injection.

IVTA has also been studied in particular conditions. Kivilcim et al. [235] performed IVTA injections at doses of 1, 2 or 4 mg in vitrectomized and silicone-filled rabbit eyes. The electroretinograms and histologic sections in all groups were normal, and no drug was visible in the vitreous cavity at the end of the 140-day period (average) in eyes injected with 4 mg of TA.

Clinical Studies: TA as Medical Device (Vitrectomy)

In several studies, intraocular TA was used intraoperatively during pars plana vitrectomy to visualize the inner limiting membrane, epiretinal membranes and remnants of the vitreous base [207, 214, 219, 220, 236]. Yamamoto et al. [216] found that using TA during vitrectomy may facilitate both the removal of the epiretinal membrane around the macular hole and the separation of the residual vitreous cortex from the retina in highly myopic eyes with retinal detachment. Birinci [236] retrospectively reviewed the data on 72 patients (75 eyes) who accepted triamcinolone-assisted pars plana vitrectomy and cataract surgery for proliferative diabetic retinopathy. Postoperatively, visual acuity improved in 65 eyes (86.7%) and complications consisted of mild iritis in 8 eyes (10.7%), recurrent vitreous hemorrhage in 8 eyes

(10.7%), posterior capsule opacification in 7 eyes (9.3%), transient intraocular pressure increase in 6 eyes (8.0%), iatrogenic retinal tear in 6 (8.0%) eyes and epiretinal membrane in 5 eyes (6.7%). It was also reported that triamcinolone-assisted vitrectomy was tried by a 25-gauge vitrectomy system and showed good results during 6 months of follow-up [237].

It may be of importance not to use IVTA in situations where the inner limiting membrane of the retina is removed since a study by Jaissle et al. [238] suggested that IVTA may exhibit a potentially cell-damaging effect if the limiting membrane is not present. It remains unclear whether the risk of a postoperative infectious endophthalmitis after triamcinolone-assisted vitrectomy is increased.

Clinical Studies: TA as Drug Treatment for Macular Edema

Diabetic Macular Edema

For decades, studies have suggested that IVTA may be useful to temporarily increase visual acuity in patients with diffuse DME [18, 19, 21–34]. The most convincing evidence came from a prospective, double-masked, placebo-controlled and randomized trial by Sutter et al. [34]. Eighteen of 33 eyes (55%) treated with triamcinolone (4 mg) gained 5 or more letters of best-corrected visual acuity compared with 5 of 32 eyes (16%) treated with placebo ($p = 0.002$). Macular edema was reduced by 1 or more grades as determined by masked semiquantitative contact lens examination in 25 of 33 treated eyes (75%) versus 5 of 32 untreated eyes (16%; $p < 0.0001$).

Ciardella et al. [25] performed an intravitreal injection of 4 mg of TA into 30 eyes of 22 consecutive patients with DME refractory to laser treatment. The mean visual acuity improved from 0.17 ± 0.12 at baseline to 0.31 ± 0.17 , and the mean macular thickness measured by optical coherence tomography decreased from $476 \pm 98 \mu\text{m}$ at baseline to $331 \pm 147 \mu\text{m}$ at the 6-month follow-up. A progressive reduction in the number and size of the hard exudates was noted after intravitreal TA in all patients. Similar results were reported in studies performed by Micelli et al. [32], Karaçorlu et al. [28], Lee and Yang [30], Gharbiya et al. [196] and Negi et al. [45].

Larsson et al. [49] did not find a correlation between the improvement in visual acuity and the reduction in foveal thickness ($r = 0.05$; $p = 0.8$) after a single intravitreal injection of 4 mg of triamcinolone in DME. Correspondingly, a study looking for predictive factors for the

change in visual acuity after IVTA injection found that the more marked the macular edema and the less marked the macular ischemia, the higher the increase in visual acuity after the injection [43]. The varying degree of macular ischemia may explain why some patients do not show a marked improvement in vision despite a regression of the macular edema and thickness. A multiple linear regression analysis revealed that improvement in visual acuity after IVTA injection was 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.

The appropriate dose of IVTA for DME is a controversial topic. Both Hauser et al. [239] and Audren et al. [240] showed that the use of the higher 4-mg dose of IVTA does not have enough advantages over the lower 1- or 2-mg dose. However, Lam et al. [241] published a comparison between 4- and 8-mg doses and showed that the higher dose had a more sustained effect on both visual acuity and central macular thickness although with a trend to more ocular hypertensive responses. Using a dose of about 20 mg of TA, 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 [36]. Using a dose of 4 mg of TA, the duration of the reduction in macular thickness as measured by optical coherence tomography was less than 6 months [31].

Several studies were performed to compare the efficacy and safety between IVTA and intravitreal bevacizumab [242], between IVTA and focal/grid photocoagulation [243–245], between IVTA plus photocoagulation and IVTA or photocoagulation alone [246], and between IVTA and vitrectomy with internal limiting membrane peeling [247]. In a randomized study, Avitabile et al. [53] compared the outcome after IVTA injection with macular laser grid photocoagulation for the treatment of cystoid macular edema due to diabetic retinopathy and retinal vein occlusion. After IVTA treatment, visual acuity significantly improved and the central macular thickness significantly decreased. In the macular grid laser study, visual acuity remained unchanged. The groups receiving triamcinolone had better visual acuity and lower central macular thickness values at all time points during follow-up. Recently, both the published 2-year [244] and 3-year [243] follow-up results of a randomized study by the DRCR.net (Diabetic Retinopathy Clinical Research Network) group did not indicate a benefit from IVTA relative to focal/grid photocoagulation in patients with DME. Moreover, Lam et al. [246] performed a randomized comparative study and found that combined treatment with

IVTA plus grid laser did not yield a greater central macular thickness reduction or best-corrected visual acuity improvement at 6 months than IVTA alone. However, if IVTA and intravitreal bevacizumab were combined, a significantly greater macular thickness reduction in comparison with standard laser treatment was observed in another randomized study [248]. Recently, Kim et al. [247] showed that vitrectomy combined with inner limiting membrane removal had a better long-term efficacy than a single IVTA injection at 6 months after surgery. Shimura et al. [242] showed IVTA at a dose of 4 mg was better at reducing DME and improving visual acuity than a dose of 1.25 mg of bevacizumab within 6 months after injection. Nowadays, a multicenter, randomized and controlled trial (the TIME study) is in progress, which should be the first randomized prospective clinical trial to compare the effectiveness of IVTA with inner limiting membrane peeling [249].

So far, it has remained unclear whether and how intensively TA crystals injected into the vitreous body may influence the vitreoretinal interface. One may suspect that, due to their weight, the crystals may lead to a posterior vitreous detachment if the vitreous has not already been detached prior to the injection. A posterior vitreous detachment may have as a disadvantage the possibly increased risk of rhegmatogenous retinal detachment. So far, however, there have been no reports in the literature on a markedly elevated rate of retinal rhegmatogenous detachments as a complication in the follow-up of patients who received an IVTA injection [250]. The advantages of a posterior vitreous detachment in patients with diabetic retinopathy may be a reduction in macular edema, as suggested by studies on pars plana vitrectomy in patients with diffuse DME, and a decreased risk of retinovitreal proliferations.

Branch Retinal Vein Occlusion

In an exponentially increasing number of case series studies and nonrandomized comparative studies, IVTA has been used for the treatment of BRVO [80–92, 251]. Özkiris et al. [86] evaluated the efficacy of IVTA injection on persistent macular edema in BRVO that failed to respond to previous laser photocoagulation. During a mean follow-up time of 6.2 ± 1.0 months, the best-corrected logarithm of the minimal angle of resolution improved significantly ($p < 0.001$) from 1.01 ± 0.16 at baseline to 0.62 ± 0.22 at the final follow-up.

Recently, there have been two reports [252, 253] from different departments showing an encouraging effect of IVTA combined with laser photocoagulation in eyes with

macular edema after BRVO. In the report by Riese et al. [252], at 6 months after treatment, a gain of 1 or more logarithmic lines was achieved in 16/24 eyes (67%) and a gain of 3 lines or more was achieved in 8/24 eyes (33%), and the median central foveal thickness decreased from 423 μm at baseline to 266 μm ($p = 0.001$). Designed in a randomized way, Parodi et al. [253] compared the effectiveness of subthreshold grid laser treatment with infrared micropulse diode laser alone or in combination with IVTA for the treatment of macular edema secondary to BRVO. At the 12-month evaluation, 10 patients of the combination group (91%) and 8 of the laser alone group (62%) gained at least 10 letters (2 lines) in visual acuity. The mean number of lines gained was 3.4 and 1.3 in the combination group and in the laser alone group, respectively.

A recent randomized study compared the functional and anatomical outcomes of arteriovenous sheathotomy and IVTA for macular edema associated with BRVO. The between-group differences in average ETDRS (Early Treatment of Diabetic Retinopathy Study) score, total macular volume and foveal thickness changes were significantly better at 1 month after treatment in the IVTA group ($p = 0.026$, $p < 0.001$ and $p = 0.001$, respectively), at which time IVTA patients had better vision and anatomical outcomes than those in the sheathotomy group [254].

All studies on IVTA for BRVO mentioned above have the serious flaw that they do not have a strict randomized design, and they often did not clearly differentiate between the nonischemic type and the ischemic type of the disease. Recently, the results of a multicenter and randomized clinical trial of 411 BRVO participants, the SCORE (Standard Care versus Corticosteroid for Retinal Vein Occlusion) study, has been published [255]. There was no difference identified in visual acuity at 12 months for the standard care group (grid photocoagulation in eyes without dense macular hemorrhage, and deferral of photocoagulation until the hemorrhage clears in eyes with dense macular hemorrhage) compared with the triamcinolone groups; however, the rates of adverse events (particularly elevated intraocular pressure and cataract) were highest in the 4-mg group. Therefore, the authors recommended that grid photocoagulation should remain the benchmark against which other treatments are compared in clinical trials for eyes with vision loss associated with macular edema secondary to BRVO.

Central Retinal Vein Occlusion

After the first reports on the use of IVTA for the treatment of CRVO by Greenberg et al. [99] and Jonas et al.

[104], the number of reports on the use of IVTA as therapy of CRVO have increased exponentially [93–111]. In a prospective nonrandomized comparative study on 11 eyes with CRVO receiving an intravitreal injection of TA, compared with 6 eyes of a control group without intravitreal injection of TA, the gain in visual acuity was significantly ($p = 0.003$) higher in the study group [103]. This confirms results of other reports on the beneficial effect of intravitreal TA on macular edema and visual acuity in patients with CRVO [81–99]. The results additionally suggest that the increase in visual acuity after IVTA injection may not last permanently in eyes with CRVO. 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. In a similar manner, Williamson and O'Donnell [111] found that intravitreal TA at a dose of 2 mg was effective in reversing cystoid macular edema and improving visual acuity in recent-onset nonischemic CRVO in the first 6 months, but this was not sustained over the following 6 months.

Another positive effect of intravitreal TA in eyes with ischemic CRVO may be a direct or indirect antiangiogenic effect, possibly decreasing the risk of neovascularization [208, 256–266].

A recent nonrandomized comparative study [267] revealed that the therapeutic effects displayed no significant difference between the IVTA group and the intravitreal bevacizumab group with regard to visual results ($p = 0.240$) and macular thickness decrease ($p = 0.832$), and IVTA seemed to cause more adverse events than bevacizumab, which was consistent with our own results [268].

Recently, the results of the SCORE study [269], a multicenter and randomized clinical trial of 271 CRVO participants, showed that the odds of achieving a gain in visual acuity letter score of 15 or more from baseline to 12-month follow-up were 5.0 times greater in the 1-mg group than in the observation group ($p = 0.001$), and 5.0 times greater in the 4-mg group than in the observation group ($p = 0.001$); there was no difference identified between the 1- and 4-mg groups ($p = 0.97$). The rates of elevated intraocular pressure and cataract were similar for the observation and 1-mg groups, but higher in the 4-mg group. The authors concluded that IVTA is superior to observation for treating vision loss associated with macular edema secondary to CRVO.

Pseudophakic Cystoid Macular Edema

Phacoemulsification with the implantation of an intraocular lens can be complicated by severe postoperative

cystoid macular edema. The latter has usually been treated with topical, peribulbar and systemic applications of steroids or nonsteroidal antiinflammatory agents. Recently, IVTA has been used for the treatment of persisting pseudophakic cystoid macular edema [169–174]. Patients who developed cystoid macular edema after cataract surgery and who received an IVTA showed an increase in visual acuity from 0.26 ± 0.13 to a mean best visual acuity of 0.60 ± 0.19 [174]. 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 IVTA treatment.

Clinical Studies: TA for Proliferative Retinopathies

Pars Plana Vitrectomy for Proliferative Diabetic Vitreoretinopathy Combined with Intravitreal TA

Due to the antiinflammatory and antiangiogenic effects of TA, it 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 [270]. A following nonrandomized comparative investigation consisted of 32 eyes undergoing pars plana vitrectomy with IVTA and 32 control eyes which were matched to the study eyes for preoperative and intraoperative parameters and underwent pars plana vitrectomy for proliferative diabetic retinopathy without IVTA [17]. The study and control eyes did not vary significantly in their rates of postoperative retinal detachment, repeated pars plana vitrectomy, postoperative enucleation and phthisis bulbi, and in their best postoperative visual acuity, visual acuity at the end of the study, and gain in visual acuity. Future randomized investigations may readdress the question whether adding intravitreal triamcinolone to pars plana vitrectomy may be helpful in the postoperative stabilization of the eye and in reducing the risk of postoperative cystoid macular edema and neovascularization.

Pars Plana Vitrectomy for Proliferative Vitreoretinopathy Combined with Intravitreal TA

In a pilot study, IVTA was applied in combination with pars plana vitrectomy to the treatment of proliferative vitreoretinopathy [14]. During the follow-up period (mean: 1.64 months), intraocular inflammation and postoperative pain were significantly less severe in the

study group. The study suggested that IVTA with most of the vehicle removed may not be toxic to intraocular structures, and that it reduces postoperative intraocular inflammation. In a following study, however, the redetachment rate was about 30% [16], so that up to now, IVTA has not generally been shown to be markedly useful in combination with pars plana vitrectomy for proliferative vitreoretinopathy. Enaida et al. [212] used TA in combination with pars plana vitrectomy and found that between the study group with TA (n = 94 eyes) and the control group without TA (n = 83 eyes), there were no significant differences in the frequency of improved vision after surgery, the rate of intraocular pressure higher than 21 mm Hg after the operation, and the frequency of additional filtering surgeries. The study group had a slightly lower incidence of reoperations caused by preretinal fibrous membrane formation than the control group. Summarizing the clinical reports available, it remains unclear whether IVTA suppresses the proliferation of retinal pigment epithelium cells *in vivo*.

Clinical Studies: TA in Other Ocular Diseases

Exudative AMD

IVTA has been discussed to be a possibly useful adjunct to the therapy of exudative AMD [116–152] since previous studies had shown that TA may have an antiangiogenic and antiedematous effect [112–115, 258–260, 262–266]. Both neovascularization and retinal edema are characteristics of exudative AMD.

Penfold et al. [116] were the first to inject TA intravitreally in an effort to treat exudative AMD medically. In 1998, Challa et al. [117] evaluated the safety and efficacy of IVTA after a follow-up of 18 months in patients with exudative AMD considered unsuitable for laser photocoagulation. In the nonrandomized clinical pilot study, 30 eyes of 28 patients were treated with an IVTA injection (4 mg). Of the 20 eyes with initial visual acuity of 0.10 or better, vision was stabilized in 11 eyes (55%), while 6 eyes (30%) suffered severe visual loss (6 or more lines). Similar results of a possibly positive effect of IVTA on exudative AMD were reported in a randomized clinical trial by Danis et al. [118] and in other case series studies and nonrandomized comparative investigations [119, 121, 125, 126, 128, 135, 152]. One of these studies looked for factors influencing visual acuity after an intravitreal injection of TA as treatment of exudative AMD [126]. A postinjection increase in visual acuity was significantly ($p < 0.001$) 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. The effect of IVTA on visual acuity in patients with exudative AMD lasted about 6–8 months if a dose of about 20 mg was used. If, after that time, visual acuity decreased again, some patients received a repeated injection of about 20 mg of TA followed by a reincrease in visual acuity [125].

The results of these nonrandomized studies are partly in contrast to those of a double-masked, placebo-controlled, randomized clinical study by Gillies et al. [123] which determined whether a single intravitreal injection of 4 mg of TA can safely reduce the risk of severe visual loss in patients with classic choroidal neovascularization associated with AMD. The whole study population included 75 study eyes receiving IVTA and 76 control eyes without treatment. The development of a severe loss of vision of 30 or more letters by survival analysis on an intention-to-treat basis was the main outcome measure. Gillies et al. [123] did not find 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 TA than in those receiving placebo 3 months after treatment although no difference was noted after 12 months. Although there were differences between the studies in the type of subfoveal neovascularization, the dosage of TA, and the timing of the follow-up examinations, the randomized controlled study by Gillies et al. [123] may be a landmark study cautioning against the use of TA as a monotherapy for exudative AMD. In agreement with Gillies et al. [123], a recent follow-up study on 205 patients who received IVTA as a monotherapy for the treatment of exudative AMD reported that visual acuity at 6, 9 and 12 months after the injection was significantly ($p < 0.001$) lower than visual acuity at the baseline of the study [136]. The mean loss at 6 months was 1.4 ± 3.8 Snellen lines, at 9 months it was 2.5 ± 4.6 lines, and at 12 months after the injection it was 2.6 ± 4.0 lines. It was concluded that a single high-dose intravitreal triamcinolone injection may stabilize visual acuity in patients with neovascular AMD for about 3 months but may eventually be associated with a loss in visual acuity.

The studies mentioned above were the reason for initiating multicenter studies to evaluate the triamcinolone/photodynamic therapy combined treatment: the VISTA trial led by Rick Spaide, the VERTACL trial led by Karl Csaky at the National Eye Institute, and a third trial fund-

ed by a pharmaceutical company. Recent estimates suggest that about 70–90% of all verteporfin photodynamic treatments for exudative macular degeneration are combined with an intravitreal injection of TA.

In general, in the era of intravitreal use of bevacizumab for the treatment of exudative AMD, triamcinolone monotherapy seems to be no longer up to date.

Cataract Surgery on 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 IVTA [115]. In the postoperative period, visual acuity increased, and without additional retinal ablative treatments, the iris neovascularization markedly regressed within the first 5 weeks after surgery. The study suggested that IVTA may be a useful adjunctive treatment tool in eyes with iris neovascularization undergoing cataract surgery, and that IVTA may have an antiangiogenic effect.

Uveitis

Chronic uveitis has usually been treated by topical or systemic application of steroids. Topical treatment, however, often has not been sufficiently effective in suppressing intraocular inflammation and reducing 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 IVTA for other indications, TA has also been applied to eyes with chronic therapy-resistant uveitis [159–168, 175–177, 197, 199, 200, 204, 271–275]. These diseases include Adamantiadis-Behçet's disease [199, 200]: Karaçorlu et al. [199] performed an intravitreal injection of TA (4 mg) in 10 eyes of 10 patients with cystoid macular edema due to Behçet's disease. At the 1-, 3- and 6-month follow-ups, foveal thickness was significantly reduced. None of the eyes had lost vision at 1 month, and 8 eyes (80%) showed improvement in visual acuity. At the 3- and 6-month follow-ups, 3 eyes (30%) remained stable, and the other eyes had maintained the improved acuity. Kramer et al. [200] reported on 3 patients with acute severe exacerbations of noninfectious panuveitis and vitritis due to Adamantiadis-Behçet's disease who were treated with IVTA injections alone or as an adjunct to sys-

temic 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.

Other diseases for which IVTA has been used are Eales' disease [204], the Vogt-Koyanagi-Harada syndrome [165], chronic sympathetic ophthalmia [175, 176] acute sympathetic ophthalmia [177], adult Coat's disease [197] and other diseases [168].

Other Conditions

IVTA has been applied as treatment for foveal telangiectasia. In two reports, IVTA increased visual acuity, while in a third report only 1 out of 2 patients experienced an increase in visual acuity [181, 182]. Smithen and Spaide [183] reported a combined treatment of photodynamic therapy with verteporfin and IVTA injection (4 mg) for subfoveal neovascularization secondary to bilateral idiopathic juxtafoveal telangiectasias. Leakage in the late phase of fluorescein angiography resolved in an attenuation of telangiectatic vessels and an improvement in visual acuity from 20/200 to 20/50. At 9 months after 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.

In a recent report on a patient presenting with longstanding cystoid macular edema after penetrating keratoplasty suggests that IVTA may be an additional tool in the treatment of longstanding therapy-resistant cystoid macular edema after intraocular surgery besides phacoemulsification [198]. The beneficial effects of triamcinolone-assisted vitrectomy during the management of retained nuclei by phacofragmentation were shown by Kaynak et al. [276]. An additional advantage of intraocular steroids to the treatment of cystoid macular edema after penetrating keratoplasty may be the suppression of an immunologic graft reaction as recently described [180, 277].

In contrast to ocular hypertension, which can often successfully be cured by a whole array of antiglaucomatous medical and surgical methods, progressive ocular hypotony can be an untreatable condition eventually leading to blindness and painful phthisis bulbi. In an attempt to use a side effect of steroids as a desired effect, TA was injected intravitreally in 3 eyes with longstanding prephthisical ocular hypotony [156]. In all 3 patients, intraocular pressure and visual acuity increased after the

injection, associated with a stabilization of the eyes. This may suggest that in some eyes with longstanding prephthisical ocular hypotony, IVTA can be beneficial by increasing intraocular pressure and stabilizing the eye [156–158].

The antiangiogenic effect of TA was observed in an investigation of 14 eyes with neovascular glaucoma due to proliferative diabetic retinopathy or ischemic CRVO [113]. All patients received an intravitreal injection of about 20 mg of acetamide as the only procedure ($n = 4$ eyes), or in combination with additional procedures such as goniosynechiolysis ($n = 1$) and transscleral peripheral retinal cryocoagulation. Postoperatively, the degree of iris neovascularization decreased significantly ($p = 0.02$). Considering only the 4 patients for whom the intraocular cortisone injection was the only procedure performed, the mean intraocular pressure decreased from 26.5 ± 12.1 mm Hg to 21.75 ± 11.3 mm Hg. This report on the possible use of IVTA for adjunct treatment of neovascular glaucoma has been supported by recent investigations [112, 114, 115].

Further indications for which the intravitreal use of TA has been reported are ocular ischemic syndromes [184, 185], cystoid macular edema due to retinitis pigmentosa [187–189], radiation retinopathy [178, 179] and others [218].

Adverse Events

Postinjection Infectious Endophthalmitis

The frequency of postinjection infectious endophthalmitis as reported in recent studies ranged between 0/700 and 8/992 (0.87%) [278–286]. The risk of an infectious endophthalmitis may partly depend on the setting of the injection itself. The studies suggest that if the injection is performed under sterile conditions, the risk of an infection may be less than if the injection is performed at the slit lamp without special precautions being taken.

Histologically, eyes with IVTA 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 [279]. Between both areas, there is a sharp demarcation line. It is the morphallaxia-like histology in which a dense infiltration by granulocytes is sharply demarcated by tissue areas in which inflammatory cells are almost completely missing. Such a histology, normally characteristic for the demarcation and destruction of necrotic

anemic tissue as in the intrauterine resorption of a dead fetus, may be explained by the intraocular presence of high concentrations of TA. As a steroid, it may have inhibited the immigration of granulocytes into those areas in which the TA crystals are present. A 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 a massive infiltration of all ocular structures by inflammatory cells. The morphallaxia-like morphology of infectious endophthalmitis in eyes with IVTA may be paralleled by the clinical observation that patients with infectious endophthalmitis after an IVTA injection usually show almost no pain, which is rather uncommon for infectious endophthalmitis in eyes without intraocular steroids [284]. The lack of inflammatory cells migrating into the eye may be the histologic correlate of the clinical observation [278–286].

With respect to susceptibility to infectious endophthalmitis, a recent experimental study showed that rabbit eyes with IVTA have a significantly higher rate of apparent intraocular infections than rabbits without IVTA if both groups were inoculated with *Staphylococcus epidermidis* organisms [287]. Concerning the multiple use of TA-containing bottles, another investigation showed that even after 24 h of exposure to a benzyl alcohol preservative, 4 of 5 challenge organisms demonstrated moderate growth in the bottle so that the use of multidose containers of triamcinolone for intravitreal injections was discouraged [288].

Postinjection Pseudoendophthalmitis

TA crystals can mimic a so-called pseudohypopyon if they penetrate from the vitreous cavity into the anterior chamber [14, 97, 173, 289–292]. The diagnostic problem is the differentiation between a painless hypopyon caused by a postinjection infectious endophthalmitis and a pseudohypopyon due to TA crystals. Using high-magnification slit-lamp biomicroscopy usually reveals the crystalline structure of TA. TA 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 damage to the trabecular meshwork by the crystals. If the intravitreal injection is performed in the direction of the center of the vitreous cavity, a pseudohypopyon may only rarely occur. If, however, the injection touches the posterior chamber, the TA crystals may not be trapped by the vitreous body but may partly be washed into the anterior chamber.

Secondary Ocular Hypertension, Secondary Steroid-Induced Open-Angle Glaucoma

One of the two most common side effects of IVTA is the steroid-induced elevation of intraocular pressure [106, 293–306]. A prospective clinical interventional comparative nonrandomized study included 260 consecutive patients (293 eyes) receiving an intravitreal injection of 20–25 mg of TA as treatment for diffuse DME, exudative AMD, retinal vein occlusions, uveitis and cystoid macular edema [300]. Intraocular pressure readings higher than 21, 30, 35 and 40 mm Hg, respectively, were measured in 94 (36.2%), 22 (8.5%), 11 (4.2%) and 4 (1.5%) of the patients. The triamcinolone-induced elevation of intraocular pressure could be treated by antiglaucomatous medication in all but 3 eyes (1.0%), for which filtering surgery became necessary. About 40% of the patients developed secondary ocular hypertension, starting about 1 week after the injection in a few eyes, and about 1–2 months after the intravitreal injection of 20–25 mg of TA in most eyes which had developed ocular hypertension. Using this dose, the increase in intraocular pressure lasted about 7–9 months, after which the intraocular pressure measurements returned to the normal range without any further antiglaucomatous medication taken. In a multiple regression analysis, younger age was a significant factor contributing to the TA-induced increase in intraocular pressure.

Unexpectedly, the postinjection rise in intraocular pressure did not vary significantly between patients with a preinjection 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 preinjection antiglaucomatous treatment in the glaucoma group prevented a higher increase in intraocular pressure, or the megadose of 20–25 mg of intravitreally injected TA made baseline differences between the glaucoma group and the nonglaucomatous group disappear. If further studies confirm the finding, one may infer that, depending on the clinical situation and the severity of the macular disease, a diagnosis of chronic open-angle glaucoma may not be a major contraindication to IVTA.

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 dose of about 20 mg of TA. Although not systematically investigated in the present study, many eyes included in the investigation showed ophthalmoscopically

visible TA crystals in the vitreous for as long as the increase in intraocular pressure lasted. This suggests that when the TA 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 the reaction of intraocular pressure after topical applications of corticosteroids [307].

Those patients who received a second injection of 20–25 mg of TA showed a reaction of intraocular pressure similar to that after the first injection [300]. This suggests that if, after a first injection, the intraocular pressure remained within the normal range, it may also remain within the normal range after a second injection. In a similar manner, if the intraocular pressure increased after the first injection, a similar rise in intraocular pressure may be expected after a second injection.

Comparing studies using different doses of TA for intravitreal injection may suggest that the higher the dose, the longer the duration of steroid-induced ocular hypertension [106, 293–306]. If further studies confirm the assumption that the frequency of secondary ocular hypertension after an IVTA injection may not markedly depend on the dose used, one may assume that even relatively low TA doses are already high enough to occupy all steroid receptors. One has to take into account that the eye constitutes about 0.01% of the body volume. Assuming an equal distribution of TA 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 of TA is equal to a quarter of a kilogram injected intragluteally.

Rhegmatogenous Retinal Detachment

Since TA is injected into the vitreous cavity, leading to a rearrangement of the structure of the vitreous body, and because an abnormal vitreous may exert traction on the retina, 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 of TA as treatment of exudative AMD, DME, retinal vein occlusions, persistent pseudophakic cystoid macular degeneration and uveitis, none of the eyes developed a rhegmatogenous retinal detachment or retinal lesions [308]. This held true in particular (1) for the inferior midperipheral area of the fundus where the TA crystals had settled in the preretinal vitreal cortex, (2) for the superior midperipheral and peripheral fundus where a vitreous traction might be induced by the weight of the TA crystals settled at 6 o'clock, and (3) for the far

periphery of the fundus where retinal traction by the vitreous, if incarcerated into the injection site, might have resulted in reinjections [299, 309, 310].

Postinjection Steroid-Induced Cataract

Besides secondary triamcinolone-induced ocular hypertension/temporary secondary open-angle glaucoma, cataract may be one of the two most common side effects of intravitreal triamcinolone [298, 311, 312]. In a recent study on 144 phakic eyes which consecutively received intravitreal injections of about 20 mg of TA for diffuse DME, exudative AMD and BRVO, cataract surgery was performed on 20 eyes (13.9%) 17.4 ± 9.1 months (median: 12.7 months; range: 8.0–35.5 months) after the intravitreal injection [312]. Out of the 20 eyes undergoing cataract surgery, 19 (95%) had received 1 intravitreal injection, and 1 eye (5%) had received 2 previous injections. It was concluded that in the elderly population of patients with exudative AMD, diffuse DME or BRVO, intravitreal high-dose injections of TA lead to clinically significant cataract with eventual cataract surgery in about 15–20% of the eyes within about 1 year after the intravitreal injection. In an analysis of longitudinal data from a randomized, double-masked, placebo-controlled trial of intravitreal triamcinolone for AMD, Gillies et al. [298] compared 57 phakic eyes in the treatment group (4 mg TA) with 54 phakic eyes in the control group. They found that a progression of posterior subcapsular cataract by 2 or more grades in the treatment group occurred significantly more often among 16 intraocular pressure responders (51% after 2 years) than among 37 nonresponders (3%; $p < 0.0001$). There was no significant progression of posterior subcapsular cataract in the placebo group or the opposite eyes of the treatment group. A progression of cortical cataracts also occurred significantly more often among responders than nonresponders (15 vs. 3%; $p = 0.015$). The percentage of progressions of nuclear cataracts (13 vs. 3%) was not significantly different between intraocular pressure responders and nonresponders ($p = 0.3$). The authors concluded that, although steroid-related cataracts were unlikely to develop in eyes that do not experience an elevation of intraocular pressure after intravitreal triamcinolone, those eyes that do also have a very high risk of rapidly experiencing posterior subcapsular lens opacification. They postulated that this strong association suggests a similar mechanism responsible for the development of steroid-induced posterior subcapsular cataract and for the elevation of intraocular pressure. In a retrospective, interventional case-control study, Çekiç et al. [311] assessed cataract

progression after intravitreal triamcinolone injections. They found that single intravitreal triamcinolone injections induced posterior subcapsular cataract development, whereas multiple injections resulted in all-layer cataract progression.

Central Serous Chorioretinopathy

Since steroids may be a risk factor for central serous chorioretinopathy, the question arises whether IVTA may lead to an increased frequency of central serous chorioretinopathy [313, 314]. In a previous case report, a patient was described who developed central serous chorioretinopathy after vitrectomy with IVTA for DME [46]. It remained unclear whether it was a noncausal coincidence or whether the intravitreal steroid had led to the development of central serous chorioretinopathy. In another previous report on a patient who showed longstanding central serous chorioretinopathy continuously recurring for 6 years, an IVTA injection did not result in a resolution of the subfoveal accumulation of fluid, suggesting that on this type of macular disorder, IVTA may not have a therapeutically positive effect [195].

Toxic Effects

The intraocular use of Kenalog has not been approved by the FDA [229]. The preservative in Kenalog-40 is 0.99% benzyl alcohol [229], which may potentially be toxic to the retina and lens. A study by Kai et al. [315] investigated vehicle toxicity in New Zealand rabbits. In this study, TA with vehicle, either reduced or not, was injected into the vitreous cavity of rabbits. A significant increase in lens density and declining amplitudes of electroretinographic waves were observed in the vehicle-containing groups. Moreover, transmission electron microscopy showed that mitochondria of photoreceptors were swelling and ruptured in the vehicle-containing group compared with the control group; nevertheless, the reduced vehicle groups were normal. Similar results were observed in the reports by Macky et al. [316] report, in which pigmented rabbits were used, and by Lang et al. [317].

Direct toxic effects of TA on the retina and optic nerve have not yet been observed, independently of the dose used. Correspondingly, a recent safety and efficacy study of an intravitreal fluocinolone acetonide sustained-release delivery device used for the treatment of cystoid macular edema in patients with uveitis, as well as other clinical and experimental studies have not shown any toxic effect of intraocular steroids [159, 299]. The same was found by Hida et al. [8] and Tokuda et al. [318]. It may be of importance that TA is usually not found in the se-

rum shortly after its intravitreal application, suggesting that major systemic side effects may not be very probable [319].

However, recent studies conducted by Yeung et al. [320, 321] reported on a possible cytotoxic effect of TA. The authors found that TA caused a significant reduction in cell numbers throughout the whole range of concentrations when retinal pigment epithelium cells were exposed to it for more than 1 day. Compared with dexamethasone and hydrocortisone, TA showed the higher relative toxicity.

Safety of IVTA Including High-Dose Reinjections

In a case series study including 46 patients who received at least 2 intravitreal injections of about 20 mg of TA for the treatment of diffuse DME, exudative AMD, secondary angle-closure glaucoma due to iris neovascularization, CRVO, BRVO, noninfectious uveitis, Coats' disease and exudative retinal detachment of unknown etiology [308], the second injection was carried out 6.7 ± 3.4 months after the first, and 9 eyes received a third injection 8.0 ± 4.6 months after the second, 2 eyes received a fourth injection 9.5 and 10.8 months after the third, respectively, and 1 eye received 6 injections altogether. After all of these reinjections, no complications or side effects other than those already known to occur after a single IVTA were detected. After the first, second and third injections, 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 mm Hg after the first injection did not show an elevation of intraocular pressure after a repeated injection. The mean maximal intraocular pressures after the first, second and third injections did not vary significantly ($p > 0.50$). The results suggest (1) that intravitreal high-dose 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, (2) that the increase in intraocular pressure may not be more marked after a repeated injection than after the first injection, (3) and that side effects or complications may not occur more frequently after reinjections of TA than after a primary intravitreal high-dose injection.

Discussion and Conclusions

Intravitreal versus Sub-Tenon Application of TA

Several studies have addressed the question whether, instead of an intravitreal injection, a sub-Tenon injection

could have the same results as an intravitreal injection by increasing visual acuity while avoiding the risks of an intraocular procedure [60, 88, 131, 322–324]. Most of them agree that the sub-Tenon injection results in a lower intraocular concentration and a shorter duration of action compared with the intraocular injection. As one of the side effects of a sub-Tenon injection, ptosis and orbital fat prolapse have been reported [324].

Purification of TA

As already mentioned before, TA is not available without preservatives to date, and it remains unclear whether so-called sterile endophthalmitis may be associated with preservatives such as benzyl alcohol. Several techniques to remove the preservative have been described. All these methods have the disadvantage that the dose eventually ready for injection is too imprecise [63, 157, 325–327].

Conclusions

IVTA may open new avenues of treatment of intraocular edematous and neovascular diseases [328]. Since there have remained many open questions so far, the procedure may still be regarded as an experimental technique until randomized studies will eventually have proven the benefit of the therapy. The open issues include questions such as what may be the best dosage for which disease and for which clinical situation. In most studies on IVTA, a dose of 4 mg has been used. In a few studies, a dose of about 20 mg of filtered TA has been used. Comparing the studies with each other may suggest that the frequency and severity of side effects may not be markedly different between the doses used, and that the duration of the side effects, particularly of secondary ocular hypertension, depends on the dose. Other unanswered questions are whether the proliferation of retinal pigment epithelium cells is hindered in high concentrations of TA and, paradoxically, furthered in low concentrations [329]. What is the best mode of application of TA? Is the sub-Tenon 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 an accidental injection of TA 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 IVTA, together with previous clinical experiences of the use of intravitreal antibiotics and virustatic drugs, makes one understand that retinal diseases, par-

ticularly macular disorders, become locally treatable diseases. Unbelievably high intraocular concentrations of drugs become achievable, and systemic side effects may mostly be avoided. Future directions may include the combined applications of IVTA with photodynamic

therapy, possibly also with other intravitreal antiangiogenic medications, for the treatment of exudative AMD, and the intraocular application of TA in slow-release devices, possibly with a trigger mechanism to release the drug if necessary.

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