Posterior sub-Tenon's triamcinolone injections in the treatment of uveitis

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CLINICAL STUDY

Abstract

Purpose **This is the first study reported in the United Kingdom to investigate the efficacy and safety of posterior, sub-Tenon's triamcinolone acetonide injections in the treatment of posterior and intermediate uveitis.**

Methods **Twenty-eight posterior sub-Tenon's triamcinolone injections (40 mg) were given and the results analysed with a 6 month prospective follow-up in 13 cases.**

Results **At 6 weeks follow-up, objective improvement in visual acuity occurred in 25 eyes ($p < 0.05$). Vitreous cellular activity was diminished in 21 eyes ($p < 0.05$). In most cases improvement was observed within 2 weeks of injection. No patient required repeat triamcinolone injection within 3 months and all patients previously treated with systemic immunosuppression were able to decrease or discontinue this treatment. Complications included transient elevation of intraocular pressure in 4 patients and persistent mild ptosis in 2 patients.**

Conclusions **We have demonstrated that posterior sub-Tenon's triamcinolone injection significantly decreases cystoid macular oedema, with a corresponding increase in visual acuity, in patients with posterior uveitis. Systemic immunosuppression may be reduced or discontinued with the avoidance of associated systemic side effects, and the technique has a high level of patient acceptability.**

Key words Macular oedema, Steroid, Sub-Tenon's, Triamcinolone, Uveitis

Posterior uveitis often requires treatment by systemic immunosuppression, which carries a risk of many side effects some of which may be life-threatening. If possible, it is best to avoid systemic therapy, particularly if the intraocular inflammation is relatively mild. The alternative treatment methods include periocular steroid injections either to the orbital floor or into the posterior sub-Tenon's space. These techniques allow a high concentration of a long-acting steroid preparation to be placed in close proximity to the posterior part of the globe. The risk of systemic side effects with these techniques is minimal although some local side effects may occur. The posterior sub-Tenon's route may carry a slightly greater risk of globe perforation than orbital floor injections, but it allows the steroid to be placed in direct contact with the globe and therefore might achieve a higher intraocular concentration. Despite relatively widespread use, there are very few reports in the literature on the efficacy and side effects of posterior sub-Tenon's triamcinolone in the treatment of uveitis.

Patients and methods

An initial retrospective case note review of 10 consecutive posterior sub-Tenon's triamcinolone injections performed over a 12 month period was carried out at the Prince Charles Eye Unit. This was followed by a prospective study of an additional 18 consecutive injections, performed over a 4 month period, from the Medical Eye clinic at the Oxford Eye Hospital. When analysed separately there was no significant difference in outcome or complication rate between the retrospective and prospective groups at 2, 6 or 12 weeks post-injection. Treatment and follow-up in the two groups was carried out using an identical protocol as outlined below. Therefore, demographic data and results for each group are combined and presented together.

Patient eligibility included a decrease in Snellen visual acuity to 6/9 or less due to cystoid macular oedema and the presence of active intermediate or posterior uveitis. The uveitic diagnostic category for each eye injected is shown in Table 1.

A total of 28 injections were given to 28 eyes of 25 patients (3 patients received bilateral injections). Mean age was 42 years (range 20–68 years) and there were 14 female and 11 male patients. Mean duration of macular oedema was 3.6 years (range 1 month to 15 years). Patients excluded from this study include 1 patient with

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Table 1. *Diagnostic categories of patients undergoing posterior sub-Tenon's triamcinolone injection*

	No. of patients	No. of eyes
Intermediate uveitis	10	11
Panuveitis	15	17
Idiopathic	(7)	(8)
Associated with Behçet's disease	(5)	(6)
Associated with sarcoidosis	(3)	(3)
Total	25	28

sufficiently severe uveitis to have been commenced on systemic immunosuppression at the same time as being given a sub-Tenon's injection, thus making it difficult to determine the relative contribution of each treatment. Two patients who had received a periocular injection of steroid within the preceding 12 months were also excluded to prevent a dosing effect. In patients with bilateral disease severe enough to require bilateral treatment, the worse eye was injected first followed 6 weeks later by the second eye.

Of a total of 25 patients, 14 were on systemic immunosuppressive therapy prior to sub-Tenon's injection. This included 9 patients on systemic prednisolone, 3 patients on systemic prednisolone and azathioprine, 1 patient on systemic prednisolone and cyclosporin and 1 patient on azathioprine alone. If a positive response was seen at either the 2 or 6 week review following injection then systemic therapy was gradually decreased or discontinued.

Baseline assessment of all patients included a complete ophthalmic examination together with measurement of best corrected Snellen visual acuity, near acuity and intraocular pressure (IOP), assessment of vitreous cellular activity and degree of macular oedema. The visual acuity was recorded by independent observers as the smallest line on the Snellen eye chart for which the patient correctly identified at least half the letters.

Vitreous cellular activity was measured and scored by biomicroscopic examination of the anterior vitreous, according to the following criteria. The light intensity of a standard slit lamp biomicroscope was set at maximum illumination with a slit setting of 3 mm long by 1 mm wide and magnification of ×16. The number of cells visible per field was then counted and given a score as follows: 1 = 1–5 cells per field, 2 = 5–10 cells per field, 3 = 10–20 cells per field, 4 = 20–50 cells per field. Almost all vitreous cell counts were performed by one of the authors (V.T.) in an attempt to decrease inter-observer variation.

The severity of macular oedema was assessed clinically as routine flourescein angiography was felt not to be appropriate. For this reason, the severity of macular oedema was not analysed in the assessment of response to treatment.

All posterior sub-Tenon's injections were given by one ophthalmologist (V.T.) experienced in the technique. In each case 40 mg (1 ml) of triamcinolone acetonide (Kenalog, Squibb Pharmaceuticals) was placed superotemporally under topical anaesthesia using the technique described by Nozik[1] and Smith.[2] The patient was asked to look inferonasally while the upper lid was elevated allowing good exposure. The injection was given with a short (5/8 inch) 25G needle mounted on a 2 ml syringe. With the bevel towards the globe, the needle was passed through the superior bulbar conjunctiva, as far posteriorly as could be easily visualised, into the sub-Tenon's space in the superotemporal fornix. The tip of the needle was then advanced to the hub with a wide sweeping action, pivoting at the point of insertion, maintaining the needle as close to the globe as possible. If the limbus was seen to rotate during advancement of the needle it was assumed that some superficial scleral fibres had been engaged; the needle was then withdrawn a few millimetres and then reinserted more superficially. In all cases a standard dose of 40 mg was given (Figs. 1, 2).

In the prospective group, patients were evaluated at 2, 6 and 12 weeks following injection; further follow-up was as determined clinically, with 13 patients completing 6 months of follow-up. In the group of patients studied retrospectively only 2, 6 and 12 week follow-up results were complete and accurate enough to be analysed.

Examination at each follow-up visit included measurement of best corrected Snellen visual acuity, IOP and vitreous cellular activity.

Results

Pre-injection visual acuities ranged from 6/9 to count fingers; visual acuity results at 6 weeks for 28 injections are shown in Fig. 3. Overall, 22 (78.6%) injections resulted in an improvement of vision, often particularly noticed for near vision, with a subjective decrease in floaters. A 2 line increase in Snellen acuity was achieved in 12 (43%) cases. Visual acuity was unchanged in 6 cases and none had a decrease in visual acuity. In most cases the onset of both subjective and objective improvement in visual acuity was within 2 weeks of injection (range 3 days to 4 weeks).

Visual acuity results at 12 weeks for 25 injections are presented in Fig. 4. Overall, 21 (84%) injections resulted in an improvement in visual acuity, 3 cases were unchanged and 1 patient had a decrease in visual acuity due to progression of a pre-existing posterior sub-capsular lens opacity. A 2 line increase in Snellen acuity was achieved in 10 (40%) cases. Two patients failed to attend for follow-up at 12 weeks and 1 had been inadvertently discharged at 6 weeks with a Snellen visual acuity of 6/6.

Of 18 injections given in the prospective group, 13 were available for analysis at 6 months as shown in Fig. 5. In addition to the 3 patients lost to follow-up at 12 weeks, 1 patient had relapsed and required repeat posterior sub-Tenon's triamcinolone injection at 3 months. This patient was excluded from further follow-up. An additional patient underwent cataract surgery at 4 months post-injection and was also excluded from further follow-up. Of 13 patients who completed 6

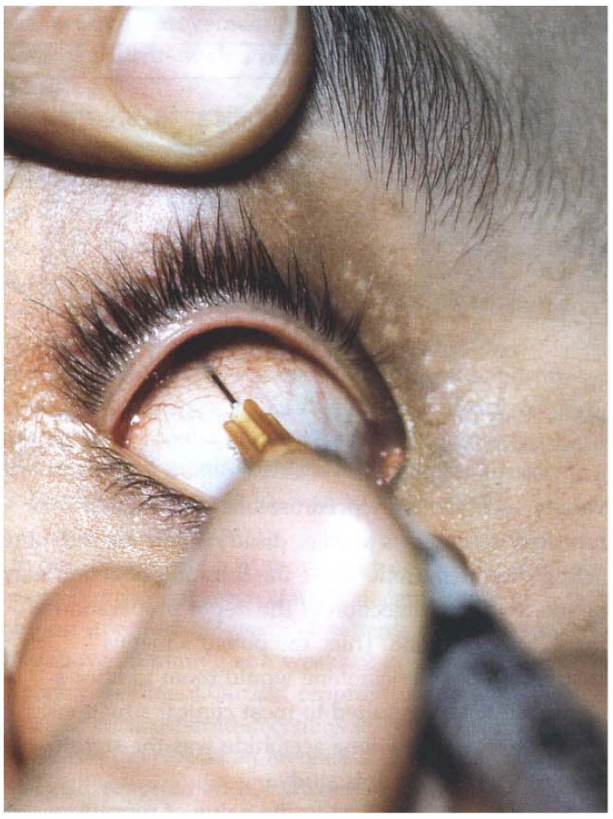

Fig. 1. *Posterior sub-Tenon's triamcinolone injection given with a 25G needle via a superotemporal approach to the right eye.*

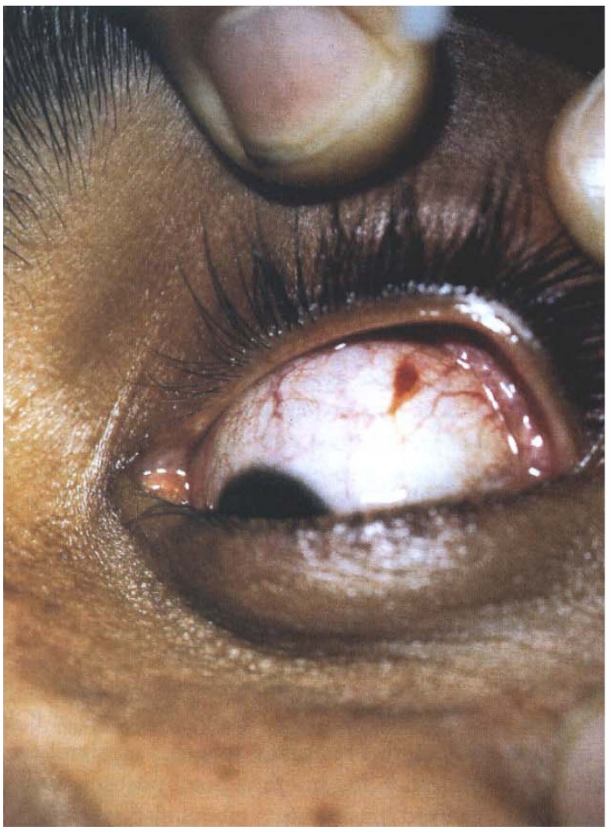

Fig. 2. *Photograph of another patient immediately following posterior sub-Tenon's injection to the left eye. If given correctly no steroid is visible following the injection.*

months of follow-up, 11 maintained a better visual acuity than before the injection, in one the visual acuity was unchanged and one had decreased visual acuity due to cataract.

Due to the heterogeneous nature of the different uveitis categories, further analysis with respect to patient age, sex, pre-injection visual acuity or duration of disease was not considered to be appropriate.

Mean vitreous cell scores are shown in Fig. 6. The mean pre-injection vitreous cell score was 1.64, at 6 weeks it was 0.73, at 12 weeks 0.55 and at 6 months 0.65. The case which relapsed at 3 months, requiring further injection, is excluded from the 6 month follow-up results.

Prior to sub-Tenon's injection, 14 patients were on systemic immunosuppressive therapy. At 12 weeks post-injection, 8 patients had decreased their regimen and 6 had discontinued systemic immunosuppression altogether. No patient required an increase in systemic immunosuppression within 3 months of sub-Tenon's injection. One patient relapsed at 3 months and a further 2 patients relapsed and required a repeat injection at 7 months.

Minor complications included transient conjunctival oedema, sub-conjunctival haemorrhage and mild temporary ptosis immediately following injection. During the month following injection 2 women (28 and 56 years) developed ipsilateral, permanent mild upper lid ptosis which did not cover the visual axis. In each case the injection had been uncomplicated and the ptosis appeared to be due to a disinsertion of the levator palpabrae superioris aponeurosis. The younger patient had a well-documented pre-existing ptosis that became more marked following injection.

Mean pre-injection IOP was 15.7 mmHg compared with 18.5 mmHg at 6 weeks; however, this trend did not reach statistical significance (Fig. 7). At 12 weeks and 6 months, mean IOP was little changed compared with baseline. Four patients developed IOP greater than 25 mmHg. Two of these patients were treated successfully with temporary topical monotherapy (beta blockers) and in the other 2 the IOP returned to normal without treatment.

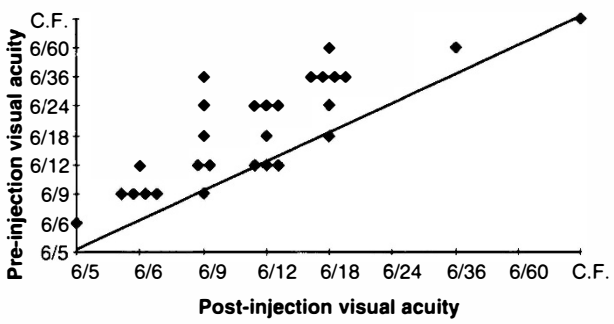

Fig. 3. *Snellen visual acuity at 6 weeks following sub-Tenon's triamcinolone injection* (n = 28).

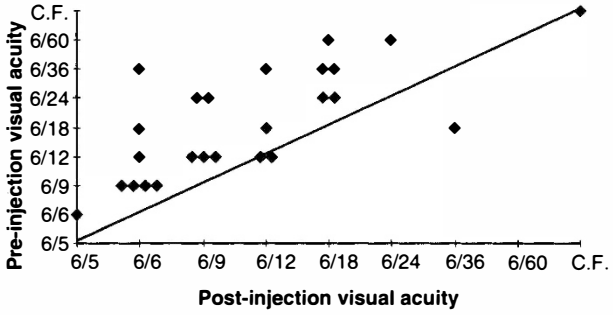

Fig. 4. *Snellen visual acuity at 12 weeks following sub-Tenon's triamcinolone injection* (n = 25).

Statistics

All statistical analysis was carried out using S-Plus software[3] and linear mixed effects models as described by Vonesh.[4] Vitreous cell counts were analysed with paired *t*-tests, which revealed a significant drop in cell count from pre-injection to 6 weeks ($p < 0.05$). Analysis with paired *t*-test and a linear mixed effects model revealed no significant differences between the 6 weeks, 12 week and 6 month results ($p = 0.32$). Analysis of IOP results using analysis of variance revealed no significant change post-injection for any time point post-injection ($p = 0.13$). A mixed linear effects model also revealed no significant trend in IOP post-injection ($p = 0.48$). Visual acuity data were transformed to an inverse fractional scale and analysed with a mixed linear effects model. A statistically significant improvement in mean visual acuity was seen at each time point post-injection ($p < 0.01$).

Discussion

Posterior sub-Tenon's injection of steroid allows a high concentration of drug to be delivered to the posterior segment of the eye via trans-scleral absorption, with a minimal risk of systemic side effects. Intraocular concentrations are higher than those obtained via systemic administration, particularly when the eye is inflamed.[5–7]

There are essentially three types of injectable corticosteroid available to the clinician. These are: (1) the water-soluble short-acting variety such as dexamethasone, (2) an aqueous suspension such as triamcinolone (Kenalog) and (3) the long-acting depot

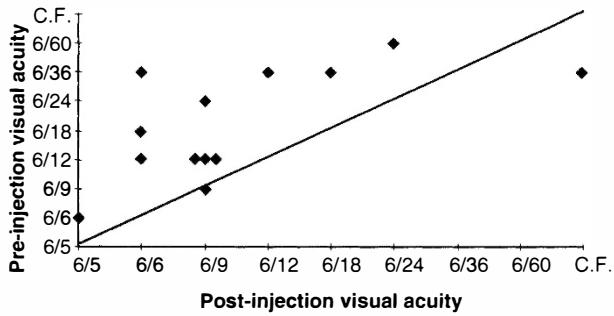

Fig. 5. *Snellen visual acuity at 6 months following sub-Tenon's triamcinolone injection* (n = 13).

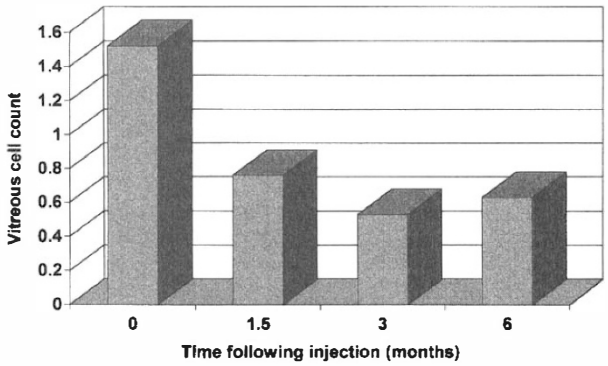

Fig. 6. *Mean vitreous cell scores following posterior sub-Tenon's triamcinolone injection.*

variety such as methylprednisolone. The necessity for repeated injections is a major disadvantage for the short-acting dexamethasone while the duration of action may be too long after injection of the depot preparation of methylprednisolone. Thus, the potent aqueous suspension of triamcinolone would seem to offer a compromise better suited to most clinical situations. For this reason triamcinolone acetonide was the steroid preparation used in this study.

Previous studies attest to the value of repository steroids for the treatment of inflammatory disease but few objective data are available regarding its efficacy and potential complications. Schlaegel and Weber[8] studied 67 eyes in 46 patients with pars planitis that were treated with periocular methylprednisolone acetate injections, systemic corticosteroids or a combination of both. In their series 57 (85%) of 67 eyes either retained visual acuity better than 20/40 or had an improvement of 2 Snellen lines or more. Nozik[1] reported a series of patients in which there was a 69% improvement rate with periocular injections of repository corticosteroids. However, this series was heterogeneous with respect to type of inflammatory disease, corticosteroid used and injection site. In a retrospective study on the effect of posterior sub-Tenon's triamcinolone injections on 20 patients with intermediate uveitis by Helm and Holland,[9] a Snellen

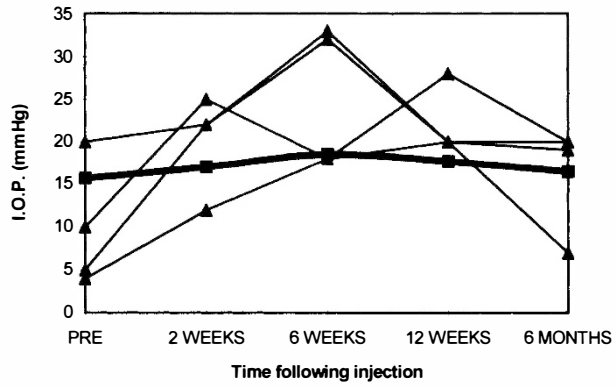

Fig. 7. *Intraocular pressure (IOP) following posterior sub-Tenon's triamcinolone injection. Squares, mean IOP; triangles, IOP readings for the 4 patients who developed pressure responses greater than 25 mmHg.*

visual acuity improvement of 2 lines or more was found in 67% of patients with a mean time to improvement of 3 weeks.

In our series of 28 single injections to 28 eyes, at 6 weeks post-injection 22 patients (78.6%) reported a subjective improvement in vision that was confirmed on Snellen visual acuity testing. The onset of visual improvement occurred in most cases at 2–3 weeks post-injection. Improvement in vitreous activity scores coincided with improvement in visual acuity and was maintained until 12 weeks post-injection (Fig. 6). Although visual acuity was maintained in patients with a follow-up of 6 months, subjective vision and degree of mean vitreous cellular activity started to deteriorate between 3 and 6 months. This would suggest a mean duration of maximum efficacy in most cases of approximately 4 months.

In our series mean IOP showed a trend to elevation at 6 weeks but did not reach statistical significance at any time post-injection. However, 4 patients developed IOP levels above 25 mmHg at 6 weeks, 2 of whom required temporary treatment. Nozik[1] reported the results of periocular corticosteroid injections in 175 cases of uveitis: only 3 cases developed an increase in IOP post-injection. Schlaegel[10] reported an IOP increase in 5 of 10 patients, each of whom had received between 19 and 44 injections to each eye via the inferior cul-de-sac. Schlaegel's study emphasises the risks associated with multiple injections, particularly when the steroid is placed anteriorly.

Glaucoma secondary to periocular corticosteroids tends to be of delayed onset and long duration. In Herschler's series of 11 patients with ocular hypertension secondary to periocular corticosteroid injection[11] the mean time to detection of increased IOP was 9.4 weeks, and mean duration was 3.2 months. However, 10 of 11 cases had received an anterior sub-Tenon's injection and only 1 had received a posterior sub-Tenon's injection. In the case reported by Herschler[12] marked elevation of IOP occurred after an injection of dexamethasone followed by two injections of triamcinolone, all given to the anterior sub-Tenon's space. This patient was subsequently shown to be a steroid responder. We feel this emphasises the need to place triamcinolone injections in the posterior sub-Tenon's space where they are potentially more efficacious and also avoids direct absorption into the anterior segment. Herschler excised the visible, anterior depot triamcinolone in this case and demonstrated using biochemical assay that approximately 10% of the original triamcinolone was active at 4 months. This would tend to confirm our clinical findings of a continued effect from a posterior sub-Tenon's triamcinolone injection up to 4 months.

It is interesting that in our series 2 of the 4 patients with marked IOP elevation at 6 weeks were hypotonous prior to injection with IOPs of 5 and 6 mmHg. The increase in IOP as vitreous cellular activity decreases would suggest that production of aqueous increases as intraocular inflammation decreased. These chronically inflamed eyes probably had a compromised trabecular meshwork or partial angle closure resulting in an elevation of IOP as ciliary production increased. An alternative explanation is that IOP elevation is steroid-induced in susceptible individuals. Such a response is probable in cases of intractable ocular hypertension secondary to repository steroid injections given to the anterior sub-Tenon's space.[11–13]

In cystoid macular oedema, increased perifoveal capillary permeability causes an accumulation of fluid that can be seen clinically and on flourescein angiography. Inflammatory mediators have been hypothesised to cause the perifoveal capillary leakage and for this reason corticosteroids may have a direct effect on leakage at the macula, as well as an effect on vitreous cellular activity, both contributing to an improvement in visual acuity in eyes with posterior uveitis. Jennings *et al.*[14] studied the effect of posterior sub-Tenon's injection of methylprednisolone and triamcinolone on blood–retinal barrier permeability in 10 patients with cystoid macular oedema secondary to uveitis. Using fluorescein angiography and vitreous fluorophotometry they found an improvement in blood–retinal barrier permeability in 50% of cases. However, this decrease in permeability was not always associated with an improvement in visual acuity, and in 4 eyes visual acuity improved without measurable decrease in vascular permeability. They suggest other factors may play a role, such as retinal hypoxia and swollen Müller cells.

Freeman *et al.*[15] suggested using B-scan ultrasound to confirm accurate placement of posterior sub-Tenon's corticosteroid injection against the sclera in the region of the macula. Using this technique to evaluate the position of methylprednisolone injections they confirmed more accurate placement using a superotemporal route rather than an inferotemporal approach. They also demonstrated movement of steroid inferiorly from the initial site of injection, slightly above the posterior pole, to a position adjacent to the macula. We evaluated this technique on 6 patients receiving triamcinolone injections but did not find it reliable in detecting the depot site. This is probably due to the better definition of the echolucency produced by methylprednisolone as compared with triamcinolone. Freeman *et al.*[15] also reported difficulty in detecting triamcinolone and suggested the better echolucency of methylprednisolone may be related to its more viscous nature.

Riordan-Eva and Lightman[16] published a retrospective series evaluating the efficacy of orbital floor steroid injections in a heterogeneous group of patients with posterior uveitis. They found a 2 line improvement in Snellen visual acuity in 35% (19/54) of injections to 33 eyes. A great variability in response to injection was found in this study, with a poor response to an initial injection being followed by a good response to a second injection in some cases. We have achieved a slightly better 2 Snellen line improvement rate 43% (12/28 injections) using a posterior sub-Tenon's approach. However, our results appear to be more predictable, with patients not usually requiring multiple injections to obtain a positive response and few patients losing visual

acuity. This may be due to a different patient population, but could also be the result of achieving a higher intraocular concentration of steroid using the sub-Tenon's approach as the depot lies directly against the posterior sclera. Animal studies[17] have shown that subconjunctival hydrocortisone injections penetrate intraocular tissue more rapidly with much higher intraocular concentrations than do injections placed within the anterior orbital fat.

A recent report by Weijtens *et al.*[18] suggested that periocular steroid injections may result in significant systemic steroid levels and a risk of systemic side effects. If the most significant route of action for periocular steroid injections was via systemic absorption then an improvement of visual acuity would also be expected in fellow eyes with active uveitis. Helm *et al.*[9] studied this possibility and found no significant change in visual acuity of fellow eyes in patients with bilateral uveitis receiving contralateral posterior sub-Tenon's triamcinolone injections. This has also been our experience in patients with bilateral uveitis, who showed no improvement in the fellow eye following unilateral injection but did respond to subsequent injection to that side. We have also seen a rapid improvement in steroid-related side effects in patients who decreased or stopped systemic medication following posterior sub-Tenon's injection. Weijtens' study was performed on non-inflamed eyes prior to routine vitrectomy and this may be one factor in the explanation of what appears to be a poor trans-scleral absorption of steroid in their series. Relevant animal studies are contradictory, with some suggesting equally high intravitreal steroid concentrations in fellow eyes following contralateral injection[19,20] while Hyndiuk and Reagan[21] found intravitreal concentrations following intramuscular injection to be only 1–11% of the levels found following peribulbar injection.

Traditionally it has been advocated that bilateral disease should be treated with systemic immunosuppression rather than bilateral depot injections. In our series 3 patient received consecutive bilateral sub-Tenon's injections with good effect and we feel that the advantages offered by depot as opposed to systemic treatment are just as valid in bilateral disease. The main advantage of using depot injections in the treatment of posterior uveitis is the avoidance of the numerous systemic complications associated with immunosuppression using oral corticosteroids or other agents. Of 14 patients on systemic immunosuppression prior to injection in our series 8 (57%) were able to decrease systemic treatment and 6 (43%) were able to discontinue it altogether. As the sequelae of systemic side effects may overshadow those of the ocular disease, the local nature of sub-Tenon's injections may allow posterior uveitis to be treated at an earlier stage, helping arrest and possibly reverse damage to the eye. In addition this form of treatment is cheap, readily available and requires a minimum of monitoring with no requirement for support from other medical practitioners as may be required in systemic immunosuppression.

All our patients had low- or medium-grade uveitis, more severe cases being treated concurrently with systemic immunosuppression. In milder cases posterior sub-Tenon's injection appears to give surprisingly long-term control of disease, removing the need for systemic therapy altogether. In some cases the very high intraocular concentration of steroid is perhaps inducing remission, at least in the medium term, by switching off the inflammatory process. We have seen a similar phenomenon in children with anterior uveitis associated with juvenile chronic arthritis treated with anterior sub-Tenon's injections of triamcinolone (J.J. Kanski, unpublished data). In more severe cases it is our policy to maintain patients on a relatively safe low level of background systemic immunosuppression and to treat acute exacerbations with posterior sub-Tenon's injection. This combined approach not only decreases the side effects of systemic immunosuppression but also avoids the greater potential for local complications associated with multiple injections.

In this mostly prospective trial we have demonstrated that posterior sub-Tenon's triamcinolone injection significantly decreases ocular inflammation, with a corresponding increase in visual acuity, in patients with posterior uveitis. Systemic immunosuppression may be reduced or discontinued with the avoidance of associated systemic side effects and the technique has a high level of patient acceptability. The significant complications include a short-term risk of IOP elevation and a risk of ptosis. Although not found in our experience the advantage of a more predictable positive response rate than in injections given via the orbital floor route may be offset by a higher risk of globe perforation. This is one of the few studies in the literature to examine the effects of individual injections in a prospective manner, but it is limited in number and the heterogeneous uveitis categories. A controlled prospective trial comparing orbital and posterior sub-Tenon's routes would be recommended. We also await further studies on the potential systemic effects of periorbital steroid injections.

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