Use of intravitreal injection of triamcinolone acetonide in the treatment of age-related macular degeneration

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Age-related macular degeneration (AMD) is now considered an important and leading cause of blindness among elderly patients in developed and developing countries. AMD has two forms, dry and wet; both can lead to visual loss. However, occurrence of subfoveal choroidal neovascular (CNV) membrane in the wet form results in severe visual impairment.

Treatment options for choroidal neovascularization are available in order to maintain and in some cases improve vision. Photodynamic therapy (PDT) has been used to treat both classic and occult membranes. It has known to cause choroidal hypoperfusion and production of vascular endothelial growth factor.

Intravitreal steroid can possibly reduce the damage caused due to these undesirable effects. In the recent past, intravitreal injection of triamcinolone acetonide (IVTA) has been used extensively as an adjunct to PDT in AMD in order to reduce the number of PDT sessions and evaluate possible beneficial effects on vision.

This article reviews the pharmacological attributes of triamcinolone, available evidence of its use as monotherapy or combination therapy to treat AMD, ocular side-effects thereof and ongoing clinical trials on IVTA.

Key words: Age-related macular degeneration, choroidal neovascularization, intravitreal steroid

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Pharmacological Attributes

Chemical composition
Triamcinolone is a synthetic steroid of the glucocorticoid family having a fluorine instead of hydrogen atom in the ninth position.

Photodynamic therapy with verteporfin has been shown by the TAP study to be effective in the treatment of predominantly classic subfoveal CNVM. Verteporfin in PDT (VIP study) showed it to be so in occult CNVM. In general, patients do require multiple sessions (3.5 to 5 sessions on an average) of PDT, thereby hiking the cost. Studies have also revealed that PDT could cause choroidal hypoperfusion and upregulate the production of vascular endothelial growth factor (VEGF). Yet, what detrimental effects these changes have on vision remains speculative.

In the recent past, intravitreal injection of triamcinolone acetonide (IVTA) has been used extensively as an adjunct to PDT in AMD in order to reduce the number of PDT sessions and evaluate possible beneficial effects on vision.

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This article reviews the pharmacological attributes of triamcinolone, available evidence of its use as monotherapy or combination therapy to treat AMD, ocular side-effects thereof and ongoing clinical trials on IVTA.
Technique of intravitreal injection

It is preferable to give intravitreal triamcinolone under an aseptic condition to minimize the potential risk of endophthalmitis. Preoperative topical antibiotics can be used as per the physician’s discretion. Topical povidone iodine application enhances safety.7,8

Commercially available triamcinolone can be used for injection. To prevent inflammation due to the vehicle benzyl alcohol, the drug can be passed through a Millipore filter or can be centrifuged; however, in such methods, the concentration of the drug and its dosage may not be accurate. High performance liquid chromatography can precisely determine the concentration.9

The injection is loaded into a tuberculin syringe and a 30-G needle is used for the injection. The procedure is done under topical anesthesia. It is injected 3.5-4 mm from the limbus, usually in the inferotemporal quadrant. Fundus evaluation after the procedure is performed to examine the arterial perfusion at the optic nerve head and to determine the need for anterior chamber paracentesis. Topical use of antibiotics is continued for a week after the injection. In the postoperative period, measurement of intraocular pressure (IOP) is recommended for two to three months.10

Clinical Evidence

Use of IVTA as monotherapy

There have been studies with small sample sizes on the treatment of subfoveal CNVM due to AMD, with IVTA. It was first described by Penfold et al.,11 in a pilot study using IVTA in 30 eyes, not amenable to laser photocoagulation. The overall visual outcome was better in the treatment group than in the untreated group.

Table 1 summarizes the results of published reports. In all these studies, there was no masking of investigators and patients. The duration of follow-up was only up to one year. The only study with a large number (n=151) showed that though the size of membrane decreased with IVTA, there was no significant reduction in the risk of developing severe visual loss. Two were randomized control trials and the one with a larger sample size did not show any significant difference between cases and controls.

The efficacy of IVTA monotherapy remains controversial.

Use of IVTA as a combined therapy (PDT and IVTA)

Photodynamic therapy with verteporfin has been shown to be effective in the treatment of choroidal neovascularization secondary to AMD [Fig. 1]. Though the leakage from the neovascular complex, on fluorescein angiogram, declines with treatment, moderate to severe vision loss is noted after PDT. This can be due to collateral hypoxic damage to the adjacent choriocapillaris and retinal pigment epithelial atrophy following PDT. There is also release of VEGF following PDT which can cause transient visual disturbance secondary to hyperpermeability induced by it.20 This was demonstrated by multifocal electroretinography.21

Triamcinolone acetonide due to its anti-angiogenic and anti-inflammatory effects can reduce the re-perfusion of CNVM and also reduce the edema secondary to inflammation. Spaide et al.,22 in their pilot study of PDT with IVTA showed improvement in visual acuity. Subsequently, there have been a number of reports of IVTA combined with PDT for all types of membranes due to AMD [Table 2].

These studies indicate that combined treatment as a first line of management reduces the need for multiple sessions of PDT, avoids further vision loss and improves visual acuity. However, reduction in visual acuity of three or more Snellen lines was noted in two studies.26,31 Except one,30 all of the published studies were nonrandomized. So, the results need to be interpreted cautiously before making a clinical decision of using IVTA combined with PDT.

Table 1: Studies of monotherapy with intravitreal injection of triamcinolone acetonide in age-related macular degeneration

| Reference | Lesion type | No. of eyes | Treatment | Outcome |
|-----------|-------------|-------------|-----------|---------|
| Penfold et al.11 | Subfoveal and juxtafoveal unsuitable for laser | 30 | Single 4 mg | Overall VA outcome better than published data for untreated |
| Challa et al.12 | Subfoveal and juxtafoveal unsuitable for laser | 30 | Single 4 mg | Rate of development of severe visual loss less |
| Danis et al.13 | Subfoveal unsuitable for laser | 16 treated, 11 control | Single 4 mg | VA better in treated group at three and six months |
| Ranson et al.14 | Extrafoveal recurrent | 14 | Single 4 mg | VA remained stable for one year |
| Gillies et al.15 | Any classic component | 75 treated, 76 control | Single 4 mg | No effect on risk of visual loss at 12 months. Change in size of membrane less in treated eyes but not at 12 months |
| Jonas et al.16 | Predominantly or total occult, classic | 71 | Single 25 mg (six had two injections) | VA increased, especially one to three months after injection |
| Jonas et al.17 | Subfoveal | 115 treated, 72 control | Single 25 mg | VA increased significantly in study group |
| Jonas et al.18 | Occult or predominantly occult subfoveal | 13 treated, 24 control | 25 mg, second dose 3-18 months later | VA increased significantly after first and second injection in study group |
| Jonas et al.19 | Minimally classic or occult subfoveal | 20 - one eye treated, fellow eye control | 20 mg | VA gain in treated eyes |

VA - Visual acuity
Figure 1: A 57-year old male with reduced vision following cataract surgery. On examination, he was diagnosed to have classic subfoveal choroidal neovascular membrane. FFA showed classic subfoveal membrane (top panel). He underwent PDT with IVTA following which his vision had improved by 1 line and the membrane has reduced in size. FFA showed reduction in size (bottom panel). OCT (middle panel) showed marked reduction in thickness of CNVM following treatment. He underwent a second sitting of PDT with IVTA.

Ocular Complications

(a) Due to injection procedure

Endophthalmitis

Both infectious and sterile endophthalmitis were reported. In one study the incidence of culture-positive endophthalmitis was 0.87%, while in other reports no case was observed; this difference could be due to following strict asepsis during the administration of the drug and partly due to prophylactic use of antibiotics. Sterile endophthalmitis could occur due to solvent agent. Pseudo hypopyon occurs due to triamcinolone crystals entering the anterior chamber.

(b) Due to the triamcinolone

Glaucoma

IOP elevation is reported in 19 to 43% of eyes after IVTA. It occurs most often between one and three months of injection. Jonas et al. reported IOP greater than 21 mm of Hg, 30 mm of Hg, 35 mm of Hg and 40 mm of Hg in 41.2%, 11.4%, 5.5% and 1.8% patients respectively. Rise in IOP is well controlled with one to two topical anti-glaucoma medications; around 3% need filtering surgery.

Cataract

Following IVTA, progression of cataract has been reported in 0 to 57%. One study has shown that progression of cataract could be associated with increased IOP. Cataract surgery after IVTA does not harbor a markedly elevated frequency or a markedly changed profile of surgical complications.

Constraints of using IVTA

- A cause of concern with the use of IVTA is the vehicle benzyl alcohol which can cause inflammatory responses. There have been methods described to remove it; however, the concentration of the drug obtained after removal is not uniform. We usually do not undertake measures to purify the drug, however, some others use only the purified form. These need to be standardized.
- Various investigators have given the injection at various intervals following PDT. More research with respect to its ideal timing, frequency and dosage will help standardize the procedure.
• The drug has a propensity to cause rise in IOP and cataract. Hence careful evaluation and follow-up is needed.
• There is as yet no satisfactory answer to the question: how frequently can IVTA be repeated?
• Non-availability of randomized clinical trial, a gold standard in evaluating the efficacy of IVTA.

Ongoing Clinical Trials

• VERTACL (Verteporin Triamcinolone for AMD, sponsored by the National Eye Institute, Bethesda, MD)
  * Study design: This is a masked, randomized, multi-center clinical study of participants randomized to one of the following treatment arms:
    * 1.25 mg intravitreal bevacizumab at baseline (visit 0) and then at each of weeks 6, 12 (month 3), 18, 26 (month 6), 32, 38 (month 9), 45 and 52 (month 12).
    * 1.25 mg intravitreal bevacizumab + half-fluence verteporin-PDT + 1 mg preservative-free triamcinolone acetonide (TAC-PF) at baseline (visit 0), then as needed at months 3, 6, 9, 12 with 1.25 mg intravitreal bevacizumab alone as needed at weeks 6, 18, 32 and 45.
  * Primary objective: To investigate whether, compared to bevacizumab alone, combination bevacizumab, PDT, TAC-PF therapy results in a similar functional outcome and reduces the number of intravitreal injections in participants with neovascular AMD. The results of this investigation will contribute substantially to planning future definitive studies on anti-VEGF/PDT/steroid combination therapies.

• ViSTA (Visudyne with intravitreal triamcinolone acetonide under Richard Spaide).

To determine whether PDT in combination with 4 mg intravitreal triamcinolone will reduce the average loss from baseline of best corrected visual acuity (BCVA) as compared with PDT without intravitreal triamcinolone at 12 months in subjects with occult subfoveal and minimally classic subfoveal CNVM secondary to AMD. The IVTA will be given as either a 1mg or 4 mg dose. This study will also evaluate the safety of verteporin in treatment in patients with CNVM.

With the recent invasion of the VEGF inhibitors, triamcinolone has taken a back seat in the treatment armamentarium. These anti-VEGF drugs have undergone randomized control trials and in the current clinical scenario stand a better chance.

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