REVIEW ARTICLE

Using Steroids in Diabetic Macular Edema: A Guide for Steroid Application in Clinical Practice

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Article Information

Received: 24 March 2016
Accepted: 29 April 2016
Plagiarism software: Turnitin

Keywords:
DME, Diabetic Macular Edema, steroids, intravitreal, retina, ophthalmology, eye care, diabetes

ABSTRACT
Diabetic macular edema is a multi-pathogenic diseases which vascular endothelial growth factor (VEGF) may play the main role in most of the cases and treatment with Anti VEGF is warranted, where in long standing edema inflammation maybe the main pathogenic factor and treatment with Anti VEGF may not achieve optimum results and steroids can be used to address the inflammatory mechanism, there are three classes of intravitreal steroids which help us to individualize treatment for each patient never the less we have to take into account that all intravitreal steroids may cause cataract formation and glaucoma.

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INTRODUCTION

Since mid-90s Intravitreal steroids such as triamcinolone was used off-label to treat diabetic macular edema (DME) were laser photocoagulation was the standard of treatment, after 2005 anti-VEGF become treatment of choice as studies have shown its efficacy, since then we are living in anti-VEGF era, but clinical studies and practice shown that some patients are partial or non-responsive to anti-VEGF treatment may be due to lack of VEGF roll and more inflammatory role in pathogenesis in some cases of diabetic macular edema and the presence of a new steroid slow release implants have rethink the treatment of DME in some cases.

Role of Inflammatory Process in DME Pathogenesis

When DME is chronic the main pathological factor is inflammation that may lead to diffuse leakage and damage to the neural tissue including photoreceptor loss and interim inflammatory mediators such as TNF-α, IL-1b, IL-6, IL-8, IP-10 and MCP-1[1] are up regulated more than VEGF where inflammation in diabetes does not resolve by itself and tissue stress is exacerbated which will lead to further injury and accumulation of sub retinal microglia which interim is important factor for leukostasis with increasing cytotoxic effect and inducing more leakage.[2]

Access this article online	
Website: www.actamedicainternational.com	Quick Response code
DOI: 10.5530/ami.2016.2.33	

As in certain cases of DME the inflammatory process is the main driver that why treating such cases with VEGF blockage agents may not lead to improvement and treatment with steroids may have a larger role.

Triamcinolone Acetonide

Intravitreal Triamcinolone Acetonide (IVTA) has a half-life of 18.6 days and may persist at levels sufficient to exert clinical effect for up to 4 months but with potential complications such as glaucoma and cataract formation.

IVTA has been studied in a lot of clinical trials, The Diabetic Retinopathy Clinical Research Center Network (DRCR.net) have investigated IVTA use in several clinical trials such as comparing 1.0-mg and 4.0-mg doses of intravitreal triamcinolone acetonide with focal or grid photocoagulation retreatment was

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provided for persistent or new edema at four-month intervals and they concluded that short term visual improvement in 4.0 mg arm but in long-term results IVTA didn't appear to be beneficial when comparing it to focal laser treatment.[3]

Protocol I by DRCR.net has investigated Ranibizumab plus Prompt or Deferred Laser or Triamcinolone plus Prompt Laser for Diabetic Macular Edema and they concluded that IVTA + prompt laser (in the long term) in pseudophakic eyes, is more effective than laser alone but frequently increases the risk of intraocular pressure elevation, however Ranibizumab with prompt or deferred laser is more effective.[4]

TADMO study showed that IVTA can be effective in resolving macular edema in cases were deemed to have "refractory" in DRCR.net which are not responsive to laser therapy with beneficial effect persists for up to 2 years.[5]

The Rational use of IVTA

Besides the cheap price and 4 months durability of Triamcinolone Acetonide, Clinical studies have shown that IVTA can be effective in pseudophakic patients when combined with focal laser and in cases of refractory edema but has short term effect with potential complications such as glaucoma and cataract formation.

In real world practice IVTA with prompt focal laser can be used in the absence of anti-VEGF availability in pseudophakic patients with no history of glaucoma.

IVTA can be considered in cases of refractory edema which failed to respond to all other available treatments.

Dexamethasone

Dexamethasone700-µg intravitreal implant is a biodegradable polymer, extended-release which may have an exert clinical effect for up to 4 months with more predictable risk if intraocular pressure when it compare it with IVTA, it 1st gained FDA approval to treat macular edema due to retinal vein occlusion then it gained FDA approval for non-infectious uveitis and lastly in year 2014 it gained FDA approval for DME treatment.

Multiple clinical trials have investigated the safety and efficacy of intravitreal Ozurdex (Dexamethasone700-µg intravitreal implant) for DME treatment such as MEAD where they recruited central DME patients with BCVA ranged from 20/50 to 20/200 and patients were randomized 1:1:1 to dexamethasone implant 0.7 mg, dexamethasone implant 0.35 mg, or sham, and they were followed for three years with retreatment no more than 6 months and they concluded that patents that gained 15 ETDRS letters and more from base line and reduction of central retinal thickness was more in the dexamethasone implant 0.7 mg arm.[6]

The BEVORDEX study reported a 12-month results of a randomized head-to-head clinical trial that compared dexamethasone implant with bevacizumab, and they concluded that both arms had comparable 10 letters gain but there was substantial visual loss in Ozurdex arm due to cataract formation while the Bevacizumab required more frequent injections.[7]

The CHAMPLAIN study studied 55 patients with history of pars plana vitrectomy and resistant DME they concluded that single 0.7 mg dexamethasone implant can improve vision and reduce leak up to 26 weeks with BCVA improvement of more than 10 letters in 30% of patients within the 1st 8 weeks.[8]

Another study has evaluated the efficacy of Ozurdex in pregnant woman with DME and they concluded that 0.7 mg dexamethasone implant improve vision and reduction of foveal thickness without significant increase of intraocular pressure.[9]

The DRCR.net protocol U is currently recruiting participants to study the short-term effects of combination dexamethasone intravitreal implant + Ranibizumab therapy on visual acuity and retinal thickness in comparison with that of continued Ranibizumab therapy alone in eyes with persistent central-involved DME and visual acuity impairment despite previous anti-VEGF treatment.[10]

The rational use of dexamethasone intravitreal implant.

As dexamethasone intravitreal implant has the safest profile in contrast to other intravitreal steroids along with it is 4 months durability it can be our 1st choice to address the inflammatory component of DME in psedophakic patients with no history of glaucoma.

In real world practice dexamethasone intravitreal implant can be used in cases of pseudophakic patients with no history of glaucoma and DME don't respond to several (6 injections) Anti VEGF treatment as those edemas are deemed as refractory and chronic where inflammatory process is the main driver and not VEGF.

Dexamethasone intravitreal implant can be used to lower the frequency of intravitreal injections to lower the cost burden in other words an Anti VEGF can be administered at the baseline and then dexamethasone intravitreal implant can be inserted to maintain the dryness of the macula up to 4 months to lower the cost burden of 4 more intravitreal injections.

Dexamethasone intravitreal implant can be considered to treat DME in patients are planned for cataract surgery, so implant is placed prior to cataract surgery and hence the implant is releasing dexamethasone slowly it will dry the macula along with its anti-inflammatory effect after cataract surgery which virtually should protect against inflammation.

Dexamethasone intravitreal implant is a great option to treat DME in patients with history of parsplana vitrectomy as half-life of other drugs are reduced due to vitreous absence and The CHAMPLAIN study showed its efficacy.

When a pregnant woman between gestational weeks 9 and 23 has moderate to severe central DME, dexamethasone intravitreal implant is a great option for treatment as its 4 months durability with minimal systemic exposure can spare the patient the retinal scars which induced by focal laser as treatment with Anti VEGF has no proven safety.

Fluocinolone Acetonide Implant

In contrast to dexamethasone implant Fluocinoloneacetonide implant is not biodegradable and has 36 months of extended release with higher risk of cataract and glaucoma where it gained FDA approval for DME treatment in year 2014 for 0.19mg implant.

FAME study has compared[11] two doses (0.5 & 0.2) of a fluocinoloneacetonide intravitreal implant and sham injections in a patients persistent DME despite previous macular laser treatment, they concluded that percentage of patients with improvement of ≥15 letters from baseline are 31.9% (0.5 μg/d), 33.0% (0.2 μg/d), and 21.4% (sham), FAME has reported that diabetic patients treated with Fluocinoloneacetonide implant slowed the progression of retinopathy as after 36 months 31% of patients were treated with sham arm showed progression of diabetic retinopathy where only 17% showed progression in Fluocinoloneacetonide implant arm.[12]

The Rational use of Fluocinoloneacetonide Intravitreal Implant.

The extended durability of the fluocinoloneacetonide up to 36 months with higher risk of unpredicted increase of intraocular pressure, increase rate of cataract formation and expensive price make the use of this intravitreal implant in selected cases only such as pseudophakic patients with chronic DME and no history of glaucoma that have been treated with dexamethasone intravtreal implant several times with recurrent edemas and show no increase of intraocular pressure.

Keep in mind as fluocinoloneacetonide implant is at a low dose which may need additional Anti VEGF to control edema in some cases.

Complications

Cataract: When treating with intravitreal triamcinolone the probability of cataract formation is 50 to 80% when using 4 mg while lower dose of triamcinolone may reduce the rate of cataract formation,[13] virtually all patients treated with fluocinoloneacetonide intravitreal implant developed cataract[14] and 67% of patients who treated with dexamethasone intravitreal implant.[15]

Increase of intraocular pressure: When treating with intravitreal triamcinolone there is a risk of increased intraocular pressure by 33%-68% when using 4 mg while lower dose of triamcinolone may reduce the rate of increased intraocular pressure,[16] while only 34% of patients who treated with dexamethasone intravitreal implant however 4.8% of patients treated with fluocinoloneacetonide intravitreal implant required incisional surgery for glaucoma.

In real clinical practice the family history of glaucoma and patients that presented with open angle glaucoma may be at risk of increased ocular pressure after corticosteroid administration.[17]

CONCLUSION

Diabetic macular edema can be persisted to Anti VEGF and laser treatment up to 40% of cases and thus maybe due to more prominent inflammatory role than VEGF in pathogenesis in those cases.

When addressing inflammatory mechanism in our management we usually use intravitreal corticosteroids agents, we have to weigh the advantages and disadvantages

Table 1: A table to compare Pros and Cons of each corticosteroid agent

Agent	PROS	CONS
Dexamethasone intravitreal implant	Has a safer profile as it has more predictable increase of IOP with good efficacy	Cataract formation, and some time it needs repeated injections to achieve dry macula
Fluocinolone acetonide intravitreal implant	Extended durability up to 36 months	Cataract formation, Expansive and more prone to increase IOP which may need incisional glaucoma surgery to control, in addition of reduced effect due to low dose
Intravitreal triamcinolone acetonide	Cheap and available	Cataract formation, non predictable increase of IOP, floaters and it may lose effect in repeated injections

of each agent when tailoring the treatment to our patients (Table 1).

In summary the dexamethasone may have a safer profile as it has a predictable increase of intraocular pressure and better efficacy in pseudophakic patient with no history of glaucoma but a repeated injection is needed so if the patient needs several implant to maintain macular dryness with no signs of increased intraocular pressure then intravitreal implant of fluocinoloneacetonide can be injected as it had extended durability up to 36 months, where intravitreal triamcinolone acetonide is preserved for refractory cases in the absence of other former agents and no history of glaucoma.

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How to cite this article: Marashi A. Using steroids in diabetic macular edema: A guide for steroid application in clinical practice. Acta Medica International. 2016;3(2):171-174.

Source of Support: Nil, **Conflict of Interest:** None declared.