Corticosteroids for the Treatment of Diabetic Macular Edema

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Abstract Diabetic macular edema (DME) is a leading cause of vision loss throughout the world. Three different corticosteroids have been used in the treatment of diabetic macular edema: triamcinolone acetonide, dexamethasone, and fluocinolone acetonide. Intravitreal injection of all three corticosteroids is associated with a similar side effect profile including worsening/formation of cataract, elevation of intraocular pressure, pseudo-endophthalmitis, and infectious endophthalmitis. Sustained-release implants of corticosteroids have recently been studied, and one has recently received FDA approval as the first corticosteroid for the treatment of diabetic macular edema. This review will address some of the major studies evaluating corticosteroids for DME and will focus on studies published within the last 2 years.

Keywords Diabetic macular edema · Corticosteroids · Triamcinolone acetonide · Fluocinolone acetonide · Dexamethasone · Intravitreal injection

Introduction

Diabetic retinopathy (DR) is a leading cause of vision loss in the developed world. Based on a population estimate from 2005 to 2008, 28.5 % of adults over the age of 40 with diabetes in the United States have DR with an overall prevalence of 3.8 % [1]. Diabetic macular edema (DME) carries a significant burden of vision loss in patients with

diabetes and can manifest in patients with any degree of DR. Estimates of the prevalence of DME in patients with diabetes range from 10 to 20 % [2, 3]. The prevalence of clinically significant macular edema (CSME) in adults over the age 40 with diabetes in the United States is 2.7 % [1]. Approximately half of all patients with untreated DME will lose two or more lines of vision within 1 year [4].

DME is defined as thickening of the macula due to accumulation of fluid in the retina. The pathogenesis of DME is complex and multifactorial with several proposed mechanisms causing capillary leakage following breakdown of the blood retinal barrier [5]. An inflammatory component is suspected with the association of select cytokines including but not limited to vascular endothelial growth factor (VEGF), interleukin-6, intercellular adhesion molecule 1, platelet-derived growth factor, protein kinase C, pigment epithelial-derived factor, and basic fibroblast growth factor amongst many others [6–10]. Retinal vessel leukostasis, alterations in vascular endothelial cell tight junctions, pericytes, and glial cells are also felt to play a role [11]. Furthermore, the interaction of anatomic structures, such as the vitreous, epiretinal membranes, internal limiting membrane, and posterior hyaloid, may be a factor in causing DME [11].

Given the significant morbidity associated with DME, multiple treatment methodologies have been studied. Control of blood sugars along with focal laser photocoagulation was the standard of care for over 25 years based on the results of the Early Treatment for Diabetic Retinopathy Study, which showed that early focal laser for patients with CSME resulted in a reduction in the proportion of patients losing three lines of vision [12]. Unfortunately, laser photocoagulation is less successful at restoring visual acuity that has been lost, and patients continue to lose vision over time despite focal laser therapy [13–15].

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Anti-VEGF therapy has now emerged as front-line therapy to treat DME in many centers worldwide. In 2012, intravitreal ranibizumab (IVR, Lucentis®, Genentech, South San Francisco, CA) became the first pharmacotherapy for the treatment of DME approved by the United States Food and Drug Administration (FDA) based on the results of the RISE and RIDE trials [16•]. Prior to this, intravitreal bevacizumab (IVB, Avastin®, Genentech, South San Francisco, CA) had been used as an off-label treatment, as it has also shown efficacy in the treatment of DME and is still used off-label [17–19]. Intravitreal aflibercept (Eylea®, Regeneron, Tarrytown, NY) has recently shown efficacy for the treatment of DME in the VIVID and VISTA trials and was approved by the FDA in July 2014 [20•]. The VIVID and VISTA trials showed similar efficacy for the monthly and every 2-month dosing regimen of aflibercept [20•]. These three agents are effective, but result in a high treatment burden due to the frequent monthly or bimonthly dosing regimens resulting in potentially high drug costs. Furthermore, there is still a significant portion of patients who are non-responders to anti-VEGF therapy, presumably due to the multifactorial nature of DME [16, 20•, 21].

Corticosteroids are non-specific anti-inflammatory agents that address not just VEGF-mediated vascular leakage of fluid into the retina, but also inhibit other inflammatory cytokines, reduce capillary permeability, and inhibit leukostasis [22–29]. Three different corticosteroids have been investigated for the treatment of DME: triamcinolone acetonide, dexamethasone, and fluocinolone acetonide [30]. Various routes have been investigated to administer corticosteroids for the treatment of DME including peribulbar injection, intravitreal injection, and sustained-release intravitreal implants. This review will address some of the major studies evaluating corticosteroids for DME and will focus on studies published within the last 2 years.

Periocular Versus Intravitreal Injections

Intravitreal injection of corticosteroids includes a number of side effects and risks including progression/induction of cataract, increase in intraocular pressure (IOP), pseudo-endophthalmitis, and endophthalmitis [31–34]. All of these risks are increased in diabetic patients. Posterior subtenons injections (PSTI) provide a periocular depot with a reduced side effect profile and have been investigated as a potentially safer option for the treatment of DME. A few initial studies investigating the role of PSTI of triamcinolone in the treatment of DME showed promising results with improvement in vision [35–38] and reduced side effects compared to intravitreal injection of triamcinolone

(IVTA) [39, 40]. The Diabetic Retinopathy Clinical Research Network (DRCR.net) performed a phase II, randomized, prospective, pilot study (Protocol E) to determine the safety and efficacy of PSTI of triamcinolone either alone or in combination with focal laser in mild DME which failed to find a benefit of PSTI of triamcinolone and noted significant adverse effects from the injections including elevated IOP and blepharoptosis [41]. This study only included patients with good visual acuity; so PSTI of triamcinolone may still be a useful adjunct for diffuse diabetic macular edema with poor visual acuity when performed prior to grid focal laser, as has been suggested by other studies [42, 43]. The duration of effect has been found to be longer following IVTA compared to PSTI [44, 45]. A few studies have found that PSTI of triamcinolone are associated with an increase in IOP but the degree of IOP increase to be lower than IVTA [46, 47]. Other side effects reported after PSTI of triamcinolone include reactivation of infectious retinitis [48], cutaneous hypopigmentation [49], retinal and choroidal vascular occlusion [50], infectious crystalline keratopathy [51], herpetic keratitis [52], orbital abscess [53–55], encapsulated cyst [56], and infectious scleritis [57].

Triamcinolone Acetonide

Three different formulations of triamcinolone acetonide have been tested in various clinical trials: Trivaris® (Allergan, Irvine, CA), Triesence® (Alcon, Ft. Worth, TX) and Kenalog® (Bristol-Myers Squibb, Princeton, NJ). Kenalog is not our preferred choice of drug for intravitreal injection due to the presence of preservative. Trivaris is no longer commercially available in the United States. Triesence is preservative-free and is our preferred formulation of triamcinolone acetonide for intravitreal injection. The majority of the studies discussed used Triesence unless specifically noted.

The DRCR.net performed a randomized, prospective clinical trial (Protocol B) comparing two doses (1 and 4 mg) of IVTA (Trivaris) monotherapy to focal laser photocoagulation and found that IVTA was associated with better vision at 4 months but with increasing time, the focal laser group had better visual acuity [14]. This was especially evident at 3 years [58]. Additionally, the focal laser group had a much lower incidence of cataract and glaucoma. Another prospective, randomized clinical trial by the DRCR.net (Protocol I) found IVTA plus prompt laser to be superior to laser alone at 24 weeks but the treatments were equivalent at one and 2 years [59, 60•]. The lack of difference at 2 years may have been due to the development of cataract after IVTA. IVR plus either prompt or delayed laser was associated with better vision compared to laser

alone at all time points. Subgroup analysis of pseudophakic eyes showed that IVTA plus prompt laser was as effective as IVR with a lower treatment burden.

Recent studies have expanded our knowledge in the use of IVTA. O'Day et al. reported a prospective, randomized trial treating patients with IVTA plus focal laser and evaluating baseline characteristics (age, gender, best-corrected visual acuity, glycosylated hemoglobin, phakic status, central macular thickness (CMT), and IOP) predictive of the number of treatment needed over a 2-year period and only found having higher baseline CMT was associated with an increased number of treatments [61]. IVTA was studied in DME eyes unresponsive to bevacizumab and was found to improve visual acuity at one and 2 months, but not at 3 months, after treatment, with multivariate analysis showing that increased aqueous levels of intraocular interleukin-8 pre-treatment were associated with increased efficacy [62].

Intravitreal anti-VEGF therapy has been compared with IVTA injections. A pilot study comparing a single injection of 4 mg IVTA versus 3 monthly injections of IVB found no significant difference between the two groups in visual acuity or retinal thickness at 3 months [63]. A randomized trial comparing 3 monthly injections of 2.5 mg IVB versus a single injection of 8 mg IVTA followed by two sham injections and then a PRN treatment protocol for both groups found similar visual acuity at 6 months but significantly worse vision in the IVTA group at 1 year [64]. The difference in visual acuity may have been due to cataract formation in the IVTA group versus differential effects of the two medications on the angiogenic versus inflammatory pathways. A recent meta-analysis by Zhang et al. of eight studies comparing 4 mg IVTA vs either 1.25 or 1.5 mg IVB found a significant visual benefit of IVTA versus IVB at 4, 8, 12, and 24 weeks; however, the improvement in central macular thickness was only significant at 4 weeks in the IVTA group versus bevacizumab [65]. It is unclear why visual acuity was better in the IVTA group but the CMT was not significantly different between the two groups.

Saeed reported the results of an Egyptian randomized trial of 34 eyes from 34 patients with intractable DME without vitreomacular traction comparing vitrectomy with removal of the posterior hyaloid plus 4 mg IVTA and 1.25 mg IVB at the end of procedure versus macular focal laser performed 2 weeks after 4 mg IVTA plus 1.25 mg IVB. In this study, visual acuity was found to be better in the vitrectomy group at month 3, equal at month 6, and worse at 1 year; meanwhile, central retinal thickness was better at all time points in the laser group except for month 3 [66]. They concluded that the combined treatment of IVTA, IVB, plus focal laser was superior to vitrectomy combined with the same injections. The vitrectomy group

had a higher cataract rate that could have accounted for the worse vision at 1 year.

There appears to be a significant difference in the pharmacokinetics and pharmacodynamics between different triamcinolone acetonide preparations with increased particle size correlating with increased durability and efficacy [67]. A new, simple technique of using centrifuge-concentrated IVTA (Triesence) found triamcinolone to be present in the vitreous for a median of 3 months longer compared to non-concentrated IVTA [68]. This technique may be useful to get a sustained duration of action after IVTA and avoid the need for repeat injections.

Other ocular effects of IVTA have recently been studied and found to be significant. A randomized, prospective trial found that IVTA was associated with a sustained reduction of choroidal thickness in patients with DME; the choroidal thickness remained unchanged after IVB [69]. Color Doppler imaging of ocular hemodynamics after IVTA and IVB found that the end diastolic volume decreases in the ophthalmic artery and posterior ciliary arteries after IVTA while peak systolic velocity and end diastolic volume decrease significantly in the ophthalmic artery after IVB [70]. The significance of the changes in choroidal thickness and blood flow is unclear but both suggest diabetes-associated vascular alterations may be more selectively steroid-responsive rather than to anti-VEGF agents. A trial evaluating the refractive changes after pharmacologic resolution of DME using both anti-VEGF agents and IVTA found the spherical equivalent change to be insignificant after resolution of DME [71]. The authors recommended giving spectacle correction to patients at any time during ongoing therapy. An exploratory analysis found that both IVTA and IVR are associated with a reduced risk of worsening of proliferative diabetic retinopathy, but felt that the risk profile of the drugs did not warrant their use for this purpose [72].

The economic impact of DME steroid pharmacotherapy has received increasing attention. A cost effectiveness analysis of anti-VEGF therapy with IVR versus triamcinolone either alone or combined with focal laser found IVR plus laser to be the most cost effective therapy with an incremental cost effectiveness ratio of \$12,410 per quality-adjusted life-year over IVTA plus laser [73]. In addition, laser or IVTA monotherapy was found to be less effective and more costly than combination therapy [73]. Another cost effectiveness analysis found IVTA to be at least as effective as focal laser for visual acuity $<20/200$, IVTA plus focal laser to be equivalent to anti-VEGF in pseudophakic eyes, and less frequent treatment with aflibercept to give equivalent visual acuity results as more frequent treatment [74]. An analysis of the DRCR.net Protocol I trial found IVR plus either prompt or delayed laser to be more cost effective for phakic patients with an incremental

cost of \$3,084 per letter gained over 2 years and IVTA plus prompt laser more cost effective for pseudophakic patients not at high risk for glaucoma [75]. For pseudophakic patients, ranibizumab plus deferred laser was the only treatment superior to IVTA plus prompt laser, but had an incremental cost of \$14,690 per letter gained which was not felt to be justifiable for the small incremental gain of 1.36 letters over 2 years.

Elevation of IOP and cataract formation are the two most common side effects after IVTA; younger male patients with higher baseline IOP were found to have the greatest risk for elevation in IOP whereas eyes with prior vitrectomy were less likely to have elevated IOP [76]. Elevation of IOP that is recalcitrant to maximal medical therapy can be successfully managed by vitrectomy to remove the steroid from the eye [77]. Endophthalmitis after intravitreal injection of IVTA is reported to occur at a similar rate as after other intravitreal injections with no difference in the rate in the office versus operating room settings and an overall rate of endophthalmitis after intravitreal injection of 0.043 % [78]. No benefit is found with topical antibiotics before or after intravitreal injections and there is a trend toward an increase in the rate of endophthalmitis with the use of topical antibiotics [79, 80]. Sterile endophthalmitis after IVTA is characterized by an immediate granulocytic infiltration, with an increased incidence with the use of preservative-containing solutions [81]. Prior vitrectomy, prior IVTA injection, internal limiting membrane peeling, and pseudophakia were associated with an increased risk of sterile endophthalmitis [82]. In general, visual outcomes are good after treating the eye acutely as if it was infectious endophthalmitis [83]. Other recently reported, though rare, side effects of intravitreal injection of triamcinolone include persistence of crystals on the surface of the retina for multiple years resembling crystalline retinopathy [84], reactivation of viral retinitis [85], intraocular hemorrhage, retinal detachment, and fulminant toxoplasmic retinochoroiditis [86].

Dexamethasone

Despite having a slightly increased duration of effect compared to anti-VEGF agents, IVTA is still limited in its duration of action in the eye. Sustained-release corticosteroid implants have been developed to reduce the treatment burden on patients and mitigate the risk of repeat intravitreal injections. It has been suggested that sustained low-dose release of corticosteroid into the vitreous may be more efficacious compared to higher bolus doses seen after IVTA injection [87]. A bioerodible dexamethasone implant (Ozurdex[®], Allergan, Inc, Irvine, CA) has recently become the first corticosteroid FDA approved for the treatment of

DME. It releases steroid into the vitreous cavity for approximately 6 months with peak concentrations in the first 2 months [88]. A study using optical coherence tomography-based monitoring of CMT to determine the ideal retreatment interval after injection of the dexamethasone implant found a rapid and dramatic effect on macular edema for about 8 weeks and a modest effect up to week 32; the ideal retreatment point was felt to be week 20 [89].

Two large, randomized, prospective clinical trials evaluating the safety and efficacy of the dexamethasone implant to sham treatment in DME found the percentage of patients meeting the primary endpoint of a greater than 15 letter improvement in vision to be 22.2 % and 18.4 % after the 0.7 and 0.35 mg dexamethasone implants, respectively; 12.0 % met the same endpoint after sham treatment [90••]. A mean of approximately four treatments was needed during the 3 years of the trial. The mean reduction in CMT was similar (~110 µm) with the two doses of dexamethasone implants and significantly better than sham treatment (~40 µm). Over three times, as many patients developed cataracts after the dexamethasone implant compared to sham. An increase in IOP of >10 from baseline was noted in 27.7 and 24.8 % for the 0.7 and 0.35 mg doses, respectively, but was controlled with medications or monitoring, and trabeculectomy was needed only in two patients for the 0.7 mg dose and one patient for the 0.35 mg dose. Callahan et al. reported on a randomized, controlled trial evaluating eyes treated with the dexamethasone implant and focal laser versus focal laser alone found a greater proportion of patients gaining at least ten letters in the combination group at months one and nine, but no difference at 1 year [91]. The results from these trials led the FDA to approve the 0.7 mg dexamethasone implant for use in pseudophakic patients with DME or phakic eyes scheduled to undergo cataract surgery.

The newer design of the dexamethasone implant injector was found to require lower force for scleral penetration compared to the old design [92, 93]. Despite the larger gauge and use of a tunneled incision, dexamethasone implant injection was not found to be more painful than anti-VEGF injection [94].

Aphakic and pseudophakic eyes are at risk of anterior migration of the dexamethasone implant with vitrectomized patients being at much higher risk [95–98]. Anterior migration of the implant is associated with corneal decompensation, pain, elevated IOP, and misidentification as a hypopyon. Fortunately, the implant can often be surgically repositioned into the vitreous cavity, but in select cases, surgery may be required to remove the displaced implant. The dexamethasone implant has also been found to be trapped anterior to the anterior hyaloid face and between the posterior capsule and a silicon oil bubble, in both cases it spontaneously relocated to the inferior

vitreous cavity without any other complications [99, 100]. Fragmentation of the implant has been noted to occur during injection or shortly thereafter; fortunately, this does not change the rate or duration of drug delivery in the eye [101–104]. Inadvertent injection of the dexamethasone implant into the crystalline lens can be safely and successfully managed by standard cataract extraction with phacoemulsification [105, 106].

Fluocinolone Acetonide

Two different sustained-release fluocinolone acetonide (FA) devices have been studied in the treatment of DME: a non-bioerodible, extended release, implantable FA device (Retisert®, Bausch and Lomb, Rochester, NY) which needs to be surgically implanted in the operating room and a much smaller, non-bioerodible, injectable FA insert (Iluvien®, Alimera, Alpharetta, GA) which can be injected as an outpatient procedure. The FA device is currently only approved in the US for the treatment of non-infectious posterior uveitis [107]. The Iluvien FA insert is approved for the treatment of DME in parts of Europe but has been rejected by the FDA twice. The most recent letter from the FDA to the manufacturer was promising and the manufacturer has submitted the insert for approval a third time.

The Retisert FA device releases 0.59 µg/day of FA over the 3-year lifespan of the device [107] providing a constant release of drug which avoids the peak and trough effect of steroid solutions injected into the vitreous or bioerodible implants. There have been a few studies evaluating the efficacy and safety of the FA device in DME. A 4-year, randomized, prospective study of the FA device versus additional laser in cases of persistent DME, despite focal laser 12 weeks prior to study entry, met the primary endpoint of a greater than 15 letter gain of VA at 6 months and the secondary endpoints of reduction of CMT and DR severity score [108]. However, the side effect profile was notable for 91 % of phakic patients needing to have cataract extraction during the study, 61.4 % of patient having IOP elevation greater than 30, and 33.8 % requiring surgery for control of IOP. The device requires implantation in the operating room and the high incidence of IOP elevation requiring surgical intervention has limited the use of this device in routine clinical practice.

The Iluvien FA insert releases 0.2 or 0.5 µg of FA over the three-year lifespan of the insert [109] and is injected via a modified needle system similar to IVTA. The ocular concentration of drug for both concentrations peaks at 1 week and remains at that level for 2 months prior to declining to a steady state level for at least 12 months [109]. Two randomized, prospective, sham injection controlled trials (FAME) evaluating the efficacy and safety of

the 0.2 and 0.5 µg FA inserts found both doses to meet the primary study endpoint with 28 % of patients achieving a greater than 15 letter gain in visual acuity compared to 16 % in the sham group [110]. At 2 years, the mean improvement in visual acuity was 4.4 and 5.4 letters for the 0.2 and 0.5 µg doses, respectively, compared to 1.7 letters for sham. The rate of incisional glaucoma surgery was 3.7 and 7.6 % for the 0.2 and 0.5 µg, respectively. The results at 3 years were similar [111•]. Unfortunately, nearly all phakic patients required surgery by 3 years. In a subgroup analysis, the low-dose (0.2 µg) insert was found to be more effective for patients with DME of greater than 3 years duration compared to those with DME of less than 3 years duration [112]. This is significant as it represents a treatment option for patients with DME that is recalcitrant to other treatment options.

Conclusion

IVTA is an effective off-label treatment option for refractory DME in pseudophakic patients. The duration of effect is longer than after anti-VEGF injection or PSTI of triamcinolone but reinjections are needed after three to 6 months. The duration of effect seems to be greater with increased dose of injected triamcinolone but the increase in intraocular pressure is also greater with increasing doses of IVTA. The dexamethasone implant is the first FDA approved corticosteroid for DME but it is only approved for pseudophakic patients or those scheduled for cataract surgery. The increase in IOP with the dexamethasone implant is less severe than the IOP increase seen with IVTA injection. The FA insert is available for use in a limited number of countries at this time; FDA approval has been denied in the past, but seems promising based on the last letter to the manufacturer. Approval of this device in the US would be a significant addition to the range of choices available to physicians for the treatment of chronic DME as it has shown significant promise in treating chronic DME which has traditionally been recalcitrant to treatment. The fluocinolone insert also represents a significant decrease in treatment burden as it is active for 3 years with caution to the fact that nearly all patients will develop a cataract requiring surgery within 3 years and the risk of IOP increase is significant though it is less for the low-dose insert.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Zhang X, Saaddine JB, Chou CF, Cotch MF, Cheng YJ, Geiss LS, et al. Prevalence of diabetic retinopathy in the United States, 2005–2008. *JAMA*. 2010;304(6):649–56. doi:[10.1001/jama.2010.1111](https://doi.org/10.1001/jama.2010.1111).
2. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556–64. doi:[10.2337/dc11-1909](https://doi.org/10.2337/dc11-1909).
3. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology*. 1995;102(1):7–16.
4. Ferris FL 3rd, Patz A. Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol*. 1984;28(Suppl):452–61.
5. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. *Semin ophthalmol*. 1999;14(4):223–32. doi:[10.153/SOPH01400197](https://doi.org/10.153/SOPH01400197).
6. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology*. 2009;116(1):73–9. doi:[10.1016/j.ophtha.2008.09.037](https://doi.org/10.1016/j.ophtha.2008.09.037).
7. Joussen AM, Poulaki V, Le ML, Koizumi K, Esser C, Janicki H, et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. *FASEB J*. 2004;18(12):1450–2. doi:[10.1096/fj.03-1476fje](https://doi.org/10.1096/fj.03-1476fje).
8. Murata T, Ishibashi T, Khalil A, Hata Y, Yoshikawa H, Inomata H. Vascular endothelial growth factor plays a role in hyperpermeability of diabetic retinal vessels. *Ophthalmic Res*. 1995;27(1):48–52.
9. Qaum T, Xu Q, Joussen AM, Clemens MW, Qin W, Miyamoto K, et al. VEGF-initiated blood-retinal barrier breakdown in early diabetes. *Invest Ophthalmol Vis Sci*. 2001;42(10):2408–13.
10. Funatsu H, Yamashita H, Noma H, Mimura T, Yamashita T, Hori S. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. *Am J Ophthalmol*. 2002;133(1):70–7.
11. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol*. 2009;54(1):1–32. doi:[10.1016/j.survophthal.2008.10.001](https://doi.org/10.1016/j.survophthal.2008.10.001).
12. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol*. 1985;103(12):1796–806.
13. Aiello LP, Edwards AR, Beck RW, Bressler NM, Davis MD, Ferris F, et al. Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*. 2010;117(5):946–53. doi:[10.1016/j.ophtha.2009.10.002](https://doi.org/10.1016/j.ophtha.2009.10.002).
14. Diabetic Retinopathy Clinical Research N. A randomized trial comparing intravitreal triamcinolone acetate and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*. 2008;115(9):1447–9. doi:[10.1016/j.ophtha.2008.06.015](https://doi.org/10.1016/j.ophtha.2008.06.015).
15. Lee CM, Olk RJ. Modified grid laser photocoagulation for diffuse diabetic macular edema. Long-term visual results. *Ophthalmology*. 1991;98(10):1594–602.
16. • Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119(4):789–801. doi:[10.1016/j.ophtha.2011.12.039](https://doi.org/10.1016/j.ophtha.2011.12.039). Results from the two phase III randomized clinical trials evaluating ranibizumab for DME that led to approval of ranibizumab for DME.
17. Diabetic Retinopathy Clinical Research N, Scott IU, Edwards AR, Beck RW, Bressler NM, Chan CK, et al. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology*. 2007;114(10):1860–7. doi:[10.1016/j.ophtha.2007.05.062](https://doi.org/10.1016/j.ophtha.2007.05.062).
18. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology*. 2010;117(6):1078–86, e2. doi:[10.1016/j.ophtha.2010.03.045](https://doi.org/10.1016/j.ophtha.2010.03.045).
19. Rajendram R, Fraser-Bell S, Kaines A, Michaelides M, Hamilton RD, Esposti SD, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol*. 2012;130(8):972–9. doi:[10.1001/archophthol.2012.393](https://doi.org/10.1001/archophthol.2012.393).
20. • Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS et al. Intravitreal Aflibercept for Diabetic Macular Edema. *Ophthalmology*. 2014. doi:[10.1016/j.ophtha.2014.05.006](https://doi.org/10.1016/j.ophtha.2014.05.006). Results from the two phase III randomized clinical trials evaluating aflibercept for DME that led to approval of aflibercept for DME.
21. Dabir SS, Das D, Nallathambi J, Mangalesh S, Yadav NK, Schouten JS. Differential systemic gene expression profile in patients with diabetic macular edema: responders versus non-responders to standard treatment. *Indian J Ophthalmol*. 2014;62(1):66–73. doi:[10.4103/0301-4738.126186](https://doi.org/10.4103/0301-4738.126186).
22. Antonetti DA, Wolpert EB, DeMaio L, Harhaj NS, Scaduto RC Jr. Hydrocortisone decreases retinal endothelial cell water and solute flux coincident with increased content and decreased phosphorylation of occludin. *J Neurochem*. 2002;80(4):667–77.
23. Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. *Exp Eye Res*. 2005;80(2):249–58. doi:[10.1016/j.exer.2004.09.013](https://doi.org/10.1016/j.exer.2004.09.013).
24. Fischer S, Renz D, Schaper W, Karliczek GF. In vitro effects of dexamethasone on hypoxia-induced hyperpermeability and expression of vascular endothelial growth factor. *Eur J Pharmacol*. 2001;411(3):231–43.
25. Nauck M, Karakiulakis G, Perruchoud AP, Papakonstantinou E, Roth M. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *Eur J Pharmacol*. 1998;341(2–3):309–15.
26. Nauck M, Roth M, Tamm M, Eickelberg O, Wieland H, Stulz P, et al. Induction of vascular endothelial growth factor by platelet-activating factor and platelet-derived growth factor is down-regulated by corticosteroids. *Am J Respir Cell Mol Biol*. 1997;16(4):398–406. doi:[10.1165/ajrcmb.16.4.9115750](https://doi.org/10.1165/ajrcmb.16.4.9115750).
27. Silva PS, Sun JK, Aiello LP. Role of steroids in the management of diabetic macular edema and proliferative diabetic retinopathy. *Semin Ophthalmol*. 2009;24(2):93–9. doi:[10.1080/08820530902800355](https://doi.org/10.1080/08820530902800355).
28. Tamura H, Miyamoto K, Kiryu J, Miyahara S, Katsuta H, Hirose F, et al. Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina. *Invest Ophthalmol Vis Sci*. 2005;46(4):1440–4. doi:[10.1167/iovs.04-0905](https://doi.org/10.1167/iovs.04-0905).
29. Wang K, Wang Y, Gao L, Li X, Li M, Guo J. Dexamethasone inhibits leukocyte accumulation and vascular permeability in retina of streptozotocin-induced diabetic rats via reducing

- vascular endothelial growth factor and intercellular adhesion molecule-1 expression. *Biol Pharm Bull.* 2008;31(8):1541–6.
30. Schwartz SG, Flynn HW Jr. Pharmacotherapies for diabetic retinopathy: present and future. *Exp Diabetes Res.* 2007;2007:52487. doi:[10.1155/2007/52487](https://doi.org/10.1155/2007/52487).
 31. Cekic O, Chang S, Tseng JJ, Akar Y, Barile GR, Schiff WM. Cataract progression after intravitreal triamcinolone injection. *Am J Ophthalmol.* 2005;139(6):993–8. doi:[10.1016/j.ajo.2005.01.022](https://doi.org/10.1016/j.ajo.2005.01.022).
 32. Wingate RJ, Beaumont PE. Intravitreal triamcinolone and elevated intraocular pressure. *Aust N Z J Ophthalmol.* 1999;27(6):431–2.
 33. Gillies MC, Kuzniarz M, Craig J, Ball M, Luo W, Simpson JM. Intravitreal triamcinolone-induced elevated intraocular pressure is associated with the development of posterior subcapsular cataract. *Ophthalmology.* 2005;112(1):139–43. doi:[10.1016/j.ophtha.2004.07.017](https://doi.org/10.1016/j.ophtha.2004.07.017).
 34. Nelson ML, Tennant MT, Sivalingam A, Regillo CD, Belmont JB, Martidis A. Infectious and presumed noninfectious endophthalmitis after intravitreal triamcinolone acetonide injection. *Retina (Philadelphia, Pa).* 2003;23(5):686–91.
 35. Verma LK, Vivek MB, Kumar A, Tewari HK, Venkatesh P. A prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in the treatment of diffuse diabetic macular edema. *J Ocul Pharmacol Ther.* 2004;20(4):277–84. doi:[10.1089/1080768041725308](https://doi.org/10.1089/1080768041725308).
 36. Bakri SJ, Kaiser PK. Posterior subtenon triamcinolone acetonide for refractory diabetic macular edema. *Am J Ophthalmol.* 2005;139(2):290–4. doi:[10.1016/j.ajo.2004.09.038](https://doi.org/10.1016/j.ajo.2004.09.038).
 37. Entezari M, Ahmadi H, Dehghan MH, Ramezani A, Bassirnia N, Anissian A. Posterior sub-tenon triamcinolone for refractory diabetic macular edema: a randomized clinical trial. *Eur J Ophthalmol.* 2005;15(6):746–50.
 38. Javadzadeh A. The effect of posterior subtenon methylprednisolone acetate in the refractory diabetic macular edema: a prospective nonrandomized interventional case series. *BMC Ophthalmol.* 2006;6:15. doi:[10.1186/1471-2415-6-15](https://doi.org/10.1186/1471-2415-6-15).
 39. Choi YJ, Oh IK, Oh JR, Huh K. Intravitreal versus posterior subtenon injection of triamcinolone acetonide for diabetic macular edema. *Korean J Ophthalmol.* 2006;20(4):205–9.
 40. Ozdek S, Bahceci UA, Gurelik G, Hasanreisoglu B. Posterior subtenon and intravitreal triamcinolone acetonide for diabetic macular edema. *J Diabetes Complications.* 2006;20(4):246–51. doi:[10.1016/j.jdiacomp.2005.06.015](https://doi.org/10.1016/j.jdiacomp.2005.06.015).
 41. Chew E, Strauber S, Beck R, Aiello LP, Antoszyk A, Bressler N, et al. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study. *Ophthalmology.* 2007;114(6):1190–6. doi:[10.1016/j.ophtha.2007.02.010](https://doi.org/10.1016/j.ophtha.2007.02.010).
 42. Shimura M, Nakazawa T, Yasuda K, Shiono T, Nishida K. Pretreatment of posterior subtenon injection of triamcinolone acetonide has beneficial effects for grid pattern photocoagulation against diffuse diabetic macular oedema. *Br J Ophthalmol.* 2007;91(4):449–54. doi:[10.1136/bjo.2006.106336](https://doi.org/10.1136/bjo.2006.106336).
 43. Chung EJ, Freeman WR, Azen SP, Lee H, Koh HJ. Comparison of combination posterior sub-tenon triamcinolone and modified grid laser treatment with intravitreal triamcinolone treatment in patients with diffuse diabetic macular edema. *Yonsei Med J.* 2008;49(6):955–64. doi:[10.3349/ymj.2008.49.6.955](https://doi.org/10.3349/ymj.2008.49.6.955).
 44. Yalcinbayir O, Gelisken O, Kaderli B, Avci R. Intravitreal versus sub-tenon posterior triamcinolone injection in bilateral diffuse diabetic macular edema. *Ophthalmologica.* 2011;225(4):222–7. doi:[10.1159/000324714](https://doi.org/10.1159/000324714).
 45. Nan K, Sun S, Li Y, Qu J, Li G, Luo L, et al. Characterisation of systemic and ocular drug level of triamcinolone acetonide following a single sub-Tenon injection. *Br J Ophthalmol.* 2010;94(5):654–8. doi:[10.1136/bjo.2009.172106](https://doi.org/10.1136/bjo.2009.172106).
 46. Iwao K, Inatani M, Kawaji T, Koga T, Mawatari Y, Tanihara H. Frequency and risk factors for intraocular pressure elevation after posterior sub-Tenon capsule triamcinolone acetonide injection. *J Glaucoma.* 2007;16(2):251–6. doi:[10.1097/IJG.0b013e31802d696f](https://doi.org/10.1097/IJG.0b013e31802d696f).
 47. Hirano Y, Ito T, Nozaki M, Yasukawa T, Sakurai E, Yoshida M, et al. Intraocular pressure elevation following triamcinolone acetonide administration as related to administration routes. *Jpn J Ophthalmol.* 2009;53(5):519–22. doi:[10.1007/s10384-009-0692-5](https://doi.org/10.1007/s10384-009-0692-5).
 48. Yamamoto Y, Kato Y, Tabuchi H, Fukushima A. Case of cytomegalovirus retinitis aggravated by sub-Tenon injection of triamcinolone acetonide with subsequent metastatic liver cancer. *Clin Ophthalmol (Auckland, NZ).* 2013;7:411–5. doi:[10.2147/OPTH.S41361](https://doi.org/10.2147/OPTH.S41361).
 49. Gallardo MJ, Johnson DA. Cutaneous hypopigmentation following a posterior sub-tenon triamcinolone injection. *Am J Ophthalmol.* 2004;137(4):779–80. doi:[10.1016/j.ajo.2003.09.044](https://doi.org/10.1016/j.ajo.2003.09.044).
 50. Moshfeghi DM, Lowder CY, Roth DB, Kaiser PK. Retinal and choroidal vascular occlusion after posterior sub-tenon triamcinolone injection. *Am J Ophthalmol.* 2002;134(1):132–4.
 51. Hollander DA, Clay EL, Sidikaro Y. Infectious crystalline keratopathy associated with intravitreal and posterior sub-Tenon triamcinolone acetonide injections. *Br J Ophthalmol.* 2006;90(5):656. doi:[10.1136/bjo.2005.087270](https://doi.org/10.1136/bjo.2005.087270).
 52. Hashizume K, Nabeshima T, Fujiwara T, Machida S, Kurosaka D. A case of herpetic epithelial keratitis after triamcinolone acetonide subtenon injection. *Cornea.* 2009;28(4):463–4. doi:[10.1097/ICO.0b013e31818a7d9a](https://doi.org/10.1097/ICO.0b013e31818a7d9a).
 53. Azarbod P, Mohammed Q, Akram I, Moorman C. Localised abscess following an injection of subtenon triamcinolone acetonide. *Eye (London, England).* 2007;21(5):672–4. doi:[10.1038/sj.eye.6702671](https://doi.org/10.1038/sj.eye.6702671).
 54. Engelman CJ, Palmer JD, Egbert P. Orbital abscess following subtenon triamcinolone injection. *Arch Ophthalmol.* 2004;122(4):654–5. doi:[10.1001/archophth.122.4.654](https://doi.org/10.1001/archophth.122.4.654).
 55. Kusaka S, Ikuno Y, Ohguro N, Hori Y, Tano Y. Orbital infection following posterior subtenon triamcinolone injection. *Acta Ophthalmol Scand.* 2007;85(6):692–3. doi:[10.1111/j.1600-0420.2007.00959.x](https://doi.org/10.1111/j.1600-0420.2007.00959.x).
 56. Chan CK, Mohamed S, Tang EW, Shanmugam MP, Chan NR, Lam DS. Encapsulated triamcinolone cyst after subtenon injection. *Clin Experiment Ophthalmol.* 2006;34(4):360–2. doi:[10.1111/j.1442-9071.2006.01223.x](https://doi.org/10.1111/j.1442-9071.2006.01223.x).
 57. Gharaee H, Khalife M, Poor SS, Abrishami M. Infectious scleritis after subtenon triamcinolone acetonide injection. *Ocul Immunol Inflamm.* 2011;19(4):284–5. doi:[10.3109/09273948.2011.584010](https://doi.org/10.3109/09273948.2011.584010).
 58. Diabetic Retinopathy Clinical Research N, Beck RW, Edwards AR, Aiello LP, Bressler NM, Ferris F, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol.* 2009;127(3):245–51. doi:[10.1001/archophthol.2008.610](https://doi.org/10.1001/archophthol.2008.610).
 59. Diabetic Retinopathy Clinical Research N, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology.* 2010;117(6):1064–77. doi:[10.1016/j.ophtha.2010.02.031](https://doi.org/10.1016/j.ophtha.2010.02.031).
 60. Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology.* 2011;118(4):609–14. doi:[10.1016/j.ophtha.2010.12.033](https://doi.org/10.1016/j.ophtha.2010.12.033). Two year results from the randomized trial of tria of triamcinolone plus laser versus ranibizumab plus laser versus laser alone.

61. O'Day R, Barthelmes D, Zhu M, Wong TY, McAllister IL, Arnold JJ, et al. Baseline central macular thickness predicts the need for retreatment with intravitreal triamcinolone plus laser photocoagulation for diabetic macular edema. *Clin Ophthalmol* (Auckland, NZ). 2013;7:1565–70. doi:[10.2147/oph.s47424](https://doi.org/10.2147/oph.s47424).
62. Jeon S, Lee WK. Effect of intravitreal triamcinolone in diabetic macular edema unresponsive to intravitreal bevacizumab. *Retina* (Philadelphia, Pa). 2014. doi:[10.1097/iae.0000000000000109](https://doi.org/10.1097/iae.0000000000000109).
63. Tas M, Oner V, Alakus MF, Turku FM, Iscan Y, Yuksel K. Single injection of triamcinolone versus three repeated injections of bevacizumab for treatment of diabetic macular edema. *Int Ophthalmol*. 2013;33(4):375–80. doi:[10.1007/s10792-012-9709-z](https://doi.org/10.1007/s10792-012-9709-z).
64. Kriechbaum K, Prager S, Mylonas G, Scholda C, Rainer G, Funk M et al. Intravitreal bevacizumab (Avastin) versus triamcinolone (Volon A) for treatment of diabetic macular edema: one-year results. *Eye* (London, England). 2014;28(1):9–15, quiz 6. doi:[10.1038/eye.2013.242](https://doi.org/10.1038/eye.2013.242).
65. Zhang Y, Ma J, Meng N, Li H, Qu Y. Comparison of intravitreal triamcinolone acetonide with intravitreal bevacizumab for treatment of diabetic macular edema: a meta-analysis. *Curr Eye Res*. 2013;38(5):578–87. doi:[10.3109/02713683.2013.767351](https://doi.org/10.3109/02713683.2013.767351).
66. Saeed AM. Combined vitrectomy and intravitreal injection versus combined laser and injection for treatment of intractable diffuse diabetic macular edema. *Clin Ophthalmol* (Auckland, NZ). 2013;7:283–97. doi:[10.2147/oph.s37781](https://doi.org/10.2147/oph.s37781).
67. Zacharias LC, Lin T, Migon R, Ghosn C, Orilla W, Feldmann B, et al. Assessment of the differences in pharmacokinetics and pharmacodynamics between four distinct formulations of triamcinolone acetonide. *Retina* (Philadelphia, Pa). 2013;33(3):522–31. doi:[10.1097/IAE.0b013e3182647f69](https://doi.org/10.1097/IAE.0b013e3182647f69).
68. Ober MD, Valijan S. The duration of effect of centrifuge concentrated intravitreal triamcinolone acetonide. *Retina* (Philadelphia, Pa). 2013;33(4):867–72. doi:[10.1097/IAE.0b013e31826b0bee](https://doi.org/10.1097/IAE.0b013e31826b0bee).
69. Sonoda S, Sakamoto T, Yamashita T, Otsuka H, Shirasawa M, Kakiuchi N, et al. Effect of intravitreal triamcinolone acetonide or bevacizumab on choroidal thickness in eyes with diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2014;55(6):3979–85. doi:[10.1167/iov.14-14188](https://doi.org/10.1167/iov.14-14188).
70. Shahin M, Gad MA, Hamza W. Impact of intravitreal triamcinolone acetonide versus intravitreal bevacizumab on retrobulbar hemodynamic in patients with diabetic macular edema. *Cutan Ocul Toxicol*. 2014;33(1):49–53. doi:[10.3109/15569527.2013.796478](https://doi.org/10.3109/15569527.2013.796478).
71. Deak GG, Lammer J, Prager S, Mylonas G, Bolz M, Schmidt-Erfurth U. Refractive changes after pharmacologic resolution of diabetic macular edema. *Ophthalmology*. 2014;121(5):1054–8. doi:[10.1016/j.ophtha.2013.11.026](https://doi.org/10.1016/j.ophtha.2013.11.026).
72. Bressler SB, Qin H, Melia M, Bressler NM, Beck RW, Chan CK, et al. Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. *JAMA Ophthalmol*. 2013;131(8):1033–40. doi:[10.1001/jamaophthalmol.2013.4154](https://doi.org/10.1001/jamaophthalmol.2013.4154).
73. Pershing S, Enns EA, Matesic B, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of treatment of diabetic macular edema. *Ann Intern Med*. 2014;160(1):18–29. doi:[10.7326/m13-0768](https://doi.org/10.7326/m13-0768).
74. Smiddy WE. Clinical applications of cost analysis of diabetic macular edema treatments. *Ophthalmology*. 2012;119(12):2558–62. doi:[10.1016/j.ophtha.2012.09.015](https://doi.org/10.1016/j.ophtha.2012.09.015).
75. Dewan V, Lambert D, Edler J, Kymes S, Apte RS. Cost-effectiveness analysis of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2012;119(8):1679–84. doi:[10.1016/j.ophtha.2012.01.049](https://doi.org/10.1016/j.ophtha.2012.01.049).
76. Sonmez K, Ozturk F. Complications of intravitreal triamcinolone acetonide for macular edema and predictive factors for intraocular pressure elevation. *Int J Ophthalmol*. 2012;5(6):719–25. doi:[10.3980/j.issn.2222-3959.2012.06.13](https://doi.org/10.3980/j.issn.2222-3959.2012.06.13).
77. Okka M, Bozkurt B, Kerimoglu H, Ozturk BT, Gunduz K, Yilmaz M, et al. Control of steroid-induced glaucoma with surgical excision of sub-Tenon triamcinolone acetonide deposits: a clinical and biochemical approach. *Can J Ophthalmol*. 2010;45(6):621–6. doi:[10.3129/i10-055](https://doi.org/10.3129/i10-055).
78. Tabandeh H, Boscia F, Sborgia A, Ciraci L, Dayani P, Mariotti C, et al. Endophthalmitis associated with intravitreal injections: office-based setting and operating room setting. *Retina* (Philadelphia, Pa). 2014;34(1):18–23. doi:[10.1097/iae.0000000000000008](https://doi.org/10.1097/iae.0000000000000008).
79. Bhavsar AR, Stockdale CR, Ferris FL 3rd, Brucker AJ, Bressler NM, Glassman AR. Update on risk of endophthalmitis after intravitreal drug injections and potential impact of elimination of topical antibiotics. *Arch Ophthalmol*. 2012;130(6):809–10. doi:[10.1001/archophthalmol.2012.227](https://doi.org/10.1001/archophthalmol.2012.227).
80. Cheung CS, Wong AW, Lui A, Kertes PJ, Devenyi RG, Lam WC. Incidence of endophthalmitis and use of antibiotic prophylaxis after intravitreal injections. *Ophthalmology*. 2012;119(8):1609–14. doi:[10.1016/j.ophtha.2012.02.014](https://doi.org/10.1016/j.ophtha.2012.02.014).
81. Otsuka H, Kawano H, Sonoda S, Nakamura M, Sakamoto T. Particle-induced endophthalmitis: possible mechanisms of sterile endophthalmitis after intravitreal triamcinolone. *Invest Ophthalmol Vis Sci*. 2013;54(3):1758–66. doi:[10.1167/iov.12-11247](https://doi.org/10.1167/iov.12-11247).
82. Ahn SJ, Kim TW, Ahn J, Huh JW, Yu HG, Chung H. Associated factors and treatment outcome of presumed noninfectious endophthalmitis occurring after intravitreal triamcinolone acetonide injection. *Graefes Arch Clin Experiment Ophthalmol*. 2013;251(3):715–23. doi:[10.1007/s00417-012-2111-8](https://doi.org/10.1007/s00417-012-2111-8).
83. Marticorena J, Romano V, Gomez-Ulla F. Sterile endophthalmitis after intravitreal injections. *Mediators Inflamm*. 2012;2012:928123. doi:[10.1155/2012/928123](https://doi.org/10.1155/2012/928123).
84. Zarifa R, Shaikh S, Kester E. Persistence of triamcinolone crystals after intra-vitreous injection: benign crystalline hyaloidopathy. *Indian J Ophthalmol*. 2013;61(4):182–3. doi:[10.4103/0301-4738.112166](https://doi.org/10.4103/0301-4738.112166).
85. Zghal I, Malek I, Amel C, Soumaya O, Bouguila H, Nacef L. Viral retinitis following intravitreal triamcinolone injection. *J Fr Ophthalmol*. 2013;36(7):e129–32. doi:[10.1016/j.jfo.2012.08.015](https://doi.org/10.1016/j.jfo.2012.08.015).
86. Rush R, Sheth S. Fulminant toxoplasmic retinochoroiditis following intravitreal triamcinolone administration. *Indian J Ophthalmol*. 2012;60(2):141–3. doi:[10.4103/0301-4738.94059](https://doi.org/10.4103/0301-4738.94059).
87. Yilmaz T, Cordero-Coma M, Lavaque AJ, Gallagher MJ, Padula WV. Triamcinolone and intraocular sustained-release delivery systems in diabetic retinopathy. *Curr Pharm Biotechnol*. 2011;12(3):337–46.
88. Chang-Lin JE, Attar M, Acheampong AA, Robinson MR, Whitcup SM, Kuppermann BD, et al. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Invest Ophthalmol Vis Sci*. 2011;52(1):80–6. doi:[10.1167/iov.10-5285](https://doi.org/10.1167/iov.10-5285).
89. Mathew R, Pearce E, Muniraju R, Abdul-Hey A, Sivaprasad S. Monthly OCT monitoring of Ozurdex for macular oedema related to retinal vascular diseases: re-treatment strategy (OC-TOME Report 1). *Eye* (London, England). 2014;28(3):318–26. doi:[10.1038/eye.2013.287](https://doi.org/10.1038/eye.2013.287).
90. •• Boyer DS, Yoon YH, Belfort R, Jr., Bandello F, Maturi RK, Augustin AJ et al. Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema. *Ophthalmology*. 2014. doi:[10.1016/j.ophtha.2014.04.024](https://doi.org/10.1016/j.ophtha.2014.04.024). *Results from the three year trial of the*

- Ozurdex dexamethasone implant that led to it becoming the first corticosteroid approved for the treatment of DME.*
91. Callanan DG, Gupta S, Boyer DS, Ciulla TA, Singer MA, Kuppermann BD, et al. Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology*. 2013;120(9):1843–51. doi:[10.1016/j.ophtha.2013.02.018](https://doi.org/10.1016/j.ophtha.2013.02.018).
 92. Meyer CH, Liu Z, Brinkmann CK, Rodrigues EB, Bertelmann T. Penetration force, geometry, and cutting profile of the novel and old Ozurdex needle: the MONO Study. *J Ocul Pharmacol Ther*. 2014;30(5):387–91. doi:[10.1089/jop.2013.0231](https://doi.org/10.1089/jop.2013.0231).
 93. Eaton AM, Gordon GM, Booth D, Wafapoor H, Avery RL. Injection force comparison of the old and new dexamethasone implant insertion needles in porcine eyes and synthetic sclera. *Ophthalmic Surg Lasers Imaging Retina*. 2014;45(3):232–8. doi:[10.3928/23258160-20140430-01](https://doi.org/10.3928/23258160-20140430-01).
 94. Moisseiev E, Regenbogen M, Rabinovitch T, Barak A, Loewenstein A, Goldstein M. Evaluation of pain during intravitreal Ozurdex injections vs intravitreal bevacizumab injections. *Eye (London, England)*. 2014. doi:[10.1038/eye.2014.129](https://doi.org/10.1038/eye.2014.129).
 95. Khurana RN, Appa SN, McCannel CA, Elman MJ, Wittenberg SE, Parks DJ, et al. Dexamethasone implant anterior chamber migration: risk factors, complications, and management strategies. *Ophthalmology*. 2014;121(1):67–71. doi:[10.1016/j.ophtha.2013.06.033](https://doi.org/10.1016/j.ophtha.2013.06.033).
 96. Kishore SA, Schaal S. Management of anterior chamber dislocation of dexamethasone implant. *Ocul Immunol Inflamm*. 2013;21(1):90–1. doi:[10.3109/09273948.2012.736589](https://doi.org/10.3109/09273948.2012.736589).
 97. Collet B. Management of ozurdex in the anterior chamber. *JAMA Ophthalmol*. 2013;131(12):1651–2. doi:[10.1001/jamaophthalmol.2013.5610](https://doi.org/10.1001/jamaophthalmol.2013.5610).
 98. Vela JJ, Crespi J, Andreu D. Repositioning of dexamethasone intravitreal implant (Ozurdex) migrated into the anterior chamber. *Int Ophthalmol*. 2012;32(6):583–4. doi:[10.1007/s10792-012-9604-7](https://doi.org/10.1007/s10792-012-9604-7).
 99. Wai Ch'ng S, Padroni S, Banerjee S. Anterior vitreous displacement of the intravitreal dexamethasone implant (Ozurdex). *Eye (London, England)*. 2014;28(2):238–9. doi:[10.1038/eye.2013.270](https://doi.org/10.1038/eye.2013.270).
 100. Banerjee PJ, Petrou P, Zvobgo TM, Charteris DG. Spontaneous relocation of a trapped retrolenticular slow-release dexamethasone implant (Ozurdex) in a silicone oil-filled eye of a pseudophakic patient. *Eye (London, England)*. 2014. doi:[10.1038/eye.2014.84](https://doi.org/10.1038/eye.2014.84).
 101. Agrawal R, Fernandez-Sanz G, Bala S, Addison PK. Desegmentation of Ozurdex implant in vitreous cavity: report of two cases. *Br J Ophthalmol*. 2014;98(7):961–3. doi:[10.1136/bjophthalmol-2014-304866](https://doi.org/10.1136/bjophthalmol-2014-304866).
 102. Rishi P, Mathur G, Rishi E. Fractured Ozurdex implant in the vitreous cavity. *Indian J Ophthalmol*. 2012;60(4):337–8. doi:[10.4103/0301-4738.98734](https://doi.org/10.4103/0301-4738.98734).
 103. Roy R, Hegde S. Split Ozurdex implant: a caution. *Can J Ophthalmol*. 2013;48(1):e15–6. doi:[10.1016/j.jcjo.2012.03.033](https://doi.org/10.1016/j.jcjo.2012.03.033).
 104. Donmez O, Parlak M, Yaman A, Saatci AO. Splitting of a Dexamethasone Implant (Ozurdex) following the Injection. *Case Rep Ophthalmol Med*. 2013;2013:247949. doi:[10.1155/2013/247949](https://doi.org/10.1155/2013/247949).
 105. Berarducci A, Sian IS, Ling R. Inadvertent dexamethasone implant injection into the lens body management. *Eur J Ophthalmol*. 2014;24(4):620–2. doi:[10.5301/ejo.5000436](https://doi.org/10.5301/ejo.5000436).
 106. Coca-Robinot J, Casco-Silva B, Armada-Maresca F, Garcia-Martinez J. Accidental injections of dexamethasone intravitreal implant (Ozurdex(R)) into the crystalline lens. *Eur J Ophthalmol*. 2014;24(4):633–6. doi:[10.5301/ejo.5000439](https://doi.org/10.5301/ejo.5000439).
 107. Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL. Treatment of posterior uveitis with a fluocinolone acetonide implant: three-year clinical trial results. *Arch Ophthalmol*. 2008;126(9):1191–201. doi:[10.1001/archophth.126.9.1191](https://doi.org/10.1001/archophth.126.9.1191).
 108. Pearson PA, Comstock TL, Ip M, Callanan D, Morse LS, Ashton P, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology*. 2011;118(8):1580–7. doi:[10.1016/j.ophtha.2011.02.048](https://doi.org/10.1016/j.ophtha.2011.02.048).
 109. Campochiaro PA, Hafiz G, Shah SM, Bloom S, Brown DM, Busquets M et al. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. *Ophthalmology*. 2010;117(7):1393–9, e3. doi:[10.1016/j.ophtha.2009.11.024](https://doi.org/10.1016/j.ophtha.2009.11.024).
 110. Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626–35, e2. doi:[10.1016/j.ophtha.2010.12.028](https://doi.org/10.1016/j.ophtha.2010.12.028).
 111. •• Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125–32. doi:[10.1016/j.ophtha.2012.04.030](https://doi.org/10.1016/j.ophtha.2012.04.030). *Three year results of the clinical trial evaluating the FA insert for DME.*
 112. Cunha-Vaz J, Ashton P, Iezzi R, Campochiaro P, Dugel PU, Holz FG, et al. Sustained Delivery Fluocinolone Acetonide Vitreous Implants: Long-Term Benefit in Patients with Chronic Diabetic Macular Edema. *Ophthalmology*. 2014. doi:[10.1016/j.ophtha.2014.04.019](https://doi.org/10.1016/j.ophtha.2014.04.019).