Review Article

Current intravitreal therapy and ocular hypertension: A review

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To determine the effect of commonly used intravitreal agents on immediate and long-term IOP elevations and their association, if any, with glaucoma. Literature searches in PubMed and the Cochrane databased in January 2020 yielded 407 individual articles. Of these, 87 were selected for review based on our inclusion criteria. Based on the evidence provided, 20 were assigned level I, 27 level II, and 22 level III. Eight articles were rejected because of poor quality, insufficient clarity, or irrelevance based on standardized protocols set out by the American Academy of Ophthalmology. The studies that reported on short-term IOP elevation (i.e., between 0 and 60 min) showed that an immediate increase in IOP is seen in all patients who receive anti-VEGF agents or triamcinolone acetonide when measured between 0 and 30 min of intravitreal injection and that the IOP elevation decreases over time. The data on long-term IOP elevation were mixed; Pretreatment with glaucoma medications, anterior chamber tap, vitreous reflux, longer intervals between injections, and longer axial lengths were associated with lower IOP elevations after injection of anti-VEGF agents, while the position of the implant vis-à-vis, the anterior chamber was important for steroid therapy. Data were mixed on the relationship between IOP increase and the type of intravitreal injection, number of intravitreal injections, preexisting glaucoma, and globe decompression before injection. There were no data on the onset or progression of glaucoma in the studies reviewed in this assessment. However, some studies demonstrated RNFL thinning in patients receiving chronic anti-VEGF therapy. Most, if not all, intravitreal agents cause ocular hypertension, both in the short term and long term. The functional consequences of these observations are not very clear.

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Intravitreal injection of therapeutic agents has in recent times become the mainstay of therapy for a variety of macular diseases. The treatment options available to the physician today are varied, as are their indications and applicability. An important consideration with any therapy is the attendant adverse effect; the development of ocular hypertension being one of them. This adverse effect assumes importance in light of the fact that the development of ocular hypertension and subsequent glaucoma can offset the gains achieved courtesy intravitreal therapy. It is important, therefore, to be aware of the degree of risk associated with a particular therapeutic agent and the benefits that may accrue with continuation or cessation thereof. This review has been proposed with the intention of reviewing current literature with reference to ocular hypertension and the risk factors that may predispose one to its occurrence.

Description of Evidence

Literature searches were conducted on January 1, 2020 in the PubMed and Cochrane Library databases. A total of 287 articles were found. The following search terms were used: Intraocular pressure OR glaucoma OR ocular hypertension OR IOP OR visual field analysis OR RNFL analysis OR antivascular endothelial growth factor OR anti-VEGF OR angiogenesis inhibitors Avastin/bevacizumab OR Lucentis/Accentrix/ranibizumab OR Eylea/Aflibercept OR dexamethasone implant/Ozurdex or ILUVIEN/fluocinolone acetonide OR intravitreal insert or cohort studies OR randomized studies OR Case Series OR controlled trial. Filters used were Humans, English. Articles that did not assess intravitreal injections were excluded, and a total of 107 articles were found eligible for review. These articles were initially screened using their titles and abstracts, and 87 were selected for full-text review. The following inclusion criteria were used: 1) the study reported on original research and 2) the population consisted of at least 20 adults (>18 years)

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treated with one or more of the aforementioned intravitreal therapeutic agents. Articles evaluating neovascular glaucoma were excluded. Since this was a review of published articles, ethics committee approval was not required.

The panel assigned a rating to each article based on the level of evidence therein using standardized protocols.[1] Based on the level of evidence, 20 articles were assigned level, 27 level II, and 22 level III. A total of eight articles were excluded, either on the grounds of poor study design or irrelevance. Metaanalyses and reviews were not rated separately.

Questions for Assessment

The assessment attempts to address the following questions: (1) What is the effect of various medications in current use for intravitreal therapy on short- and long-term IOP and does it predispose patients to glaucoma? (2) What are the risk factors for development of ocular hypertension with various intravitreal medications.

This review article focuses exclusively on current therapy and does not include analyses on therapeutic agents now considered obsolete or intravitreal agents that are not in practical use as of today.

Intravitreal Anti-VEGF Therapy

Sustained intraocular pressure (IOP) rise following intravitreal anti-VEGF injections is a known phenomenon with several publications addressing this issue in part or whole.[1-5] There is a certain measure of discrepancy in reporting insofar as the potential risk factors as well as definitions of IOP rise are concerned.[6-8] With numerous publications on the subject, it is only natural that contrasting outcomes are noted in studies conducted across the globe[1-8]; the most disputed among risk factors for IOP rise being the number of injections administered and the treatment interval[2] between consecutive injections. When one factors in the indication, the anti-VEGF agent used, the phakic status, the anterior chamber angle status, family history of glaucoma, and other characteristics,[1,2] it is evident that the condition (IOP rise) and analysis thereof is a complex phenomenon.

Despite a plethora of literature[5-36] on the subject, a recently published review[1] highlights the lack of a comprehensive overview and hazards analysis of risk factors and IOP rise.

Sustained IOP rise with aflibercept and ranibizumab use for AMD has been documented and studied[16]; studies have thrown up conflicting reports as regards the risk factors studied for IOP rise. Indeed, some studies do not report of any sustained IOP rise following anti-VEGF injections.[1,2,6,8] The most studied and documented risk factors are the number of injections and the treatment interval, followed by lens status, presence of vein occlusion,[2] preexisting glaucomatous disease, and angle chamber depth. Literature[31] suggests the following mechanisms for the development of ocular hypertension after intravitreal therapy: trabecular alterations over repeated peaks of IOP with multiple injections, trabecular congestion due to antibodies, silicone micro-droplets, protein aggregation with bevacizumab, and a chronic trabeculitis or a trabecular autoimmune reaction. These factors along with several probable mechanisms that we describe subsequently may have had a collaborative effect.

Short-term IOP fluctuations consequent to increased intraocular volume upon injection can also adversely affect RNFL thickness. Conversely, pretreatment with topical IOP lowering medication has shown to maintain IOP immediately after injection within the normal range (i.e., 21 mm Hg or less). The functional significance of these RNFL thickness changes are not immediately clear; studies do demonstrate perimetric defects,[32] especially superior rim thinning in eyes that require continued intravitreal therapy. However, this risk must be viewed in tandem with the threat to vision upon cessation of intravitreal anti-VEGF therapy. Another point to be taken into consideration is the role of anterior chamber paracentesis[17] during the procedure; a simple test is confirmation of light perception on table. Absence of light perception is a definite indication for anterior chamber paracentesis on table. This is readily achieved with the use of a 30 gauge needle and can be done safely in phakic eyes as well. It is important to fix the globe well before needle insertion, especially in phakic eyes, to avoid inadvertent lens touch and subsequent cataract formation. This is also a useful manoeuvre in patients who have already manifest an IOP rise, and the aim is to avoid a surge in IOP intraoperatively.

Additionally, most studies that do report IOP rise are ones that follow patients over a mean of 84 weeks. We demonstrate an association between sustained IOP rise and the following: older age, male sex, South Asian ethnicity, narrow angles, preexisting glaucoma, >6 injections, AMD and RVO, use of ranibizumab, concentration of ranibizumab injected, and switch to ranibizumab or bevacizumab. Patients manifesting a short-term IOP rise were not necessarily predisposed to develop sustained IOP rise. Patients who had sustained IOP rise with anti-VEGF therapy were not predisposed to develop IOP rise with the dexamethasone implant.

Pretreatment[10,11,17] with IOP lowering medications or ocular massage has been suggested for short term IOP rise; the long-term effect of this measure is unknown. Typically, IOP can increase up to 50 mm Hg in the first 5 min after injection and returns to baseline 45 min post-injection. RNFL thinning[18] has been suggested as a short-term consequence of acute IOP fluctuations. Also, vitreous reflux[19] is said to play a role in reducing immediate rise in IOP. Most studies that advise preemptive lowering of IOP did not look at the long-term consequences of these measures on sustained IOP rise or their role in preventing visual field defects.[1] This suggests that the cause for RNFL thinning as described by Martinez de la Casa and associates is probably short-term IOP rise.

A short treatment interval appears to influence IOP rise as per the study by Mathalone *et al*. They reported an incidence of sustained IOP rise of 11% (comparable to our study). Overall, 22 patients in their series were noted to have IOP rise. Other studies, including our own analysis,[33] do not seem to suggest that the treatment interval can influence IOP rise.

The anti-VEGF agent used has generated considerable interest, with reasonably consistent findings reported from various studies. Bevacizumab[1,2,15,20] has been noted by most authors to lead to sustained IOP rise followed by ranibizumab.[1,2] Our data corroborate with past literature in that ranibizumab has a higher probability of causing sustained IOP rise when compared with aflibercept[1,2,20]; only one study (with insufficient numbers) reports that ranibizumab is

not associated with IOP rise.[8] We also determine in our study through multivariate analysis that switching to ranibizumab or bevacizumab increases the chances of the patient developing sustained IOP rise, whereas switching to aflibercept does not.[7] This agrees well with past reports and may have something to do with the structure of ranibizumab. Also, per our analysis, switching to the dexamethasone implant after primary therapy with anti-VEGF agents does not increase the probability of IOP rise, regardless of the agent used (ranibizumab or aflibercept). This finding is somewhat in conflict with the discussion by Dedania and associates[2] wherein they discuss past literature.

The outcome of research on the number of injections and its influence on long-term IOP rise is mixed; some studies suggest that this is a consideration,[23] while other authors reject this theory.[24,25] Even the average number of injections to IOP rise fluctuate between 6[26] and 24.[22,23]

The concentration of the injected drug, a consideration only with ranibizumab in the South Asian region in our study (given that aflibercept is only used in a dose of 0.5 mg), seems to correlative positively and independently with sustained IOP rise. A literature search using the key words "anti-VEGF agent, IOP, ranibizumab, drug volume, 0.3 mg, 0.5 mg ml, age-related macular degeneration, macular edema, sustained IOP rise, long-term IOP rise" on PubMed, Scopus, and the Cochrane Database on September 11, 2019 failed to reveal any study that looks at the concentration of injected ranibizumab and IOP rise. This has probably something to do with greater probability of trabecular meshwork obstruction with higher drug concentrations.

Whereas a narrow anterior chamber angle predisposed the patient to sustained IOP rise in our study, the axial length seemingly did not. Short term IOP rise has been associated with short eyes and narrow chambers,[27] but its influence on long-term IOP rise does not seem to have been adequately addressed.

Preexisting glaucoma and sustained IOP rise seem to have a controversial association,[1,2] with some studies reporting a strong correlation and another reporting none. Studies that report no influence of preexisting glaucoma on long-term IOP rise generally have small numbers.[1] A family history of glaucoma was reported to be a risk factor by Hoang and associates[24]; Dedania *et al*.[2] suggest that their exclusion of three patients with glaucoma might have confounded the results. Whereas one study reports the average time to IOP rise to be 39 weeks in glaucoma patients,[27] we noted the time to be 25 weeks on an average in our analysis. Whereas preexisting glaucoma appeared to be a risk factor for sustained IOP rise in our study, a family history of glaucoma did not seem to predispose a patient to long-term IOP rise. Unlike the findings of Kim and associates,[5] a low baseline IOP did not seem to predispose the patient to sustained IOP rise. AMD and RVO, however, were strongly associated with sustained IOP rise. Patients with AMD in our study tended to receive on an average a greater number of injections probably leading to a greater buildup of degradation microparticles and causing a rise in IOP. Additionally, we hypothesize that the development of AMD reflects an overall degenerative process affecting the eye and that this affects trabecular meshwork outflow as well, causing a buildup of microdegradation products and leading to the development of ocular hypertension. The hypothesis that alteration of trabecular outflow facility with steroid use may influence sustained IOP rise after anti-VEGF injections probably needs further evaluation.

The extreme variations in reports on long-term IOP rise along with the risk factors responsible for it as reported in literature are testimony to the complexity of this disease process.[1,2,19-26] Studies vary in their structure, number, indications, inclusion, and exclusion of certain groups of patients (glaucomatous eyes, for instance) and their definitions of IOP rise.[1,2] RNFL thickness has not shown to vary significantly in literature published earlier.[28] Unlike most reports on dexamethasone implant-induced transient ocular hypertension,[29,30] the rise in IOP with anti-VEGF agents seems to be chronic, sustained, thereby suggesting a higher chance of progression to glaucomatous changes, the lower incidence overall of ocular hypertension with anti-VEGF therapy notwithstanding.

Repeat intravitreal injections affect Bruch's Membrane opening, cup size, and other optic disc changes typically considered to be clinical signs of glaucomatous optic neuropathy.[34] The discussion thus far is applicable to a large extent to the new molecule on the horizon as well: Brolucizumab. Preliminary studies[35] report an incidence of ocular hypertension around 5.6%. Logically, the same precautions and prophylaxis should work as containment of sustained IOP rise with brolicizumab although detailed analyses will follow once physicians around the world publish their real-life experience. The role of gender and ethnicity in trabecular meshwork function along with the proposed hypothesis needs further study. At present, the inference that we may draw from this analysis is that all patients on chronic intravitreal anti-VEGF therapy, regardless of indication, choice of drug or the presence or absence of glaucoma should be carefully monitored for IOP rise, and therapy instituted at the earliest. In patients with established ocular hypertension/glaucoma, it might be prudent to consider pretreatment (prophylaxis) with IOP lowering medications at the time of injection and to continue IOP lowering therapy during the course of anti-VEGF treatment and thereafter. Our recent publication deals with these issues in some detail.[33]

Steroids and Ocular Hypertension

Ocular hypertension is a known consequence of steroid administration irrespective of the molecule or route of administration used,[33,36-38] albeit with varying degrees of IOP elevation. The mechanisms involved therewith are complex, but the most accepted theory is the modification or blockage of the ultrastructure of the trabecular meshwork that impedes aqueous outflow by inhibition of proteases and phagocytosis of trabecular meshwork making the extracellular matrix of the trabecular meshwork less permeable.

The Intravitreal Dexamethasone Implant

Pivotal studies[39-42] that established the role of the dexamethasone implant (Ozurdex, Allergan, Irvine, CA) in uveitis, diabetic macular edema, or macular edema secondary to vein occlusion report that up to a third of patients receiving intravitreal therapy may develop ocular hypertension at some point in time during therapy and follow up. The peak in IOP typically occurs a mean of 60 days after the injection. Patients with preexisting ocular hypertension or glaucoma tend to respond

early and more to implant injection, with 50–100% of patients demonstrating some measure of IOP spike, especially those on dual or triple therapy with IOP lowering medications.

A third of patients on monotherapy for preexisting IOP elevations tend to develop a rise in IOP.[43] Typically, patients who demonstrate a rise in IOP post injection tend to do so after the first or second injection, and of these, nearly 87% manifest a spike of 6 mm Hg or more. Past analyses show that there is little or no cumulative risk of IOP rise with the dexamethasone implant, i.e., if the patient does not manifest an IOP spike with the first or second injection, there is little risk of development of ocular hypertension with future injections. "Late" responders, i.e., people generally have one of the predisposing risk factors discussed subsequently. An overwhelming majority of the cases can be managed with topical therapy; only a handful require systemic therapy or some form of incisional surgery for IOP control.

Risk factors[29,43] for development of ocular hypertension secondary to the dexamethasone implant include younger age (<60 years), male gender, presence of type 1 diabetes mellitus, vein occlusion or uveitis, and patients already on dual or triple therapy for ocular hypertension/glaucoma. Type II diabetics on the other hand are not necessarily predisposed to IOP rise.

Additionally, our analysis of IOP rise and the dexamethasone implant[29] demonstrates that the position of the dexamethasone implant in-situ is an important determinant of and independent risk factor for IOP rise; the closer the implant lies to the ciliary body, the greater the chance of developing ocular hypertension. This finding is in line with the theory that the entry of the steroid molecule in the anterior chamber is an essential component of the development of ocular hypertension. Further evidence for this is provided by the rates of incisional surgery in patients who receive the RETISERT versus those who receive the fluocinolone acetonide intravitreal insert (ILUVIEN); a lower dose and a more posterior placement of the depot preparation reduces the rate for incisional surgery for uncontrolled ocular hypertension from 33% for patients who receive the RETISERT implant to approximately 5.6% for patients who received the ILUVIEN implant.[44] Additionally, eyes with the implant positioned closed to the ciliary body may manifest IOP spikes as early as 3 days post injection.[29] Vitrectomized eyes probably show increased clearance of drug from the intravitreal cavity and the presence or absence of vitreous does not influence IOP rise.[33,36]

An important limitation of all retrospective analyses must be taken into account; it is possible that missed follow-ups explain the lower incidence of ocular hypertension when compared with validation or pivotal studies such as the MEAD study; the SAFODEX study documented an incidence of around 17%; we noted an incidence of approximately 20%. The MEAD study, for instance, noted that almost a third of patients demonstrated ocular hypertension at some point in time during the course of follow-up. The MEAD study was a prospective study with strict follow-up regimes and therefore recorded an incidence of ocular hypertension that is probably closer to the real incidence. Conversely, real-life studies depict a scenario that is more prevalent, and therefore more relevant; not every spike in IOP is clinically significant and a more relaxed follow-up schedule should be able to pick up in timely manner clinically significant elevations of IOP (>25 mm Hg, as agreed upon by most authors). Finally, there appears to be some ethnic predisposition to the development of ocular hypertension per the GEODEX-IOP study,[45] wherein it was demonstrated that south Asians and Latinos have a greater propensity to develop ocular hypertension, especially when an IOP >25 mm Hg is an inclusion criterion. There is no particular racial predisposition if one considers and IOP >20 mm Hg. A genetic predisposition to develop ocular hypertension secondary to steroid administration is known.[44] The dexamethasone implant and its association with ocular hypertension have been well studied in patients with glaucoma and in patients who are known steroid responders as well[46,47]; the results are largely encouraging in that most patients who did demonstrate an IOP rise responded well to medical management and incisional surgery was seldom required. Steroid induced ocular hypertension in uveitis[46-49] needs to be looked at with a different perspective; presences of peripheral anterior synechiae may adversely influence the frequency and severity of IOP spikes, necessitating surgical intervention. In our series discussed earlier,[29] the solitary patient who received trabeculectomy for IOP control was a case of pan-uveitis with peripheral anterior synechiae affecting trabecular outflow.

Triamcinolone Acetonide

Preservative-free triamcinonolone acetonide has been used for a variety of retinal conditions and has been used intravitreally, subconjunctivally, and in the subtenon space. Several studies[50-61] have documented its cataractogenesis and IOP spikes. Intravitreal triamcinolone acetonide injections can cause both short-term IOP fluctuations and persistent ocular hypertension, the former being related in part to the volume of the injected drug and the latter a "pharmacopathological" response. Younger age, preexisting glaucoma, narrow angles, and a history of diabetes mellitus are clinically evident risk factors[52,60,61] associated with IOP rise in patients.

The short-term rise in IOP[50] immediately postoperatively logically follows an increase in intraocular volume and is absent/low in eyes that demonstrate vitreous reflux immediately after injection. In a series of 38 eyes who had received intravitreal triamcinolone, Benz and associates measured IOP with Goldmann applanation tonometry preoperatively and then immediately postoperatively as well as 2, 5, 10, 20, and 30 min after injection. They concluded that eyes that do not demonstrate vitreous reflux at the site of injection tend to show, on average, a spike of around 20 mm Hg or more from baseline immediately after injection and that it tends to normalize over 30 min. This is not unlike what we have elaborated upon for short-term IOP rise consequent to intravitreal anti-VEGF injections.[33] Additionally, there are reports[51] of a "Postop day 4 IOP rise" in a few patients who were part of the triamcinolone arm in the Diabetic Retinopathy Clinical Research Network study groups. This appears to be transitory, and the authors do not suggest more stringent follow-up protocols or therapy for the same.

Long-term development of ocular hypertension with triamcinolone acetonide follows closely the pattern noted with other intravitreal steroid injections, such as the dexamethasone implant. This typically happens between weeks 2 and 5 post injection. In a retrospective analysis[61] involving 929 eyes of 841 patients, the cumulative incidence of IOP rise >21 mm Hg

in patients receiving multiple injections rose from 28.8% at 6 months to 44.6% at 24 months. Preexisting glaucoma would naturally translate into a higher probability of IOP spikes, and the severity of the spikes are also greater. Conversely, approximately 28% eyes had IOP elevation >25 mm Hg at 2 years after initiation of therapy. Finally, a quarter of these eyes required IOP lowering medications at 2 years. This does not necessarily imply a cumulative rise in IOP secondary to multiple injections; it is more reflective of a diminishing sample size. Only three eyes ever required incisional surgery for uncontrolled IOP rise. IOP rise does not preclude further injection as long as the IOP rise can be satisfactorily controlled medically; for patients who have received incisional surgery to counter IOP rise, the need and permissibility for further steroid injections can be decided on a case-to-case basis.

Triamcinolone crystals have been observed to remain in the vitreous cavity for a period of 12 weeks post injections and even longer in some cases, as noted clinically and pharmacologically by Sophie and Beer.[57] It follows that patients must be monitored for the said time period.[56-58] The persistence of triamcinolone crystals does not correlate with pharmacologic activity. In patients with persistent IOP elevations refractory to medical or surgical therapy, vitrectomy and evacuation of the triamcinolone crystals may be considered as the last option (*ultima ratio*). The subtenon route[59] might be associated with a lower incidence of ocular hypertension. The efficacy and safety of the subtenon route depends upon the exact plane of injection; inadvertent subconjunctival injection may actually raise the IOP to a greater extent than the subtenon space itself. Vitrectomized eyes show increased uptake and excretion of triamcinolone acetonide and may correspondingly demonstrate a lower and ill-sustianed rise in IOP.[62]

Intravitreal triamcinolone continues to be used regularly in developing countries with poor/absent health insurance systems because it is cheap and readily available. A reasonable alternative is posterior subtenon injection of the said drug, which, as discussed earlier, can lessen or delay the occurrence of ocular hypertension but is said to be less effective than the intravitreal route. In countries with universal healthcare systems,[12] triamcinolone acetonide has largely been replaced with the safer dexamethasone implant. However, it continues to be an important alternative for therapy of uveitis, diabetic macular edema, and retinal vein occlusion in developing countries with little or no insurance support. Currently, we can infer that 0.05 ml (2 mg) or 0.1 ml are the two most commonly used doses and that a higher dose correlates with a higher risk of IOP rise. Close follow-ups, especially in younger patients and those with DME and uveitis, are recommended. Vitrectomy as a probable treatment option should be thought of whenever IOP control with medical therapy is no longer possible. The possibility of triamcinolone crystals[63] entering and obstructing the trabecular meshwork must also be kept in mind, and the infero-temporal site of injection is the most preferred.

ILUVIEN

The ILUVIEN insert (an intravitreal insert of fluocinolone acetonide) has had a limited release worldwide and has primarily been studied for two major indications: Uveitis and DME. The use of the insert has reduced the number of interventions required to manage uveitis and DME.[64]

Ocular hypertension is one of the most common adverse events associated with the use of intraocular steroids, and the ILUVIEN insert is no exception.[44,64-74] Up to 13% of patients might have an IOP of >30 mmHg[70] (range of occurrence, 7-50%).[64,74,75]

No ocular hypertension was present in the fellow untreated eye when specifically assessed.[71] In the FAME study, IOP increased in 37.1% of patients who received the 0.2-µg/day FA implant (n = 375) and in 11.9% of those who received placebo (n = 185). A >30-mmHg rise in IOP was more frequent in patients who received the 0.2-µg/day FA implant ($P < 0.001$) than in those who received placebo in the overall population and in those without prior ocular corticosteroid exposure.[44,64-71] A posthoc analysis showed that glaucomatous optic nerve changes were not dissimilar between the patients in the two arms of the trial.[73] A recent multicentre study from three European countries (United Kingdom, Germany, and Portugal) published by the IRISS group confirmed the results of the FAME study: about 23% of patients required IOP-lowering medication without clinically significant changes in the cup-to-disc ratio (CDR).[67] However, a small percentage of patients in IRISS (5.2%) had a baseline IOP of >21 mmHg, which was an exclusion criterion in the FAME trials.

The need for glaucoma drops varied from 0 to 15%, with some larger series having an even higher rate.[44,64-77] These higher rates are more in accordance with the FAME study, in which 26% of patients required glaucoma drops. A need for glaucoma surgery despite appropriate topical treatment was seen in up to 14.3% of cases.[44] Careful patient selection remains critical to avoid complications related to ocular hypertension.

Intraocular hypertension in vitrectomized eyes was assessed by Meireles *et al*.[77] in a retrospective study of 26 eyes with a mean follow-up of 255 days. A mean IOP change of 1.4 mmHg was found between baseline and the last visit (range, −9.0 to +8.0 mmHg), with eight eyes (30.7%) initiating or continuing antiglaucoma drops. Pessoa *et al*.[70] performed a retrospective study of 43 eyes (24 vitrectomised and 19 nonvitrectomized eyes) with a mean follow-up of 8.5 months and reported no significant difference in the IOP changes between the two groups; however, vitrectomized eyes exhibited a higher mean IOP elevation (1.6 vs. 0.8 mmHg).

Use of the FA implant is contraindicated in the presence of preexisting glaucoma, and it is not approved for use in steroid responders in the United States. Safety could be improved by introducing a steroid provocation test. While such a test could not absolutely predict the absence of ocular hypertension, it would highlight patients who may require surgical intervention so that they could be excluded from the treatment. In the FAME study, 6.1% of steroid-naïve patients required IOP-lowering surgery (n = 18), highlighting the importance of knowing whether patients have a strong IOP response to corticosteroid therapy.[73]

No increase in the CDR was detected with a 0.2-µg/day dose after 36 months, whereas the CDR increased by 0.1 in the 0.5-µg/day group[73] Therefore, a 0.2-µg/day dose is the implant used worldwide, but careful long-term follow-up focusing on IOP is required.

Retisert Implant (0.59 mg)

One of the first fluocinolone acetonide implants[78,79] available; it finds limited applicability today. There are better and perhaps safer alternatives available today as is evidenced by the preceding discussion. Notwithstanding, for the sake of completion, we discuss in brief the Retisert implant and its association with ocular hypertension.

Of note here is the position of the implant vis-à-vis the anterior chamber and the higher dose of fluocinolone delivered to the posterior segment of the eye when compared to the ILUVIEN implant. The anterior positioning of the implant, sutured as it is in the pars plana region, facilitates entry of the steroid molecule in the anterior chamber to a greater extent than what would be expected in cases with a more posteriorly positioned implant.[42,44] The incidence of ocular hypertension is correspondingly higher with nearly 61% of patients demonstrating IOP rise, whereas a significant proportion of these patients required incisional surgery for glaucoma. The implant is effective, but the overall availability is restricted, as is its use.

Conclusion

To conclude, intravitreal therapy, regardless of the agent or indication, does predispose the patient to the development of ocular hypertension. The risk varies with the age, gender, ethnicity, drug used, the indication, and the frequency of treatments, among other things. Barring a few exceptions, the onset is insidious and the threat of glaucomatous damage real. The common thread running through this entire discussion is careful follow-up, early intervention, and an appropriate patient counselling.

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Conflicts of interest

There are no conflicts of interest.

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