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Review article

Evidence-based guidelines for drug dosing in intravitreal injections in silicone oil-filled eyes: Pharmacokinetics, safety, and optimal dosage

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ABSTRACT

We evaluate the pharmacokinetics, safety, and optimal dosages of intravitreal agents in silicone oil (SO)-filled eyes, addressing challenges in administering such therapies. **We** assessed the pharmacological properties and safety profiles of intravitreal drugs in SO-filled eyes, deriving conclusions and guidance from available literature and expert consensus. Preclinical data suggest comparable half-lives of anti-vascular endothelial growth factoragents in SO-filled eyes, but clinical evidence is mainly from case reports and small series. Available research prioritizes standard dosages, particularly for bevacizumab (1.25 mg), supported by stronger evidence than aflibercept (2 mg) or ranibizumab (0.5 mg). Intravitreal steroids, especially dexamethasone at 0.7 mg, show efficacy and safety, while evidence for fluocinolone acetonide at 0.19 mg is limited. Intravitreal methotrexate has been reported at the dosage of 250–400 μg, with keratitis as the primary expected side effect. Case reports indicate tolerability of standard dosages of antivirals (foscarnet 1.2–2.4 mg/0.1 mL, ganciclovir 4 mg/0.1 mL) and the antibiotic combination piperacillin/tazobactam (250 μg/0.1 mL).

We offer guidance based on current, but limited, literature. Standard dosage of intravitreal agents should be carefully considered, along with close monitoring for potential side effects, which should be discussed with patients.

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1. Introduction

Silicone oil (SO) is an intraocular tamponade first introduced by Cibis in 1962 as an intravitreal implant for the surgical treatment of rhegmatogenous retinal detachment (RRD) and has been widely adopted for treating complex RRD cases.[25,26] With a molecular structure characterized by repeating siloxane units and oxygen bonds, SO possesses distinct features that enable effective retinal reattachment in complex RRD.[36,48]

With the widespread use of intravitreal injections for various conditions, specifically anti-vascular endothelial growth factor (VEGF) intravitreal injections being the most prevalent outpatient procedure in the Western countries, with approximately 7 million intravitreal injections administered each year in the USA.[52] Given the increasing incidence of RRD, it is not an uncommon scenario for patients with intravitreal SO to require intravitreal injections for associated conditions, including severe cases of proliferative diabetic retinopathy (PDR), age-related macular degeneration (AMD) with breakthrough bleeding, and proliferative vitreoretinopathy (PVR). When SO tamponade is used, the injected drug may behave differently in the posterior segment compared to eyes filled with vitreous.[38] This is because SO is a fat-soluble (lipophilic) substance, while the vitreous is a water-soluble (hydrophilic) substance; however, the full effects of replacing the vitreous with SO on the pharmacology of injected drugs are not fully understood.[56]

In recent years, as previously highlighted, the increasing utilization of intravitreal injections, particularly involving anti-VEGF agents, corticosteroids, and other intravitreal drugs, has emphasized the pressing need to elucidate the pharmacokinetic and safety profiles, as well as establish optimal dosages for these medications in eyes filled with SO.[62]

We aim to summarize the pharmacokinetic, safety and optimal dosage features of several intravitreal agents in SO-filled eyes and to provide some clear directives for their use in these patients.

2. Intravitreal anti vascular endothelial growth factor agents

Anti-VEGF agents currently represent the mainstay in the treatment of several retinal diseases, including neovascular AMD (nAMD), diabetic macular edema (DME), and retinal vein occlusions (RVO).[9] To date, 6 anti-VEGF agents have been approved by the US Food and Drug Administration (FDA) for the treatment of macular diseases: ranibizumab (Lucentis® 2013 Informa UK. Genentech, South San Francisco, CA/Roche, Basel, Switzerland) aflibercept (AFL, Eylea ®, Regeneron ®, Tarrytown, NY), and more recently brolucizumab (Beovu®, Novartis 2019), faricimab (Vabysmo®, Roche Basel, Switzerland 2022), and aflibercept 8 mg (EyleaHD®, Regeneron ®, Tarrytown, NY).[9,28] Conbercept is currently approved by China State FDA (Lumitin®, Chengdu Kanghong Biotech, China)[27]

In addition, 2 other anti-VEGF agents, ziv-aflibercept and bevacizumab approved for oncological diseases are commonly adopted in clinical practice as “off-label” treatment options for nAMD.[27] Recently, approved biosimilar agents have also been introduced into clinical practice.[79]

2.1. Pharmacokinetics

Although several studies have examined the pharmacokinetic properties of anti-VEGF in vitrectomized eyes, there is still poor evidence of their behaviour in SO-filled eyes.[20]

A study on rabbit models, analyzed 18 eyes undergoing vitrectomy with SO tamponade that then were injected with 1.25 mg bevacizumab. Bevacizumab exhibited a biphasic pharmacokinetics profile with peak concentrations observed after 14 days in the aqueous humor (4030.70 ng/mL), retina (42,171.7 ng/mL) and choroid (56,243.33 ng/mL). Peak concentration was reached after 7 days in the iris/ciliary body (52,243.33) and plasma (197.70 ng/mL), respectively. The half-life ($t_{½}$) of bevacizumab in the ocular tissues ranged from 3 to 5 days, indicating relatively rapid clearance, while the plasma $t_{½}$ from 10 to 13 days, indicating slower clearance. In rabbit eyes with oil-filled vitreous cavity, bevacizumab exhibits delayed peak concentrations with lower overall drug levels, but similar terminal half-lives as in normal eyes, suggesting a potential impact of oil on drug distribution.[83]

In a recent randomized controlled study, 13 patients with PDR underwent vitrectomy plus SO tamponade and were assigned to either subretinal or intravitreal conbercept injection at 0.5mg/0.05 mL. It was found that at the same dosage, subretinal injection led to a higher drug concentration in the aqueous humor in comparison with the intravitreal route (5.49 ± 6.11 μg/mL vs 0.42 ± 0.46 μg/mL, $p = 0.001$). Also, subretinal injection was associated with best-corrected visual acuity (BCVA) improvement by +28.59 letters 6 months postoperatively ($p = 0.028$) while the BCVA did not change significantly by intravitreal injection ($p = 0.715$). Thus, subretinal injection of conbercept led to a slower clearance rate in vitrectomized eyes with SO tamponade compared to intravitreal injection. No severe ocular adverse events were reported, and no injection related, and aqueous humor-collecting complications were reported.[85]

2.2. Safety, dosage and main indications

Presently, there are no large randomized clinical trials available. Evidence mainly comes from small series or case reports concerning the optimal dosage of anti-VEGF agents in SO-filled eyes, despite preclinical findings indicating differing pharmacokinetics in vitrectomized eyes with SO as a tamponade. While bevacizumab has provided more robust results in larger clinical studies, suggesting the possibility to adopt a standard dosage, evidence for ranibizumab and aflibercept comes from isolated case-reports.

In a small case series, 5 patients with neovascular glaucoma and SO tamponade after vitrectomy for advanced PVR were injected with intravitreal bevacizumab. Regression of iris neovascularization (INV) and normalization of IOP occurred in all the patients within 7 days, with only 1 recurrence after 10 weeks. In this case, the repeat of intravitreal bevacizumab led to successful long-term regression of INV. The authors adopted a 2.5 mg bevacizumab dose to enhance drug delivery to the peripheral retina in higher concentrations, advocating for the absence of adverse events with double the dosage reported in previous studies on choroidal neovascularization and diabetic macular edema.[54,81] Overall, intravitreal bevacizumab was effective in treating neovascular glaucoma after vitrectomy for advanced PVR. No inflammation or other complications were observed.[23]

A prospective, nonrandomized, historical-control pilot study analyzed the clinical efficacy of repeated bevacizumab injections (1.25 mg/0.05 mL) in SO-filled eyes on BCVA and anatomic outcomes in 20 eyes of 20 patients undergoing PVR related RD repair. The injection was performed intraoperatively and at postoperative months 1, 2, and 3. After 6 months, no significant differences were found in final BCVA, retinal reattachment rate and epiretinal membrane (ERM) between the SO group and the historical, age-matched control group. Furthermore, no SO injection-related adverse events, including inflammation and other ocular side effects, occurred.[41]

Differently, a single-hospital, retrospective, case-control study analyzed the effect of bevacizumab in SO filled eyes in 44 patients (46 eyes) with tractional RD. The adopted dosage of the drug was the standard 1.25 mg/0.05 mL. Intravitreal bevacizumab was injected in 20 eyes (group II). After 12 months, the average change in logMAR BCVA was larger ($p = 0.029$) in group II (−0.99 ± 0.73) than in group I (−0.56 ± 0.80). As opposed to group I, group II showed a lower mean (471.54 ± 120.14 μm vs. 363.40 ± 59.57 μm, respectively; $p = 0.001$), and mean change (−22.39 ± 203.99 μm vs. −72.40 ± 139.35 μm, respectively; $p = 0.027$), in central macular thickness (CMT), 1 month postoperatively. It was revealed that injecting bevacizumab into SO following vitrectomy at the standard dosage (1.25 mg) may promptly decrease CMT and

enhance final visual acuity. No statistically significant difference in postoperative complications (including IOP increase, vitreous hemorrhage, and fibrovascular membrane proliferation) was reported between the 2 groups.[6]

A prospective, comparative interventional study by Falavarjani and coworkers evaluated the role of bevacizumab injected into the SO at the end of retinal reattachment surgery for severe PVR associated with RRD. In this study 38 eyes of 38 patients were included, with 19 cases receiving a 1.25 mg bevacizumab injection into the SO at the end of surgery. The results indicated no significant difference in the rate of retinal redetachment between the case and control groups. Extensive subretinal fibrous proliferations were more common in the case group, but final BCVA was similar between the 2 groups. This study suggests that while intra-SO bevacizumab injection does not eliminate the risk of postoperative PVR, it does not adversely affect visual outcomes at its standard dosage.[32]

In a case series, 15 eyes of 11 patients with clinical iris neovascularizations in SO-filled eyes with PDR were injected with bevacizumab at the dosage of 1.25 mg. In all the eyes, INV completely regressed within 7 days from injection, BCVA improved in 12 eyes and the drug was well tolerated by the study sample, and IOP was controlled. Four patients experienced a recurrence of iris neovascularization, which was effectively managed with a subsequent intravitreal injection of bevacizumab at the standard commercial dosage of 1.25 mg /0.05 mL.[66]

Regarding ranibizumab, Cascavilla and coworkers described clinical efficacy of a single intravitreal ranibizumab injection (0.05 mL/0.5 mg) in a patient with myopic choroidal neovascularization (CNV) and previous successfully repaired RRD with SO as tamponade. After 2 months, they saw an increase of BCVA from counting fingers to 20/100 and the resolution of sub/intraretinal fluid by optical coherence tomography (OCT) and late leakage by fluorescein angiography (FA). No adverse events were reported, and final IOP was 16 mmHg.[10]

Similarly, Chhablani and coworkers demonstrated the complete regression of myopic CNV in a patient with SO by using a single ranibizumab injection at the dose of 0.5mg/0.05mL.[14]

Regarding aflibercept, only preliminary data at EURETINA were presented. A small retrospective case-control study evaluated the clinical efficacy of monthly intra-silicone aflibercept injections at 2 mg (0.05 mL of 40 mg/mL) on diabetic tractional retinal detachment repair. 10 eyes with SO and aflibercept injections showed improved BCVA and central macular thickness compared to 9 eyes without aflibercept treatment. While both groups had similar rates of retinal reattachment and ERM formation, aflibercept injections significantly improved CMT and final visual acuity. The study suggested potential benefits of intra-SO aflibercept injections in improving outcomes of vitreoretinal surgery for diabetic retinal detachment repair, warranting further prospective studies. No ocular adverse events were noted with aflibercept injections.[59] To date, no other larger clinical studies have investigated the optimal dosage and toxicity of ranibizumab and aflibercept in SO-filled eyes.Also, no clinical studies have investigated the optimal dosage and safety profile of the novel anti-VEGF agents brolucizumab, faricimab, and aflibercept 8 mg in SO-filled eyes.

3. Intravitreal steroids

Intravitreal corticosteroids have become an established treatment modality for a myriad of retinal conditions because of their anti-inflammatory, antiangiogenic, and anti-proliferation properties. As opposed to systemic steroid therapy, local ocular therapy has proven invaluable due to its high efficacy and safe systemic profile.[30]

There are currently several available intravitreal corticosteroid options that include triamcinolone acetonide (Kenalog, Kenacort, TRIESCENCE®, TRIVARIS®, Intracinol®), dexamethasone implant (Ozurdex®) and fluocinolone acetonide (Iluvien®, YUTIQ®).[1,47,63,68] Regarding their use in the context of SO-filled eyes, most of the current evidence focuses on triamcinolone acetonide, while studies on other intravitreal steroid implants such as dexamethasone and fluocinolone acetonide are still lacking. Clinical evidence supports the dexamethasone at standard dosages of 0.7 mg in SO-filled eyes; however, evidence for other agents, such as fluocinolone acetonide at 0.19 mg, remain more limited.

3.1. Triamcinolone acetonide

3.1.1. Pharmacokinetics

Triamcinolone acetonide (TA) is a synthetic lipophilic corticosteroid with low solubility in aqueous solution. Intravitreal use of TA was first proposed in 1979 given its advantageous pharmacokinetic profile with rapid bioavailability and extended-release characteristics.[50,75] It has since been used as a depot drug to provide sustained therapeutic drug levels within the vitreous cavity. A previous study showed that TA concentration remained measurable for a long period (up to 3 months, with a mean elimination half-life of 18.6 days) after intravitreal injection in the absence of a vitrectomy. Conversely, the half-life was considerably shorter at 3.2 days in a vitrectomized eye.[8]

Given its lipophilic nature and therefore theoretical biocompatibility with SO, TA has been trialled in several case series and suggested as an adjuvant to vitrectomy with SO tamponade for the surgical treatment of PVR and PDR.[12,45,55] Nonetheless, the exact distribution and biological effects of TA after vitrectomy surgery with SO tamponade in human eyes remain unknown.

To date, the current evidence for the pharmacokinetic profile of TA in SO is limited to *in vitro* and *ex vivo* models.[17,72] Despite both TA and SO being lipophilic molecules, they have been shown to be immiscible and this may be since SO having a lower specific weight than TA. Using an *ex vivo* pig eye model, Da and coworkers showed that the TA droplet sank to the interface of SO and aqueous shortly after injection (approximately 6 min). This droplet then remained intact in the inferior part of the SO bubble without mixing with either SO or aqueous for as long as 16 min.[17]

The stability of the TA droplet within the SO bubble appears to be dependent on its concentration. When injected at higher concentration (200mg/mL), the TA droplet sank through SO and started to sediment below the SO bubble at only 5 min after injection in an *in vitro* artificial vitreous chamber. In contrast, TA at a lower concentration (<10 mg/mL) remained stable as a droplet inside the SO bubble for several hours.[72]

In both *in vitro* studies, TA eventually precipitated out to become crystalline sediment within the drug droplet. No significant difference was found in sedimentation time between different TA concentrations although larger variation and unpredictability was observed for higher concentrations. If still within the SO bubble, the TA sediments in the drug droplet have been shown to eventually break through the interface level at about 100 min and dispersed into the underlying aqueous within a very short time leading to a transient increase in local aqueous concentration. Given the reported cytotoxic effects of high TA concentration, bolus injection of TA into SO-filled eyes is therefore likely to be harmful due to its high local concentrations on the retinal surface from sedimentation. Based on this, SO may not be a good candidate as a drug reservoir for TA.[17]

A proposed alternative to bolus injection and its potential toxic side effect is a suspension of TA in SO; however, such a preparation is time consuming and requires fresh mixing before use as the TA and SO will slowly separate over several weeks. In addition, a suspension of TA may further impair vision, especially at higher concentrations. The already reduced vision caused by SO itself would be compounded by the scattering of white TA crystals throughout the SO bubble. Thus, the clinical use of such a suspension is likely to be unfeasible.

3.1.2. Safety and tolerability

Common ocular side effects after injection of intravitreal corticosteroids such as TA include steroid-induced intraocular pressure (IOP)

rise and cataract formation. Steroid-induced IOP rise has been reported in up to 10 % of eyes treated with intravitreal TA, with higher rates observed when a higher concentration of TA is used.[34,74] In vitrectomized eyes, there is faster clearance of intravitreal TA which would theoretically translate to a more muted effect on IOP [74]; however, the incidence and severity of secondary IOP rise after intravitreal TA in such eyes remain unclear and even more so in SO-filled eyes with previous studies reporting mixed findings.[15,45,55]

IOP analysis in the context of vitrectomy with SO tamponade is further confounded by a myriad of factors including final retinal anatomical status, ciliary body function and SO emulsification.

The cataractogenic effect of TA in SO-filled eyes is difficult to evaluate from previous published studies as a large proportion of eyes were aphakic or pseudophakic at the outset. In addition, most phakic eyes underwent lens extraction as part of the surgical management with SO tamponade[2]

Sterile endophthalmitis following intravitreal TA has a reported incidence rate ranging from 0.1 % to 7.3 %,[51,80] and has been reported to be more frequent in vitrectomized eyes.[64] The incidence in SO-filled eyes, however, remains unknown as no case has been reported in the literature so far.

3.1.3. Clinical indications and dosage

The minimum effective and safest concentration of intravitreal TA in the context of SO tamponade remains to be determined. Care should be taken to extrapolate the current findings of *in vitro* and *ex vivo* models to clinical practice as these models are considered only a preliminary representation of the complex physiological condition in the human eye.[82] The pharmacokinetics in human eyes is also compounded by the influence of various disease processes (e.g., inflammation, breakdown of blood retinal barrier). Human studies on the use of adjunctive TA injection in SO-filled eyes have reported no significant increase in adverse event rates with doses ranging from 2 mg to 20 mg[12,13,44]; however, the majority of these have been small, selected case series, and further research is necessary to demonstrate the long-term efficacy and safety profile of adjunctive intravitreal TA in SO-filled eyes.

3.2. Dexamethasone and fluocinolone acetonide

3.2.1. Pharmacokinetics

There is currently a scarcity of both animal and human pharmacokinetic studies regarding intravitreal corticosteroid (dexamethasone and fluocinolone acetonide) implants in vitrectomized eyes with SO tamponade.

The only *in vitro* study to address this gap examined the behaviour of dexamethasone implant in SO. This was a basic, experimental, prospective, study in which one dexamethasone implant was placed in a test tube with 4 mL of each tamponade medium: 1000 cS, 5000 cS and heavy SO. It demonstrated an irregular drug release over a 1-year period, with significant alteration in pharmacokinetics for heavier SOs. Dexamethasone implants in conventional SO (1000 cS) were found to retain anti-inflammatory effects, whereas implants in denser SOs (2000 cS & 5000 cS) showed no antiinflammatory effect.[29] Although these findings would suggest the avoidance of intravitreal dexamethasone implant in denser SO, further *ex vivo* and human studies are required to verify this.[7]

3.2.2. Safety and tolerability and main indications

Adjunctive intravitreal dexamethasone implants in SO-filled eyes have been investigated in conditions such as PVR, PDR, and post-vitrectomy macular edema.[4,7,40] The largest prospective, randomized, controlled trial evaluated intravitreal dexamethasone implant at 0.7 mg in a sample of 140 patients with PVR and assigned them to standard (control) or study treatment (adjunct) in a 1:1 allocation ratio. After the 2-year follow-up period, no differences in primary anatomic reattachment rates (49.3 % vs. 46.3 %, adjunct vs. control; p=0.733) or visual acuity (38.3 ETDRS letters and 40.2 letters in the adjunct and control groups, respectively, p=0.812) were found, although a greater reduction in cystoid macular edema was observed at 6 months in the dexamethasone-treated group (42.7 % vs 67.2 %, p=0.004). No serious adverse events or toxicity secondary to dexamethasone implant were observed. The most common adverse event was the onset of elevated IOP in 39.2 % of the patients in the adjunct group vs 31.4 % in the control group.[7] Other smaller interventional studies have concluded that intravitreal dexamethasone implant may be beneficial for PDR and recalcitrant macular edema.[4]

As for intravitreal fluocinolone acetonide implant, the only study so far to investigate its adjunctive use in vitrectomized eyes with SO tamponade was a small retrospective case series of patients with chronic, refractive uveitic hypotony. The study concluded that treatment with intravitreal fluocinolone acetonide was feasible and well tolerated in these eyes.

Standard doses of intravitreal steroid implants (0.7 mg dexamethasone and 0.19 mg fluocinolone acetonide) were administered in all the aforementioned clinical studies comparing intravitreal injections in normal eyes with those vitrectomized with SO, showing no serious adverse event encountered and no significant increase in the rate of common side effects (e.g. elevated IOP).[19]

4. Intravitreal methotrexate

Methotrexate (MTX) is a folate analogue that inhibits dihydrofolate reductase, a enzyme involved in the synthesis of thymidylate and purine nucleotides; therefore, MTX administration leads to inhibition of rapidly dividing cells. MTX was first introduced as an antiproliferative agent; further studies confirmed its antiinflammatory effects.[11] The mechanism of action of MTX is the reduction of cell proliferation, increasing the rate of T-cell apoptosis, increasing endogenous adenosine concentrations, and altering cytokine production and humoral responses.[31]

Clinical trials examining MTX dosages have shown a range of tolerable doses, with 1 study indicating tolerance from 200 up to 1200 μg; however, prevailing evidence leans towards lower doses, particularly between 250 μg to 400 μg, demonstrating manageable ocular adverse events.

4.1. Pharmacokinetics, potential toxicity, and side effect

Intravitreal administration of MTX employs reduced doses of the compound to reduce the risk of toxicity. A study by Shen-Sampas and coworkers on 13 eyes showed a good tolerability profile combined with low corneal toxicity after injections of 400 μg MTX at an average frequency of every 7 days after vitrectomy with SO tamponade. No severe ocular adverse events were reported. Only 2 eyes (15.4 %) showed mild and asymptomatic punctate epithelial erosions during the follow-up.[69]

4.2. Main indications and dosage

Intraocular MTX has been effectively used for treatment of primary vitreoretinal lymphoma and additionally has been also used for prevention and treatment of PVR.[67,71,76] Other indications are eyes with uveitis and advanced PDR.[67]

Small, nonrandomized clinical studies have so far reported mixed results with intra-SO injection of MTX after vitrectomy for the prevention and treatment of PVR.

In 2 separate, prospective, and comparative studies, Ghasemi and coworkers administered intravitreal MTX at 250 μg into a vitreous cavity filled with SO to evaluate its effectiveness in 2 different diseases, PVR and advanced PDR. While both studies revealed no statistically significant improvement in the reduction of risk of postoperative detachment in the MTX-treated eyes, the dosage of 250 μg was well tolerated by all participants and no severe ocular side effects were referred to. The researchers speculated that higher MTX doses might provide a better therapeutic outcome without causing adverse effects, but lower doses

were employed to account for the diminished clearance in vitrectomized eyes filled with SO, thereby reducing the risk of toxicity.[22,33]

Another study administered intravitreal MTX doses ranging from 200 to 1200 mg in SO-filled eyes and found all doses to be safely tolerable.[37]

In a clinical trial conducted by Nourinia and coworkers, the efficacy of repeated intravitreal MTX injections was investigated in eyes with PVR-C. 11 participants underwent pars plana vitrectomy (PPV) followed by SO tamponade. They received 3 intravitreal MTX injections of 250 µg, at 3-week intervals and were followed-up for an average period of 9 months. During the follow-up period, all operated eyes demonstrated successful retinal reattachment and improvement in postoperative BCVA from preoperative 2.62 ± 0.04 LogMAR to 1.02 ± 0.51 LogMAR ($p=0.003$). No systemic or ocular adverse events were reported at this MTX dosage.[57]

In another observational, single-cohort study, intravitreal MTX infusion during PPV for RRD was evaluated in 29 eyes of patients at high risk for developing PVR. Inclusion criteria were patients with either tractional RD and recurrent PVR or a history of severe inflammation associated with high PVR risk. The study reported redetachment in 10 % and focal PVR in 10 % of the eyes. To achieve intraocular MTX concentrations similar to those used in intraocular lymphoma treatment (400 µg intravitreal injection of MTX into an approximately 5 mL volume of a human eye), 40 mg of MTX was added to each 500 mL balanced saline solution infusion bottle. MTX was well tolerated by the study population, and no adverse events were reported.[65]

The GUARD trial, a multicenter, randomized, controlled, adaptive phase 3 clinical study, has recently presented preliminary results. In this study, the clinical efficacy and safety of repeated intravitreal injections of ADX-2191 (MTX 0.8 %) versus historical control (routine surgical care) were examined for the prevention of PVR. Patients undergoing PPV due to recurrent retinal detachment due to PVR or open globe injury were included. ADX-2191 was administered to 68 patients, while routine surgical care was performed on 38 patients. A statistically significant decrease ($p=0.024$) in retinal detachment over 6 months was documented after 13 serial intravitreal injections of ADX-2191 over 4 months in comparison with controls. No new safety concerns arose in the trial, with ADX-2191 well tolerated, and no treatment-emergent serious adverse events observed. Punctate keratitis, which represents a common side effect of intravitreal methotrexate, was the main adverse event reported, but it was mostly mild in severity.[3]

5. Intravitreal antibiotics, antivirals and antifungals

Previous preclinical studies have shown that intravitreal antibiotic and antiviral agents present different pharmacokinetics behaviour in SO-filled eyes and the knowledge of optimal concentrations may prevent undesired potential ocular toxicity and side effects.[38,84]

Common intravitreally administered antibiotics include vancomycin, ceftazidime, amikacin and clindamycin.[49] Similarly, the most frequent antivirals used in intravitreal injections include ganciclovir, foscarnet, and fomivirsen.[53] Also, antifungal agents including voriconazole and amphotericin can be administered intravitreally.[43]

In SO-filled eyes, insights into intravitreal antiinfectious agents primarily come from preclinical studies, revealing varied pharmacokinetic profiles based on drug lipophilicity and size. Additionally, standard dosages suggested by isolated case reports underscore the tolerability and efficacy of intravitreal antiviral agents for viral retinitis and antibiotics for acute endophthalmitis.

5.1. Pharmacokinetics, potential toxicity, and side effect

The pharmacokinetic profile of vancomycin and ceftazidime in SO-filled eyes was studied by Imamura et *al.* In this preclinical study, the authors measured the concentration of intravitreal vancomycin (1 mg/0.1 mL) and ceftazidime (2 mg/0.1 mL) in vitrectomized macaque eyes filled with SO and compared it to the concentration in normal macaque eyes. To analyse the toxicity profile, endothelial cell density and electroretinogram were measured before treatment and one month after treatment. Maximum drug concentrations for in aqueous humor for vancomycin were 151.4 µg/mL (normal eyes) and 543.5 µg/mL (SO-filled eyes), for ceftazidime they were 64.6 µg/mL (normal eyes) and 1176.3 µg/mL (SO-filled eyes). The $t_{½}$ of vancomycin were 29.4 in normal eyes and 6.8 h in SO-filled eyes, while the $t_{½}$ of ceftazidime was 20.4 h in normal eyes and 3.1 h in SO-filled eyes, respectively. No alterations of endothelial cell density or electroretinogram were observed within the groups.[43] Similar results were observed in another study on cynomolgus monkeys. It was found that the time to maximum concentration of vancomycin in SO-filled eyes was shorter (2 h) than in normal eyes (24 h), while maximum concentrations reached higher peaks in SO-filled eyes compared with normal eyes.[39]

In another preclinical study, Leung and coworkers. centrifuged SO with either vancomycin (1 mg/0.1 mL) or amikacin (0.4 mg/0.1 mL). When vancomycin was mixed with SO, it maintained a concentration of 26.9 µmol/L after 24 h. In contrast, amikacin was completely extracted from the SO by centrifugation, resulting in a final concentration of zero.[49]

Another *in vitro* study analyzed the physicochemical properties of intravitreally given drugs with varying lipophilicity, including vancomycin, ceftazidime and voriconazole by comparing SO-filled eyes with porcine vitreous body. Concentrations of the drugs were measured over 24 h in aqueous and vitreous phases. Results showed that when SO was present, the concentrations of vancomycin, voriconazole and ceftazidime were significantly higher in the aqueous humor when compared with the vitreous body ($p<0.001$). When lipophilicity was increased, higher concentrations of the pharmacological agents dissolved in SO after 24 h (52.7 %, 49.1 % and 34.3 % for vancomycin, ceftazidime and voriconazole, respectively). The authors concluded that the presence of SO influences the concentration and distribution of intravitreal drugs in relation to their lipophilicity.[36]

A previous study including SO-filled rabbit eyes studied the toxicity of vancomycin, ceftazidime, and ganciclovir. They found that full- and half-doses resulted in a postoperative reduction of b-wave in electroretinograms and destruction in the histologic retinal structure, while quarter-dosage showed no alterations in electroretinogram or histologic structure.[38] Another study including rabbits examined the toxicity of ganciclovir in 3 different concentrations. They observed no histopathologic changes or alterations of scotopic electroretinogram for doses of 200 µg/0.1 mL.[21]

5.2. Main indications and dosing

The main indication for intravitreal antibiotics is the onset of endophthalmitis. For endophthalmitis management in patients with SO tamponade there is currently no conclusive therapeutic strategy.[77] Infectious endophthalmitis in SO-filled eyes has been rarely reported in literature.[24,78] In these cases, a re-operation is more commonly performed with removal of SO and wash out of vitreous cavity followed by injection of antibiotics in the fluid-filled vitreous cavity and subsequent reinjection SO.[18,86] A more common scenario in clinical settings is when patients are diagnosed with endophthalmitis, and they undergo vitrectomy with SO tamponade. In these cases, SO has been proven in various studies to display an antimicrobial activity, with a postulated mechanism of direct toxicity and nutritional deprivation for microorganisms[5,58]

In a recent case report successful treatment of endophthalmitis was achieved by vitreous cavity washout and administration of intravitreal antibiotics into the SO-filled vitreous cavity additionally to systemic antibiotic treatment. The combination of piperacillin/tazobactam was intravitreally injected with a dosage of 250 µg/0.1 mL without the onset of adverse ocular events.[35]

Another case series examined the clinical outcomes and tolerability

profile of intravitreal injections of vancomycin and ceftazidime in 2 patients with acute-onset postoperative endophthalmitis in SO-filled eyes after vitrectomy for repair of complex RRD. One patient was treated with full dosage intravitreal antibiotics, namely ceftazidime at 2.25 mg and vancomycin at 1.0 mg, while the other was injected with half of the dose for both agents due to a concern for possible retinal toxicity. The 2 treated eyes showed prompt resolution of endophthalmitis and both full and half-dose of vancomycin and ceftazidime were well tolerated by the patients with the absence of clinical signs suggestive for retinal toxicity[73]

Regarding antiviral therapy, Meshi and coworkers reported 2 patient cases with viral retinitis after RD and SO tamponade. The first HIV-positive patient was diagnosed with bilateral progressive outer retinal necrosis (PORN) and was first treated with intravitreal injections of foscarnet (2.4 mg/0.1 mL) and ganciclovir (2 mg/0.05ml) twice a week. He developed an exudative RD treated with vitrectomy and SO tamponade. Subsequently, intravitreal therapy with low dose foscarnet (1.2 mg/0.05 mL) and ganciclovir (2 mg/0.05 mL) was continued with weekly injections, in total 5 injections of each drug. The second patient was diagnosed with acute retinal necrosis (ARN) and exudative RD. After the vitrectomy with SO-tamponade, low dose foscarnet (1.2 mg/0.05 mL) weekly injections over the course of 8 weeks were given with concurrent oral antiviral and corticosteroid therapy. In both cases long-term retinitis control could be achieved.[53]

Another case report described a patient with recurrent ARN after a RRD and treatment with vitrectomy and SO tamponade. Successful disease control was achieved with unadjusted doses of intravitreal ganciclovir (4 mg/0.1 mL, 2 injections within one week and another injection 6 weeks later) and foscarnet (2.4 mg/0.1 mL, 4 weekly injections) with concurrent oral antiviral therapy.[42] (Tables 1–2)

6. Discussion

The potentially distinct behaviour of intravitreal drugs in SO-filled eyes, attributed to the contrasting lipophilic nature of SO and the hydrophilic nature of vitreous fluid, presents a complex clinical

Table 1
Main clinical studies involving intravitreal agents in patients with silicone oil-filled eyes.

Intravitreal drug	Dose	Study design and patients enrolled	Primary endpoints	Safety profile
Bevacizumab(41)	1.25 mg	Prospective, non-randomized, IVT bevacizumab given at month 1, 2 and 6. 20 patients with PVR	At 6 months, no significant differences in final BCVA, retinal reattachment rate and ERM between the SO-group and the historical, age-matched control group.	No SO injection-related adverse events
Bevacizumab(6)	1.25 mg	Retrospective, case-control study in 44 patients (46 eyes) with tractional RD.	After 12 months, the change in logMAR BCVA was greater ($p = 0.029$) in bevacizumab patients (-0.99 ± 0.73) than in age-matched control group (-0.56 ± 0.80). and mean change was lower (-22.39 ± 203.99 μm vs. -72.40 ± 139.35 μm, respectively; $p = 0.027$), in CMT	No SO injection-related adverse events
Bevacizumab(66)	1.25 mg	Prospective case series in 15 eyes of 11 patients with INV	In all the eyes, INV completely regressed within 7 days from injection, BCVA improved in 12 eyes and the	Bevacizumab was well tolerated by the all the patients and IOP was controlled.
Triamcinolone (44)	4 mg	Prospective, case series in 13 eyes of 12 patients with PDR	At last follow-up visit (4.7 months) retina was attached in 10 of the 13 eyes and BCVA improved in 4 eyes and remained stable in 5 eyes	Mean IOP remained stable during follow-up. Steroid crystals visible at month 1
Triamcinolone (55)	4 mg	Prospective, non-comparative study in 24 eyes of patients with PVR grade C2 or greater	87.5 % eyes had attached retinas at the 11-month final follow up visit. Visual acuity improved in all patients following surgery	No increases in IOP and other ocular side effects reported
Dexamethasone (7)	0.7 mg	2-year, single-center, prospective, participant- and surgeon-masked randomized trial in 140 patients with PVR grade C	Anatomic success comparable between the 2 groups (49.3 % vs. 46.3 %, adjunct vs. control; odds ratio, 0.89; 95 % $p = 0.733$). At 6 months, fewer adjunct patients had CME (42.7 %) or a foveal thickness of >300 μm (47.6 %) compared with controls (67.2 % and 67.7 %, respectively, $p = 0.004$, $p = 0.023$)	No serious adverse events in both groups. Proportion patients undergoing cataract operation was 75.8 % in adjunct vs 86.1 % in control at month 6.Episode of IOP increase in 45.7 % in adjunct vs 31.4 % controls
Dexamethasone (4)	0.7 mg	Prospective, randomized study in 52 eyes of 52 patients with PDR and vitreomacular traction syndrome	At 6 months, no significant difference in the PVR development rate between the groups ($p < 0.05$). BCVA improvement was significantly higher in dexamethasone group ($p > 0.05$)	No IOP increase and other ocular adverse vents reported
Fluocinolone acetonide(19)	0.19 mg	Retrospective, case series on 13 eyes of 11 patients with chronic refractory uveitic hypotony	The increase in IOP relative to the baseline IOP was statistically significant at 6 and 12 months. At the 6- and 12-month visits, the mean BCVA remained stable at 20/800 ($p = 0.74$) and 20/600 ($p = 0.34$)	No intraoperative complications and severe adverse ocular events reported
MTX(33)	250 μg	Prospective comparative study in 38 eyes of 35 patients with PDR	Retinal re-detachment occurred in seven eyes (36.8 %) in the MTX group and eight eyes (42.1 %) in controls ($P = 0.74$). Mean change in BCVA was 0.04 ± 0.71 and 0.39 ± 0.70 logMAR in the MTX and the control group, ($p = 0.14$).	MTX 250 μg was well tolerated by all the participants and no severe ocular side effects
MTX(22)	250 μg	Prospective comparative study in 44 eyes of 44 patients with PVR grade C	Retinal redetachment occurred in one eye (4.5 %) in the MTX group and five eyes (22.7 %) in the control group ($p = 0.18$). The change in BCVA was similar between the two groups at final visit ($p = 0.15$)	MTX 250 μg was well tolerated by all the participants and no severe ocular side effects
MTX(65)	400 μg	Retrospective in 29 eyes of recurrent PVR (n=22) or history of severe inflammation associated with high risk PVR	At 27 months, the retinas of 26 of 29 eyes (90 %) remained attached while three eyes required another reattachment procedure.	No complications attributable to MTX occurred during a mean follow-up of 27 months.

BCVA= Best-corrected visual acuity; CMO=Central macular edema; CMT=central macular thickness; IOP= Intraocular pressure; MTX=Methotrexate; PDR=Proliferative vitreoretinopathy; PVR=Proliferative vitreoretinopathy;

challenge.[85] This contrast highlights the intricate nature of administering intravitreal therapies in SO-filled eyes, emphasising the need for a comprehensive exploration of their pharmacological properties, safety profiles, and optimal dosing regimens. This imperative is particularly significant due to the growing prevalence of intravitreal injections, necessitating meticulous scrutiny to ensure their effectiveness and safety in clinical practice.[60] Among various treatment options, dexamethasone and intravitreal MTX have collected more consistent evidence from clinical trials and multiple clinical series; in contrast, evidence for other agents relies predominantly on anecdotal case series or isolated case reports. Such variability in evidence poses significant challenges in formulating clinical guidelines, underscoring the complexities involved in drawing definitive recommendations from the current evidence.

The recommended dose of intravitreal dexamethasone implant, typically administered at 0.7 mg, has shown efficacy in reducing cystoid macular edema in SO-filled eyes. Clinical studies, including a randomized clinical trial, have provided evidence of this and its tolerability, with minimal adverse effects observed. Remarkably, research indicates no notable escalation in severe adverse events, such as elevated IOP, with no significant differences observed between the dexamethasone treatment group and the control group, thus implying a favourable safety profile.[4,7]

Another lipophilic corticosteroid, TA, has been explored as an adjunctive therapy with SO tamponade for conditions like PVR and PDR; however, uncertainties persist regarding its distribution and effects in SO-filled eyes. In fact, while *in vitro* and *ex vivo* studies suggest stability of this molecule within SO, concerns arise regarding potential toxicity, including crystalline sediment formation and localized cytotoxic effect and therefore the relative high frequency of ocular side effects, namely steroid-induced IOP elevation and cataract formation; however, in human studies a dose ranging from 2 mg to 20 mg has been shown to be not associated with the above mentioned ocular side effects and can be considered safe in SO-filled eyes[12,17,72]

While dexamethasone efficacy and safety are well-documented, evidence for fluocinolone acetonide in vitrectomized eyes with SO tamponade is limited to a small retrospective case series in patients with chronic uveitic hypotony. This suggests feasibility and tolerability at the standard dosage of 0.19 mg, but further studies are needed to validate its safety and efficacy.[19]

Based on the available evidence, we advocate for the adoption of standard dosages of intravitreal steroids, including 0.7 mg of dexamethasone, which has demonstrated the most consistent efficacy. TA is recommended in doses ranging from 2 to 20 mg, while fluocinolone acetonide is suggested at 0.19 mg. These recommendations aim to provide clarity and guidance regarding the use of intravitreal steroids in eyes with SO, where these doses have shown to mitigate the risk of adverse ocular events.

Preclinical evidence on anti-VEGF agents highlighted varied pharmacokinetics, emphasizing the need for precise dosing strategies. Although preclinical studies have highlighted a comparable half-life of anti-VEGF agents including bevacizumab in SO-filled eyes in comparison with nonvitrectomized eyes, there is emerging evidence indicating that SO might influence the distribution of the drug within the vitreous cavity[66,83]; however, some clinical studies have highlighted that repeated intravitreal bevacizumab injections at the standard dosage (1.25 mg) preserved the clinical efficacy of the molecule and were well-tolerated, suggesting a similar half-life of the drugs in SO-filled eyes.[6,66] While repeated intravitreal bevacizumab injections at the standard dosage (1.25 mg) have shown preserved efficacy and good tolerance in SO-filled eyes, caution should be exercised regarding potential increases in IOP and inflammation secondary to SO or anti-VEGF agents.

Although isolated, small case series demonstrated a good clinical efficacy and tolerability profile of intravitreal bevacizumab at double-dosage (2.5 mg) in the management of iris neovascularization and IOP in neovascular glaucoma post-PVR vitrectomy, further substantiation through comprehensive research is warranted before endorsing this dosage in clinical practice.[6]

To date, most of the evidence regarding the clinical efficacy, optimal dosage, and toxicity of ranibizumab and aflibercept agents is based on isolated case reports and small spontaneous retrospective case-series. In these studies, the mentioned anti-VEGF agents have been employed at their standard dosage with clinical efficacy and absence of side effects[10,14]; however, the limited sample size, the non-randomized design of the studies, and the absence of evidence across various retinal exudative conditions, such as nAMD and DME are significant limitations hindering the ability to derive consistent conclusions.

Therefore, we advise physicians to consider these limitations and potential risks when utilizing intravitreal anti-VEGF agents in SO-filled eyes. We recommend adhering to a standardized dosage regimen for these drugs, even in eyes filled with SO. In this regard, while there is more substantial evidence supporting the use of a standard dosage for bevacizumab, there is less definitive evidence available for ranibizumab and aflibercept.

In regard to MTX, clinical trials suggest varying doses, with one study indicating tolerability with dosages ranging from 200 up to 1200 μg[37]; however, most of the lower doses, particularly ranging from 250 μg to 400 μg, demonstrating tolerable ocular adverse events.[22,33,65] The large, multicenter, randomized GUARD trial revealed an acceptable safety profile and comparable tolerability to standard of care of intravitreal MTX 0.8 %, with punctate keratitis being the most frequent mid adverse event.[16]

Based on the available evidence, we suggest considering a dosage range of 250 μg to 400 μg for intravitreal MTX administration in SO-filled eyes; however, to ensure optimal treatment outcomes and safety, it is crucial to tailor dosing based on individual patient characteristics, including ocular pathology and risk profile.

To date, most of the evidence for intravitreal anti-infectious agents derives from preclinical studies, highlighting that the different lipophilicity and size of drugs (from the hydrophilic antibiotic vancomycin to the lipophilic antifungal agent voriconazole) lead to different pharmacokinetic behaviours in SO-filled eye models.[36,39] Isolated case reports provided evidence of good tolerability for intravitreal antiviral agents at standard dosage in case of viral retinitis (foscarnet 1.2–2.4

Table 2
Recommended doses of intravitreal drugs with related level of evidence and grade of recommendations in silicone-oil filled eyes (OCEBM Levels of Evidence).

Medication	Doses recommended	Level of evidence	Grade of recommendations
Bevacizumab	1.25 mg	IIb	B
Conbercept	0.5 mg	II a	B
Ranibizumab	0.5 mg	IV	C
Aflibercept	2 mg	IV	C
Triamcinolone acetonide	2–20 mg	III	D
Dexamethasone	0.7 mg	I	A
Fluocinolone Acetonide	0.19 mg	III	C
Methotrexate	250–400 μg	IIa	B
Vancomycin	0.5–1.0 mg	IV	D
Ceftazidime	1.13–2.25 mg	IV	D
Piperacillin/ Tazobactam	250 μg/0.1 mL	IV	D
Foscarnet	1.2–2.4 mg/0.1 mL	IV	D
Ganciclovir	4 mg/0.1 mL	IV	D

Grade of recommendations
A = Consistent level 1 studies
B = Consistent level 2 or 3 studies or extrapolations from level 1 studies
C = Level 4 studies or extrapolations from level 2 or 3 studies
D = Level 5 evidence or troubling inconsistent or inconclusive studies at any level

mg/0.05 mL, ganciclovir 4 mg/0.1 mL) and antibiotics in case of acute endophthalmitis (piperacillin/tazobactam 250 μg/0.1 mL).[35,42] In this regard, in the rare case of endophthalmitis onset in SO-filled eyes, the most frequently chosen approach remains the reoperation for SO removal, the administration of intravitreal antibiotics, and the reinjection of SO; in the 2 cases presented by Steinmetz, a successful resolution of endophthalmitis was obtained with either half or full doses of a single intravitreal injection of vancomycin (0.5–1 mg) and ceftazidime (1.13–2.25 mg) (81).

Based on the current evidence limited to isolated case reports, we recommend to cautiously adopt the above-mentioned dosage of antibiotic and antiviral agents in case of endophthalmitis and viral posterior uveitis; however, careful consideration of individual risk factors, including the severity of infection and potential risks of retinal toxicity, is also essential to determine the appropriate dosage. We also deem that larger-scale clinical trials are needed to provide higher levels of evidence regarding the optimal dosage of intravitreal agents in SO-filled eyes.

Previous research has highlighted the presence of a distinct sub-SO fluid layer beneath the SO in the eye, characterized by unique biological properties such as higher cytokine concentrations and lower levels of ferrous iron compared to the anterior chamber fluid.[46,70] These differences may also contribute to the varying behaviour of intravitreal drugs in eyes filled with SO. Despite knowledge of drug pharmacokinetics in the aqueous humour of eyes filled with SO, precise drug concentrations beneath the SO remain poorly explored. Furthermore, the absence of histological studies further complicates our comprehension of this ocular environment. We deem that addressing this gap in our knowledge may be essential in the near future to refine appropriate treatment strategies and optimize patient outcomes during vitreoretinal procedures.

While the evidence is sparse, it is also important to discuss the occurrence of SO emulsification following intravitreal injections. Proteins such as albumin significantly reduce the interfacial tension between SO and aqueous humor, facilitating emulsification, which can occur within months. This is a particular safety concern in cases where SO tamponade is maintained for extended periods.[61] Considering that follow-up duration and timing of SO removal are critical factors, future research should focus on long-term effects of intravitreal injections on SO stability and developing strategies to minimize emulsification and its associated complications.

In summary, ongoing research is crucial to optimize dosages and understand safety profiles, particularly in patients with SO tamponade. Discussion with patients about any medication used in SO-filled eyes is recommended, along with considering the limited evidence available.

7. Method of literature research

A comprehensive literature search was conducted to identify all published studies on these topics from database inception until February 2024. The following databases were searched: Medline, PubMed, Web of Science Core Collection, and the Cochrane Library. Controlled vocabulary and keywords related to "silicone oil" "silicone oil tamponade" “densiron” were used in combination with terms referring to intravitreal, anti-vascular endothelial growth factors (anti-VEGF), corticosteroids, dexamethasone, fluocinolone, triamcinolone, methotrexate, and antibiotics. No language or publication status restrictions were imposed. After screening 121 retrieved records, relevant articles were reviewed in full by the authors and included based on relevance to this review. Reference lists of eligible articles were hand-searched for additional studies. Ongoing clinical trial registries (e.g., www.clinicaltrials.gov) were also searched to identify research in progress.

The evidence for the recommended doses of intravitreal drugs was graded according to the OCEBM Levels of Evidence. The evidence for each drug was reviewed independently by a panel of 5 experienced ophthalmologists. Each grader assessed the evidence based on factors such as study design, sample size, methodological quality, and specific relevance to the topic

The overall kappa value was 0.76, indicating substantial agreement among the graders. Additionally, all the authors checked the available manuscript and agreed with the level of evidence assigned. If there was any disagreement, this was addressed with a discussion until reaching a consensus.

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Declaration of Competing Interest

None

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