

Intravitreal Injections form a big part of any Retina practice. The aim of this course is to run through the different categories of intravitreal injections with representative examples of each. Along with specific indications. The course will also discuss the Indian preferred practice patterns on this subject. The Chief Instructor is a senior Retina Surgeon with an experience of more than 25 years in this field. He is also a mentor for many Retina Fellows from India & abroad. The course flow is given below:

No.	Topic	Speaker	Time
01	Introduction of the topic and the faculty	Dr. Mukesh Porwal	05 min
02	Innovator molecules	Dr. Himanshu Shukla	10 min
03	The Biosimilars	Dr. Umesh Bhammarkar	10 min
04	Multimodal agents	Dr. Raunaq Poonia	10 min
05	Antibiotics	Dr. Ravi Dharamdasani	10 min
06	Steroids	Dr. Mukesh Porwal	10 min
07	Antimetabolites	Dr. Reha Vijay	10 min

The course will provide an overview of the categories of intravitreal injections, their indications and some practical take-home tips in the presentations and discussion.

INNOVATOR MOLECULES

These are the original researched molecules developed by pharmacological companies and studied extensively with clinical trials for specific actions in the human eye in specific clinical indications. We aim to discuss mainly the innovator Anti-vascular endothelial growth factor (Anti-VEGF) and other agents in treating neovascular age-related macular degeneration and diabetic macular edema through intravitreal injections.

A. Anti-VEGF Agents

- Pegaptanib** (Macugen, 2004)
 It is a 40-kDa RNA aptamer that selectively binds to the VEGF165 isoform. While it was a first-of-its-kind therapy, it is now obsolete due to limited efficacy compared to newer agents that bind all VEGF-A isoforms.
- Ranibizumab** (Lucentis/Accentrix, 2006)
 It is a 48-kDa recombinant humanized immunoglobulin G1k isotype monoclonal antibody fragment (Fab) designed specifically for ocular use. It binds to all VEGF-A isoforms. Due to its small size, it has excellent retinal penetration. Ranibizumab ruled the Anti-VEGF space for long and has spawned many biosimilars molecules copying its effects.
- Aflibercept** (Eylea, 2011)
 A 115-kDa fusion protein (VEGF-Trap) that acts as a decoy receptor for VEGF-A, VEGF-B, and placental growth factor (PlGF). It has a higher binding affinity for VEGF-A than ranibizumab and bevacizumab and a longer duration of action, allowing for less frequent injections (e.g., every 8 weeks after initial monthly doses).
- Brolucizumab** (Beovu/Pagenax, 2019)
 A 26-kDa single-chain antibody fragment (scFv) that binds all isoforms of VEGF-A. Smallest approved molecule, allowing for a higher molar concentration (11x higher than aflibercept) to extend injection intervals, but carries a higher risk of intraocular inflammation.
- Faricimab** (Vabysmo, 2022)
 A 150-kDa bispecific antibody designed for the eye, targeting both VEGF-A and Angiopoietin-2 (Ang-2). Inhibits two pathways, enabling extended, less frequent dosing (up to every 16 weeks).
- Conbercept** (Lumister, 2013)
 A fusion protein similar to aflibercept, but with an extra domain (domain 4 of VEGFR2) to increase binding affinity for VEGF-A, VEGF-B, VEGF-C, and PlGF. A Chinese innovation, not yet available in India.

B. Molecules beyond VEGF:

- **Angiopoietin/Tie-2 pathway modulation**
Improves vascular stability and reduces leakage
- **Complement inhibitors** (Geographic Atrophy)
 - Targeting complement cascade dysregulation
- **Plasma kallikrein inhibitors** (DME)
 - Potential role in anti-VEGF suboptimal responders

Current status of Innovator molecules

- Innovator molecules are reshaping intravitreal therapy beyond conventional anti-VEGF agents.
- The future lies in sustained delivery and multi-pathway modulation.
- Intravitreal therapy has evolved beyond conventional anti-VEGF to bispecific agents, long-acting platforms, and gene-based therapies.
- Indian retinal practice prioritizes durability, safety, affordability, and real-world outcomes.
- Next-generation agents such as brolicizumab, faricimab and high-dose aflibercept may help reduce injection burden.
- Careful patient selection and vigilant monitoring are essential to safely adopt newer molecules.
- The future of intravitreal therapy lies in multi-pathway targeting, sustained delivery, and personalized treatment strategies.

THE BIOSIMILARS

- Retinal vascular diseases are a leading cause of preventable blindness worldwide
- Anti-VEGF biologics have revolutionized outcomes, but high cost limits long-term use
- Many patients require repeated, lifelong intravitreal injections
- Biosimilars offer a scientifically validated, cost-effective alternative
- Their role is increasingly critical in resource-limited settings like India

Objectives

- To understand the science behind biosimilars
- To review efficacy, safety, and regulatory approval
- To explore their current and future role in ophthalmic practice

“The challenge today is not whether anti-VEGF works—but how many patients can afford to receive it consistently.”

The talk will explore all aspects of Biosimilars in detail and give their current status.

MULTIMODAL AGENTS

Degenerative eye conditions such as age-related macular degeneration (AMD), diabetic retinopathy, and retinal vein occlusion are major contributors to significant vision loss. The last decade in the treatment of vascular pathologies of the retina has largely been limited to one cytokine: the vascular endothelial growth factor (VEGF) and its interaction with the receptor by blocking the downstream pathway. Though anti-VEGF agents have saved millions of eyes from going blind to these pathologies, there have been a subset of patients who did not have optimal response to this therapy.

This suboptimal response to anti-VEGF therapies can be pinpointed to two reasons, the first being, administration of inadequate therapy due to a multitude of reasons, and other being non-response of the disease to injection. While there have been various regimens that are being tried to provide lesser number of injections without compromising outcomes such as Treat and Extend (T&E) to counteract the first scenario, tackling the second problem requires novel therapeutic targets to be identified and analyzed for their role in inflammation and angiogenesis.

Faricimab, a novel bispecific antibody, offers potential solutions to these challenges. Engineered to simultaneously bind and neutralise Angiopoietin-2 (Ang-2) and VEGF-A, faricimab targets two key pathways involved in nAMD pathogenesis. This dual mechanism of action could provide a more comprehensive therapeutic effect and durable response, potentially reducing the frequency of treatment.

Pharmacology of Faricimab

Faricimab concurrently targets angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A), disrupting two pivotal signaling pathways in the pathogenesis of these conditions. Faricimab binds and neutralises both VEGF-A which is a key driver of neovascularisation and vascular permeability and Ang-2 which is a critical regulator of vascular stability. Accordingly, the simultaneous inhibition of these pathways offers the potential for comprehensive therapeutic efficacy compared to existing VEGF-A inhibitors. Dosage: Initial dosing is 6mg every 4 weeks followed by extending dosing intervals based on clinical response.

Clinical trials for Faricimab

Faricimab has been evaluated in several clinical trials like TENAYA and LUCERNE (for nAMD), YOSEMITE, RHINE, AVENUE (for DME), and BALATON and COMINO (for RVO). Overall, faricimab has shown promising results in treating these conditions, with a favorable safety profile and potential for extended dosing intervals.

INTRAVITREAL ANTIBIOTICS

Rationale

Intravitreal antibiotics are used to deliver high concentrations of antimicrobial agents directly into the vitreous cavity to treat infectious endophthalmitis. Prompt therapy is crucial to preserve vision.

Pathogenesis and Role of Intravitreal Delivery

Microorganisms introduced into the vitreous proliferate rapidly in a nutrient rich environment.

Systemic antibiotics do not reliably achieve therapeutic vitreous levels in most cases of endophthalmitis.

Intravitreal antibiotics deliver high local concentrations at the site of infection with minimal systemic exposure.

Indications of Intravitreal Antibiotics

- Acute Post operative Endophthalmitis (any intraocular Surgery)

- Post Intravitreal injection infection

- Traumatic endophthalmitis

- Endogenous endophthalmitis

To be administered immediately after Vitreous tap/ biopsy and culture sampling, then tailor/ modify therapy once organism is identified. Diagnostic sampling: Vitreous tap is taken before antibiotic injection for Gram/KOH stain and culture-PCR

Common intravitreal Antibiotic Agents and Therapeutic Doses

Agent	Spectrum covered	Intravitreal Dose
Vancomycin	Gram Positive	1 mg/ 0.1 ml
Ceftazidime	Gram Negative	2.25 mg/ 0.1 ml
Voriconazole	Fungal	50-100 mcg/ 0.1 ml
Amphotericin B	Fungal	10 mcg/ 0.1 ml
Dexamethasone*	Anti-inflammatory	400 mcg/ 0.1 ml

*May be used in selected bacterial cases, avoid in fungal

Repeat intravitreal antibiotics may be considered after 48-72 hrs if needed.

Injection protocols and newer antibiotics will also be discussed in the talk.

STEROIDS

Intravitreal steroids form a vision-restoring therapy in many ocular conditions. Corticosteroids are well known for their antiangiogenic, antiedematous, and anti-inflammatory properties. Consequently, the drugs have been widely used in the treatment of many retinal diseases since the early 1950s. Later, intravitreal steroids emerged as an essential tool, allowing for optimal drug efficacy when given locally. The topical or local route offers the great advantage that there is no significant systemic side effect.

Randomized studies have properly shown that steroids are very effective in the treatment of posterior segment diseases such as retinal vascular occlusion, diabetic macular edema, and uveitis. For controlling the disease activity and improving the visual outcome. Today because of the anti-inflammatory, antiangiogenic, and anti-permeability properties, steroids are an attractive therapeutic option for vascular and inflammatory retinal diseases. Recent advances in ocular drug delivery methods led to the development of intraocular implants, which help to provide prolonged treatment with a continuous drug release.

Many now use intravitreal steroids for the treatment of various posterior segment disorders, not only when other therapeutic methods have failed, but more and more as a first-line therapy. Steroids are sometimes used in combination with other drugs like antibiotics in endophthalmitis and anti-VEGF agents in some recalcitrant cases of exudative age related macular degenerations. Intra-operative use of triamcinolone as a surgical adjunct to highlight the vitreous and its attachments is also well known.

Short-acting dexamethasone solution, intermediate acting triamcinolone suspension and long-acting dexamethasone implants are the current commonly used intravitreal steroid therapies. Newer implants containing fluocinolone acetonide are not yet available in India.

Though steroids can have a rapidly visible improvement both in the retinal morphology as well as visual acuity, they can contribute to secondary glaucomas and cataracts in some patients, particularly those with chronic or recurrent conditions needing repeated injections. Checking for a IOP rise with a course of topical steroids before injecting intravitreally may help in detecting some of these 'steroid-responders'.

Specific case examples with pathologies responding well to intravitreal steroids will be highlighted with appropriate imaging before and after injection in the course.

ANTIMETABOLITES

Intravitreal antimetabolites offer targeted intraocular immunosuppression in situations where corticosteroids are ineffective, contraindicated, or associated with unacceptable side effects. Their role is selective but clinically important.

Why Consider Intravitreal Antimetabolites?

Local drug delivery allows high intraocular concentrations with minimal systemic exposure. These agents are particularly useful in unilateral disease, steroid responders, and conditions requiring steroid-sparing strategies.

Methotrexate: The Principal Agent

Methotrexate remains the most widely used intravitreal antimetabolite. It exerts anti-inflammatory effects through inhibition of folate metabolism and downstream cytokine suppression.

- Typical dose: 400 µg / 0.1 mL
- Duration of action: approximately 2–3 months
- Role: local disease control rather than systemic protection

Clinical Indications

Established indications:

- Vitreoretinal lymphoma (local control)
- Noninfectious posterior uveitis (steroid-intolerant cases)
- Proliferative vitreoretinopathy (adjunctive use)

Rare or emerging indications (adjunctive use only):

- Tubercular choroiditis
- Serpiginous-like choroiditis
- Post-infectious inflammatory sequelae
- Necrotizing viral retinitis following antimicrobial control

Treatment Protocols (Practical Overview)

Protocols vary by indication. Lymphoma typically requires an induction and maintenance schedule, while uveitis and PVR are treated with individualized dosing and close follow-up.

Safety and Toxicity

The most frequent adverse effect is corneal epithelial toxicity, particularly with repeated dosing. This is usually reversible and can be mitigated with lubrication, dose spacing, and folate supplementation.

Alternative Non-Biologic Agents

Sirolimus has demonstrated efficacy in reducing intraocular inflammation and vitreous haze, though visual gains are inconsistent. Calcineurin inhibitors remain investigational with limited human data.

Key Teaching Points

DOs:

- Use antimetabolites as steroid-sparing or adjunctive therapy
- Counsel patients regarding corneal side effects
- Reserve use for carefully selected cases

DON'Ts:

- Substitute for antimicrobial therapy
- Expect systemic disease control
- Use indiscriminately in bilateral disease

Take-Home Message on Antimetabolites

Intravitreal antimetabolites occupy a focused but valuable role in retinal practice. Methotrexate remains the primary agent, with cautious expansion into select inflammatory and proliferative conditions.

This Instruction course on Intravitreal Injections will discuss and debate all practical points pre and post-injections, including the preparation, precautions, procedure and protocols.