World class Indian Ranibizumab

RAZUMAB™
Ranibizumab 0.5mg Injection

Revives Vision, Empowers Possibilities

Approved medication for
wAMD, DME, RVO & mCNV

Revived Vision of
35,000*+ Eyes

Abridged Prescribing Information

Active ingredient: Razumab contains Ranibizumab solution for intravitreal injection 10 mg/mL vial (2.3 mg/0.23 mL). Indication: Wet Age-Related Macular Degeneration (wAMD), Diabetic Macular Edema (DME), Macular Edema Following Retinal Vein Occlusion (RVO), Visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM). Dose and method of administration: Ranibizumab 0.5 mg (0.05 mL of 10 mg/mL Ranibizumab solution) is recommended to be administrated by intravitreal injection once a month (approximately 28 days). Contraindications: Ocular or periorcular infections and hypersensitivity to Ranibizumab. Warnings and precautions: Endophthalmitis, retinal detachments, increases in intraocular pressure and thromboembolic events. Adverse reactions: The most frequently reported ocular adverse reactions following injection of Ranibizumab are: eye pain, ocular hyperaemia, increased intraocular pressure, vitritis, vitreous detachment, retinal haemorrhage etc. Drug interactions: Drug interaction studies have not been conducted with Ranibizumab. Use in specific populations: Pregnancy Category C. Nursing Mothers: It is not known whether ranibizumab is excreted in human milk. Overdosage: More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen. Incompatibilities: In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Storage and handling instruction: Store refrigerated between 2 °C to 8 °C in the carton to protect from light. Do not shake. The preparation should not be allowed to freeze. Keep out of reach and sight of children.

1. Myopic Choroidal Neovascularization*  

*Internal Data
Guidelines for the manuscript submission in
VRSI Newsletter

Original articles:
These include randomized controlled trials, intervention studies, studies of screening and diagnostic
test, outcome studies, cost effectiveness analyses, case-control series, and surveys with high response
rate. The text of original articles amounting to up to 3000 words (excluding Abstract, references and
Tables) should be divided into sections with the headings Abstract, Key-words, Introduction, Material
and Methods, Results, Discussion, References, Tables and
Figure legends.

Case reports / Challenging case /Innovations / Instruments /Techniques
New, interesting, challenging, rare cases, innovations, instruments and techniques can be reported.
They should be unique and providing learning point for the readers. Manuscripts with clinical
significance or implications will be given priority. These communications could be of up to 1000 words
(excluding Abstract and references) and should have the following headings: Abstract (unstructured),
Key-words, Introduction, Case, Discussion, Reference, Tables and Legends in that order.

The manuscript could be of up to 1000 words (excluding references and abstract) and could be
supported with up to 10 references. Case Reports could be authored by up to four authors.

Mail to vishalisara@yahoo.co.in, anandrjn@gmail.com
From the President’s Desk

Dr. A. Giridhar
Medical Director
Giridhar Eye Institute, Kochi
giridhareye@gmail.com

Dear Members:

Greetings from Vitreo Retinal Society-India.

This issue of VRS-I newsletter focuses on Intravitreal Injections in vitreo retinal practice. This probably is the most important and relevant issue pertaining to vitreo retina today. It has become the most common intra ocular procedure worldwide with increase in numbers each year. It is reported that an estimated 5.9 million injections were given in the United States alone last year, highlighting the need for safe and practical guidelines and also the urgent need for practicing evidence based medicines to identify proper indications for administering intravitreal injections. I would therefore like to appreciate the initiative of Prof. Vishali and team to bring out an issue of this very important subject. Hope all the members will find this issue relevant and useful.
Dear Friends:

Greetings from VRSI!! I hope that you enjoyed the first issue of our newsletter, which was brilliantly compiled by Dr. Vishali Gupta. I am delighted to know that the second issue of VRSI newsletter in 2018 is being published. I am sure that you will find the articles extremely valuable for your daily practice, and to provide the best care to your patients. I take this opportunity to request you all to submit your interesting cases, articles and innovations to the VRSI newsletter, which will help improve the scientific knowledge base of our members.

Preparations for our XXVII annual meeting at Jaipur from Nov 29 to Dec 2, 2018 are under way. The abstract submission and registration sites are open. Numerous International and National faculty have already confirmed their participation. I request you all to participate enthusiastically in the activities of VRSI.
From the Convenor
Scientific Committee Desk

Dr. Vishali Gupta MD
Professor (Retina, Vitreous and Uvea)
Advanced Eye Centre,
Post Graduate Institute of Medical Education
and Research, Chandigarh-India- 160012
Tel: +91-172-2747837 FAX: +91-172-2747837
e-mail: vishalisara@yahoo.com
vishalisara@gmail.com

Dear Members:

It gives me great pleasure in bringing out the second newsletter of VRSI for the year 2018. The first newsletter focused on the theme of operating rooms that was greatly appreciated by the members. I would like to thank all the members of VRSI for their support and efforts and hard work in helping us to bring out these newsletters on time and giving the practical tips that are generally learnt from the experiences and cannot be learnt from the literature or google.

So, for the second newsletter, we have chosen a theme based on Intravitreal Injections as these injections have become the 'soul' of treating retinal pathologies. I am certain that many of our young members would find this newsletter very useful for their day to day practice with lots of practical tips from our senior members.

Once again, I would like to thank all the busy vitreous retinal surgeons who have taken time out of their busy practices to contribute to the Newsletter and making it possible for us to get the newsletter out on time. We sincerely hope that you enjoy reading it and look forward to your feedback that would help us in improving the quality.
GUIDELINES FOR INTRAVITREAL INJECTIONS

Raja Narayanan

The incidence of post-injection endophthalmitis though low, is of great concern as there is a dramatic increase in the number of injections performed annually in India. The risk of cluster endophthalmitis is high as multiple patients may receive injections from the same vial in a single session. This is relevant in cases of multi-dosing vial such as bevacizumab. Bevacizumab (Avastin®, Roche, Basel, Switzerland) is a recombinant humanized monoclonal antibody approved by the Food and Drug Administration (FDA) for the intravenous treatment of colorectal cancer. The recommendations made in this guidelines are based on the Best Practices followed and published worldwide. The aim of these guidelines is to provide safe intravitreal injection of Bevacizumab (Bevacizumab) to our patients. Though these guidelines are not legally binding, these guidelines are highly recommended as this document formed the basis for DCGI to repeal its alert that allowed us to use bevacizumab again in our patients. The injection should be performed in a sterile environment and should be done by Ophthalmologists, who have the knowledge and training of performing safe intravitreal injections and have the ability and the facilities to manage any adverse events that may arise after such an injection. Following document discusses the recommended way Bevacizumab should move from the Distributor into doctor’s clinic/hospital and further used as an intravitreal injection. It will help you achieve the goal of safe delivery of sterile Bevacizumab.

A. PROCURING & STORING THE BEVACIZUMAB VIAL

1. Purchase drug from a ROCHE authorized distributor only on a proper bill that documents the lot number and matches with the lot number on the carton. It is best to avoid switching dealers for the sole purpose of discounted price. Check the authorization letter of the dealer.

2. It should be stored at the hospital in an exclusive refrigerator at 2–8°C with temperature display, power backup, and a temperature log. Do not store any non-drug related items, such as food and beverages, microbiology or pathology samples, blood and blood products, in the same refrigerator. Electronic data loggers are available in the market to monitor the temperature. The refrigerator should ideally be lockable and access to this should be possible only to few certified people.

3. A separate register should be kept to keep record of Bevacizumab usage. This should have following information

   a) Name of the Person who transferred the vial to the refrigerator

   b) Record of Utilization of the vial with the lot number, aliquot preparation date and samples sent for culture and their reporting.

   c) If the culture comes positive, report to the distributor and VRSI office.

B. HOW TO USE THE BEVACIZUMAB VIAL

Once the authenticity is confirmed, carefully open the vial and check that the lot number and expiration date on the vial matches that on the carton. Also ensure the vial does not look tampered and look at the contents of the vial for anything unusual.

OPTIONS FOR PREPARING BEVACIZUMAB

Option 1:
Prepare aliquots in class 1000 environment under a class 10 laminar flow hood

Option 2:
Fractionation and Aliquoting:

Place of Fractionation
We suggest opening a vial and preparing the required number of injections in 1ml syringes under sterile conditions (ideally under ISO class 5 conditions):
• Clean Room with Laminar flow Hood
• Compounding Isolator
• Sterile Operation Theatre with HEPA filter or Laminar flow with filter.

Steps of Aliquoting
• Open the cap of the vial. Clean the Rubber Stopper with Sterilium/70% Isopropyl Alcohol. The swab used for cleaning also must be sterile. A 20/23 G needle/mini spike device is inserted in the rubber stopper of the vial by a scrubbed paramedical staff/ophthalmologist in the operation theatre with mask and cap. The scrubbing and gowning should be as for any intraocular surgery. The vial must be held upside down by non-scrubbed personnel in the operation theater wearing a cap and mask.

• Do not talk while the procedure is being done.

• The scrubbed staff should withdraw 0.2 ml of Bevacizumab in a 1 ml disposable syringe without injecting any air in the vial. All other aliquots are similarly prepared.

• Cap it with a 30 G needle. Ensure there is no remnant air in the syringe. The needle could be optionally bent/capped by a sterile cap.

• Do not withdraw less than 0.2 ml per syringe. All syringes should be prepared by withdrawing drug from a single puncture of 20/23 G needle.

• The prepared capped syringes with the drug must be stored in ETO sterilized sealed pouches and then placed in a sterile autoclavable container. Each sterile box should have a label with name of the drug, batch number, date of preparation of the syringe and date of expiry, (which is 2 weeks from the date of preparation).

• Even if all the injections are to be consumed the same day by different surgeons in the same hospital, they should be maintained between 2-8°C.

• A freshly opened 29/30/31 G needle should be used at the time of performing the Intravitreal injection.

A separate register for maintaining a log of usage of Bevacizumab must be maintained in the operation theater. This includes medical record number, name of the patient, name of surgeon, and indication for use, and the batch number with expiry of the syringe.

At the time of aliquoting, two syringes must be sent for culture and sensitivity testing. If there is no growth on culture after 48 hours, the batch of syringes can be released for use in patients.

It is preferable to keep the vial for a month before destroying it. The vial should be destroyed rather than just discarded to prevent its misuse. Destroy the labeling sticker on the vial with a permanent marker or remove it physically before discarding the vial.

Option 3.
Withdraw Bevacizumab directly from the vial using a 30 G needle by strict aseptic technique (after having cleaned the rubber stopper with Sterilium or 70% Isopropyl alcohol) in a sterile OT and inject. Ensure that before you start injecting the first aliquot, send a sample for culture and sensitivity, wait 48 hrs to obtain a negative culture. The injection can be done only if the culture is clear. This technique has limited published data, but is useful as a precaution against contaminated spurious drugs. In any case, vials with visible contaminants, altered color, and broken seal should never be used. The vial should always remain stored after use in its carton and in an airtight plastic container at 2-8°C.

It is recommended that both for technique 2 and 3, a culture is to be sent on day 1, wait for 48 hours for culture report before using the aliquots or the vial. The 30 G needle used for injection should be a new one and not the one with which the aliquot was stored. The vial or the aliquots can be stored, kept and used for a maximum duration of two weeks.

• Discard the empty vial after one month– it is NOT to be re-used

C. Intravitreal injection guidelines

1. Pre-op preparation and precautions:

• Patient screening & precautions:
  • The need and choice of Intravitreal injection should be tailored to the individual patient according to the best clinical judgment of the attending/injecting eye specialist.
  • All patients should be screened to ensure a patent nasolacrimal duct and negative regurgitation test.
  • Patients with active infection of the ocular adnexa (blepharitis, meibomitis) or a blocked nasolacrimal duct/positive regurgitation test are at high risk for endophthalmitis and should be treated for the active infection first. Injection should be scheduled after the active infection is treated.
  • Surgical/procedural time-out to verify the patient’s name, Intravitreal agent and laterality should be practiced before injection for each patient.
  • Bilateral injections on the same day are NOT recommended and injection for the other eye should be preferably planned 3 days later.
• Patients with uncontrolled systemic conditions like uncontrolled diabetes should first be treated for it. While there is no strict cut-off value for blood sugar, injections should be given with the same precautions as for any intra-ocular surgery.

• Antibiotics: Routine use of topical antibiotics for a day prior to the injection are not recommended. However, in special circumstances such as debilitated or immuno compromise patients, topical antibiotics may be prescribed.

• Patient preparation:

  • Consent: An informed written consent should be taken from all patients undergoing the injection after explaining the procedure and the risks involved. Off label use of Bevacizumab should be included in the consent and explained to the patient.

  • Each patient should be given a cleaned OT gown, protective cap and booties before entering the preoperative holding area/operating room.

**Time of Using the Aliquoted Bevacizumab**

• While the Aliquots are waiting to be used they should be maintained in sterile, packed pouches in a sterile container at 2-8 C. Local logistics need to be worked out by the injecting surgeons.

• The drug is not to be stored for more than 15 days.

**2. Steps of Injection**

1. **It is recommended to do the injection procedure in an operation theater or a sterile room designated for such procedures taking all precautions as are taken for any intraocular surgery.** We do not recommend Intravitreal injection Bevacizumab in an office setting.

2. Evidence suggests that prophylactic antibiotics are not better than the use of povidone iodine 5% drops. We recommend mandatory cleaning and draping. Use 10% povidone-iodine to clean the skin and periorcular adnexa and 5% povidone iodine drops to be instilled in the conjunctival sac for a contact period of 3 minutes.

3. Please instill one drop of proparacaine eye drops in the eye before instilling povidone-iodine drop.

4. Patients with known povidone allergy can have fluoroquinolone eye drop instilled 3 times in the eye starting 30 minutes prior to the injection.

5. The surgical area should be draped using sterile linen and a separate plastic sticking eye-drape for each patient to isolate the field.
   - A sterile speculum should be used to prevent contact of the eyelashes and eyelid margins with the injection site and needle.
   - Topical anesthetic drops should be preferred over anesthetic gel as the latter may interfere with povidone-iodine contact with the conjunctiva/injection site.
   - Reapply povidone-iodine after anesthetic drop use. Before the injection, povidone-iodine (5%) should have been the last agent applied to the intended injection site.
   - Routine anterior chamber paracentesis is NOT recommended.

6. The injecting physician must wear surgical attire, gloves, cap and mask. Talking should be minimal during the injection procedure.

7. Draping should be done after a minimum of 2-3 minutes of povidone iodine painting. This is to provide adequate exposure time for the povidone iodine to act against pathogens.

8. During the waiting time of 2 minutes, one can prepare the caliper marking, and make the final adjustment of volume of Bevacizumab with a fresh 29/30 G needle.

9. Do not hesitate to re-drape if eyelashes have not been completely tucked under the drape.

10. Take a final time-out to confirm the name of the patient and the correct eye to be injected.

11. It is preferable to inject under an operating microscope.

12. Any quadrant can be chosen for injection. Sterile calipers should be used to mark 3–4 mm from limbus (depending on lens status) to mark the injection site.

13. Post injection, the cul de sac can again be flushed with povidone iodine or the injection site dabbed with a povidone iodine soaked sterile swab.

14. The eye can be patched with povidone iodine 5% drops for 2 hours after injection.

15. Post-injection antibiotic and its use is left to the discretion of the Ophthalmologist treating the case. However, in patients with poor lid hygiene, or debilitating systemic status, topical antibiotic eye drops for 5 days are recommended.

**3. Post-operative precautions:**

- Proper lid hygiene should be maintained in the post-op period
- Post-injection IOP should be monitored and topical antiglaucoma may be prescribed for post-injection IOP spike as and when warranted.
- All patients should be given a discharge card
mentioning the injection details, postoperative instructions, symptoms of infection (pain, redness, dimness of vision, swelling, discharge, etc.) and 24-hour emergency contact information.

- Patients should be instructed to avoid washing of eyes for 24 hours.
- After each day, all the instruments and linen after thorough cleaning and drying should be autoclaved for the next day.
- Follow-up of each patient should be tailored as per the indication for the Intravitreal injections.

D. Postoperative Management

1. Patients may be examined within 3 days after injection. If the patient is unable to come for any reason, the patient must be asked to report to the nearest ophthalmologist immediately if there is unusual pain, redness, or drop in vision at any time. These instructions must be given in writing to the patient and it must be ensured that they, or the accompanying attendant have understood it.

2. We suggest a good examination of anterior segment using slit lamp for any cells in the anterior chamber or anterior vitreous. Fundus should be examined using indirect ophthalmoscopy for any exudates, floaters, or new onset peripheral retinal hemorrhages or vasculitis.

3. Please check the intra-ocular pressure at each visit.

4. Patients should be instructed to avoid head bath for 1 day post injection and swimming for 3 days post injection.

5. In case the patient is due for injection in both eyes, it should be done at an interval of 3 days.

Cautions

- *Injections for ROP are not covered in these guidelines.*
- *Anti-VEGF injections should be deferred in pregnant women.*
- *Caution should be exercised in patients with increased risk of thromboembolic phenomenon or recent history of stroke or myocardial infarction, as for any other intra-ocular surgery.*
- *Injections should be deferred in patients with uncontrolled blood sugar levels as it may increase the chances of endophthalmitis. However, there is no evidence-based guideline for a cut-off of blood sugar or HbA1c level.*
- *Patient should be informed about higher risk of endophthalmitis in uncontrolled diabetes. If the patient wishes to proceed with the injection due to unavoidable circumstances, the above discussion should be documented in the consent prior to the injection. Such patients may be given pre and post-injection topical antibiotics as an additional precaution.*

**Don’ts**

Do not buy drugs from a non-authorized Distributor

Do not inject Bevacizumab in Office/OPD room. Considering the varied circumstances in India we have taken a conscious decision of performing intravitreal injections in sterile setting of an operating room or similar area.

Do not transport partially used vials in ice packs. Do not transport Alliquoted syringes of Bevacizumab. If a surgeon is practicing at multiple centers, it is recommended that each center be equipped to fractionate Bevacizumab. If this is not feasible, it is recommended that the patient be taken to the nearest center where Bevacizumab is available.

Do not store Bevacizumab vial for re-use once it’s seal is broken.
The vitreoretinal fraternity is currently in the process of deciding if it trusts AntiVEGF products from manufacturers other than the company holding the patent for it. This situation has arisen due to a combination of factors, first being the fact that the statutory period for the validity of the patent is close to expiry in the US and EU and second, the availability of a cheaper drug manufactured by an Indian company. While this is an occasion for pride that our industry has manufactured such a product, many of us wish to convince ourselves of the safety and efficacy of this substitute product and therefore have a lot of unanswered questions.

Firstly is it a generic or a biosimilar? What difference does it make, after all, its just semantics isn’t it? Not Really, it’s not just semantics. A generic drug implies a drug with a chemical origin where the ingredients are easily measured chemicals that can be standardized with regard to effect, distribution and pharmacokinetics. The drug can be mixed and formulated in exactly the same proportions as the patented drug (called the innovator product). Since the components of the drug are easily measured and produced, their effects are easy to standardize and relatively predictable. The constituents of the generic drug are therefore, identical to the innovator molecule. The licensing of these drugs flows an abbreviated process where the generic does not have to replicate all the data that was needed to license the innovator molecule. Most countries have robust and simple working laws to license generic products.

Biosimilars on the other hand, are products that are NOT identical to the innovator molecule. The reason for this is that the source of the drug is a biological process and not a chemical one. All biological processes, whether animal, plant or cell origin, have an inherent variability. Therefore, it is virtually impossible to create an identical product. The innovator molecule itself had an inherent variability in its product but that variability is rigorously evaluated, measured and controlled during the original licensing application (also called a New Drug Application). Since there is an inherent variability, it has been very difficult for Licensing Authorities around the world to evolve any law to deal with this class of drugs. All that exist are guidelines. In India, The CDSCO (which contains the DCGI) is the organization that deals with this issue, however, a large number of other agencies are also stakeholders in the decision making process. As a result of the difficulties faced in standardizing products and their effects, there is no law as yet that governs the licensing of Biosimilars. There is however a set of Guidelines, Published by CDSCO in 2016 that deals with the topic. This supersedes the earlier guidelines and has certain differences from it that impact the process and are important for us to understand. (Table 1)

So, what exactly is the process?

First the generic manufacturer has to submit an application for permission to license a biosimilar. Then it has to be proven that the product is SIMILAR to the innovator molecule. How dissimilar can a biosimilar be from the innovator or reference product? This is the million dollar question to be answered and it is the one not adequately answered. There is no information in the biosimilar guidelines that clearly lays down the limits of variability in structure or function that will bind the application process. Maybe it is impossible to do so and each molecule has its own limits that are to be assessed on a case to case basis, but this point seems to have been glossed over in the guidelines. However, the new guidelines do mention that the variability or parameters have to be in accordance with international guidelines. This allows some degree of standardization of outcome evaluation.

The next step in the process is to furnish data regarding the manufacturing process and establish the stability and variability of the process. This would call for stringent record
Downstream processing involves molecular biology, and upstream includes the cell lines, clones, etc. This includes excipients, packaging details, and any interactions during the process. The details will include molecular biology issues and upstream and downstream process development data. What is this data and why is it so important that it has specifically been added in the latest guidelines? This is fairly detailed data that breaks down the manufacturing process into its steps and ensures that there is consistency, reproducibility, and stability of the product. Most importantly, the company has to demonstrate that it can manufacture three batches of the product that are similar enough to be used in preclinical and clinical trials.

**How is identity and purity established?**

The biosimilar manufacturer has to provide data on every step of the manufacturing process and the stability of the cell banks, clones, etc. This includes excipients, packaging details, and any interactions during the process. The details will include molecular biology issues and upstream and downstream process development data. What is this data and why is it so important that it has specifically been added in the latest guidelines? This is fairly detailed data that breaks down the manufacturing process into its steps and ensures that there is consistency, reproducibility, and stability of the product. Most importantly, the company has to demonstrate that it can manufacture three batches of the product that are similar enough to be used in preclinical and clinical trials.

**How is the quality of the product assessed?**

Quality is assessed broadly by analytical (in vitro) methods, preclinical studies, and clinical studies. The analytical methods used are wide-ranging, however, the guidelines mention that the latest and "State of the art" methods be used to detect even "slight differences" in relevant quality attributes. What are these quality attributes? These are

1. **Critical quality attributes** that have a direct impact in the clinical efficacy and safety
2. **Key quality attributes** that may not affect the clinical and safety considerations, but have a bearing on the quality of the manufacturing process and its consistency

An important point clarified by the guidelines is that all these studies should be carried out using the biosimilar, the reference molecule, and controls for each assay or experiment. This reference molecule need not be licensed in India as per the recent guidelines and this is an important change. The guidelines also focus on excellent documentation and verification of processes to guarantee the standard of the finished product.

Some of the most important data that needs to be submitted prior to consideration for clinical trial is PK (Pharmacokinetics) and PD (Pharmacodynamics) Data. These studies are mandatorily head to head comparative studies. The important issues in this section are

1. **The PK and PD studies** that involve drugs used in cumulative doses or where drugs may be substituted must be studied in multiple doses or in crossover studies to prove that the generic drug behaves the same as the reference biologic even on interchangeability or repeated doses. This, in fact, is extremely relevant for biosimilars relevant to ophthalmology.
2. **The PK and PD data** is so important that it forms the basis for application for clinical trials of the drug and if the PK and PD data is very robust, the regulating authority is empowered to provide a waiver for the requirement for a clinical trial. PK and PD data is generated through small scale in vivo trials in healthy volunteers or patients.

The Clinical assessment of a Generic molecule is done through comparative clinical trials and also post-marketing surveillance. One of the points of controversy has been the number of patients studied in these trials have been low. It was assumed that this was somehow an indicator of inadequate oversight. However a look at the guidelines, both in the US and India, suggests that the number of patients that are mandated to be studied in these trials range from between 100 to 200. Yes, this is appreciably lesser than the innovator molecule but the aims are different. Post marketing surveillance is important since many adverse effects surface in appreciable numbers only on more widespread use of the drug, hence the manufacturer needs to demonstrate a robust post-marketing surveillance program.

**How robust is our regulator and how do we compare with other countries?**

The USFDA is very conservative when granting approvals to generic molecules and has approved very few. India and its CDSCO on the other hand has approved a significantly larger number (Table 2). How has this happened? One point of view could be that USFDA is compromised by pharma lobbies and the Indian regulator is trying to provide for the poor and break the hegemony of Big Pharma. This would imply that CDSCO is largely impervious to pharma influence. The other viewpoint is that CDSCO simply has inadequate experience, staffing and standardization to conduct a rigorous enough evaluation. I will leave it up to the reader to judge. Some incidents, though, need to be mentioned in this regard. A USFDA inspection of a
plant that produces a biosimilar that is already licensed in India, resulted in a slew of observations about the quality of the plant. Then how was this drug licensed in India, when it was manufactured at the same plant? Is it that the FDA is biased against Indian companies or is the Indian regulator too lax. How does one decide? Another telling point is that all approval data in USA is in the public domain. In India it is not, so concerned citizens like us cannot verify the quality or quantity of data provided to CDSCO. I tried to access this data on my own and could not, whereas I was able to access it on the FDA website. At the least, we still need more transparency. An overview of the decision making process and the kinds of observations and oversight carried out by CDSCO can be estimated from the minutes of the meetings available online.

In conclusion, biosimilars are here to stay, the price benefit lies in the range of 20-30% and govt policy will naturally veer towards these products. The guidelines are robust and provide for adequate assessment prior to licensing approval. However, as with all things in India, the actual application of these guidelines by the regulatory body will need to be seen in time. As a society VRSI will still have a role to alert regulators to adverse post marketing effects and also spread awareness of the same.

<table>
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<tr>
<th>2016 guideline</th>
<th>Impact</th>
<th>Relevance to us</th>
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<tbody>
<tr>
<td>POST MARKETING SURVEILLANCE</td>
<td>This has become the most important change in emphasis in comparison to the previous guidelines. Companies are now mandated to have a surveillance program and establish safety as the primary endpoint even after marketing the drug</td>
<td>Post marketing adverse events ought to be reported to the regulator.</td>
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<tr>
<td>Manufacturing : Upstream process</td>
<td>Has been described in detail with objective parameters. Most importantly, has become more stringent. For example, companies now have to reveal in detail the components they use to manufacture the drug, including media etc. Thus was not mandatory earlier</td>
<td>Brings the guidelines in consonance with international standards. Reduces the space available for discretionary powers.</td>
</tr>
<tr>
<td>Clinical studies</td>
<td>Detailed criteria established that lay down the process for comparison of the drugs and also criteria on which preclinical testing will be assessed</td>
<td>Aligns with international standards. Introduces objective criteria, reduced scope for waivers and ambiguity.</td>
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<tr>
<td>Extrapolation</td>
<td>All indications for the reference drug can be applied for in the new drug</td>
<td>Use of the biosimilar across indications is possible and makes the approval process for other indications easier.</td>
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<tr>
<td>Shelf life</td>
<td>Shelf life to be supported by real data. If data is available only for 12 months, then shelf approved will be 12 months. To approve shelf life of 24 months, data for 24 months should be available</td>
<td>Improves standards and makes decisions evidence based.</td>
</tr>
<tr>
<td>Patients numbers</td>
<td>Number of patients required for each stage of the clinical and post marketing surveillance is specified</td>
<td>Removes ambiguity, reduces scope for manipulation.</td>
</tr>
<tr>
<td>INTERCHANGABILITY – During therapy with the reference biologic, can the biosimilar be used interchangeably in the course of the treatment?</td>
<td>Needs specified crossover trials that interchange the drugs and establish similarity of effect. The current guidelines are a little vague on this point and the policy document only mentions this in passing. USFDA, however specifies this very clearly.</td>
<td>Especially relevant for ophthalmology. No such crossover trials have been done. These biosimilars are approved as standalone drugs and not as substitutes—this is just semantics since they will certainly be used as interchangeable drugs. This point is never highlighted.</td>
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Table 1: Highlights of the 2016 guidelines
Currently, no biosimilars of ranibizumab or aflibercept are licensed by other countries. Many products are undergoing evaluation for licensing. INTAS has applied for USFDA approval for RAZUMAB.

Table 2: Approved Biosimilars

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>Reference drug</th>
<th>Biosimilar name</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>INDIA</td>
<td>RANIBIZUMAB</td>
<td>RAZUMAB</td>
<td>INTAS</td>
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<td></td>
<td>BEVACIZUMAB</td>
<td>ZYBEV</td>
<td>CADILA</td>
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<td>KRABEVA</td>
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Welcome to

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- Symposium by 'ASRS'
- Symposium by 'The Egyptian Vitreoretina Society'
- Symposium by 'Asia Pacific Society of Ocular Oncology and Pathology'
- Session by "Retnet India"
- Fluorescein Conference
- Challenging cases & Videos
- Roundtables and Panel Discussion
- Workshops on Retinal procedures
- Fellows Forum
- Mentorship for budding Retina Surgeons

29th November - 2nd December 2018, Jaipur
White Dot Syndrome – An Update

Ezhil Vathani N. MS, Parthopratim Dutta Majumder MS, Anmol Naik MS, DNB, FICO, Jyotirmay Biswas MS, FMRF, FNAMS, FIC Path, FAICO

1 Fellow, Shri Bhagwan Mahavir Vitreo-retinal services, Sankara Nethralaya, Medical Research Foundation, Chennai, Tamil Nadu, India.
2 Senior Consultant, Department of Uvea and Ocular Inflammation, Sankara Nethralaya, Medical Research Foundation, Chennai, Tamil Nadu, India.
3 Director, Uvea and Ocular Pathology, Sankara Nethralaya, Medical and Vision Research Foundations, Chennai, Tamil Nadu, India.

The white dot syndrome (WDS) is an umbrella term for a group of inflammatory disorders characterised by ‘whitish-yellow’ inflammatory lesions located at the level of outer retina, retinal pigment epithelium (RPE) and choroid. Various clinical entities have been included under the term WDS. A considerable overlap exists between these clinical entities.

In this short review, we have discussed about the clinical characteristics and management of few WDS: acute posterior multifocal placoid pigment epitheliopathy (APMPPE), serpiginous choroiditis (SC), diffuse unilateral sub-acute neuroretinitis (DUSN), birdshot chorioretinopathy (BC), multiple evanescent white dot syndrome (MEWDS), punctate inner choroidopathy (PIC), multifocal choroidopathy with panuveitis (MCP) and acute zonal occult outer retinopathy (AZOOR).

APMPPE is an uncommon, idiopathic bilateral disease which affects young healthy adults. There is no gender predilection. Association with HLA-B27 and HLA-DR2 has been reported. It is typically preceded by an influenza-like illness (50%). Patients present with sudden onset of bilateral, asymmetrical decreased visual acuity and photopsia. The fellow eye is affected within few days or weeks. Anterior segment is quiet with mild to moderate vitritis. Fundus examination reveals yellow-white creamy lesions in the posterior pole ranging in size from 0.5 to several disc diameters. These lesions spontaneously become less opaque within 2-3 weeks and develop pigment changes at the level of RPE. A rapid improvement in visual acuity may occur during this time. New lesions may appear in a linear or radial pattern up to the equator. A role of systemic vasculitis has been attributed in majority of the cases.

FFA may reveal early hypofluorescence probably due to both the opacification of retinal pigment epithelium (RPE) and choroidal non-perfusion followed by late staining.

Indocyanine green angiography (ICGA) reveals hypofluorescence of the active and healed lesions, indicating the role of choroidal non-perfusion in APMPPE. EOG is abnormal. The diagnosis of APMPPE is based on the typical clinical presentation and FFA findings.

Fig. 1: Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

Legend:
A – Fundus picture showing yellow-white creamy lesions at the posterior pole B and C – Fluorescein angiography images demonstrating early hypofluorescence (B) and late staining (C)

In general, no treatment is required for APMPPE as it is a self-limiting condition. Most individuals have good visual prognosis with spontaneous visual recovery within 3-6 weeks. Recurrences are rare. Systemic treatment has been suggested in cases with foveal involvement and associated central nervous system (CNS) vasculitis. Long term vision loss in patients with APMPPE is found to be due to extensive RPE depigmentation and clumping. APMPPE needs to be differentiated from serpiginous choroiditis. While APMPPE is an acute condition which usually does not recur, serpiginous choroiditis is recurrent and relentlessly progressive.
SERPIGINOUS CHOROIDITIS (SC):

Serpiginous choroiditis (SC), formerly known as geographical helicoid peripapillary choroidopathy (GHPC), is a bilateral, asymmetrical, chronic, progressive, inflammatory condition affecting the choroid and retinal pigment epithelium. It affects healthy patients from second to seventh decades of life. Its etiology is unknown. There is no known sex predilection. It seems to be associated with increased frequency of HLA-B7 and retinal S-antigen and reports of various auto-immune vasculitides suggest it to be an autoimmune mediated occlusive vasculitis. A possible association with herpes virus has also been postulated. An elevation of factor VIII – von willebrand antigen has been found to be in a small series of patients. In tuberculosis (TB) endemic areas, macular or peripheral lesions may be present without peripapillary involvement. The term multifocal serpiginoid choroiditis (MSC) has been recently proposed for this infective variant to distinguish it from the typical peripapillary serpiginous choroiditis (SC) which is believed to be autoimmune mediated.

Symptoms include blurred vision, photopsia, paracentral scotomas, metamorphopsia and visual field loss. On examination, the anterior segment is quiet with mild vitritis. Fundus examination shows asymmetric bilateral, characteristic grey-white lesions in the peripapillary and macular region at the level of RPE and choriocapillaries with a pseudopodial or geographic extension from the peripapillary area into the posterior fundus. It has a peripapillary (Fig. 2A) and a macular variant (Fig. 3) depending on which area is predominantly involved. Typically both healed and active lesions are seen with activity located adjacent to atrophic scars. The active lesions may be associated with shallow sub-retinal fluid. As the acute lesions clears, extensive atrophy of the choriocapillaries, retinal pigment epithelium and retina is seen. Recurrent attacks are typical with a centrifugal extension. The healed inactive chorio-retinal lesions appear as well demarcated geographic areas with or without pigment epithelial hyperplasia. Late complications include sub-retinal fibrosis and choroidal neovascularization (CNV) usually occurring at the border of an old scar. Visual acuity drops markedly if the fovea is involved. FFA shows early hypofluorescence and the late staining of the active edge of the lesion that may extend centrally (Fig. 2B, 2C - left), ICGA reveals hypofluorescence throughout all phases of the study for both acute and old lesions (Fig. 2B, 2C – right). Fundus autofluorescence (FAF) is useful in monitoring the disease activity with new lesions appearing hyperautofluorescent, at the edge of an old lesion which is hypautofluorescent. Electrophysiologic studies are usually normal.

Fig. 2: Peripapillary serpiginous choroiditis

Legend:
A - Fundus photograph showing the characteristic grey-white lesions in the peri-papillary
B and C – FFA and ICGA images: FFA demonstrating early hypofluorescence and late staining of the active edges (left) and ICGA demonstrating hypofluorescence throughout all phases for active lesions (right)

Fig. 3: Macular serpiginous choroiditis

Legend:
A: Clinical fundus picture
B: Autofluorescence showing lesion at the centre with hyperautofluorescence at the edges; suggesting central healed lesions and peripheral active lesions.

Due to the relapsing and progressive nature of the disease, treatment is aimed at treating acute episodes with steroids and preventing recurrences with the use of immunomodulatory therapy. Since the disease is usually bilateral, oral systemic steroids are preferred for active lesions. Macular or foveal involvement may warrant use of intravenous methylprednisolone followed by tapering oral steroids.
Periocular, intravitreal corticosteroids or intravitreal implants like fluorocinolone acetonide implants may also be used. Long term management involves prolonged use of immunosuppressants, most commonly cyclosporine/azathioprine/chlorambucil/cyclophosphamide under supervision of an internist. The multifocal serpiginoid choroiditis variant is usually infective with tuberculosis being the most common etiology. These patients should be investigated for TB and may need treatment with anti-tubercular therapy (ATT) for at least 9 months with a short course of oral steroids. ATT has shown to decrease number of recurrences in such cases. Immunosuppressives are preferably avoided in TB associated SC. Intravitreal anti-VEGF agents and photodynamic therapy are important therapeutic modalities for the treatment of associated CNVM.

AMPIGINOUS CHOROIDITIS:

Ampiginous choroiditis has been described as clinical entity involving features of both acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and serpiginous choroiditis (SC) in relatively young patients, occurring predominantly in males. The first cases were described by Jones et al, who used the term relentless placoid chorioretinitis (RPC) and the first group to coin and use the term ampiginous choroiditis was Nussenblatt et al. These patients have evidence of numerous posterior and peripheral retinal lesions predating or occurring simultaneously with macular involvement. Older, healing pigmented lesions are often accompanied by the appearance of new active white placoid lesions (Fig. 3A). All these cases demonstrate prolonged periods of activity, resulting in more numerous lesions in hundreds scattered throughout the fundus at different stages of activity. Growth of subacute lesions and appearance of new lesions continue for 5-24 months after initial examination.

Diagnostic criteria:

- Yellowish white placoid lesions with geographic borders occurring in the mid periphery, unlike serpiginous choroiditis. The posterior pole may be involved later in the disease and rarely this may be the initial presentation.
- These lesions are much smaller than serpiginous choroiditis and APMPPE.
- The lesions are recurrent, unlike in APMPPE.
- FFA characteristics are markedly different. The active lesions show central hypofluorescence with hyperfluorescent margins (Fig. 3B). They do not show blocked fluorescence as in APMPPE.

Fig. 4: Ampiginous choroiditis

Legend:

A: FFA demonstrating central hypofluorescence with hyperfluorescent margins
B: ICGA demonstrating hypofluorescence throughout the lesion

DIFFUSE UNILATERAL SUBACUTE NEURO-RETINITIS (DUSN):

An ocular inflammatory syndrome described by Gass in 1978, it is postulated to be caused by the movement of a single nematode parasite in the sub-retinal space. It is termed as diffuse unilateral subacute neuroretinitis (DUSN) because of the inflammatory changes in the optic nerve and retina. It commonly occurs in children and young adults. Unilateral visual loss, often with central or paracentral scotomata, is the primary symptom. The accompanying vitritis will often produce complaints of floaters. DUSN has two distinct stages. The early stage is characterized by inflammatory signs such as papillitis, multifocal chorioretinitis, and mild to moderate vitritis. Clusters of multiple grey-white or yellow-white lesions in the deep retina that fade within days were found in the majority of the patients. Progressive pigment epithelial changes occur with resolution of the active lesions. The late stage is characterized by narrowing of vessels, sheathing, optic nerve pallor and focal or diffuse changes in the RPE. CNV and sub-retinal fibrosis can occur.

FFA demonstrates the RPE changes well. Active lesions are hypofluorescent in the early stage and stain at a later stage (Fig. 5). Mild leak may occur from the optic nerve any areas of active retinal involvement. ERG is moderately to severely affected, but not extinguished. Direct visualization of the nematode can be made on fundus examination or scanning laser ophthalmoscopy.
The causative agent of DUSN is often suspected to be a toxocaral species. Baylisascaris procyonis, the larval form of an intestinal parasite of raccoons, multiple intestinal round worms (ascarides) from a variety of animal species can probably produce DUSN. Also, Ophidascaris, Polydephis, Travassoascaris and Hexametra species must be considered as the etiological agent of DUSN.

Laser photocoagulation of visualized nematodes should be attempted in all cases. It is helpful in halting the progression, and improvement of visual acuity if lasered in the early phase. Corticosteroids provide transient control of inflammation, but leads to recurrence of symptoms and progression of visual loss. Also a reinfection with a second nematode may be suspected in patients who have completed a previous photocoagulation. Antihelminthic therapy not only decreases the inflammation but also immobilises the sub-retinal nematode and facilitates laser photocoagulation. Oral Thiabendazole (22 mg/kg twice daily for two to four days with a maximum dose of 3g) is successful in moderate to severe inflammation. Albendazole (200 mg twice daily for 30 days) may be a better tolerated alternative. Antihelminthic therapy not only decreases the inflammation but also immobilises the sub-retinal nematode and facilitates laser photocoagulation.

**Legend:**

FFA showing RPE changes and the mid phase showing hyperfluorescent dots

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**BIRDSHOT CHORIORETINOPATHY:**

It has also been called vitiliginous chorioretinitis and is not seen in India. This syndrome usually affects healthy young women, between the third and sixth decades of life. It is thought to have a highly probable auto-immune etiology with nearly 90% of patients having HLA-A29 allele, S-antigen CD8+, the highest association of any HLA antigen with a human disease. The research criteria for the diagnosis of birdshot chorioretinopathy formulated by an International Consensus Conference. Patients with BC present with decreased vision which may be out of proportion with the clinical findings. Since intraocular inflammation can be very mild and the spots are not always prominent in the early stages, the symptoms could be dismissed and there is often a delay in diagnosis. Fundoscopy reveals the characteristic multifocal, hypopigmented, ovoid, cream-coloured lesions at the level of the choroid and RPE in the post equatorial fundus, typically nasally and inferiorly to the disc. The term “birdshot” was given by Ryan and Maumenee because lesions radiate from the optic nerve and follow the larger choroidal vessels in a pattern similar to a shotgun scatter of a birdshot. Retinal vasculitis is an important component of the disorder. Vasculitis involves the large and small vessels in the posterior fundus which is typical, especially in the early stage of the disease. Retinal haemorrhage or exudation is rare and most of the retinal vascular change is arteriolar and venular narrowing. Optic disc edema and CME may be present. Late complications include optic atrophy, epiretinal membrane (ERM) formation and rarely choroidal neovascular membrane. Chronic stages show well defined atrophy characteristically without pigments.

**Legend:**

Multiple hypopigmented, ovoid, cream-coloured lesions at the level of the choroid and RPE, radiating from the disc to the periphery

FFA provides important diagnostic and prognostic information. It helps in detecting subtle features of active inflammation such as retinal vasculitis, optic disc leakage and
CME. Early stages of FFA could be normal or demonstrate ‘Quenching’ of vessels, venous hyperfluorescence, extensive late intra-retinal and disc leakage. ICGA showing hypofluorescent, fuzzy vessels indicates activity.

Progressive visual field loss and abnormal electroretinogram (ERG) results are commonly seen with extended follow up, suggesting that a more diffuse retinal dysfunction occurs and the visual loss is not by the presence of CME alone. For this reason full field ERGs and visual fields are more useful parameters in following the disease course and response to therapy than only the changes in fundus or visual acuity. The disease course is generally marked by multiple exacerbations and remissions. Hence the long term visual prognosis is guarded.

Treatment of an active disease is the initial administration of systemic corticosteroids, and low doses of cyclosporine; some patients also require treatment with azathioprine. Low doses of systemic steroids and intravitreal triamcinolone are given for refractory cystoid macular edema. Complications include CNV, progressive vascular attenuation, macular edema or optic nerve atrophy. Differential diagnosis includes sarcoidosis and Vogt-Koyanagi Harada disease.

MULTIPLE EVANESCENT WHITE DOT SYNDROME (MEWDS):

Multiple evanescent white dot syndrome is an idiopathic, unilateral, inflammatory disorder of retina affecting young healthy moderately myopic women in their second to fourth decades of life. This condition is preceded by a viral prodromal illness in one-third of cases. There is no known racial or hereditary association. Patients present with acute, painless, unilateral decrease in vision, photopsias, and central or paracentral scotomas corresponding to an enlarged blind spot. On examination, RAPD, quiet anterior segment with mild vitritis, disc edema and rarely vascular sheathing may be seen. Funduscopy reveals multiple, discrete, perifoveal white to orange spots of 100 – 200 µm at the level of RPE or deep outer retina during the acute phase. These spots fade away and are frequently missed but leave behind granular macular pigmentary change which is pathognomonic. CNV may rarely develop. FFA shows early punctate hyperfluorescence and disc capillary leakage and late punctate staining (Fig. 7A), characteristically in a wreath like pattern. ICVA shows typical multiple hypofluorescent spots throughout the fundus that are more numerous than those seen clinically or FFA (Fig. 7B). FAF shows hypofluorescent spots in greater number than clinically seen. OCT shows dome shaped reflective lesions corresponding to the clinical white dot at the level of the photoreceptors which ultimately disappears. ERG reveals profoundly decreased ‘a’ wave amplitude and early receptor potential amplitude in the acute phase of the illness which indicates widespread photoreceptor dysfunction and these return to normal in the recovery phase. The recovery without any residual scarring occurs in 2 -10 weeks without treatment. Residual blind spot enlargement disproportionate to clinical findings would be persistent. Recurrences are uncommon.

Fig. 7: Multiple Evanescent White Dot Syndrome (MEWDS)

PUNCTATE INNER CHORIOIDOPATHY (PIC):

Punctate inner choroidopathy is a bilateral idiopathic inflammatory disease of the choroid affecting young healthy myopic women. It was described by Watzke et al in 1984 in association with Epstein-Barr virus and with HLA-DR2 positivity. Patients present with blurred vision, photopsias or paracentral scotomas. Funduscopy reveals bilateral, multiple, small, well defined, yellow-white lesions of 100-200 µm in size in the posterior pole. The lack of inflammation is the hallmark of PIC. Cells and flare in the anterior chamber and vitreous cavity are typically absent. Serious retinal detachment may occur overlying an active lesion. These lesions heal with punched out scars and a depigmented halo.

FFA of acute lesions reveal early focal hyperfluorescence which does not increase in size and late staining. CNV shows late leakage. Healed stage will reveal window defects. FFA shows more lesions than seen clinically. ICG shows numerous hypofluorescent spots in the middle and late phases. ICG reveals even more lesions than FFA. OCT shows CNVM & CME if present. FAF resembles MCP but limited in posterior pole. Recurrences are common and visual prognosis is guarded.

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Treatment is aimed at controlling the inflammation in the active stage. Systemic steroids are used in the active stage of the disease. Immunosuppressants are used if the patient is not tolerant to steroids or if recurrences occur. CNV occurs in 40-75% of patients. Extra-foveal CNV is treated with diode laser, PDT, or anti-VEGF injections in combination with oral steroids. No treatment is required if the lesions are not sight threatening. Submacular tranlocation surgery had been tried like in some sub-macular diseases but recurrence of CNV has been reported.

**Fig. 8: Punctate Inner Choroidopathy (PIC)**

Multiple, small, well defined, yellow-white lesions in the posterior pole (A) with early focal hyperfluorescence in FFA (B) in 2 cases of PIC

**MULTIFOCAL CHOROIDITIS AND PANuveitis (MCP):**

Multifocal choroiditis and panuveitis is an idiopathic inflammatory chronic, bilateral, asymmetric disorder of choroid and retina with delayed development in the fellow eye. It typically affects myopic middle aged women between second to sixth decade of life with photopsia and decreased vision and poor prognosis. Though it is a panuveitis, it is classified as WDS due to its characteristic appearance. The cause of MCP is unknown. It has been hypothesized that an exogenous pathogen may sensitize an individual to antigens within the photoreceptors, retinal pigment epithelium or choroid. Subsequent exacerbations may occur without an inciting pathogen. A viral etiology involving herpes simplex and Epstein-Barr virus has been postulated but not proved. MCP simulates presumed ocular histoplasmosis syndrome but the difference is the active inflammation in the anterior chamber and the presence of vitritis. Acute MCP lesions are characterised by yellow-white lesions involving the choroid and outer retina in the posterior and peripheral regions which progresses to punched out chorio-retinal scars with pigmented borders measuring 50-100µm in size. It can mimic PIC, but the lesions are not confined to the posterior pole alone. Patients with multifocal choroiditis can progress to develop CME, CNV, ERM formation and sub-retinal fibrosis. Diffuse subretinal fibrosis (DSF) is characterized by a coalescence of lesions and broad zones of subretinal fibrosis.

**ACUTE ZONAL OCCULT OUTER RETINOPATHY (AZOOR):**

AZOOR is a syndrome consisting of one or more zones of outer retinal dysfunction that occurs in young to middle age aged patients and progresses to develop retinal cell death. Two pathogenic mechanisms; first - common genetic hypothesis of autoimmune/inflammatory diseases (Jampol’s hypothesis) and second - primary infection of retinal photoreceptors (Gass’ hypothesis) have been proposed but none has been proven. Patients are typically young myopic women presenting with acute visual field loss and photopsias in one or both eyes. The photopsias in AZOOR can be very distinctive with patients describing them as movement of colours or lights within the area of visual field loss. Patients typically have an apparently normal fundus on initial examination, making the diagnosis very difficult. There may be mild vitritis with moderate diminution of vision. It starts as a unilateral disease which eventually progresses to be bilateral. FFA may be entirely normal in the early phase of the disease, showing only a prolonged retinal circulation time. As the disease progresses, diffuse areas of RPE changes ensues causing hyperfluorescence or salt & pepper or granularity or patchy
hyper-hypofluorescence and window defects corresponding to the zones of RPE dearrangement. FAF is useful in the follow up of the patients. It shows areas of central hypoautofluorescence corresponding to areas of chorioretinal atrophy with peripheral hyperautofluorescence seen at the border of an expanding lesion due to the presence of lipofuscin-laden cells that predicts RPE cell death. OCT shows an irregularity of the inner-outer segment (ISOS junction) photoreceptor line in the areas of retinal involvement. The outer retinal dysfunction can be documented by visual fields which shows large, superior, temporal and occasionally central zones of visual field loss. The scotomas often increase in size within a few days to weeks and then stabilize. ERG will be abnormal not only at the photoreceptor-RPE complex but also at the inner retina level. Typically a delayed 30 HZ flicker ERG and a reduction in the EOG has been the classic symptomatology and helpful in the diagnosis of the disease avoiding extensive neurological evaluation. Recurrences are common in one third of the patients. Visual field abnormalities typically stabilizes in three fourth of the patients and partially improve in 25%. It is unclear whether treatment with systemic steroids or immunomodulators alters the disease course or visual outcome. The other WDS diseases like MEWDS, MCP, OHS, PIC, acute macular neuroretinopathy and acute idiopathic blind spot enlargement syndrome are often grouped under AZOOR complex of diseases due to similar clinical pictures.

**Fig. 9: Acute Zonal Occult Outer Retinopathy (AZOOR)**

**Legend:**
A: Fundus picture showing an area of altered reflex at the posterior pole
B: Fundus autofluorescence demonstrating gradually increasing area of hyperautofluorescence from the fovea to the margin of the lesion

**NON WHITE DOT SYNDROME LIKE MIMICKING LESIONS:**
Some of the non-white dot like lesions may also mimic white-dot syndromes. Examples include like sarcoidosis (Fig. 10) and military tuberculosis (Fig. 11) of the choroid. Systemic features and ancillary investigations usually help to rule out these conditions.

**Fig. 10: Healed sarcoid nodule of the choroid**

**Legend:**
A. Fundus photograph showing multiple cream coloured round to oval lesions in a case of protean sarcoidosis.
B. Fundus fluorescent angiography and Indocyanine green angiography showing hypofluorescent lesions corresponding to fundus lesions

**Fig. 11: Miliary tuberculosis of the choroid**

**Legend:**
Fundus photograph showing multiple military tubercles in the choroid in a case of military tuberculosis of the lung.
Conclusion:
The white dot syndromes are a distinctive group of disorders affecting the retina, retinal pigment epithelium, and choroid. They present significant diagnostic and therapeutic challenges to the clinician. Careful observation of signs, documentation of findings, long follow-up of cases and appropriate treatment of reactivation with steroids and immunosuppressives are needed for successful management of a white dot cases.

References:
Intravitreal Injections For Managing Retinal Inflammation And Infections

Dr. Padmamalini Mahendradas, Dr. Arpitha Pereira, Dr. Bhujang K Shetty
Narayana Nethralaya, Bengaluru, India

Introduction

Intravitreal drug delivery refers to injection of the drug directly into the vitreous cavity. In doing so, it bypasses the systemic metabolism, thus increasing the drug bioavailability within the eye and also avoids the systemic adverse effects of the drug. Intravitreal injections are commonly used to treat retinal inflammations and infections.

Retinal inflammation can present as retinitis, retinochoroiditis or choroiditis. Retinal infections can be caused by a wide range of organisms such as bacteria, fungi, viruses and even parasites. (Table 1)

Technique of intravitreal injections

Intravitreal drug injections as a procedure involves not only the actual drug implantation into the vitreous cavity but also involves thorough counselling of the patient giving them a clear idea regarding the visual prognosis post the injection. One should proceed with the intended drug injection only after obtaining an informed consent from the patient.

Post preliminary tests and counselling for intravitreal injections the actual injection delivery is carried out in the operating room. After thorough hand scrubbing and using sterile gloves, intravitreal injections are prepared according to their individual defined protocols under strict aseptic conditions.

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**INTERAVITREAL DRUGS IN INFECTIONS AND INFLAMMATION**

**INFECTIONS**
- Anti Bacterial: Vancomycin, Amikacin, Cefazidime, Moxifloxacin, Piperacillin, Tazobactrum
- Anti Viral: Ganciclovir, Foscarnet, Cidofovir
- Anti Fungal: Amphotericin B, Voriconazole
- Anti Parasites: Clindamycin

**INFLAMMATION**
- Cortico Steroids: Dexamethasone, Triamcinolone, Acetonide
- Immunosuppressive Drugs: Methotrexate, Sirolimus
- Biologicals: Adalimumab, Infliximab
- Anti VEGF: Bevacizumab, Ranibizumab, Afibercept
- NSAIDs: Ketorolac, Diclofenac
Topical anaesthetic (Proparacaine 0.5%) eye drops are instilled after crosschecking the patient information and the laterality of the eye. This is followed by painting the eye with povidone iodine and drapping. Lid speculum is applied. The area intended as the injection site is measured from the limbus using callipers. The distance from the limbus depends on the phakic status of the eye and marking of the site on the sclera needs to be meticulous to avoid complications like lens touch. Using a 30G needle directed towards the mid-vitreous cavity, pars plana is penetrated (Figure 1 & Table 2) and the required amount of drug is injected from a 1 ml drug loaded tuberculin syringe. The needle is then withdrawn and a cotton tip applicator is applied to the injection site. In case of intraocular pressure being high after drug delivery into the vitreous cavity, anterior chamber paracentesis may be needed.

Preparation of commonly used Intravitreal drugs

For preparing the right formulation of drugs for intravitreal injections, one must follow a few common guidelines. It is always recommended that the drug must be prepared by the surgeon himself/herself under aseptic conditions using sterile gloves. As the preparation requires precise quantisation of the drugs, it is advisable to have a reference chart of the drug formulation within easy access of the surgeon. Injections are prepared using 1 ml tuberculin syringe with detachable needles.

A.) ANTIBIOTICS

1.) Vancomycin 1mg/0.1ml
   The drug is available as a powder in strength of 500 mg. 10ml of 0.9 % NaCl is added to 500mg of Vancomycin. Then 2ml of this solution is added to 8ml of 0.9% NaCl solution. Now, 0.1ml of the resultant solution, which has a concentration of 1mg/0.1ml, is used.

2.) Ceftazidime 2.25mg/0.1ml
   First 10ml of 0.9 % NaCl is added to 500mg of Ceftazidime powder. Then, 1.2 ml of the saline is added to the resultant solution. Take 1 ml of this solution is added to. Now 0.1 ml of the solution having a concentration of 2.25mg/0.1ml is used for injection.

3.) Amikacin 0.125mg/0.1ml
   The drug is available in strength of 100mg in a 2ml vial. Just 0.08 ml of the solution (4 mg) is taken into a Tuberculin syringe and then made up to 1 ml by adding sterile saline or water for injection into the syringe. So now we have 4 mg in 1 ml and so 0.1 ml will be having 0.4 mg, which is the required dose.

4.) Moxifloxacin 200 μg /0.05ml
   To prepare a concentration of 200 μg/0.05ml of moxifloxacin, 0.05 ml of 0.5% moxifloxacin (preservative free) is directly taken from topical preparations under sterile condition

5.) Imipenem 50–100 μg / 0.05 ml
   Its available in powder form with 250 mg in a vial. To this vial 100 ml of distilled water is added. Now 0.2 ml of this solution is taken and diluted with 0.3 ml of sterile water. For injection purpose, 0.05 ml of the solution is used.
6.) Piperacillin/Tazobactam  225 μg /0.1ml
   It begins with adding 10ml of distilled water to 2.25g of Piperacillin-tazobactum powder. This is followed by adding 0.9ml of saline to 0.1 ml of the solution. Now 0.9 ml distilled water is added to 0.1 ml of the solution. For injection, 0.1 ml of the resultant solution is used.

B.) ANTIFUNGALS
1.) Amphotericin B  0.005mg/0.1ml
   A 50mg vial of amphotericin B is reconstituted with 10 ml of 5% dextrose. Then 0.1ml of this solution is withdrawn and diluted with 9.9 ml of 5% Dextrose. Now concentration is 500 µg in 10 ml (50 µg /ml) which can be used for injection.

2.) Voriconazole 0.01mg/0.1ml
   First 3 ml of water is added to 30 mg of Voriconazole. Then, 0.1ml of the solution which has a concentration of 0.01mg or 1µg/0.1ml is used.

C.) ANTIVIRALS
1.) Ganciclovir 2000µg /0.1ml
   The drug is available in 500 mg vial to which 10 ml of sterile water is added. Then 0.4 ml of the solution is added to 0.6 ml of water. For injection, 0.1 ml of the final solution is used.

2.) Foscarnet 2.4 mg/0.1 ml.
   Take 0.1ml of the drug (2.4mg/ml vial) and inject.

D.) ANTIParasitic
1.) Clindamycin 1mg /0.1ml
   The drug is available in 600 mg /4ml ampoule. 0.2ml of it is withdrawn to which 2.8ml of sterile water is added. 0.1 ml of this solution is used.

E.) CORTICOSTEROIDS
1.) Dexamethasone 0.4mg/0.1ml
   Take 0.1ml solution (0.4mg/0.1ml) from Dexamethasone vial having drug concentration of 4mg/ml

2.) Triamcinolone acetonide: 4mg /0.1ml
   Take 0.1ml solution (4mg in 0.1ml) from Triamcinolone acetonide vial having drug concentration of 40mg/ml.

F.) OTHERS
1.) Methotrexate 400 microgram in 0.1ml
   First 4.2 ml of 0.9% NaCl is added to 0.8 ml of the drug (25mg/ml vial) and then 0.1 ml of the drug (400 µg in 0.1 ml) is used for the injection.

DISCUSSION
Intravitreal Antibiotics
Intravitreal antibiotics are the mainstay of treatment in the management of infectious endophthalmitis. Various antibiotics have been used for the same. The details have been summarised in Table 3.

For post-operative endophthalmitis, usually a combination of two antibiotics are given intravitreally, one for staphylococcus, most common organism causing bacterial endophthalmitis and other for gram negative bacilli. A commonly used intravitreal antibiotic drug combination is of vancomycin (1mg/0.1ml) and Ceftazidime (2.25mg/0.1ml). Though amikacin can be used in place of ceftazidime, however it poses a higher risk of macular toxicity.

Figure 2
A 63 year old male presented with the complaints of pain and decreased vision in the left eye

2a&2b anterior segment photographs showing the presence of cells in the anterior chamber and exudates in the anterior vitreous cavity

2C: B scan ultrasound showed low to medium reflective echoes in the vitreous cavity with thickening of the choroid in the left eye
## Table 3: Commonly used Intravitreal antibiotics and their spectrum of action (1)

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Drug</th>
<th>Recommended dose (microg/0.1 ml)</th>
<th>Half-life (h) in vitreous</th>
<th>Frequency of repeat injections (h)</th>
<th>Susceptible microorganisms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-inflamed phakic eyes</td>
<td>Inflamed eyes</td>
<td>Aphakic vitrectomy</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Amikacin</td>
<td>400</td>
<td>NA</td>
<td>NA</td>
<td>24 to 48 Aerobic GNBs, Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>2</td>
<td>Ampicillin</td>
<td>5,000</td>
<td>NA</td>
<td>NA</td>
<td>48 GPC, enterobacteria, therapeutic option for infections caused by MDR pathogens</td>
</tr>
<tr>
<td>3</td>
<td>Cephazolin</td>
<td>2,250</td>
<td>6.5 h</td>
<td>10.5 h</td>
<td>24 GPC, GPB, E. coli, Proteus, H. influenza</td>
</tr>
<tr>
<td>4</td>
<td>Ceftazidime</td>
<td>2,250</td>
<td>NA</td>
<td>NA</td>
<td>48 to 72 Aerobic GNBs, GPBs including Pseudomonas</td>
</tr>
<tr>
<td>5</td>
<td>Cefuroxime</td>
<td>1,000</td>
<td>NA</td>
<td>NA</td>
<td>48 to 72 GPC, GPB, GNC, GNB including Pseudomonas aeruginosa, penicillinase-producing N.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ciprofloxacin</td>
<td>100</td>
<td>3.5 to 5.5 h</td>
<td>1.2 h</td>
<td>12 Broad-spectrum activity against aerobic Gram-positive and Gram-negative bacteria, Actinomycetes, Nocardia spp.</td>
</tr>
<tr>
<td>7</td>
<td>Clindamycin</td>
<td>1,000</td>
<td>40 h</td>
<td>NA</td>
<td>72 GPCs - staphylococci, pneumococci; GPBs - Bacillus; GNBs - Bacteroides, Fusobacterium;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>resistance - enterococci, Enterobacteriaceae, Clostridium, Toxoplasma gondii</td>
</tr>
<tr>
<td>8</td>
<td>Chloramphenicol</td>
<td>2,000</td>
<td>NA</td>
<td>NA</td>
<td>24 Gram-negative bacteria, Rickettsia, Borellia recurrentis; moderately active against</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gram-positive bacteria and Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>9</td>
<td>Gentamicin</td>
<td>200</td>
<td>40 to 60 h</td>
<td>20 to 40 h</td>
<td>&lt;40 h 72 to 96 Aerobic GNBs</td>
</tr>
<tr>
<td>10</td>
<td>Imipenem</td>
<td>50 to 100</td>
<td>NA</td>
<td>NA</td>
<td>72 MDR GPB, GNBs including Pseudomonas aeruginosa, therapeutic option for infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>caused by MDR pathogens</td>
</tr>
<tr>
<td>11</td>
<td>Moxifloxacin</td>
<td>200</td>
<td>1.72 h</td>
<td>Prolonged</td>
<td>12 Broad-spectrum activity against Gram-positive and Gram-negative organisms</td>
</tr>
<tr>
<td>12</td>
<td>Penicillin</td>
<td>2 to 4,000 units</td>
<td>NA</td>
<td>NA</td>
<td>48 Broad-spectrum activity against Gram-positive organisms, Spirochaetes</td>
</tr>
<tr>
<td>13</td>
<td>Piperacillin/tazobactam</td>
<td>225</td>
<td>NA</td>
<td>NA</td>
<td>NA Effective GNBs, Staphylococcus epidermidis and Pseudomonas aeruginosa; therapeutic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>option for infections caused by MDR pathogens</td>
</tr>
<tr>
<td>14</td>
<td>Tobramycin</td>
<td>200 to 400</td>
<td>NA</td>
<td>NA</td>
<td>72 Aerobic Gram-negative organisms</td>
</tr>
<tr>
<td>15</td>
<td>Vancomycin</td>
<td>1,000</td>
<td>25.5 to 56 h</td>
<td>48 h</td>
<td>9.8 h 72 Active against GPCs - MRSA and MDR Staphylococcus epidermidis</td>
</tr>
<tr>
<td>16</td>
<td>Meropenem</td>
<td>0.5</td>
<td>2.6 h</td>
<td>NA</td>
<td>NA Pseudomonas, Bacteroides, Clostridia, Listeria, Enterobacteriaceae</td>
</tr>
</tbody>
</table>

Table 3: Commonly used Intravitreal antibiotics and their spectrum of action (1)

GPC, Gram-positive cocci; GPB, Gram-positive bacilli; GNB, Gram-negative bacilli, GNC, Gram-negative cocci; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*; NA, not available, h hours
ANTIFUNGALS

Amphotericin B (AMB)

AMB belongs to the family of polyene macrolide antibiotics and was the first broad-spectrum antifungal agent to be discovered. Isolated in the 1950s, AMB is produced by the actinomycete, Streptomyces nodosus. AMB acts by increasing cell permeability through the formation of pores or channels in the fungal cell membrane upon binding to ergosterol and by promoting oxidative action on cells, thus altering their metabolic functions. It also binds to cholesterol in human cells, which is the main reason for its side effects. For the treatment of fungal endophthalmitis, intravitreal injection of AMB is the therapy of choice.

The recommended dose ranges from 1 to 10 mcg/0.1ml and may be repeated weekly. In vitrectomised patients, the dosing regimen should be reduced to every 3 or 4 days. Clinical and experimental studies demonstrate the safety and efficacy of this route of administration; however, there are reports of toxicity and retinal necrosis, which are probably dose dependent. It is the first choice in the treatment of fungal endophthalmitis caused by yeasts or filamentous fungi.

Voriconazole

Voriconazole, a triazole acts by inhibiting P450 enzymes thus blocking the synthesis of ergosterol in the fungal plasma membrane. It has broad spectrum activity against moulds and yeast. Commonly, intravitreal doses ranging from 50-200 μg/0.1ml repeated every 48 hours have been used to treat fungal endophthalmitis. Intravitreal voriconazole has been found to cause small foci of retinal necrosis in animal studies. We have reported the use of intravitreal voriconazole in the management of retinochoroidal granuloma due to fungal infection.

Figure 4

A 58 years female has retinochoroiditis in the left eye following IV infusion
Vila Arteaga J et al., in their case study had a significant and rapid improvement in patient treated with single dose of injection intravitreal voriconazole (100 μg/0.1 ml) for aspergillus chorioretinitis, obviating the need for vitrectomy.

Echinocandins are semisynthetic lipopeptides that inhibit the synthesis of glucan in the fungal cell wall through non-competitive inhibition of the enzyme 1,3-β-glucan synthase, causing osmotic imbalance and cell lysis. This class of drugs includes caspofungin and micafungin. (10,11). Caspofungin exerts its fungicidal effect against spp. in a concentration-dependent manner over a broad concentration range in vivo. A few case reports have described the use of intravitreal caspofungin. Intravitreal injections of 50 μg/0.1 ml caspofungin repeated at 48-h intervals has been used in a cases of fungal endophthalmitis (12,13). Studies in rabbit eyes have shown it to be non-toxic to the retina. (14)

**GCV inhibits viral replication mainly through two mechanisms: a) GCV triphosphate inhibits viral DNA polymerase, thereby halting the formation of deoxyguanosine triphosphate, and hence the replication of virus. b) The drug also can directly combine with DNA chains and prevents further viral replication.** (15)

**Foscarnet**

Foscarnet interferes with the exchange of pyrophosphate from deoxynucleoside triphosphate by binding to a site on the herpesvirus DNA polymerase or HIV reverse transcriptase enzymes, thus inhibiting viral replication. It needs to be administered twice a week at a dose of 2.4 mg/0.1 mL (shorter half- life) for 3 weeks. Maintenance doses of the same are administered once a week. It has been found to be useful in CMV retinitis resistant to ganciclovir (22,24). For the injection, the commercial preparation of foscarnet for intravenous infusion is used directly because it is already diluted to the appropriate concentration for intraocular injection (2.4 mg/0.1 mL). It has also been used successfully in the treatment of acute retinal necrosis (25,26). Combinations of high-dose intravitreal ganciclovir (3.0 mg twice a week) and foscarnet (2.4 mg twice a week) may be effective in patients who fail to respond or are intolerant to conventional therapy. (23)

**Fomivirsen**

Fomivirsen inhibits cytomegalovirus replication by means of inducing an antisense mutationin the viral genome. It binds to the target mRNA and inhibits IE2 protein synthesis, which further inhibits virus replication. It has been studied for intravitreal use in patients with CMV retinitis, especially in situations where conventional therapy is contraindicated. However, the drug has been withdrawn from the market. (27)
Cidofovir

The long half-life and potent anti-CMV activity of Cidofovir make it an attractive drug for intravitreal injection. But many studies report encouraging results without much serious adverse effects with 10 to 15 microgram injections. But many studies report encouraging results without much serious adverse effects with 10 to 15 microgram injections. Cidofovir causes uveitis and hypotony. (28)

Antiparasitic

Clindamycin

Clindamycin works primarily by binding to the 50s ribosomal subunit of bacteria and disrupting the organism’s protein synthesis. Intravitreal Clindamycin (1 mg/0.1 mL) has been used to treat toxoplasmic chorioretinitis where there was intolerance to the systemic medications or disease progression despite systemic antimicrobial treatments. Treatment with a single injection was associated with resolution of vitreous inflammation within six weeks. (28)

Lasave et al. have reported functional and anatomical improvement in 12 patients (eyes) with posterior pole or zone one toxoplasmic chorioretinitis treated weekly or every four weeks (in pregnancy) with intravitreal clindamycin (1.5 mg/0.1 mL) and dexamethasone (0.4 mg/0.1 mL). Patients were controlled for 24 months. (29)

In Brazil, Zamora et al. recently reported resolution of toxoplasmic retinochoroiditis with intravitreal injection of clindamycin and dexamethasone in 16 patients. Choudhury et al. described the use of intravitreal trimethoprim/sulfamethoxazole for treating toxoplasma retinochoroiditis in four patients with no evidence of retinal toxicity. (30)

Sulfamethoxazole/trimethoprim

Intravitreal trimethoprim and sulfamethoxazole with dexamethasone has been used as an alternative treatment for recurrent ocular focal toxoplastic retinochoroiditis.

The formulation used was the commercially available intravenous suspension (400 mg of sulfamethoxazole and 80 mg of trimethoprim) that was fractionated into separate vials containing 0.1 mL of 8 mg sulfamethoxazole and 1.6 mg of trimethoprim. A 0.1 mL solution containing 400 mg of preservative-free dexamethasone was prepared for each injection. (31)

Intravitreal Corticosteroids

Uveitic cystoid macular edema (CME), posterior uveitis, retinal vascular occlusion and uveitis are the ocular pathologies where intravitreal corticosteroids are frequently used due to their well-documented antiangiogenic, anti-oedematous and anti-inflammatory properties.

Currently, there are various methods to deliver corticosteroids to the vitreous cavity and retina: intravitreal triamcinolone acetonide (IVTA) and dexamethasone as well as intraocular drug implants: 0.7 mg dexamethasone implant (Ozurdex®; Allergan Inc., Irvine, CA, USA), 0.59 mg flucinoloneacetonide implant (FAi) (Retisert®; Bausch & Lomb Inc., Rochester, NY, USA), and 0.019 mg FAi (ILUVIEN®; Alimera Sciences Limited, Aldershot, UK). These implants help to provide prolonged

Figure 5

A 51 yrs /F floaters in OS. BCVA in OD is 6/6 and OS is 6/18 with normal IOP. She is a known case of Psoriasis.

Figure 5A: Montage colour fundus photograph of the left eye revealed active retinitis adjacent to the area of chorioretinal scar in a case of toxoplasmosis.

Figure 5 B SDOCT revealed the presence of posterior vitreous cells, vitreous membrane hyperreflective in the retinal layer corresponding to the area of retinitis with increased choroidal thickness with hyperreflectivity with after shadowing in the area of chorioretinal scar.

Figure 5C. Following treatment with intravitreal clindamycin and dexamethasone there is healing of the retinochoroiditis lesion in the left eye with disappearance of posterior vitreous cells with decreased choroidal thickness.
treatment with controlled drug release, thus proving to be a rather efficacious drug delivery system.

**Intravitreal triamcinolone acetonide (IVTA)**

IVTA is able to effectively deliver corticosteroids to the vitreous and retina while avoiding the side effects associated with systemic therapy. In a retrospective noncomparative interventional case series of 65 eyes, Kok et al reported the effects of 4 mg/0.1 ml IVTA on uveitic CME in the short term. It was found that best-corrected visual acuity (BCVA) improved at a mean of 4 weeks with the improvement being greater in younger patients as well as in those who had CME for a shorter period of time. The main adverse ocular event observed was raised IOP. (33)

Tuncer et al also performed a retrospective case series of 18 eyes with panuveitis secondary to Behçet’s disease, which did not respond or were intolerant to systemic medications. The authors reported that there was an increase in mean BCVA following the injection. Resolution of intraocular inflammation was also achieved after a mean of 25.4 days. Retinitis, vasculitis, as well as macular edema were resolved at the end of 1 month. However, recurrence of uveitis occurred at a period of 10–18 months. Ocular adverse events of cataracts and raised IOP were also observed as in previous studies (34)

Therefore, IVTA can be useful in NIU where patients are intolerant or nonresponsive to systemic medications and is also advisable in unilateral disease. Typically in bilateral patients, systemic immunosuppression is considered by most uveitis specialists.

**Dexamethasone**

Dexamethasone intravitreal injection has been used in the dose of 0.4mg/0.1ml along with intravitreal antibiotics in the treatment of endophthalmitis. It has a short half-life of 3.48 hours so its use in the treatment of non-infectious uveitis has been taken over by dexamethasone implant (Ozurdex)

**Flucinolone Acetonide (FAI)- Retisert**

The 0.59 mg FAI (Retisert®; Bausch & Lomb Inc.) is an FDA-approved nonbiodegradable implant that is designed to maintain a sustained release of drug for 30 months. The Multicenter Uveitis Steroid Treatment (MUST) trial is the largest randomized comparative trial to date regarding the efficacy, safety, and impact on quality of life of the FAI in comparison with systemic immunosuppression. About 479 uveitic eyes of 255 patients were observed over a period of 24 months. Vision-related quality of life was superior in patients with FAI at 6 months, but this advantage narrowed by the end of 24 months with minimal difference between the two. Intraocular inflammation control was also achieved in most eyes by 9 months in each intervention. However, the implant achieved better control compared with the systemic immunosuppression. Regarding adverse effects, patients treated with the implant were four times more likely to have an increased IOP, absolute IOP of >35 mmHg and increased need for medications and surgery to lower the IOP while 17% of eyes developed glaucoma. Cataract developed in almost all the phakic eyes at the end of 24 months. (35)

It is found that FAI does not seem to confer a substantial advantage in the improvement of BCVA but is advantageous in intraocular inflammation control. The use of the implant also allows for reduction in systemic medications. However, in patients with bilateral disease, the cost of bilateral FAI was greater than that of systemic corticosteroids. (36) Therefore, given that the FAI has minimal advantage in visual outcomes and avoidance of systemic side effects from systemic corticosteroids, with additional ocular adverse events such as raised IOP and cataract development coupled with increased cost for bilateral disease, alternate forms of treatment such as newer implants or systemic agents may be preferable as a first-line treatment in patients with bilateral non infectious uveitis (NIU)

**Dexamethasone implant**

The 0.7 mg dexamethasone implant (Ozurdex®; Allergan Inc) is an FDA-approved biodegradable dexamethasone implant. The implantation of the dexamethasone implant can be performed as an outpatient procedure, and it maintains sustained release for up to 6 months

**Figure 6**

A 36 yrs male is a case of right eye retinal vasculitis with aortic valve stenosis

6A Wide field colour fundus photograph of the right eyes showing intravitreal dexamethasone implant in a case of idiopathic retinal vasculitis.

The HURON trial, a multicenter randomized controlled trial reported by Lowder et al evaluated the effect of 0.7 mg dexamethasone implant in 77 eyes over a period of 26 weeks in improving Vitreous haze (VH) as the primary outcome. There was a statistically significant improvement in BCVA in eyes implanted with 0.7 mg dexamethasone compared with the controls. The implant also proved its ability to control ocular inflammation as 47% of eyes achieved a vitreous haze
A 36 year male is a case of bilateral multifocal serpiginoid choroiditis due to probable ocular inflammatory CNVM in the left eye. In a retrospective case series of 18 eyes, the effect of 0.7 mg dexamethasone implant on persistent uveitic CME was studied. There was improvements in BCVA with a complete resolution of CME at 1 month. However, CME recurred at a median time interval of 201 days. Adverse events noted in the study included an increase in IOP in 11% of eye. Similar outcomes were observed in study by Lam et al and Ratra et al.

Agarwal et al studied the role of dexamethasone implant in management of Tubercular uveitis in a retrospective analysis of 19 eyes. They concluded that intravitreal dexamethasone implant was safe and efficacious as an adjunct to ATT in reducing the central macular thickness, vitritis, and progression of choroiditis lesions in paradoxical worsening of multifocal serpiginous choroiditis.

The FAI and dexamethasone implants both show relatively similar efficacy with regard to their effect on BCVA and inflammation control. Recurrence rates seem to be higher in the FAI group, but the difference have not shown to be statistically significant.

**Intravitreal Non steroidal anti inflammatory drugs (NSAIDS)**

**Ketorolac 4 mg/0.1ml**

It has been used in patients with chronic uveitis and has shown a good response. However, a limiting factor for this medication is its short half-life; therapeutic levels remain only for two days in the vitreous.

**Diclofenac 500 micrograms/0.1ml**

It has been used in the eyes of patients with refractory uveitis macular edema with no signs of ocular toxicity at 8 weeks follow up.

**Anti vascular endothelial growth factor (VEGF)**

VEGF is a major regulator of angiogenesis and vascular permeability and is strongly implicated in the development of uveitic macular edema of various origins. Most of the case series and small studies published on this topic describe its use as a second line agent. Choroidal neovascularization (CNV) is also a well-known complication of uveitis and various studies have evaluated the efficacy and safety of intravitreal anti-VEGF in the treatment of CNV secondary to uveitis.
Intravitreal bevacizumab has also been suggested as an effective supplementary therapy to topical bromfenac eyedrops. (47)

Rahimi et al compared 1.25 mg IVB and 4 mg IVTA on their effect on uveitic CME that was not responding to topical corticosteroids in an RCT. Both IVB and IVTA resulted in improvements in BCVA and CRT, however IVTA was significantly better than IVB in decreasing CRT. IVTA resulted in statistically significantly greater rise in IOP as opposed to IVB, which had minimal effect on IOP. (48)

Intravitreal Aflibercept has been evaluated in a pilot study of 15 eyes affected by CNV associated with chorioretinitis. Patients were treated with aflibercept (2mg/0.1mL) pro renata and observed over a 12-month follow-up period. They showed a positive clinical effect (improved BCVA, Reduced CRT) and the drug was well tolerated. (50)

As of now there are no studies comparing the clinical efficacy or safety of available antiangiogenic agents (bevacizumab, ranibizumab, and afibbercept) in uveitic macular edema.
**IMMUNOSUPPRESSIVE AGENTS**

**Methotrexate**

Methotrexate is an anti-metabolite that is commonly used for the treatment of rheumatoid arthritis and cancer. Intravitreal methotrexate was first introduced for the treatment of intraocular lymphoma. Currently, intravitreal injection of methotrexate has been used to treat uveitis.

In the pilot study of 15 eyes, Taylor et al reported that intravitreal methotrexate (400 micrograms/0.1 ml) resulted in an improvement in BCVA and ocular inflammation as well as CRT with significant effects seen within 1 week except in two patients. A relapse occurred in 30% of patients at a median time of 4 months necessitating a repeat injection which showed improvement within 2 months. There were no instances of raised IOP. Corneal epitheliopathy occurred in one pseudophakic patient while opacification of lens occurred in another patient (unrelated to the methotrexate injection). (51)

Furthermore, a study published by Bae and Lee confirmed the efficacy of intravitreal methotrexate in the treatment of refractory retinal vasculitis due to Behçet’s disease. (52)

**Sirolimus**

Sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation.

In a phase III, randomized, double-masked, active-controlled study, patients with active non-infectious uveitis (NIU) of the posterior segment were assigned intravitreal sirolimus 1:1:1 at doses of 44 (active control), 440, or 880 µg, administered on days 1, 60, and 120. Intravitreal sirolimus 440 µg demonstrated a significant improvement in ocular inflammation with preservation of BCVA in subjects with active NIU of the posterior segment. (53)

As of now there are no studies comparing the clinical efficacy or safety of available antiangiogenic agents (bevacizumab, ranibizumab, and aflibercept) in uveitic macular edema.

**IBIOLOGICS**

**Infliximab**

Infliximab, an anti-tumor necrosis factor agent, is a chimeric monoclonal antibody usually used systemically for the treatment of autoimmune diseases.

Farvardin et al, treated 10 eyes of 7 patients with chronic persistent non-infectious uveitis who were unresponsive to conventional medications. The patients were administered intravitreal injection of 1.5 mg/0.15 mL infliximab and followed up for 6 months. The study showed that while intravitreal infliximab improved the visual acuity and decreased the central macular thickness, its effect is only temporary. (54)

Use of single intravitreal injection of infliximab (1 mg/0.05 mL) for sight-threatening relapsing uveitis in Behçet disease has also provided good results (55).

Wu et al reported a case series of 7 patients with refractory CME post cataract surgery treated with intravitreal infliximab. By 6 months of follow-up, the visual acuity of these patients improved and the macular thickness was reduced (56). However, Gigant demonstrated that low-dose (0.5 mg/0.5 mL) intravitreal infliximab was not well tolerated and was both immunogenic and probably retinotoxic (57).

Adalimumab binds to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. It has been studied for the treatment of 13 eyes with active NIU where in patients were injected with adalimumab at 0, 2, then every 4 weeks for total of 26 weeks. IVA was effective in controlling the inflammation, decreasing the macular edema, and improving the best corrected visual acuity in the majority of eyes in this series (58).

**Conclusion**

Early diagnosis and early intervention with appropriate intravitreal drugs in a sterile environment can achieve good control of retinal inflammation and infections.

**References:**


48. Rahimi M, Shahrzad SS, Banifatemi M. Comparison of intravitreal injection of bevacizumab and triamcinolone


**Corresponding Author:**

**Dr. Padmamalini Mahendradas**

Head, Uveitis and Ocular Immunology

Narayana Nethralaya

121/c, Chord Road

Rajaji Nagar 1st R Block

Bengaluru 10

560010

Email: m.padmamalini@gmail.com
Abstract
Intravitreal injections have been described in eyes with retinoblastoma, intraocular lymphoma, intraocular metastasis, radiation side effects, and neovascular glaucoma secondary to intraocular tumors. Intravitreal chemotherapy for intraocular tumors provides enhanced local effect and minimal systemic adverse effects. The indications, chemotherapeutic agents used and the side effects associated with these agents have been described in this chapter.

Introduction
Different routes of drug delivery have been employed for the treatment of intraocular tumors and their complications. A specific dose provides an optimal concentration of the drug in the vitreous cavity to achieve maximal tumoricidal activity with limited systemic toxicity.

Indications
Retinoblastoma- Vitreous seeds
Intraocular lymphoma(disease limited to the eye)
Intraocular metastasis
Choroidal neovascular membrane associated with tumors
NVI/NVG due to intraocular tumors/radiation
Others: Tumor associated macular edema, Radiation retinopathy, radiation maculopathy, radiation papillopathy.

Retinoblastoma
Vitreous seeds are resistant to treatment with systemic chemotherapy and hence are a poor prognostic factor. Intravitreal chemotherapy has emerged as a new successful treatment option for the management of vitreous seeds. It was initially described in 1960s with the use of Thiotepa and Methotrexate. In 1987, Kaneko published his results of successful in vitro use of L-phenyl alanine mustard in treatment of retinoblastoma in comparison to methotrexate, doxorubicin, mitomycin, vincristine, 5-fluorouracil.

Intravitreal chemotherapy has been widely accepted due to the safety enhanced technique described by Munier et al, which involves anti-reflux measures such as utilizing small gauge needles and cryotherapy at the injection site. Intravitreal chemotherapy has not only improved ocular salvage rates but also resulted in visual optimization.

Currently, the main indications for intravitreal chemotherapy include the following:
1. Vitreous seeds non-respondent to systemic chemotherapy,
2. Recurring vitreous seeds post systemic chemotherapy

The chemotherapeutic agents commonly used in retinoblastoma are melphalan (20-40 µg) and topotecan (8-20 µg). Various studies by different authors have found intravitreal chemotherapy to be effective in treating vitreous seeds up to the rate of 90% (80 to 100%). With intravitreal chemotherapy, globe salvage rates as high as 68% have been achieved. However, higher doses are associated with higher toxicity rates. In our institute, we treat patients of recurrent/refractory retinoblastoma with intravitreal melphalan as monotherapy or in combination with topotecan.

It was earlier speculated that intravitreal injection in eyes with retinoblastoma leads to tumor spread, but there are no such instances reported till date. On the contrary, it has been proven experimentally that with proper technique of intravitreal injection, there is hardly any risk of spread of malignancy.
Vitreoretinal lymphoma (VRL)

Methotrexate (400µ), is commonly used intravitreal agent for primary vitreoretinal lymphoma. The frequency of injection can vary from biweekly to monthly, depending on the stage of the disease and response to treatment. The regimen described by Smith et al, involves twice-weekly intravitreal methotrexate injections given for 1 month during the induction phase, followed by a consolidation phase of weekly methotrexate injections given for 1 month. Subsequently, a maintenance phase involves monthly methotrexate injections for 1 year.

Rituximab (1mg/0.1ml) when delivered intravitreally has been shown to cross the retina effectively with lesser side effects. Methotrexate and Rituximab can be used as a combination therapy in the same sitting, or alternately. Intravitreal targeted delivery of chemotherapeutic agents in primary VRL avoids the risks and complications associated with radiation exposure.

Thiotepa also has been used successfully with Methotrexate in prolonging remission.

Anti-VEGF Agents

Angiogenesis is essential for the survival and growth of newly dividing cells. Proangiogenic factors like vascular endothelial growth factor (VEGFs) bring about vascular proliferation. Anti-VEGF agents inhibit this process resulting in tumor regression and reduce the risk for metastasis.

Anti-VEGF agents bevacizumab, ranibizumab have been used successfully for vascular regression in neovascular glaucoma secondary to primary intraocular malignancy and also in uveal metastasis. Encouraging results following treatment of secondaries of Multiple myeloma, bronchial carcinoma, breast carcinoma, renal cell carcinoma, nasopharyngeal carcinoma with anti-VEGF agents have been reported. In contrary, Maudgil et al has reported failure of metastatic tumors to respond to intravitreal bevacizumab in 4 out of 5 cases and hence do not recommend intravitreal bevacizumab as the primary therapy in choroidal metastasis.

Choroidal neovascular membranes complicating intraocular tumors like choroidal osteoma have been successfully treated with intravitreal anti-VEGF agents. Anti-VEGF agents have also been used in treating vasoproliferative tumors. Macular edema associated with benign tumors like Congenital simple hamartoma of the retinal pigment epithelium (RPE) have been treated with anti-VEGF agents. Anti-VEGF agents are also used for treatment of radiation related retinopathy and maculopathy. Finger et al have reported 14 cases of radiation optic neuropathy following plaque therapy for choroidal melanoma. Improvement in visual acuity, resolution of papillary hemorrhages and disc edema were noted in these cases following treatment with bevacizumab.

Intravitreal steroids- Intravitreal triamcinolone acetonide and dexamethasone implants have been successfully used to treat radiation macular edema after proton beam therapy.

Procedure

Using a 30/32 G needle mounted on a tuberculin syringe the drug with desired dosage is injected into the vitreous cavity at an age-appropriate distance from the limbus. The site for injection is chosen to be away from the site of tumor/ tumor seeds. On withdrawal of the needle, triple freeze thaw cryotherapy is applied to the needle site. The globe is then gently shaken to allow distribution of the drug within the vitreous cavity. Optionally, the procedure may involve creating a transient hypotony by anterior chamber paracentesis prior to injection, and copious irrigation of the eye following the injection.

Complications

A. Associated with the procedure: Lens touch, vitreous hemorrhage, retinal break, retinal detachment, endophthalmitis.

B. Associated with the drug:

1. Methotrexate: can cause corneal epitheliopathy and cataract. Rare complications include uveitis, vitreous
hemorrhage, sterile endophthalmitis, maculopathy. Oral folic acid supplementation has been recommended to reduce corneal epithelial toxic effects associated with methotrexate.

2. Melphalan: can cause cataract, iris atrophy, chorioretinal atrophy, vitreous and subretinal hemorrhage, hypotony, phthisis bulbi, salt-and-pepper retinopathy, retinal toxicity, blunted ERG response and rarely, retinal detachment. The complications were higher when higher dose of 50µg was used. Darkly pigmented eyes are suspected to suffer greater toxic damage. Toxicity resulting from intravitreal melphalan has been graded. Grade I being salt-and-pepper retinopathy no greater than 2 clock hours of peripheral retina anterior to or at the equator. Grade II as any retinopathy extending greater than 2 clock hours anteriorly or at the equator. In grade III, the retinopathy extends posterior to the equator but spares the macula. In grade IV, the retinopathy is complicated by a maculopathy and grade V is characterized by a pan-retinopathy with optic atrophy.

3. Thiotepa can cause cataract, retinal detachment, vitreous hemorrhage, atrophic bulbi. Carboplatin can cause eyelid erythema.

4. Topotecan can cause conjunctival congestion and eyelid chemosis.

In conclusion, several interesting advances in intravitreal drug delivery for the management of intraocular tumors and their side effects have enhanced the treatment outcomes and reduced the side-effects.

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**Corresponding author:**

Pukhraj Rishi, MS, FRCS, FRCS(Ed), Senior Consultant, Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, 18 College Road, Chennai-600006, Tamil Nadu, India.

Phone: 044-28271616 FAX:044-28254180 e-mail: docrishi@yahoo.co.in

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Eye; Tumor; Intravitreal injection; Chemotherapy; Retinoblastoma; Intraocular lymphoma.
Polypoidal Choroidal Vasculopathy (PCV), first described by Yannuzzi et al in 1982, is a distinct clinical entity characterized by persistent recurrent serous leakage and haemorrhage in the macula, and is seen in the elderly population. The disorder was poorly understood earlier and had been described by various authors as recurrent pigment epithelial detachment (PED) and posterior uveal bleeding syndrome. The primary abnormality, as described by Yannuzzi et al., involves the choroidal circulation, and the characteristic lesion is an inner choroidal vascular network of vessels ending in an aneurysmal bulge visible clinically as a reddish orange spheroidal polyp like structure. More recently with improvement in choroidal imaging using Enhanced Depth Imaging and Swept Source optical coherence tomography (EDI-OCT and SS-OCT), PCV is regarded as a part of the Pachychoroid spectrum of diseases and a variant of Type I choroidal neovascularization. Pathogenesis of PCV is not fully understood, but vascular endothelial growth factor (VEGF) may have a role. Experimental studies have found markedly elevated levels of VEGF concentrations in the aqueous of PCV eyes compared to controls. Treatment modalities for PCV include verteporfin photodynamic therapy (PDT), anti-VEGF therapy and thermal laser photocoagulation, either alone or as a combination of different modalities.

Currently, PDT is widely used in the treatment of PCV, as various studies have demonstrated that PDT can result in visual improvement. Photodynamic therapy (PDT) is associated with several disadvantages. First, PCV often presents as multiple widely distributed lesions, so it might be difficult to treat all lesions, including multiple polyps and interconnecting vessels, with a single beam of PDT. Treatment of leaking polypoidal dilations only, without treating the entire vascular complex can result in persistence or worsening of exudation. Second, it can be difficult to treat nodules in the peripapillary area with a round PDT beam. Third, features commonly associated with PCV such as a large pigment epithelium detachment or a large submacular hemorrhage are not usually amenable to PDT treatment. Fourth, PCV tends to recur repeatedly, so multiple PDT treatments are often necessary, which can increase the risk of long-term choroidal atrophy. Additionally, hemorrhagic complications after PDT have been reported in up to 30% of eyes, and repeated PDT results in significant choroidal hypoperfusion.

On histopathological evaluation, PCV demonstrates hyalinization of choroidal vessels, replacement of smooth muscle component with pseudocollagenous tissue along with massive exudation of fibrin and blood. Immunohistochemical studies have revealed CD68 positive cells along the hyalinised vessels, CD34 staining revealed discontinuity of endothelium and absence of smooth muscle actin positive cells. The vascular endothelial cells in PCV are negative for vascular endothelial growth factor (VEGF), which may explain the reason for poor response to anti-VEGF therapy. Tong et al compared the VEGF levels in eyes with PCV and Wet AMD and found that the aqueous levels of VEGF were significantly lower in PCV eyes as compared to Wet AMD eyes. With the introduction of anti-VEGF drugs in ophthalmology, intravitreal anti-VEGF agents were widely used for neovascular disease such as wet age related macular degeneration and PCV. As mentioned earlier, the exact role of VEGF in pathogenesis of PCV remains unclear. Nevertheless, various anti VEGF agents including ranibizumab, bevacizumab and aflibercept have shown to have clinically significant beneficial effects in eyes with PCV. Various studies have found that anti-VEGF monotherapy may reduce sub-retinal fluid and cause stabilization of vision in eyes with PCV. Following PDT, sprouting of new vessels has been demonstrated within 24 hours itself with significant upregulation of VEGF 6 hours post-PDT. Hence, administration of intravitreal anti-VEGF agent within 24 hours following PDT results in considerable inhibition of VEGF induced re-growth of abnormal vasculature.
The EVEREST study was the first randomized controlled trial comparing standard fluence photodynamic therapy (PDT) with or without three loading doses of ranibizumab 0.5 mg and ranibizumab monotherapy in polypoidal choroidal vasculopathy (PCV). The primary endpoint was the proportion of patients with complete regression of polyps at six months, as determined by indocyanine green angiography (ICGA). The study reported a higher polyp closure rate of PDT with or without ranibizumab compared to ranibizumab alone (77.8% and 71.4% vs. 28.6%). This study established the efficacy of PDT in the closure of polyps. One limitation of EVEREST study was the short follow-up period. To overcome this limitation, EVEREST II study was designed to assess 24-month outcome of ranibizumab 0.5 mg monotherapy and ranibizumab in combination PDT for macular PCV. The 12-month data reported better visual acuity gains in combined group (8.3 lines) versus ranibizumab monotherapy group (5.1 lines). Additionally, the polyp regression rate was 69.3% in combination arm whereas 34.7% in ranibizumab monotherapy arm.

To assess the effect of PDT versus anti-vascular endothelial growth factor (VEGF) in terms of visual outcome, the LAPTOP study, a multicenter randomized controlled trial was conducted. Ninety-three patients were randomized to two arms: standard fluence PDT monotherapy arm and a ranibizumab monotherapy arm where patients received three monthly injections of 0.5 mg ranibizumab. Additional treatment was performed as needed in each arm. At 12 months, the study found a higher proportion of patients gaining more than 0.2 logMAR units in the ranibizumab arm (30.4% vs. 17.0%). In addition, the mean gain in logMAR visual acuity was also greater in the ranibizumab arm at 12 and 24 months. These two trials showed that although PDT may be more effective at polyp closure than anti-VEGF, anti-VEGF therapy seemed to be better for improving or preventing visual loss in patients with PCV.

Recent literature of aflibercept suggest that the success rate may be much higher than reported with ranibizumab. The PLANET study was a non-inferiority trial comparing the effect of intravitreal aflibercept with rescue active PDT / rescue sham PDT in 333 eyes with PCV. At 52 weeks, there was no significant difference in visual outcomes in aflibercept monotherapy arm (10.7 letters) and when combined with PDT (10.8 letters). No active polyp was detected in 81.7% of monotherapy arm and 88.9% of combination arm. Additionally, polyp regression occurred in 38.9% of monotherapy patients and 44.8% of combination therapy patients respectively which was not significant. Given the excellent visual and anatomical outcomes, the PLANET study concluded that aflibercept monotherapy was non-inferior to combination therapy with PDT.

SaymanMuslubaş et al compared the one year outcome of PDT monotherapy and PDT in combination with bevacizumab (IVB). There was no significant difference in visual acuity outcomes and the polyp regression rate (66.7% in PDT monotherapy arm and 64% in combination therapy arm) at the end of one year. Majority of the other studies of IVB for PCV are limited by their short duration of follow-up.

There have been multiple studies evaluating the ranibizumab and bevacizumab monotherapy in PCV eyes and they reported temporary stabilization of vision and reduction in exudation. The effect on polypoidal lesions or choroidal vascular changes was limited. Subsequent studies with more patients and longer follow-up reported 17% to 40% of patients achieved 15 letters or more improvement in BCVA. Most of these studies used a regimen of monthly injections for 3 months, followed by PRN over 12 months (mean number of injections ranged from 4.2 to 6.1). Polypoidal lesion regression rate of up to 40% was reported at 12 months, although abnormal choroidal vascular complexes do not seem to be affected by anti-VEGF monotherapy.

PEARL 1 and PEARL 2 were the first studies to evaluate role of ranibizumab monotherapy (0.5 mg for 12 months in PEARL 1; 2.0 mg for 6 months in PEARL 2) in PCV. The percentage of patients gaining more than 15 letters was 23% and 26% respectively in PEARL 1 and PEARL 2 respectively. None of the patients lost 15 letters and more in both the studies. Reduction in size of polypoidal lesion size was noted in 38% and 79% in the PEARL 1 and PEARL 2 studies respectively. Aflibercept has an enhanced binding affinity to VEGF-A, VEGF-B and placental growth factor as compared to ranibizumab and bevacizumab. This facilitates increased response to sub-RPE lesions such as PCV. Inoue et al has shown a polyp regression rate of 75% at end of six months in sixteen eyes. Yamamoto et al evaluated one year outcomes of 90 eyes treated with monthly aflibercept for first three months followed by two monthly doses. They demonstrated statistically significant improvement in BCVA and reduction in central retinal thickness at 12 months from baseline (p < 0.001; p< 0.001). 71.1% eyes had dry macula and polyp regression was complete in 55.4% and partial in 32.5% of eyes. The EPIC study was a 6-month prospective trial of intravitreal aflibercept in 21 eyes with PCV. The study reported stabilization of vision with / without improvement in 91% of eyes with no eyes reporting a severe vision loss (≤ 15 letters). Additionally, aflibercept monotherapy was demonstrated to be beneficial in resolution of sub-retinal fluid (72%), sub-retinal haemorrhage (75%), polyp regression (67%) and improvement of PED (87%).

Off-label use of ziv-aflibercept has also been reported in PCV. The AURORA study evaluated the 12 month outcome of conbercept in management of PCV. They found a significant improvement in visual acuity, reduction in total lesion area with a polyp regression rate of 52.9 – 56.5%.
Very few studies have compared different anti-VEGF agents head-to-head for management of PCV. Bevacizumab monotherapy has shown similar results in polyp regression rates, BCVA improvement and central macular thickness reduction in comparison with ranibizumab monotherapy by Cho et al at six months. Saito et al exhibited additional polyp regression (50%), improved BCVA and reduction in central retinal thickness after switching to aflibercept in patients’ refractory to ranibizumab. Moon et al in a retrospective analysis of 32 cases reported efficacy of Afibercept for improvement and maintenance of BCVA for PCV refractory to ranibizumab. Marcus et al reported the efficacy of 2.0 mg/0.05 ml of ranibizumab in PCV without any increase in adverse effects. However, the evidence regarding effectiveness of these therapies remains limited. Further large scale prospective studies will be required before definite guidelines can be established in this regard.

Literature has shown a superior polyp regression rate with aflibercept as compared to ranibizumab. However, in the landmark PLANET study, the polyp regression rate was 38.9% with aflibercept which is much lower than other studies in literature, and comparable to 34.7% in the ranibizumab monotherapy arm of the EVEREST II study. However, direct comparison between EVEREST and PLANET studies is limited due to differences in study design. While in EVEREST study, PDT was given as baseline, in the PLANET study it was given as a rescue therapy. Thus, the polyp regression rate with aflibercept (38.9% - 75%) is comparatively higher as compared to ranibizumab (25% - 33%). Also, the mean number of injections were very similar in the monotherapy arms of the two landmark trials, i.e. 7.3 (EVEREST II, PRN after 3 initial monthly doses) and 8.1 (PLANET, fixed bimonthly dosing after 3 initial monthly doses) respectively.

Based on level 1 evidence, active PCV should be treated with full fluence PDT with three loading doses of anti-VEGF injections. Although PDT is highly efficacious for polyp closure and reduction in lesion size, simultaneous treatment with intravitreal anti-VEGF is imperative, as it has been well established to cause a significant visual acuity improvement. Additionally, there are particular specific indications for managing PCV with anti-VEGF monotherapy. These include PCV associated small sub-macular hemorrhage(<4DD) or thin sub-macular hemorrhage(<500 µm), polyp extent not clearly defined by ICG and peri-papillary PCV

Based on the current literature, therapy with either ranibizumab or aflibercept is associated with good visual acuity outcomes with an acceptable polyp regression rate and notable reduction in disease activity. The landmark trials have demonstrated similar mean number of injections for both these agents to achieve favourable outcomes. However, direct comparison of various agents across studies should be construed with caution in view of different study designs, baseline characteristics, dosing regimens and follow-up period. Prospective, long-term head-to-head comparative studies of various anti-VEGF agents is necessary to recommend the best possible therapeutic anti-VEGF agent for optimal outcomes in PCV management.
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Macular Edema is a non-specific response of the retinal tissue to insult, and is associated with a variety of conditions, including retinal vascular occlusion (RVO), posterior uveitis, diabetic retinopathy, and Macular degeneration.

Inflammation is a key component to the pathogenesis of Macular Edema, especially in RVO, Diabetic macular edema, uveitis and wet AMD.

In RVO there is sudden increase in venous intraluminal pressure that causes increased venous pressure, that induces dilatation, flow stasis and transudation of fluid/blood into the perivascular retina.

In case of Diabetic Retinopathy, the state of hyperglycaemia leads to accumulation of sorbitol, reactive oxygen species (ROS) and other products of glucose metabolism. This leads to Leukostasis, and adhesion of leukocytes to the vascular endothelium. There is endothelial and pericyte dysfunction, with apoptotic cell death and break down of the blood retina barrier. Due to this, there is transudation of fluid and tissue hypoxia, leading to increased expression of inflammatory proteins.

Cytokines like interleukins (IL-6, IL-8, IL-1b), Gamma interferons, TNF alpha are released. They augment the process of inflammation by various methods by their intrinsic pro angiogenic nature, increase in vascular permeability, regulation of immune response, collagen production and increased oxidative stress. This leads to further leakage of fluid, Macular Edema, central retinal Inflammation thickening and neovascularization.

Corticosteroids have anti-inflammatory action in the following ways:
1. They restrict the migration of leucocytes, and stabilize endothelial tight junctions
2. Reduce capillary permeability and cause vasoconstriction
3. Inhibits production of VEGF, prostaglandins, and pro inflammatory cytokines

Corticosteroids induce the production of lipocortin, which have a negative effect on the production of prostaglandins and leukotrienes which are responsible for inflammatory reaction.

They have a more rapid onset and more profound initial effect on Macular Edema than anti-VegF agents.

Hence, corticosteroids are a good option for the treatment of Macular Edema due to inflammation of non-infectious origin.

Desired characteristics of an implantable intra vitreal drug delivery system are:
1. Controlled, sustained drug release
2. Simple insertion procedure
3. Biodegradable implant (does not need to be removed), made of an inert, non-toxic substance.
4. Long-term safety
**Ozurdex (Allergan, Inc., Irvine, CA, USA)**

Introduced in June 2009 by Allergan Inc. It is available as a prolonged release, Intra Vitreal implant containing 700 micrograms of Dexamethasone as the active substance.

It is preloaded into a single-use applicator to facilitate injection of a rod-shaped implant (NOVADUR implant) of diameter 0.46 mm x 6 mm directly into the vitreous. Matrix of the implant is biodegradable, made of polylactide-co-glycolide (PLGAs) slowly degrading to lactic acid and glycolic acid through simple hydrolysis, then further degrades into carbon dioxide and water. It releases the drug through three methods: Surface release, diffusion and bulk erosion.

The implant is contained within its own specific applicator, located in the needle (made of stainless steel) of the disposable device. The applicator consists of a plunger (stainless steel) within a needle where the implant is held in place by a sleeve (made of silicone). The plunger is controlled by a lever on the side of the applicator body. The needle is protected by a cap and the lever by a safety tab. The applicator containing the implant is packaged in a sealed foil pouch containing desiccant for protection.

The implant is delivered in a controlled manner by depressing the actuator button with the index finger. The needle is subsequently withdrawn as the puncture site self-seals. To ensure that air is not introduced into the eye, the applicator has been designed to vent air through a small gap between the implant and the inner needle wall. This allows air to move back through and out of the needle as the implant is being delivered. The small size of this gap prevents fluid from flowing out of the eye through the needle. The needle is a 22-gauge thin-wall hypodermic needle and is externally lubricated with silicone oil.

**Clinical Trials and Studies**

Before the advent of intra vitreal corticosteroid based therapies for Macular Edema, laser photocoagulation remained the benchmark of treatment. The SCORE study marked a turning point in the management of Macular Edema, since it was the first report on an effective treatment of Macular Edema due to CRVO. The SCORE study was a multicentric clinical trial, that compared the efficacy and safety of 1-mg and 4-mg doses of preservative-free intravitreal Triamcinolone with observation in central retinal vein occlusion (CRVO) participants with Macular Edema secondary to perfused CRVO. It paved the way for corticosteroids in treatment of Macular Edema secondary to non-infectious causes.

Many studies have been conducted on Ozurdex to test its efficiency and safety compared to various other existing methods of treatment. Some of these studies have been mentioned here:

- **Ozurdex Mead Study**: A Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic Macular Edema. The purpose of the study was to evaluate the safety and efficacy of Ozurdex in patients with DME. It was found that patients receiving a dexamethasone implant had a >/= 15 letter improvement in best corrected visual acuity from baseline at the end of the study. Cataract and increased IOP (mostly controlled with medication) were the most common side effects of Ozurdex implant.

- **BEVORDEX Study**: A randomized phase II clinical trial, over 12 months for a comparison between intravitreal bevacizumab versus intravitreal dexamethasone for diabetic Macular Edema. It was concluded that Dexamethasone implant achieved similar rates of visual acuity improvement compared with Bevacizumab for DME, with superior anatomic outcomes and fewer injections. It was also found that Ozurdex was a better option for pseudophakic eyes.

- **PLACID Study**: A randomised controlled trial, over 12 months to evaluate the outcome of treatment of DME with Ozurdex combined with laser photocoagulation compared with laser alone. It was found that significantly greater improvement in BCVA, as demonstrated by changes from baseline at various time points up to 9 months, occurred in patients treated with Ozurdex implant plus laser than in patients treated with laser alone.

- **Treatment of non-infectious posterior uveitis with dexamethasone intravitreal implant**: A retrospective observational study to observe the efficacy of 0.7 mcg dexamethasone implant in non-infectious posterior uveitis. It was concluded that sustained-release dexamethasone 0.7 mg intravitreal implant may be an effective treatment option for controlling intraocular inflammation.

- **Efficacy of Ozurdex implant in treatment of non-infectious intermediate uveitis**: A retrospective observational study of 20 eyes treated with Ozurdex for intermediate uveitis over 24 months. It was concluded
that Ozurdex implant was particularly useful in persistent chronic CME and vitritis due to non-infectious intermediate uveitis. It has higher safety profile and long duration of action for an average of 4–6 months.

- **SHASTA Study**: A multi-centric, retrospective, chart view study to evaluate the efficacy, safety, and reinjection interval of dexamethasone intravitreal implant in branch retinal vein occlusion and central retinal vein occlusion patients receiving ≥ 2 injections. It was concluded that patients receiving multiple implants had better visual outcome with every injection and no new safety concerns developed with multiple injection therapy.

- **GENEVA Study for RVO**: The Geneva Study, a randomized, controlled, clinical trial, conducted to evaluate the safety and efficacy of an intravitreal implant that delivers sustained levels of dexamethasone (Ozurdex), studied the largest group of RVO patients with Macular Edema (1267 patients), including 35% CRVO and 65% BRVO. The study demonstrated that this slow-release device could both reduce the risk of vision loss and improve the speed and incidence of visual improvement in eyes with Macular Edema secondary to CRVO and BRVO, with fewer side effects, such as elevation of intraocular pressure or cataract.

**Indications of using dexamethasone implant**

FDA has permitted the use of dexamethasone implantation in the following diseases:

- Diabetic Macular Edema
- Central retinal vein occlusion
- Branch retinal vein occlusion
- Non-infectious posterior uveitis

**Translation from clinical research to clinical practice**

**Diabetic Macular Edema**

In diabetic Macular Edema, most retinal specialists still start up the Intravitreal therapy with anti VEGF agents as the Mead trial results are not at par with the DRCR.net results of anti VEGF. However, in Mead trial, patients with more chronic DME was also included and implantation of dexamethasone was possible only once in 6 months, which may have tilted the results in favour of monthly anti VEGFs. Development of cataract also must have led to decrease of visual improvement in the steroid implant. In the pseudophakic group, the steroid implant results were as good as monthly anti VEGF treatment.

Hence clinically, dexamethasone implant could be used in the following situations in DME:

- Primary therapy in pseudophakes
- Patients with high-risk or recent stroke or cardiac event
- Chronic edema
- DME where recent cataract surgery is contemplated
- Bilateral DME where patient compliance is reduced
- Nonresponse or poor response with anti VEGF after about 3 injections

Primary dexamethasone implant in young phakic patients with DME, in patients with glaucoma or high IOP if possible to be avoided for risk of cataract and glaucoma.

**Retinal vein occlusion**

As in diabetic Macular Edema, Dexamethasone implant is effective in almost all cases of retinal vein occlusions. However, the risk of cataract and glaucoma with steroid implant should be weighed against the improvement of vision and central Macular thickness with anti VEGF injections.

Hence most retina specialists start treatment of RVO with anti VEGF agents. If the response is poor or if the recurrences are very frequent, it is prudent to move ahead with dexamethasone implant, especially after ruling out glaucoma.

Thus, in RVO, usually dexamethasone implant is reserved for:

- Chronic Macular Edema in RVO
- Patients with poor response to anti VEGF
- Patients with frequent need of anti VEGF even after 3 months.
- Pseudophakes
- Patients with high-risk or recent history of stroke and coronary artery disease

**Non-infectious intermediate and posterior uveitis**

Uveitis is only a final clinical sign which can occur in infection as well as inflammation and hence, it is important to differentiate the non-infectious uveitis from the infective variety by doing all the relevant investigations. Once, the infective component is ruled out, then the management strategies that we have in hand are:

- Systemic steroids
- Systemic immunosuppression
- Immunotherapy with biologics
- Intravitreal steroid implant

In most cases, it will be a combination of these management strategies that we use. In more severe and in bilateral cases, we may need systemic steroids and in cases with chronicity
and recurrence, we may need to add systemic steroid sparing immunosuppressants and even immunotherapy with biological agents. In such cases, steroid implant can be an adjutant treatment strategy to reduce the dose of immunosuppressants.

In cases with unilateral involvement or in cases with risk of infections with immunosuppression, we may consider the primary use of steroid implant. In many cases with significant vitreous haze, use of intravitreal steroid implants may improve the media clarity and thereby visual acuity. Thus, in uveitis, the use of dexamethasone implant can be summarized as:

- Primary implant in unilateral mild cases
- As an adjutant therapy to immunosuppressants and biologics
- Pseudophakes with intermediate and posterior uveitis.
- Intermediate uveitis

Risk of cataract and glaucoma should be weighed against the effect of systemic immunosuppressive treatment in the management of non-infectious posterior and intermediate uveitis.

**Side effects and Adverse drug reactions**

The ZERO Study published in 2012 in Germany was a systemic summary and analysis of clinical experience regarding complications and side effects of intravitreal administration of dexamethasone. The study concluded that this method of therapy had minimal side effects and intraocular pressure elevation was observed as the most common side effect; however, this generally did not require surgical intervention. After multiple such studies and trials a list of adverse effects have been formulated, and categorised as:

A. Ocular adverse effects

- Injection related
- Drug related

B. Systemic Side effects: Some patients developed headache after injection. However, this was considered as non-significant, and so far, for systemic adverse reactions, no specific pattern indicating safety risks with the active treatment is revealed.

**Summary**

The introduction of corticosteroids in the management of Macular Edema of vascular and non-inflammatory uveitis has revolutionised treatment modalities. Ozurdex, 0.7 mcg of sustained release dexamethasone that can be implanted intra vitreally curtails the process of inflammation and accumulation of fluid in the macula by acting on the inflammatory pathway itself. The effect of the drug is also long term as compared to other into vitreal treatments. The implant is a safe, biodegradable implant that slowly dissociates intra vitreally to release the drug. A review of various clinical trials and studies also indicates that the implant alone, or combined with laser photocoagulation provides optimum results when used for treating Macular Edema due to diabetic retinopathy, retinal vein occlusion, and non-infectious uveitis. The documented adverse effects of the drug are mainly elevated intraocular pressure and cataract. Dexamethasone implant is hence a desirable choice for treating Macular Edema of non-infectious origin in pseudophakic eyes.

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In wAMD patients
WHAT YOU START TODAY MAKES A DIFFERENCE TOMORROW

RAPID MEANINGFUL IMPROVEMENTS FROM THE FIRST DOSE

VA and ≥ 3-line gains from baseline at year 1

OUTCOMES MAINTAINED OVER TIME

Maintained visual gains from baseline up to 4 years

PROVEN RELIABILITY IN REAL LIFE SETTINGS

Real life evidence comparable to clinical trials

INNOVATIVE MODE OF ACTION