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COMMENT

Ophthalmic biosimilars and biologics—role of endotoxins

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The sterile endophthalmitis has been reported in all anti vascular endothelial growth factor (VEGF) formulations used for intravitreal therapy such as bevacizumab, ranibizumab, aflibercept, and pegaptanib, with varying incidence rate [1]. Infectious endophthalmitis is the most dreaded complication of this therapy, with an incidence of 0.029–0.058% [2]. The cumulative rate increases up to 0.843% per person when 60 intra-vitreal treatments (IVT) were administered. The rate of non-infectious or sterile endophthalmitis increased up to 0.228% per person when 20 IVTs were administered and remained stable till 60 IVTs [3].

Previously, sterile inflammation has been reported in patients receiving razumab (Intas Pharmaceuticals Ltd, Ahmedabad, India), the first biosimilar of ranibizumab approved for ophthalmic use in India. These reports led to a recall of the drug by the manufacturer and subsequent changes in the formulation [4]. Abicipar pegol, an innovative designed ankyrin repeat proteins (DARPin) molecule under evaluation, has been modified due to the high rate of intra-ocular inflammation (IOI) in clinical trials. The MAPLE trial for the drug has reported a rate of IOI at 8.9%, with 1.6% severe reaction [5]. The mechanism of the sterile endophthalmitis in anti-VEGF therapy has not been clearly understood. The cases include patients invoking immune reaction to the biological drug itself, an entity known as anti-drug antibody; or reaction to the impurities present in the drug formulation [6]. There have been several reports of cluster sterile endophthalmitis arising from intravitreal bevacizumab therapy [7–9]. Wang et al. reported cluster of sterile endophthalmitis (69%) due to counterfeit bevacizumab. On analysis of the counterfeit vial, it was found to be having 32 EU/ml of endotoxin, and endotoxin was demonstrated in the vitreous samples [7]. The FDA recommends an EL of 0.2 EU/ml for the pharmaceuticals for intraocular use [1, 10].

Endotoxins are the lipopolysaccharide complexes found in the outer cell wall of gram-negative bacteria. These endotoxins found in ophthalmic pharmaceuticals have two sources of induction, namely intrinsic and extrinsic. Intrinsic endotoxins are found to be originating from the inherent manufacturing process of the drug. Extrinsic endotoxins are introduced by improper sterilization and storage processes. These endotoxins have been proven to cause toxic anterior segment syndrome (TASS), a well-established non-infectious anterior uveitis entity following exposure to intraocular pharmaceuticals during ocular surgeries [11]. International Standards Organization (ISO) had recommended the EL to be below 0.5 EU/ml, which FDA thought not to be effective in preventing TASS and has now revised the EL to 0.2 EU/ml [1, 11]. Razumab followed ISO recommendation regarding EL. However, it further modified it as per FDA recommendation after few reports of inflammation. (Unpublished data from manufacturers).

Endotoxin-induced uveitis (EIU) is the sterile inflammation of the uveal tissue of the eye following an exposure to lipopolysaccharides of the Gram-negative bacterial cell wall. These endotoxins are intrinsic in origin as the biologics involve cell cultures to produce the molecule. Biologics such as ranibizumab and aflibercept are produced from mammalian cell lines, whereas new research molecules such as DARPins are produced from bacterial cells (*E. coli*) and thus may have a higher propensity to have intrinsic endotoxins. This could be a possible cause of the intra-ocular inflammation (IOI) in clinical trial results of abicipar. Phase 3 trials of abicipar showed an IOI rate of ~16%. Evaluation of the formulation showed *E. coli* particles as impurities,

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which led to the refinement of the formulation utilized in the subsequent MAPLE trial that resulted in a reduction of IOI of ~7.1% [5]. According to the recent data shared at the American Academy of Ophthalmology (AAO) 2019 annual meeting, the inflammation rate has come down to 1.9%. The processes to detoxify drugs produced from *E. coli* cell lines to reduce the endotoxin load themselves have a scope of significant improvement [12]. Brolucizumab, an scFv molecule that has received FDA approval, is also produced from microbial cell lines [13]. The phase 3 clinical trial of brolucizumab has shown an uveitis rate of ~2.2% [14].

The FDA recommends an EL for ophthalmic pharmaceuticals, solutions, and devices which are being used in anterior segment surgery, such as intra-ocular lens, ophthalmic visco-surgical devices, and balanced salt solutions. EIU in rabbit model has shown that vitreal cavity is ~2- to 10-fold more sensitive to endotoxin administration than the anterior chamber, and thus potentially requires a lower recommended EL [15, 16].

To the best of our knowledge, EL limits for intravitreal therapy have not been specified by the FDA, which would appear to be a deficiency. In the era of intravitreal injection and biosimilars on the horizon, it would be helpful if such recommendations were established to make these therapies safer by reducing the risk of inflammation.

Compliance with ethical standards

Conflict of interest AS conflicts of interest: CONSULTANT: Novartis India, Allergan Global, Intas India, Bayer India. NK: None. BDK conflicts of interest: CLINICAL RESEARCH: Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, ThromboGenics; CONSULTANT: Alimera, Allegro, Allergan, Cell Care, Dose, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics, jCyte, Novartis, Ophthotech, Regeneron, Revana, Theravance Biopharma. Francesco Bandello conflicts of interest: CONSULTANT: Allergan, Bayer, Boehringer- Ingelheim, Fidia Sooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss. AL conflicts of interest: CONSULTANT: Allergan, Novartis, Roche, Notal Vision, Fiorsightslabs, Beyeonics, Bayer Health Care.

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