Anti–Vascular Endothelial Growth Factor Injections and Intraocular Pressure Measurement: Should We Throw the Baby out with the Bath Water?

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For many years, observations in the clinic and numerous case reports have suggested that repeated intravitreal injections of anti–vascular endothelial growth factor drugs can lead to persistent elevation of intraocular pressure (IOP). These observations have led well-meaning investigators to wonder if large existing databases from rigorously conducted randomized trials on the efficacy and safety of the agents could be analyzed to address this issue better. Unfortunately, because change in IOP was not the primary outcome variable in these studies, one may suspect that the lack of rigor with which data on IOP were collected could tarnish any conclusions. Ophthalmology has published manuscripts venturing into this fraught area. Bakri et al1 performed a post hoc analysis of the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) studies, which compared ranibizumab with verteporfin and ranibizumab with sham injection, respectively, for the treatment of age-related macular degeneration. They reported that “Most IOP measurements were made by either applanation tonometry (49.4%) or Tono-Pen (Medtronic Solan, Jacksonville, FL) (45.5%). For the remaining patients, IOP was measured by pneumotonometry [sic], the method was missing, or a combination of methods was used.” Bakri et al ignored the robust literature demonstrating that application and Tono-Pen (Reichert Inc., Buffalo, NY) IOP readings are neither equivalent nor interchangeable.2 In the current issue (see page 1802), Freund et al3 performed a similar analysis, this time examining IOP data from the VIEW (VEGF Trap: Investigation of Efficacy and Safety in Wet AMD) 1 and VIEW 2 randomized trials comparing aflibercept with ranibizumab for age-related macular degeneration. They concluded that IOP elevation was less likely with aflibercept than ranibizumab. Like Bakri et al, they could be no more specific in terms of IOP methodology than to state that in some patients, IOP was measured by Goldmann tonometry and that in others, the Tono-Pen was used.

The glaucoma research community has long wrestled with the vagaries of IOP measurement, which include variations and inaccuracies resulting from the use of uncalibrated tonometers, the large number of personnel involved in studies, the lack of masking for IOP measurements, and the absence of more than 1 baseline IOP. For these reasons, the major trials in glaucoma therapy took great care to adhere to protocols for measuring IOP, and a consensus as to how IOP should be measured has been reached.3 Key features of the consensus include using a calibrated Goldmann tonometer for uniformity (unless the purpose of the study is to compare the accuracy and variability of more than 1 tonometer); measurement of the IOP by 2 individuals: an operator who adjusts the tonometer dial and a reader who reads and records the results (to reduce bias); and the obtaining of at least 2 measurements at each time point (to reduce the influence of continuous IOP variability). Furthermore, measurement of central corneal thickness is now an integral part of the interpretation of the IOP measurement (but without applying a corneal correction factor to IOP), and documentation of the presence or absence of glaucoma and the use of medications to lower IOP also is important.

Although the designers of these critical retina studies required that IOP data be collected as part of the trials, the data were not collected with sufficient rigor. This raises the question of what conclusions can be drawn from such poorly gathered IOP measurements when they have been designated the primary outcomes of these articles? This is the take home message of Bakri et al.1 Recommending “checking preinjection and postinjection IOP at each visit and initiating further evaluation as appropriate” makes sense to glaucoma specialists, but even tonometry in an eye that has just been penetrated with a needle is not totally benign and conceivably could increase the risk of an infection. The conclusions of Freund et al3 that aflibercept is less likely to cause IOP elevation than ranibizumab rests on shaky ground, given the IOP measurement inadequacies and an incomplete assessment of the glaucoma status of those who participated in the trials.

Analyzing an incidental outcome (IOP) from trials evaluating a different primary focus (visual acuity) is certainly not unique to studies of anti–vascular endothelial growth factor injections and IOP. One can imagine, for example, an attempt to analyze visual acuity changes after glaucoma surgery in a study in which optimal determination of visual acuity was not made part of the protocol nor was it performed, because it was not a primary focus of the study. How should journal editors and reviewers approach submissions of such research? Obviously, we believed that these 2 studies were important enough in advising us of the threat of IOP elevation to merit...
publication, but it is unlikely that further studies performed similarly would add substantially to what we know already. We hope that retina trials currently underway, and those still in the planning stages, will address IOP more rigorously to further our knowledge. If authors plan to publish studies in which IOP is the primary outcome, then their methods for obtaining IOP measurements must be improved.

References


Pictures & Perspectives

Boston Keratoprosthesis with Severe Ectasia

A 62-year-old woman with corneal scarring from Stevens-Johnson syndrome was treated with a Boston Keratoprosthesis (K-Pro). She developed corneal ectasia following Ahmed valve placement (Fig 1, arrow pointing to corneal ectasia). She underwent repeat K-Pro to stabilize her eye and allow her to wear a scleral lens. Histopathology demonstrated corneal thinning (Fig 2, asterisk). The patient had a full recovery after repeat K-Pro (Fig 3). The original implant is seen after the attached corneal tissue was removed (Fig 4).

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