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Editorial

Real-World Papers, Prophylaxis for Intravitreal Injections, Fluorescein Angiography and Neovascular Age-Related Macular Degeneration, and Anti–Vascular Endothelial Growth Factor Safety

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The first 12 issues of *Ophthalmology Retina* have been published: 6 issues (every other month) in 2017, and now we are publishing monthly in 2018. I thank our authors, reviewers, editorial board members, and journal staff for their excellent contributions and hard work.

The current issue has some very interesting articles with excellent teaching value. I would like to comment on 4 of these, including articles concerning real-world data,[1] avoiding infections with intravitreal injections,[2] the role of fluorescein angiography in the management of neovascular age-related macular degeneration (AMD),[3] and finally, the safety of ranibizumab[4] and anti–vascular endothelial growth factor (VEGF) medicines generally.

Real-World Articles: Age-Related Macular Degeneration under Treatment

Randomized clinical trials sit at the top of the hierarchy of medical research. Such trials are expensive and challenging to conduct, and there are very few good randomized clinical trial manuscripts in most journal issues. Real-world studies typically examine routine medical practice. They may collate data from insurance claims or from electronic health records. For example, the American Academy of Ophthalmology Intelligent Research in Sight database[5] provides an example of real-world data. Prospective clinical trials have inclusion and exclusion criteria and may study narrow sets of subjects. Randomized clinical trial findings are most likely to be applicable to patients who meet the eligibility criteria and who are managed according to the study protocol. The findings are likely to generalize to similar subjects treated in a similar manner. Real-world studies are messier and tend to include all comers, and treatment usually is more haphazard. These studies are easier to conduct, and sometimes the findings are quite convincing. They are usually less costly to conduct. While I tend to think "you get what you pay for," there is often good information in real-world studies. Please look in this issue at the article by Ciulla et al[1] on outcomes of anti–VEGF therapy in neovascular AMD in the United States (see pg. 645). They examined data from a very large insurance database with almost 78 000 patients with wet AMD. They found real-world neovascular AMD patients in the United States receive fewer anti-VEGF injections and experience worse visual outcomes compared with patients in randomized clinical trials. I bet this is correct. Patients miss visits and suggest excuses not to have injections, and I am sure some of the treating physicians appropriately identify reasons not to inject.

Reducing the Risk of Infection with Intravitreal Vascular Endothelial Growth Factor Injections

Endophthalmitis is rare after anti-VEGF injections. For example, the endophthalmitis rate was approximately 0.16% per injection with aflibercept in the VIEW trials[6] and 0.06% per injection in the Comparison of Age-Related Macular Degeneration Treatments Trials.[7] So, rates seem to be in the range of 1 in 1000 to 2000 injections. In this issue, Levinson et al[2] examine 7646 intravitreal injections performed by 27 retina specialists in a large vitreoretinal practice (see pg. 654). The infection rate was similar to that in the above studies, 0.09% per injection. Although neither randomized nor prospective, various ways of applying povidone iodine were used. Some surgeons used the iodine once, some reapplied but did not use a speculum, some reapplied before placing a lid speculum, and some reapplied after placing the speculum. Although we need to consider the findings with a real-world so-called grain of salt, the authors found the application of povidone–iodine after placement of the lid speculum apparently reduced the incidence of postinjection endophthalmitis approximately 7-fold compared with other aseptic protocols. If you reapply and use a speculum, maybe it makes sense to reapply after placing the speculum.

Fluorescein Angiography for Neovascular Age-Related Macular Degeneration

In another article in this issue, the main message is in the title: "Fluorescein Angiography Does Not Alter the Initial Clinical Management of Choroidal Neovascularization in Age-Related Macular Degeneration." (see pg. 659)[3] Parekh et al, from the University of Iowa, opine that use of fluorescein angiography does not seem to change the initial management of neovascular AMD. The reviewers liked the article, and I accepted it, although I do not completely agree with their conclusions. For a disease in which you may be treating a patient for 5 to 10 years with costly drugs and myriad injections and visits, I really want to be sure I have the correct diagnosis at the outset. Fluorescein angiography can help differentiate simulating conditions. And, if one is a stickler and tries to mimic

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registration trial entry criteria, one may choose to follow not yet progressing occult choroidal neovascularization. If I want to know if the choroidal neovascularization is classic or occult, I still need a fluorescein angiography examination.

Ranibizumab Safety

Finally, I would like to point to an article by Dugel et al[4] on the safety of ranibizumab in patients 85 years of age and older (see pg. 667). The authors conclude that it is safe. They studied pooled data from registration trials (ANCHOR, MARINA, PIER, SAILOR, and HARBOR). Findings included "risk of key systemic [serious adverse events] was associated with age $\geq$85 versus <85, but not with ranibizumab drug exposure. The difference between monthly versus [pro re nata] was inconclusive. There was no evidence of a dose effect." I simply comment that most registration studies are powered for efficacy. A number of anti-VEGF trials have found rates of heart attack or stroke in the 1% to 2% range both for treated and untreated participants. To detect and rule out a doubling of the risk in an important adverse event—for example, to be able to say that a 1% risk in the control patients is not increased to 2% in patients exposed to the drug—would take a sample size of approximately 5000.

Thank you for reading this issue. There is a lot to learn. Again, I thank the authors, reviewers, editors, and the editorial office team for their work and for being a part of the launch of this journal.

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Footnotes and Financial Disclosures

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Dr. Schachat is the Editor-in-Chief of *Ophthalmology Retina*.