EDITORIAL

Follow-up Non-Compliance: A Significant Risk Factor for Reduced Visual Outcomes in Patients With Diabetic Retinopathy

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DIABETIC RETINOPATHY (DR) IS THE MOST COMMON cause of blindness in working-age adults.[1] The incidence is rising, and 16 million patients are expected to be affected by 2050.[2] Over the past decade, anti-vascular endothelial growth factor (VEGF) therapy has revolutionized the treatment of DR and led to improved visual outcomes. Despite these advancements, noncompliance remains a significant barrier to effective patient care in this population.

Primary care medical literature has documented the risks of noncompliance in the diabetic population. A study from the United Kingdom showed that clinic nonattenders were more likely to be smokers, have higher A1C concentrations, and have greater morbidity.[3] Furthermore, those who missed more than 2 appointments during the study period were found to have higher all-cause mortality.

In this issue of *American Journal of Ophthalmology*, Suresh and associates[4] report on the proportion of patients with proliferative diabetic retinopathy (PDR) who were lost to follow-up (LTFU) in a single specialty retina practice. The authors examined 4,423 patients with PDR, of whom 54% and 52% were LTFU at 6 months and 12 months, respectively. The authors state that government and private insurance patients were more likely to be LTFU than self-paying patients but that age and adjusted gross income were not predictive of follow-up status.

Other studies have examined patient compliance in the DR population. A separate study examined the rate of patients LTFU who had nonproliferative diabetic retinopathy and diabetic macular edema and were receiving anti-VEGF therapy in a single large retina practice.[5] In that study of 1,632 patients, 25% were LTFU for at least 1 year. Factors associated with being LTFU included Hispanic, Pacific Islander, and American Indian ethnic minorities and an average adjusted gross income of less than $75,000. Decreasing baseline vision was also associated with patients LTFU.

In a separate report of patients presenting to an eye emergency room with PDR in a tertiary academic center,[6] the LTFU rate in 590 patients was 38%. Those with Medicaid insurance and longer encounters in the emergency room had the highest rate of being LTFU.

Patents with sight-threatening DR who are LTFU may have less favorable visual outcomes. Wubben and associates[7] evaluated the consequences of inadvertent treatment interruptions in patients receiving anti-VEGF therapy for nonproliferative diabetic retinopathy, diabetic macular edema, and PDR in a retrospective, multicenter study. All eyes had visual acuity of 20/80 or better before treatment interruption. In the study of 13 eyes in patients LTFU, reasons for treatment interruption included illness, noncompliance, and financial difficulties. Complications included vitreous hemorrhage (n = 9 of 13), neovascular glaucoma (n = 5 of 13), and tractional retinal detachment (n = 4 of 13), and 77% of eyes lost 3 lines or more of visual acuity.

Although the aforementioned studies examined real-world outcomes, compliance even in the setting of a prospective randomized clinical trial may be inadequate, despite the efforts of study coordinators and regimented visit schedules. For instance, Protocol S, the DRCR study which examined the use of anti-VEGF versus pan retinal photocoagulation (PRP) in PDR, enrolled 394 patients; however, only 65% of patients completed the study visits through 5 years.[7] Many factors contributed to this poor follow-up rate, including all-cause mortality, multiple medical issues, and voluntary participation in the long-term study. Likewise, in RISE and RIDE, approximately 15% of study patients were LTFU by the second year.[8] The DRCR and RISE and RIDE study groups, however, were populations that were chosen and maintained for optimal follow-up participation.

Although these various studies have documented the regrettably high rate and morbidity risk of patients LTFU, despite being engaged in treatment regimens that have high yield, an area that has not been investigated as

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comprehensively is why patients are LTFU. Several studies have documented the economic constraints that are an important factor in many cases.[9–13] However, there is an impression that diabetics particularly have multiple medical problems that entail commitments to many other appointment obligations besides the retina specialist, such as, for dialysis and the endocrinologist, cardiologist, podiatrist, neurovascular specialist, and others. The medical profession may be losing sight of what is being asked of the patient. Appointment fatigue, not to mention logistical constraints, are likely serious hurdles for such a patient. The vitreoretinal specialist, probably, too often loses this perspective that he or she is not the patient's only priority and maybe not even the prime medical priority.

Although data from Protocol S established that 10-year visual acuity outcomes for PDR treated with anti-VEGF therapy or PRP were noninferior, some evidence may suggest that, in diabetic populations prone to being LTFU, PRP may provide more durable visual outcomes. In the case of PDR, PRP can essentially be a "one and done" therapy, lowering the medical burden for the patient, injection-based (and other chronic) therapies may be limited in terms of compliance. Developers of future therapies would do well to consider this when designing new therapeutic approaches.

Obeid and associates[14] explored this notion in a retrospective cohort study of eyes with PDR in patients who were LTFU for more than 6 months and determined that those eyes treated with anti-VEGF therapy had a higher rate of tractional retinal detachments and neovascularization of the iris than the PRP arm.[15]

As treatment options for DR improve and expand, efforts should continue to improve follow-up and compliance. This may include a sensitivity to the underlying therapeutic design. Patients with clinical characteristics and demographics associated with being LTFU may be considered for treatments with longer duration of effect and a lower risk of visual complications in the event of being LTFU.

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