Commentary: Patterns of treatment discontinuation in neovascular age-related macular degeneration

Age-related macular degeneration (AMD), a complex disease with a wide spectrum, is the leading cause of blindness among the elderly.[1] Approximately 10% of AMD patients manifest the neovascular form—the neovascular AMD (nAMD)[2]—that requires anti-vascular endothelial growth factor (anti-VEGF) therapy. Thanks to the introduction of anti-VEGF drugs which have had a profound impact on the visual outcome of these patients than any other advancement in the past few decades, the age-standardized prevalence of blindness due to AMD declined by almost 30% from 1990 to 2020.[3]

The prevalence of AMD in the Indian population is comparable to that in Western populations in the age group of 60–79 years; and it is likely that prevalence in the 80 years and older age group is underestimated.[4] Thus, nAMD is an emerging challenge for eye care and public health professionals in India due to the country's rapidly increasing aging population with the average life expectancy of 69.9 years.[5] With the cataract-related blindness being addressed more vigorously in the communities, the demands for eye health services to address the common posterior segment diseases like nAMD will increase in the coming years.[5]

Since the approval of pegaptanib, the first anti-VEGF drug in 2004, we have encountered different anti-VEGF agents to treat this condition. Many landmark clinical trials have demonstrated visual gains over the course of 1–2 years in response to anti-VEGF treatment, utilizing frequent dosing regimens.[6] Many treatment

regimens have been subjected to adaptation in clinical practice, such as fixed dosing, *pro re nata* (PRN), and treat-and-extend. Additionally, other factors such as the choice of anti-VEGF drug, cost considerations, and changing guidelines have led to a wide variation in outcomes throughout the world.[6]

Adherence to any treatment is of utmost importance to achieve expected health care benefits. For a successful outcome with anti-VEGFs in nAMD patients, repeated intravitreal injections are often necessary over a long period of time due to their short duration of action. Hence the patients need to be compliant and should follow up regularly to receive their next scheduled dose. Though the impact of anti-VEGF therapies is impressive in clinical trials, real-world experience indicates that many patients with nAMD do not achieve similar visual outcomes due to many factors. The knowledge of these contributing factors and understanding the root causes of visual loss become very important in order to propose strategies to combat it.

One of the important reasons for visual loss in patients with nAMD is the treatment discontinuation which is highlighted by a study[7] published in this issue of the *Indian Journal of Ophthalmology*. Only 53% of patients remained in active care five years after initiation of anti-VEGF therapy in this retrospective case note review.[7] Though this study is from a single center, it studied a reasonably good number of patients. Death was found to be the commonest reason (45.6%) for treatment discontinuation. The other important reasons for treatment discontinuation in surviving patients were: early discharge due to stable disease (20.0%), and further treatment deemed futile (18.1%). The authors have also concluded that the age of >80 years was found to be another factor associated with early discontinuation. This study would have been more informative if the data and details were made available regarding the recurrence of the pathology, if observed, in those 20% of patients in whom the anti-VEGF therapy was discontinued early due to disease stabilization.

In this study, the cost of therapy is funded by the National Health Service, United Kingdom. Its findings cannot be generalized to other countries like India where the patients may need to pay the cost of therapy without health insurance coverage, which can force the patients to discontinue the treatment. An Indian study by Kelkar A *et al*.[8] has shed some light in this regard wherein it found that half of the patients were lost to followup to antiVEGF therapy, and the most common factor was "nonaffordability" in 41% of patients.

Thomas Alva Edison had said, "There's a way to do it better. Find it."

It is true that the two anti-VEGF drugs used in this study[7] represent a ground-breaking therapy which has revolutionized nAMD management and set a new standard of care. But they work primarily by targeting VEGF for a shorter duration. We have added a few more approved tools to our armamentarium to fight nAMD. These include port delivery system of ranibizumab, anti-VEGF drug of low molecular weight (i.e., brolucizumab), low-cost anti-VEGF biosimilars, and a novel drug (i.e., faricimab, a bispecific, monoclonal antibody targeting both VEGF-A and angiopoietin-2). It is hoped that these new tools may help in reducing the treatment burden and hence decrease the chances of treatment discontinuation.

It is difficult to predict which of the current and new therapies will stand the test of time. The future of anti-VEGF therapy depends on the ability to use them more effectively and efficiently, and to build upon their successes by creating next-generation therapies that address their shortcomings.

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