Progress in Retinal and Eye Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/preteyeres

Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors

Hemal Mehta[a,b,1], Adnan Tufail[c,1], Vincent Daien[a,d,1], Aaron Y. Lee[e,1], Vuong Nguyen[a,1], Mehmet Ozturk[b,1], Daniel Barthelmes[a,f,1], Mark C. Gillies[a,*,1]

[a] Macula Research Group, Save Sight Institute, University of Sydney, Sydney, Australia
[b] Royal Free London NHS Foundation Trust, London, UK
[c] Moorfields Eye Hospital NHS Foundation Trust and University College London Institute of Ophthalmology, London, UK
[d] University of Montpellier and INSERM 1061, Montpellier, France
[e] Department of Ophthalmology, University of Washington, Seattle, USA
[f] Department of Ophthalmology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

ARTICLE INFO

Keywords:
Age-related macular degeneration
Neovascular
Vascular endothelial growth factor inhibitor
Real-world outcomes
Registry

ABSTRACT

Clinical trials identified intravitreal vascular endothelial growth factor inhibitors (anti-VEGF agents) have the potential to stabilise or even improve visual acuity outcomes in neovascular age-related macular degeneration (AMD), a sight-threatening disease. Real-world evidence allows us to assess whether results from randomised controlled trials can be applied to the general population. We describe the development of global registries, in particular the Fight Retinal Blindness! registry that originated in Australia, the United Kingdom AMD Electronic Medical Records User Group and the IRIS registry in the USA. Real-world observations relating to efficacy, safety and resource utilisation of intravitreal anti-VEGF therapy for neovascular AMD are then summarised. Novel observations that would have been challenging to identify in a clinical trial setting are then highlighted, including the risk of late disease reactivation, outcomes in second versus first treated eyes, and the increased risk of posterior capsular rupture during cataract surgery in patients who have received intravitreal anti-VEGF therapy. We conclude by exploring future directions in the field. This includes the development of a global consensus on real-world outcome measures to allow greater comparison of results. Real-world neovascular AMD outcome registries can be linked with other databases to determine systemic safety or genetic predictors of treatment efficacy. Machine learning offers opportunities to extract useful insights from "Big Data" often collected in these registries. Real-world registries could be used by drug regulatory authorities and industry as an alternative to more costly and time-consuming phase 4 clinical trials, potentially allowing medication costs to be based on outcomes achieved.

1. Introduction

1.1. Natural history of neovascular age-related macular degeneration and poor prognosis with historic interventions

Age-related macular degeneration (AMD) is a leading cause of irreversible visual loss in developed countries and accounts for 7% of global blindness worldwide (Bourne et al., 2013; Bressler, 2004). The worldwide prevalence of AMD is rising as the population ages, with 288 million people projected to have either the early or late manifestations of AMD by 2040 (Wong et al., 2014). Late disease is characterised by significant loss of central vision gradually due to geographic atrophy or more rapidly due to development of neovascularisation.

Neovascular (exudative or wet) AMD is characterised by aberrant angiogenesis originating from the choroidal or, less frequently, the retinal circulation (Gass et al., 2003). These aberrant vessels are prone to leakage resulting in fluid accumulation, haemorrhage and fibrosis that can lead to rapid central visual loss compared with atrophic AMD which causes more gradual visual decline. Whilst it occurs in less than 15% of all patients with AMD, neovascular AMD was, at least before the

* Corresponding author. Macular Research Group, Save Sight Institute, University of Sydney, 8 Macquarie Street, Sydney 2000, New South Wales, Australia.
E-mail address: mark.gillies@sydney.edu.au (M.C. Gillies).

[1] Percentage of work contributed by each author in the production of the manuscript is as follows: Hemal Mehta 50%, Adnan Tufail 5%, Vincent Daien 5%, Aaron Lee 5%, Vuong Nguyen 5%, Mehmet Ozturk 5%, Daniel Barthelmes 5%, Mark C. Gillies 20%.

https://doi.org/10.1016/j.preteyeres.2017.12.002
Received 26 September 2017; Received in revised form 22 December 2017; Accepted 28 December 2017

advent of vascular endothelial growth factor (VEGF) inhibitors, the cause of over 80% of cases of blind registration (Jager et al., 2008).

The Macular Photocoagulation Study (MPS) (1982) evaluated laser photocoagulation for the management of neovascular AMD. Initially, patients with choroidal neovascular membranes outside the fovea (extrafoveal) were recruited. After 18 months of follow-up, 60% of untreated eyes versus 25% of treated eyes had experienced severe visual loss (defined as loss of six or more letters on a logarithm of the minimum angle of resolution [LogMAR] vision chart) and further recruitment was stopped as there was now clinical trial evidence that a treatment for extrafoveal neovascular AMD could reduce the risk of severe visual loss. However, after 3 years of follow-up, over half (59%) of eyes had recurrent choroidal neovascularisation documented. The MPS Group proceeded to assess laser photocoagulation for neovascular AMD lesions under the fovea (subfoveal) (1991). Even though there were larger losses in vision at 3 months in treated eyes, by 2 years only 21% of treated versus 38% of untreated eyes experienced severe visual loss. The MPS Group also observed that neovascular AMD developed in fellow eyes at a rate of approximately 5% per year during 5 years follow-up (1993).

Several other treatments for neovascular AMD have failed evaluation in randomised controlled trials. The Submacular Surgery Trials research group reported that surgery for subfoveal lesions in neovascular AMD as performed in the clinical trial did not improve or preserve visual acuity compared with observation over 2 years and therefore was not recommended for patients with similar lesions (Hawkins et al., 2004). A single dose of intravitreal triamcinolone had no effect on the risk of loss of visual acuity over 1 year in study eyes with neovascular AMD although there was a reduction in angiographic leakage at 3 months (Gillies et al., 2003). A Cochrane Review (Evans et al., 2010) of trials of external beam and plaque radiotherapy for neovascular AMD did not identify convincing evidence that radiotherapy on its own was an effective treatment.

Clinical trials with verteporfin photodynamic therapy (cold laser plus sensitising dye) were initiated in 1996. The Treatment of AMD with Photodynamic (TAP) Study (Bressler, 2002) reported 59% of eyes with predominantly classic subfoveal lesions in the verteporfin group versus 31% of eyes in the placebo group lost fewer than 15 letters vision from baseline over 2 years. The Verteporfin in Photodynamic Therapy (VIP) Study (Verteporfin In Photodynamic Therapy Study, 2001) reported 45% of eyes with occult lesions with no classic component versus 32% of eyes in the placebo group lost fewer than 15 letters of vision from baseline over 2 years.

The results of the clinical trials discussed above demonstrated that there was a major unmet need for effective treatments for neovascular AMD that could stabilise disease and potentially improve vision rather than just slow disease progression.

1.2. Real-world case reports suggested a role for vascular endothelial growth factor inhibitors (anti-VEGF) in the treatment of neovascular AMD

In 1948, Michaelson described the process of neovascularisation in the retina and hypothesised that a diffusible factor (“Factor X”) was responsible for angiogenesis in hypoxic conditions (Michaelson, 1948). Subsequent studies suggested that this Factor X was vascular endothelial growth factor (VEGF) (Senger et al., 1983; Ferrara and Henzel, 1989; Aiello et al., 1994; Miller et al., 1997; Tolentino et al., 2002).

Animal studies demonstrated inhibition of tumour cell angiogenesis could slow tumour growth (Holmgren et al., 1995; Parangi et al., 1996). One of the first anti-VEGF treatments to be developed was a humanised monoclonal antibody effective against isoform A of VEGF called bevacizumab (Avastin). After successful clinical trials demonstrated increased median survival times with systemic bevacizumab combined with chemotherapy versus chemotherapy alone, systemic bevacizumab was approved for use in the treatment of colon cancer in 2004 (Hurwitz et al., 2004).

Following the approval of a systemic anti-VEGF drug for the treatment of colon cancer and the suspected role of VEGF in neovascular AMD, clinicians used intravenous bevacizumab as an off-label treatment for neovascular AMD. In a prospective case series (Michels et al., 2005) of 18 patients treated with intravenous infusions of bevacizumab, Michels et al. reported a median increase in visual acuity of 8 letters by 12 weeks. Rosenfeld et al. (2005) subsequently published the first report of intravitreal bevacizumab for a case of recurrent neovascular AMD and reported visual benefit. Intravitreal delivery had advantages of lower drug dosage, a better systemic safety profile, easier delivery and lower cost. Retrospective case series provided further evidence that intravitreal bevacizumab might improve visual acuity in neovascular AMD (Spaide et al., 2006; Avery et al., 2006), highlighting the need for robust randomised controlled trials.

1.3. Recording distance visual acuity

Changes in distance visual acuity have been used as the primary endpoint in seminal clinical trials of anti-VEGF therapy for nAMD (see Section 1.4).

The prototype distance visual acuity chart was developed in 1862 by Dutch ophthalmologist Hermann Snellen (Falkenstein et al., 2008). “Standard vision” was defined as the ability to recognise one of his optotypes at a visual angle of 1 min of arc. The original chart was later modified to become what is now known as a Snellen chart. Although widely used, this chart has a number of limitations, such as unequal and unrelated spacing between letters and rows, inconsistent progression in letter size from one line to the next, unequal legibility of letters used, and large gaps between acuity levels at the lower end of the scale.

Bailey and Lovie (1976) introduced new principles for the design and use of letter charts for the measurement of visual acuity. They advocated that the test task should be essentially the same at each size level on the chart. Such standardisation of the test task requires the use of letters of equal legibility, the same number of letters on each row, and uniform between-letter and between-row spacing. They also advocated that, combined with the test task standardisation, there should be a logarithmic progression of letter size. These charts facilitate the use of nonstandard testing distances which might be used when there is low visual acuity or when examination room layout prevents testing at the standard distance. This type of LogMAR chart was further modified by Ferris et. al. in 1982 (Ferris et al., 1982) including use of the sans serif font to improve legibility. This LogMAR chart was adopted for the Early Treatment Diabetic Retinopathy Study (ETDRS chart) and later seminal clinical trials. The ETDRS chart is a type of LogMAR chart. Therefore, LogMAR letters can be considered equivalent to ETDRS letters. However, LogMAR letters is a more accurate term.

In a clinical trial setting refracted best-corrected distance VA readings are obtained at important time-points with standard lumination and test distances. In a real-world setting it may not be practical to carry out regular refracted best-corrected distance VA measurements and lumination levels and test distances may vary from visit to visit, potentially leading to less accurate measurements. The International Consortium for Health Outcomes Measurement Macular Degeneration Standard Set recommends recording the best of uncorrected distance VA, corrected distance VA using glasses or contact lenses, or pinhole if required in the affected eye at each clinical visit in the real-world setting (Rodrigues et al., 2016).

All visual acuity outcomes are reported in LogMAR letters in this review. Table 1 provides a conversion table between Snellen distance visual acuity and LogMAR distance visual acuity.

1.4. Seminal phase 3 clinical trials of intravitreal anti-VEGF therapy for neovascular AMD

1.4.1. Pegaptanib

One of the initial intravitreal anti-VEGF treatments developed specifically for neovascular AMD was pegaptanib (Macugen), a single