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https://doi.org/10.1007/s00417-018-4005-x

LETTER TO THE EDITOR

Past and prognosis of anti-VEGF therapy for wet age-related macular degeneration—the future has begun

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Received: 24 April 2018 / Accepted: 2 May 2018

Dear Editor,

We would like to thank Dan and Mihai Călugăru for their critical interest in our recently published work [1]. This gives us the opportunity to address the remarkable improvements that have been achieved by adopting ideal world outcomes in the therapy of exudative or wet age-related macular degeneration (AMD) using ranibizumab to the real world possibilities.

Ranibizumab was the first drug approved for the prevention of vision loss in wet AMD in 2006. The ophthalmological community believed that now a bright future had begun. Indeed, its approval revolutionized ophthalmology and opened the treatment floor for a group of vascular diseases affecting the macula that had been perceived widely untreatable by then. As we have meanwhile learned, beneficial anti-VEGF effects reach not only the macula, but eventually the entire retina [2].

Marina [3] and Anchor [4] were the first studies to show that severe vision loss and legal blindness were not any more an inevitable consequence of wet AMD. Visual gains of in average 8–11 letters were achieved and maintained over 2 years under monthly injections independent of the lesion type. This exceeded by far the limited outcome of photodynamic therapy [4]. Very soon after approval of monthly ranibizumab therapy by the FDA and European authorities, it became nevertheless evident, that in a real world, the majority of patients would not tolerate the burden of treatment associated with monthly injections, whereas the clinical care providers were struggling with highly demanding treatment densities which could barely be realized with the given infrastructure of outpatient retina clinics [5]. Anti-VEGF therapy had to learn to walk in the real world.

Those days, we had still to learn how important a consistent loading dosing with three consecutive monthly injections was for the mid- and long-term outcomes [6, 7]. Based on preclinical data, there existed, on the other hand, substantial fears as to the side effects of permanent VEGF suppression onto the maintenance of the physiological retinal and choroidal capillary network [8, 9]. Consequently, the vast majority of experts used a pro re nata (PRN) or as needed treatment strategy as a compromise between burden of treatment for the patient and feasibility for the institutions and functional stabilisation with still spectacular success compared to the spontaneous course [10].

The next lesson to learn was that this treatment strategy did reduce the number of injections, but not the burden for the patients and caregivers, since patients still had to come in monthly to assess the treatment need, based on functional stability frequently without receiving an intravitreal injection [10]. This resulted in a loss of the initial vision gain within 12 to 24 months [5, 11–13], mostly due to under-treatment [13, 14], and a limited treatment adherence [14]. Nowadays, presence of any intraretinal fluid and instability of subretinal and sub-RPE fluid in optical coherence tomography (OCT) are the gold standard for re-treatment decisions before a functional loss is registered [15, 16]. The resolution of recent OCT devices not only allows to closely follows treatment needs and success, but also potential toxic effects of therapy on an individual basis [17].

Along with these insights we learned that treatment demands of individual patients may differ widely with approximately 25% having a high treatment demand, whereas 25% respond early and very well to a small number of injections allowing to exit therapy for a while the remaining will need permanent therapy with injection intervals between 8 and 12 weeks [18, 19]. Individualisation of treatment density has become the standard concept of care [20]. Treat and extend protocols have been implemented by the majority of retina specialists, not

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Published online: 09 May 2018

because of the initial visual gain which approaches that encountered with monthly treatment, but because this strategy is likely to reduce the burden of therapy without compromising the short- and midterm functional stability [21] as experienced with PRN protocols [7, 13, 22]. This prediction has as yet to be confirmed [23].

We are aware of the tremendous way having passed from first euphorism with the then new therapeutic options to arrive at a future which is likely to maintain a widely stable retinal function for an increasing number of patients over up to a decade if they adhere to treatment [1]. Having said this, we would like to encourage Dan and Mihai Călugăru to critically question the goals achieved and thereby to contribute to further evolution in this exciting field [24, 25].

With the insights gained from systematic evaluation of 12 years of experience with ranibizumab, the community of retina specialists has learned to cope with the limitations of this amazing treatment. New switching and combination therapy strategies will allow to achieve further therapeutic benefit for virtually any vascular maculopathy thus contributing to a significant increase in vision-related quality of life of our patients [26, 27]. More importantly, incredible efforts have focussed on a closer pathophysiological understanding of the underlying retinal diseases. The corresponding pathophysiological insights are likely to further add to individualized, disease-specific targeted therapies [28] serving the prospects for further advance.

Compliance with ethical standards

Conflict of interest JGG acts as an advisor to diverse pharmaceutical companies and contributes to several clinical studies. Nevertheless, none of the authors have received direct or indirect financial support for this study or have a conflicting interest with the data that are presented in the report.

For this type of study formal consent is not required.

This article does not contain any studies with human participants or animals performed by any of the authors.

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