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Treatment for neovascular age related macular degeneration: The state of the art

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ABSTRACT

With the introduction in the clinical practice of drugs inhibiting vascular endothelial growth factor (VEGF) the visual outcomes of patients with neovascular age related macular degeneration (AMD) dramatically improved. Since 2006 repeated intravitreal injections of anti-VEGF became the standard of care for the treatment of neovascular AMD. This review provides an overview of available data form clinical trials supporting the use of anti-VEGF molecules for the treatment of this condition. Several questions remain open, in particular the regimen of treatment, the frequency of injection, the safety of the different drugs, and the poor response to the treatment in some cases. Therefore, new agents and alternative delivery are currently under evaluation.

1. Introduction

Neovascular age related macular degeneration (AMD) is characterized by the growth of choroidal neovessels that infiltrate the subretinal space. It affects 10–13% of subjects over 65 years of age in the industrialized countries. (Smith et al., 2001; Kawasaki et al., 2010) However, AMD increases in prevalence with age, thus the burden of disease is expected to increase in regions where life expectancy is highest. A population-based survey estimated AMD, as a contributing cause of blindness, increased worldwide from 4.4% (95% CI 4.0–5.1) in 1990 to 6.6% (95% CI 5.9–7.9) in 2010 (Bourne et al., 2014).

The availability of new drugs has recently revolutionized the management of patients with neovascular AMD. Several clinical trials proved the safety and efficacy of intravitreal inhibition of vascular endothelial growth factor (VEGF), a major player in the angiogenesis (Spilsbury et al., 2000; Krzystolik et al., 2002; Ferrara et al., 2007; Rosenfeld et al., 2006; Brown et al., 2006).

Since the approval of anti-VEGF pharmacotherapy in 2006, the prevalence of legal blindness and visual impairment due to AMD has been considerably reduced, removing neovascular AMD from the list of incurable diseases (Rein et al., 2009), (Chang et al., 2007), (Campbell et al., 2012). Despite the great benefit of anti-angiogenic drugs in clinical trials, it is common sense that real-life outcomes are less favorable (Frennesson et al., 2010; Bloch et al., 2012; van der Reis et al., 2011). Several questions remain open, in particular concerning treatment strategy, monitoring needs, and increasing costs of treatment (Day et al., 2011; Hawkes, 2012).

In this paper, we illustrate the current therapies and treatment regimens for neovascular AMD.

2. Methods

Ethics approval was not required for this study because only published data were included.

In this review we summarized the current available pharmacological therapies for the management of neovascular AMD, in particular, the anti-VEGF compounds that are commonly used. We included data from randomized controlled trials comparing aflibercept, bevacizumab or ranibizumab against placebo or in a head-to-head fashion. Studies had to include at least 1-year follow-up data of visual acuity and serious side effects.

To identify randomized controlled trials, we searched papers in Medline, Premedline, EMBASE, SCOPUS and the Cochrane Library. The search was last updated in October 2015.

3. Pegaptanib sodium

It is a PEGylated short (28-base) RNA oligonucleotide, an

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aptamer that binds with high specificity and affinity to the extracellular VEGF isoform VEGF-165 (Gragoudas et al., 2004; Schmidt-Erfurth et al., 2014a), (www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf).

Pegaptanib sodium 0.3 mg, given once every 6 weeks by intravitreal injection, was the first VEGF inhibitor approved by the US FDA (United States Food and Drug Administration) for the treatment of neovascular AMD and marked a new era for the treatment of this condition (www.accessdata.fda.gov/drugsatfda_docs/label/2011/021756s018lbl.pdf). The rationale is to selectively inhibit pathological leakage and angiogenesis reducing the systemic side effects (Moshfeghi et al., 2005; Schmidt-Erfurth et al., 2014a; Santarelli et al., 2015).

Pegaptanib is well tolerated in humans and has a mean intravitreal half-life of 10 days. The VISION study demonstrated the safety and efficacy of intravitreal pegaptanib sodium for the treatment of all type of choroidal neovascularization secondary to neovascular AMD (Gragoudas et al., 2004). At two year follow up, its efficacy was superior compared with PDT monotherapy, the standard of care at that time (Chakravarthy et al., 2006). Currently, pegaptanib sodium is still available and approved for the treatment of neovascular AMD. However, due to its poorer efficacy compared with other currently available anti-VEGF drugs, pegaptanib sodium is no longer recommended in the majority of cases (Schmidt-Erfurth et al., 2014a).

4. Bevacizumab

It is a full-length recombinant humanized IgG1 monoclonal antibody that binds all VEGF isoforms (Schmidt-Erfurth et al., 2014a; Schmucker et al., 2012), (www.accessdata.fda.gov/drugsatfda_docs/label/2014/125085s301lbl.pdf).

In 2004 bevacizumab was approved by the US FDA and later by EMA (European Medicines Agency) as a chemotherapeutic agent for the intravenous treatment of metastatic colorectal cancer and other neoplastic diseases (www.accessdata.fda.gov/drugsatfda_docs/label/2014/125085s301lbl.pdf).

The estimated intravitreal half-life of bevacizumab is 5.6 days, longer than ranibizumab and aflibercept (3.2 and 4.8 days, respectively), while the binding affinity is lower (0.05 to 0.2 compared to 1 and 140 for ranibizumab and aflibercept, respectively). The systemic retention is also prolonged because the presence of the FC-portion that binds to an endothelial cell receptor and is recycled (Stewart et al., 2012; Matsuyama et al., 2010; Carneiro et al., 2012; Zehetner et al., 2013).

Since bevacizumab has a similar activity to other anti-VEGF compounds, especially to ranibizumab, it was hypothesized that it could provide a less expensive but similarly efficacious alternative to approved drugs in the treatment of CNV secondary to neovascular AMD (Schmidt-Erfurth et al., 2014a; Schmucker et al., 2012). Therefore, since 2005 many uncontrolled case series reporting the effect of intravitreal bevacizumab for neovascular AMD were published (Rosenfeld et al., 2005; Avery et al., 2006).

Recently, were published the results of two independent studies of non-inferiority that compared intravitreal bevacizumab and ranibizumab with monthly or as needed regimen for the treatment of neovascular AMD. The CATT study at one year follow up demonstrated the equivalence between monthly ranibizumab and bevacizumab (+8.0 and +8.5 letters gained, respectively). Ranibizumab and bevacizumab administered as needed (+5.9 and +6.8 letters, respectively) were also equivalent. However, anatomically bevacizumab showed less effective in terms of reducing retina edema (Martin et al., 2012). At the end of the two years follow up, similar results were observed. The mean change in visual acuity was similar for both drugs, but higher for monthly than for as-needed treatment (Schmidt-Erfurth et al., 2014a). The proportion of eyes without fluid was higher (45.5%) in the ranibizumab monthly group than in the bevacizumab as-needed group (13.9%). Generally, switching from monthly to as-needed treatment resulted in a greater mean decrease in vision during year two and a lower proportion without fluid (Martin et al., 2012; Schmidt-Erfurth et al., 2014a).

Similar results were observed in the IVAN study. More than 600 patients were treated with intravitreal ranibizumab or bevacizumab given monthly or as needed. Both at one year and two year follow up bevacizumab did not meet the non-inferiority criteria and the study was inconclusive. There were no differences between drugs and treatment regimens in the changes of visual acuity and in proportion of serious systemic adverse events (Chakravarthy, 2012, 2013).

The GEFAL study confirmed these findings. This was again a non-inferiority trial between intravitreal ranibizumab and bevacizumab administered with a loading dose of three months, followed by an as-needed regimen for one year (Kodjikian et al., 2013). Bevacizumab was non-inferior to ranibizumab. However, there were no statistically significant differences in the presence of subretinal or intraretinal fluid at final evaluation, dye leakage on angiogram or change in choroidal neovascular area, but ranibizumab tended to have a better anatomic outcome (Kodjikian et al., 2013).

Safety in the use of anti-VEGF drugs is a controversial topic. Major concern is the possibility to increase the rate of cardiovascular adverse events in a population already at higher risk (Winnik et al., 2013). In human studies, Avery et al. (2014) found that the systemic exposure after the third monthly intravitreal injection was 13-fold greater for aflibercept and 70-fold greater for bevacizumab than for ranibizumab. Other reports reviewed differences in both ocular and systemic safety between intravitreal bevacizumab and ranibizumab showing that serious adverse events associated with either bevacizumab or ranibizumab injections are generally rare (Johnson and Sharma, 2013; Schmucker et al., 2012).

A recent meta-analysis evaluated the risk of major cardiovascular and non-ocular hemorrhagic events in patients with neovascular AMD, diabetes mellitus–associated macular edema (DME), or retinal vein occlusions (RVOs) treated with intravitreal anti-VEGF drugs. This review showed that intravitreal anti-VEGF molecules were not associated with significant increases in major cardiovascular or non-ocular hemorrhagic events (Thulliez et al., 2014).

With respect to safety, pooled analyses of the CATT and IVAN studies showed that mortality was lower with ranibizumab, but neither outcome differed significantly between drugs with the size of the respective study population ($p=-0.34$ and $p=-0.55$). Increased odds of experiencing a serious adverse event with bevacizumab observed in the CATT persisted in the meta-analysis ($p=-0.016$). Most importantly, the CATT and IVAN studies were not powered to identify small, but clinically significant differences in the safety of the two compounds (Schmidt-Erfurth et al., 2014a).

In conclusion, bevacizumab is substantially less expensive, but each treatment decision is—legally and medically—based on an individual agreement between treating physician and patient, and must be the consequence of a comprehensive discussion of treatment alternatives and incalculable risks. Informed consent after discussing the optimal benefit, comfort and risks and the off-label status of the drug is mandatory (Jansen, 2013).

5. Ranibizumab

It is a recombinant, humanized Fab fragment of a monoclonal antibody with a high affinity for VEGF-A. It binds to the receptor

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