Statement of the Swiss VitreoRetinal Group (SVRG) on current therapeutic options in neovascular age-related macular degeneration

S. Wolf, C. J. Pournaras, J. Garweg, H. Gerding, Y. Guex-Crosier, B. Kopp, C. Prunte, P. Senn, T. Wolfensberger

Introduction

Age-related macular degeneration (AMD) is a leading cause of severe vision loss and blindness in people aged over 50 in the developed world[1]. Visual impairment resulting from AMD affects patients' ability to perform normal daily activities, and the resulting loss of independence can have a significant impact upon their emotional well-being[2].

Neovascular AMD is characterized by abnormal growth of choroidal blood vessels beneath the macula, accompanied by increased vascular permeability and fragility[3]. This can lead to subretinal hemorrhage, fluid exudation, inflammation, detachment of the retinal pigment epithelium, and fibrotic scars, resulting in substantial vision loss[3]. Neovascular AMD is diagnosed by assessing best corrected visual acuity, biomicroscopy and fluorescein angiography. Optical coherence tomography (OCT) may complement the initial diagnosis, and, if intended to be used for follow-up monitoring, should be documented at baseline.

Recent progress in the understanding of the pathophysiology behind neovascular AMD has led to the development of new therapeutic strategies, enabling prevention of further visual deterioration and even improvements in vision. Due to the number of treatments now available for neovascular AMD, a consensus on the clinical value of each therapy is invaluable in assisting clinicians in identifying the most suitable treatment option for each patient. General evidence-based guidelines on the treatment of neovascular AMD based on data from randomized clinical trials have been previously published.[4,5,6] However, the management of AMD is a fast-changing field and it is important to keep pace with new developments.

These guidelines (summary: page 23) provide an up-to-date summary of current data on therapies for neovascular AMD, and provide clinicians in Switzerland with a basis for decision-making when treating patients with this condition.

Treatment strategies

Anti-VEGF therapy

The characteristic angiogenestic cascade underlying the development of neovascular AMD is primarily caused by vascular endothelial growth factor (VEGF) A[3,7]. VEGF-A inhibition is therefore a primary target for the treatment of neovascular AMD. Due to degradation of the anti-VEGF product by intraocular enzymes or escape to the circulation, these therapies must be administered intravitreally, with regular re-injections.

Ranibizumab

Ranibizumab (Lucentis®) is a recombinant humanized antigen binding fragment (Fab) of a murine monoclonal antibody to VEGF-A[8]. This small molecule has a reduced half-life outside the eye (t½ of less than 1 day), allowing rapid systemic elimination.[9] Ranibizumab neutralizes all active forms of VEGF-A.

A series of clinical trials has provided evidence for the efficacy and safety of ranibizumab. In the two initial Phase III studies, monthly injections of ranibizumab for 24 months led to significant improvements in visual acuity compared with sham-treated or PDT-treated patients.[10,11] The MARINA study (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD) enrolled 716 patients with neovascular AMD, who were randomized to receive 0.5 mg ranibizumab, 0.3 mg ranibizumab or sham injections. In 34% of patients receiving 0.5 mg ranibizumab, visual acuity improved by 15 or more letters, compared with 5% patients in the sham injection arm.[10] Mean change in visual acuity from baseline to month 12 was 7.2 letters in the 0.5 mg group, while patients receiving sham injections lost 10.4 letters. After 2 years' follow up, ranibizumab-treated patients still maintained the initial gain (+6.6 letters) while the sham group had continued to lose visual acuity, reaching a total loss of 14.9 letters.[10]

Similarly, in the ANCHOR study (ANti-VEGF antibody for the Treatment of Predominantly Classic CHORoidal neovascularization in AMD), which randomized 423 patients to 0.3 mg ranibizumab, 0.5 mg ranibizumab or PDT, ranibizumab-treated patients showed greater improvements compared with verteporfin-treated patients at month 12, with a mean change in visual acuity of 11.3 letters in the 0.5 mg ranibizumab group, and a loss of 9.5 letters in patients who received verteporfin therapy.[10,12] Significant benefits of ranibizumab therapy over PDT were still evident at month 24, with visual acuity improved by 10.7 letters from baseline in ranibizumab-treated patients, compared with a mean decline of 9.8 letters in PDT group.[12]

Following these two studies, further clinical studies of ranibizumab investigated treatment algorithms with less frequent injections. In a Phase IIIb, multicentre, randomized, double-masked, sham injection-controlled, 12-month study (PIER), 184 patients were given three initial monthly injections, and then received quarterly injections for the remainder of the study . Using this dosing regime, patients receiving ranibizumab experienced an initial visual acuity gain following the three monthly injections. However, mean visual acuity at month 12 was similar to baseline levels. Sham treated patients declined by 16.3 letters on the ETDRS chart over the same period. In order to directly compare the outcome of monthly treatments with that of quarterly dosing, another randomized, double-masked, 12-month study (EXCITE) was carried out in 354 patients with wet AMD. Patients were randomized to receive quarterly 0.3 mg or 0.5 mg ranibizumab or monthly 0.3 mg ranibizumab. For the first three months, all patients in all three treatment arms received monthly injections. After 12 months, visual acuity had increased by 8.3 letters within the monthly 0.3 mg ranibizumab group compared with 4.9 (0.3 mg) and 3.8 (0.5 mg) letters with the quarterly regimens. For the average patient, both quarterly regimens were not sufficient to maintain the maximal visual acuity gain resulting from the initial monthly treatment. These findings demonstrate that, for the average patient, quarterly dosing of ra-

nibizumab is insufficient to maintain the peak visual acuity achieved with initial monthly applications of ranibizumab.
Under the assumption that individual patients with neovascular AMD may suffer individual courses of disease progression, the SUSTAIN trial was designed to test the outcome of an "as needed" treatment algorithm. SUSTAIN was a 12 month study in which 513 patients were given three monthly ranibizumab injections followed by additional treatment based on a set of pre-defined retreatment criteria (a visual acuity loss of more than 5 letters or an increase in central retinal thickness of more than 100 µm). Initial results from this study showed that the initial monthly treatments resulted in a 5.8-letter visual acuity gain. However, during the subsequent period with treatments given only based on the observation of functional and/or morphological damage, visual acuity could not be maintained at this level, resulting in an average visual acuity gain of 3.6 letters at month 12. Even when more permissive re-treatment criteria were used (retreatment upon observation of "any" activity) in a case series comprising 131 eyes, the conceptual weakness of using the observation of damage as trigger of the next treatment became evident, i.e. the visual acuity gain resulting from the initial monthly treatment could not be maintained over the following period using the "as needed" approach. In fact, evidence is growing that visual acuity once lost within treatment intervals therapy may not be restored completely.
The overall safety and tolerability profile of ranibizumab is favourable. In the ANCHOR and MARINA studies, rates of serious ocular adverse events were low in both studies. Despite less stringent exclusion criteria than other clinical trials of anti-VEGF therapies (for example, unlike the pivotal studies of pegaptanib, ANCHOR and MARINA did not exclude patients with severe cardiac disease or stroke), the incidence of VEGF-related systemic adverse events was low. This was corroborated by SAILOR, a large 12-month phase IIIb safety study of ranibizumab, which included a randomized cohort and an open-label cohort and enrolled a total of 4300 patients with neovascular AMD. Patients in Cohort 1 were randomized to receive three monthly injections of either 0.3 or 0.5 mg ranibizumab, followed by retreatment as needed (based on pre-defined criteria), while patients in Cohort 2 received one dose of 0.5 mg ranibizumab and were retreated at the physician's discretion. The number of vascular deaths and deaths due to unknown cause did not differ across cohorts or dose groups. Although stroke rates were numerically higher in patients treated with 0.5 mg ranibizumab compared with 0.3 mg ranibizumab in cohort 1 (0.7% *versus* 1.2%) the difference was not statistically significant. However, concerns about possible arterial thromboembolic adverse events with anti-VEGF therapy raised by this finding prompted a meta-analysis of the MARINA, ANCHOR and phase II ranibizumab studies, which demonstrated that ranibizumab may be associated with an increased incidence of cerebrovascular accidents ($p = 0.045$; OR 3.24; 95% CI 0.96 –10.95). There was no apparent association between ranibizumab and myocardial infarction ($p = 0.193$). Because of these findings, clinicians should take additional care when treating neovascular AMD patients with a high risk of stroke with ranibizumab.

Pegaptanib sodium

Pegaptanib sodium (Macugen®) is a ribonucleic acid aptamer that competitively blocks all isoforms of VEGF-A that are 165 or more amino acids in length.[13] The highest level evidence for the efficacy and safety of pegaptanib comes from two concurrently-run prospective, randomized, multicenter, double-masked, sham-controlled pivotal studies, the VEGF Inhibition Study In Ocular Neovascularisation (VISION) trials. In these studies, visual acuity was maintained by pegaptanib treatment compared with patients receiving usual care, and the incidence of progression to legal blindness was reduced for patients continuing pegaptanib therapy for 2 years compared with those who were randomized to discontinue therapy after one year. The proportion of patients who received 2 years' pegaptanib therapy who lost more than 15 letters on the ETDRS chart from baseline during the second year of the studies was half (7%) that of patients who discontinued pegaptanib after one year and half that of those who had received usual care throughout the 2-year study duration (14% for each).
The safety profile of pegaptanib was good, with no evidence of increased systemic adverse events associated with VEGF inhibition or of serious non injection procedure-related ocular adverse events. This favourable safety and tolerability profile was sustained for up to 3 years[14].
These therapeutic benefits provided by pegaptanib compare favorable to those achieved with photodynamic therapy (PDT), with a significant number of patients with stabilized disease, but a low incidence of improvements in visual acuity.

Bevacizumab

Bevacizumab is not approved for the treatment of AMD anywhere in the world. It has been used off-label because, like ranibizumab, bevacizumab (Avastin®) inhibits VEGF-A. However, unlike ranibizumab, bevacizumab is a full-length antibody[15]; it therefore has a larger molecular weight than ranibizumab (149 kD *versus* 48 kD).[16] In comparison to ranibizumab, bevacizumab has a relatively low binding affinity for VEGF-A[17]. Bevacizumab was developed for the treatment of angiogenesis in tumours and was designed for intravenous administration[15]. The Fc portion of the IgG antibody that is bevacizumab ensures a maximal serum half-life of about 20 days.
Numerous uncontrolled prospective studies have suggested beneficial effects of bevacizumab in neovascular AMD patients, but of these only a limited number had study durations of more than 6 months, and sample sizes were always low[18]. In the only published study of bevacizumab in neovascular AMD with a duration of more than 6 months, mean visual acuity improved significantly, from 45.7 letters at baseline to 54.3 letters at 24 months ($p = 0.001$). At month 24, 47 eyes (92.2%) had lost fewer than 15 letters. These findings are similar to those seen with ranibizumab in large clinical studies, but this study was not randomized or controlled, and so must be confirmed by larger well-designed trials.
Only a few randomized controlled trials comparing bevacizumab to other therapies for neovascular AMD have been published to date. These have been short in duration (6 months or less), and have enrolled small numbers of patients, and so are considered low-ranking evidence for the clinical efficacy of bevacizumab. Findings from these randomized studies have suggested benefits of bevacizumab over PDT and PDT/triamcinolone combination therapy, and have shown similar efficacy to ranibizumab. However, larger studies with longer duration are required to determine whether initial improve-

ments in patients with neovascular AMD treated with bevacizumab over the short-term can equal those seen with ranibizumab in long-term large scale clinical trials. A number of longer-term head-to-head studies are currently ongoing that will certainly shed light on the efficacy of bevacizumab and ranibizumab. Yet, these trials appear underpowered to reveal differences in the two compounds' safety profiles.

Most currently-available information on the safety of bevacizumab for neovascular AMD is summarized by two publications: a retrospective study of published data and an internet-based adverse event reporting survey[19,20]. Although reported rates of ocular and systemic adverse events were low, it is likely that side effects were under-reported in both studies. In the internet survey, reporting of adverse events was voluntary, so patients may have failed to report adverse events due to time constraints, lack of internet access, concern over medico-legal liability or human tendency not to publicly acknowledge adverse events in clinical practice. The retrospective review was based on previously published data, and many of these publications did not provide complete reporting of side effects. In addition, the majority of these studies had durations of 3 months or less. Further studies are required to determine the safety profile of intravitreously-injected bevacizumab, especially in light of the increased risk of serious thromboembolic adverse events with intravenous administration seen in cancer patients.[21]

Photodynamic therapy

Verteporfin (Visudyne®) is a light-activated compound which is administered intravenously and is physically activated using a laser beam directed at the lesion. In contrast to photocoagulation therapy, there is a reduced risk of damage to surrounding healthy tissue. The laser is used to induce a photochemical oxidation of the vascular endothelium without a thermal component.

The pivotal phase III studies of verteporfin were the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) study[22,23] and Verteporfin in photodynamic Therapy (VIP) trial[24,25], both 24 months in duration. The TAP study enrolled patients with minimally or predominantly classic subfoveal choroidal neovascularization, and demonstrated significant benefits for verteporfin over sham treatment in terms of visual acuity, contrast sensitivity and progression of choroidal neovascularization (CNV) and leakage[23]. After 24 months, 53% of verteporfin-treated patients had lost less than 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, compared with 38% of patients in the sham treatment arm[23]. The benefit was particularly pronounced in patients with predominantly classic subfoveal lesions. The VIP trial enrolled patients with subfoveal lesions with occult components and without classic CNV[26]. Significant advantages of verteporfin over placebo were observed, of a similar magnitude to the TAP study (46% patients lost less than 15 letters, compared with 33% of controls). Patients with smaller lesions (≤ 4 MPS disc areas) or lower visual acuity derived most benefit[27].

A pooled analysis of the TAP and VIP studies demonstrated the long-term safety of verteporfin in patients with neovascular AMD. Systemic adverse events with increased incidence after verteporfin treatment compared with placebo included injection site reactions, back pain and photosensitivity, and were mostly transient and mild or moderate in nature[27].
Based on high-level evidence from the TAP and VIP studies and supporting randomized clinical trials, photodynamic therapy (PDT) with verteporfin can delay or prevent the progression of disease in patients with classic CNV, and for those with occult CNV with a lesion size of less than 4 MPS disc sizes. However, improvements in vision are rare and should not be expected.

Anti-VEGF and PDT combination therapy

Anti-VEGF therapies and PDT may be complementary, since anti-VEGF therapy targets leakage and new vessel growth, while PDT affects the lesion, inducing thrombosis and atrophy. In addition, it has been suggested that PDT might increase expression of VEGF, and so PDT treatment in conjunction with an anti-VEGF therapy might conceivably improve outcomes, resulting in longer-term benefits and reduced need for retreatments.
Best evidence for the efficacy and safety of combination therapy comes from early studies of ranibizumab. The FOCUS and PROTECT studies provided evidence that combination therapy is well-tolerated and not associated with severe vision loss or severe ocular inflammation [28,29].
The SUMMIT programme of multicentre randomized clinical trials assessing PDT and ranibizumab combination therapy is currently underway with results being only available for one of three trials comprising this programme: In MONT-BLANC a ranibizumab monotherapy was compared to a combination of PDT (standard fluence) and ranibizumab in 255 patients over 1 year. In the monotherapy arm patients were injected 3 times at monthly intervals followed by monthly visits with treatment upon retinal thickening (>/= 100µm) or functional loss (>5 letters). The initiation phase of the combination treatment consisted of 3 monthly injections with a PDT applied with the first injection followed by the second phase using fluorescein angiography, OCT (>/= 100µm increase in thickness) and functional parameters (>5 letters loss) to decide for re-treatment. The combination treatment was safe and well tolerated and the functional outcome was comparable to ranibizumab monotherapy. However, over the period of one year combination therapy did not result in a saving of ranibizumab injections or in more patients with treatment-free intervals of 3 month or more (June 14th, SOE, Amsterdam).
Still, there is limited data available on the efficacy and safety of anti-VEGF and PDT combination therapy. Results from DENALI and MONT-BLANC – two ongoing multicentre randomized controlled trials from the SUMMIT programme – are awaited before combination therapy can be recommended for the treatment of neovascular AMD.

Corticosteroids

Triamcinolone (Kenalog®) is a corticosteroid commonly used alone or in combination with PDT as an off-label treatment for neovascular AMD. Intravitreous injection of triamcinolone reduces inflammation and may also have anti-angiogenic effects[30].
The benefits of triamcinolone monotherapy appear to be transient and limited, with clinical trials detecting no differences between triamcinolone-treated and placebo-treated patients with regards to severe visual loss[30] or best corrected visual acuity at study endpoint[31]. Monotherapy with triamcinolone was associated with an increased risk of elevated intraocular pressure and progression of cataract[30,31]. Combination therapy with triamcinolone and verteporfin has yielded more promising results[32]. Early, small, non-controlled studies indicated that addition of triamcinolone to verteporfin therapy can improve outcomes and reduce the frequency of retreatment. Following these promising findings, a number of prospective, randomized clinical studies were performed, but these have provided conflicting results on the benefits of triamcinolone in addition to PDT, with some showing no visual benefits or reduction in fluorescein leakage, and some reporting improvements in visual acuity. Nevertheless, these studies did consistently report a reduced retreatment frequency with combination therapy. Combination therapy had a similar safety profile as monotherapy with triamcinolone with an increased risk of elevated intraocular pressure and progression of cataract.

Laser photocoagulation

Thermal laser surgery for neovascular AMD has been available since the 1980s[33-39]. Ablation of the vascular membrane prevents any further leakage or growth of the lesion, slowing the progression of the disease. However, an unavoidable side effect of laser surgery is irreversible collateral damage to, and scarring of, adjacent areas of the retina, which can lead to vision loss.
Evidence for the efficacy of laser surgery comes from a series of randomized controlled trials carried out by the Macular Photocoagulation Study Group[33-39], in patients with extrafoveal, subfoveal and juxtafoveal lesions.
Argon laser photocoagulation of extrafoveal lesions was shown to be beneficial in delaying loss of visual acuity for up to 5 years in a randomized clinical study totalling 236 patients with neovascular AMD. After 5 years, untreated eyes had lost a mean of 7.1 lines of visual acuity, while laser-treated eyes had lost 5.2 lines. However, recurrent neovascularization was observed in 54% of laser-treated eyes by the end of the 5-year follow-up period.
Some benefits of krypton laser treatment of subfoveal lesions were observed in two randomized clinical trials of up to 4 years duration, both in patients with and without prior laser treatment, although patients with poorer acuity and smaller lesions appeared to derive the most benefit. In patients with juxtafoveal lesions, benefits of krypton laser therapy were marred by high rates of persistent neovascularization during the first 6 weeks after treatment. The 5-year rate of recurrence was estimated to be 78%.

Submacular surgery

Submacular surgery has been investigated as a possible method of preventing further vision loss in patients with neovascular AMD. However, in a randomized trial comparing patients who underwent surgery with those who received no treatment, surgery did not improve or stabilize visual acuity in more eyes than the control group. Furthermore, the risk of developing cataract and retinal detachment increased after surgery.
Current evidence does not support the use of the surgical approach for the treatment of patients with neovascular AMD[40].

Recommendations for the management of patients with exudative AMD

Diagnosis of exudative AMD

A visual acuity test (best corrected, with normal pupils, under standardised conditions) and a clinical ocular fundus examination (biomicroscopic examination of the posterior pole of the eye in mydriasis) are the basis for all therapeutic interventions. Fluorescein angiography continues to be the "gold standard" for establishing the diagnosis and is required before all initial treatments, firstly for reasons of clear documentation of the treatment indication and even more if the diagnosis is unclear based on other measures. Photographic documentation is recommended for follow-up observation purposes before starting and after finishing each treatment series. In addition, OCT examination is considered an important adjunct, though by itself it is not a sufficient examination for diagnosis.

For the diagnosis, the decisive factors are visual acuity (best corrected visual acuity at least 0.05, no upper limit), the CNV situation (subfoveal or non-subfoveal) and the angiographic type (minimal or predominantly classic CNV or occult CNV). In occult CNV, there should be evidence of actual disease progression (subretinal haemorrhage, proven loss of visual acuity or increased size in the last three months). In addition, a differentiation of associated characteristics of the lesion such as serous detachment of the pigmented epithelium is necessary. Future therapeutic strategies could possibly also include other criteria, such as lesion size or foveal autofluorescence in decision making.

Therapy

Extrafoveal CNV

For classic CNV lacking occult components and outside the avascular zone of the fovea, thermal laser coagulation has previously been the only therapeutic option investigated in randomised clinical studies. Angiographic CNV differentiation, further developed in recent years, has, however, shown that there are frequently extrafoveal membranes with occult subfoveal components. Intravitreal injection of a VEGF inhibitor can therefore be a meaningful indication, which is also covered by the Swiss authorisation of ranibizumab and pegaptanib for the treatment of the exudative AMD.

Subfoveal CNV

The problems of comparing different studies have been intensively discussed in the literature. Even considering these methodological difficulties, there is widespread agreement that of the medications licensed under pharmaceutical law in Switzerland for the treatment of neovascular AMD, ranibizumab is the first-line therapy for the various investigated types of exudative AMD (predominantly classic CNV, minimally classic CNV or occult CNV with proven disease progression).

With regard to the functional stabilisation effects (approx. 95% in all types) and the possibility of an improvement in visual acuity (approx. 70% in all types), ranibi-

zumab provided results superior to other licensed medications. These results were, however, obtained in studies prescribing an application of ranibizumab every month over a period of two years (24 intravitreal applications). About 40% of the study patients needed further injections in the third year. Thus, the patient (and relatives) and the treating physician must be aware that a long-lasting injection therapy may be necessary, comprising (close to) monthly follow ups. Where response to ranibizumab therapy is deficient, the use of PDT or intraocular therapy with pegaptanib may represent an alternative.

Follow-up studies, treatment frequency and intervals

Follow-up, treatment intervals, repeat therapy, change of treatment

In the prescribing information for Lucentis®, administration at one month intervals is recommended. On average only this treatment frequency results in sustained long-term visual acuity gain. However, the longer term administration of monthly injections is usually not possible. Therefore, a bi-phasic approach may be used with an initial loading dose of three intravitreal applications at four-week intervals that is followed by treatments based on the clinical findings. Only in a small minority of patients will these three injections suffice to achieve a lasting stabilisation of visual acuity.

Phase 2, i.e. the maintenance phase with Lucentis® must be dependent on the individual case. Visual acuity (under standardised conditions, best-corrected, with normal pupils) and fundus findings (biomicroscopic examination of the posterior pole of the eye in mydriasis) should be tested about every 4-6 weeks. In addition, OCT examination can be a reasonable adjunct, though by itself it is not sufficient as a follow-up examination in all cases. These examinations are also very urgently required in the event of subjective deterioration. Criteria for repeated treatment are qualitative when ophthalmoscopically defined (haemorrhage, increased exudate, increased oedema, increased lesion size) in consideration of the development of visual acuity. If a deterioration in sight or the presence of metamorphopsia cannot be clearly explained by ophthalmoscopic or OCT findings, a fluorescein angiography must be carried out at least before each treatment cycle. The documentation of the fundus findings with fundus photographs is recommended every 6 months. An OCT can, as is the international norm in follow-up observation, be of additional help in evaluating possible disease progression. In addition, it must be sufficiently explained to patients that they must come in for an examination if they notice a subjective deterioration.

End or discontinuation of therapy

The end of treatment because of cicatrisation of the CNV can, in line with the above-described therapy principle, only be accepted if, after the cessation of therapy, there is no recurrence of the defined criteria for further treatment and disease progression (poorer visual acuity, new haemorrhage in the macula, increase in the macular oedema, progression or reactivation of the exudative lesions in the fluorescein angiogram). Discontinuation of therapy normally occurs, despite the absence of data on the necessary duration of therapy, if widespread subretinal fibroses or RPE atrophies are visible or if visual acuity falls irreversibly below 0.05. Exceptionally, treatment can also be indicated with visual acuity below 0.05 if there is fresh submacular haemorrhage and if, after resorption of the haemorrhage, visual acuity of more than 0.05 is expected. Discontinuation of therapy should also be considered if a further loss of visual acuity cannot be impeded (e.g. loss of visual acuity despite monthly injections) and a favourable effect on the patient's quality of life is not expected.

Treatment procedure

All injection therapies are generally administered on an outpatient basis. There may be a medical need for inpatient treatment in individual cases. The intravitreal injection is an intraocular surgical intervention, for which the same conditions must apply as in other intraocular interventions, e.g. in cataract operations or vitrectomies. There is still no evidence-based data for pre-operative prophylaxis with topical antibiotics demanded by some authors and in the prescribing information for Lucentis®, so that such a procedure is at the discretion of the surgeon. It is worth noting here that prophylaxis of this kind for Macugen® is not mentioned in the prescribing information.

Quality requirements in the implementation of anti-VEGF therapy

Intravitreal medicinal therapy for AMD is a new, cost-intensive therapy for which effective quality assurance should be carried out. The most important of the requirements suggested by the SVRS for initial, process and structural quality can be set down as follows:

Initial quality: conditions for the surgeon

- Completed further specialist doctor training for Ophthalmic surgery (FMH intrinsic value 10)
- Independent evaluation of at least 200 fluorescein angiograms (for the differential diagnosis of pathological changes of age-related macular degeneration (or of pathological myopia) or 500 fluorescein angiograms in various diseases.

Structural quality

- The treating ophthalmologist/centre should provide an SOP for indication, treatment and follow-up procedures of patients with exudative ARMD.
- For the administration of the intravitreal injection (Tarmed 08.3350), the operating theatre must fulfil the requirements of an OP I.
- 24/7 emergency service has to be provided for patients with post-injection problems (e.g. endophthalmitis, corneal abrasion). This should include capability to perform intravitreal antibiotic therapy, and co-operation with a centre that can perform vitrectomies for endophthalmitis.
- The treating ophthalmologist/centre deciding on injections should have access to photography, angiography and reasonable resolution OCT.
- The treating ophthalmologist/centre should provide evidence of the capacity to follow up all treated patients at monthly intervals as well as of > 6 re-injections per patient per year.

Documentation

The decision criteria for therapy and findings before each injection are to be documented for quality assurance by the surgeon/centre. The ongoing patient information is also to be documented.

Results quality

It is important to check the ophthalmological documentation with respect to the appropriate diagnosis on initial and further treatment, to verify the quality of the fluorescein angiograms, to set the time intervals for repeat treatment in line with the current state of scientific knowledge, and to institute adequate measures in the event of deficiencies.

Results quality should be checked by means of a registry in line with FOPH regulations. The treating ophthalmologist/centre must collect data on treatment frequency and visual outcome for each treated patient.

References

1. Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA 2004, 291(15):1900-1901.
2. Chia EM, Wang JJ, Rochtchina E, Smith W, Cumming RR, Mitchell P. Impact of bilateral visual impairment on health-related quality of life: the Blue Mountains Eye Study. Invest Ophthalmol Vis Sci 2004, 45(1):71-76.
3. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. N Engl J Med 2008, 358(24):2606-2617.
4. Chakravarthy U, Soubrane G, Bandello F et al. Evolving European guidance on the medical management of neovascular age related macular degeneration. Brit J Ophthalmology 2006, 90(9):1188-1196.
5. Mitchell PR, Korobelnik JF, Lanzetta P et al. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Brit J Ophthalmol 2009. doi:10.1136/bjo.2009.159160
6. [New aspects in the therapy of neovascular age related macular degeneration. Current position of the Retinological Society, the Germany Ophthalmologic Society and the Professional Union of Eye Doctors of Germany]. Ophthalmologe 2009, 106(5):457-464.
7. Penn JS, Madan A, Caldwel IRB, Bartoli M, Caldwell RW, Hartnett ME. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res 2008, 27(4):331-371.
8. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006, 26(8):859-870.
9. Gaudreault J, Fei D, Rusit J, Suboc P, Shiu V. Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Ophthalmol Vis Sci 2005, 46(2):726-733.
10. Brown DM, Kaiser PK, Michels M et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006, 355(14): 1432-1444.
11. Rosenfeld PJ, Brown DM, Heier JS et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006, 355(14):1419-1431.
12. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 2009, 116(1):57-65.
13. Moshfeghi AA, Puliafito CA. Pegaptanib sodium for the treatment of neovascular age-related macular degeneration. Expert Opin Investig Drugs 2005, 14(5):671-682.
14. Kourlas H, Schiller DS. Pegaptanib sodium for the treatment of neovascular age-related macular degeneration: a review. Clin Ther 2006, 28(1):36-44.
15. Presta LG, Chen H, O'Connor SJ et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997, 57(20):4593-4599.
16. Steinbrook R. The price of sight--ranibizumab, bevacizumab, and the treatment of macular degeneration. N Engl J Med 2006, 355(14):1409-1412.
17. Chen Y, Wiesmann C, Fuh G et al. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. J Mol Biol 1999, 293(4):865-881.
18. Rich RM, Rosenfeld PJ, Puliafito CA et al. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Retina 2006, 26(5):495-511.
19. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. Brit J Ophthalmol 2006, 90(11):1344-1349.
20. Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. Ann Pharmacother 2007, 41(4):614-625.
21. Ornek K, Karahan ZC, Ergin A, Tekeli A, Tekeli O. Bevacizumab sterility in multiple doses from a single-use vial. Ann Pharmacother 2008, 42(10):1425-1428.
22. TAP Study G. Photodynamic therapy of subfoveoal choroidal neovascularization in age-related macular degeneration with Verteporfin. One-Year results of 2 Randomized clinical trials - TAP report 1. Arch Ophthalmol 1999, 117:1329-1345.
23. TAP Study G. Photodynamic Therapy of Subfoveal Choroidal Neovascularization in Age-Related Macular Degeneration With Verteporfin: Two-Year Results of 2 Randomized Clinical Trials-TAP Report 2. Arch Ophthalmol 2001, 119(2):198-207.
24. VIP Study G. Verteprofin therapy of subfoveal choroidal neovascularization in pathologic myopia. 2-year results of a randomized clinical trial - VIP Report No. 3. Ophthalmology 2003, 110:666-673.
25. VIP Study G. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial--VIP report no. 1. Ophthalmology 2001, 108(5):841-852.
26. VIP Study G. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: Two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization - Verteporfin in photodynamic therapy. Report 2. Am J Ophthalmol 2001, 131:541-560.
27. VIP Study G, TAP study G. Verteprofin therapy of subfoveal choroidal neovascularization in age-related macular degeneration. Meta-analysis of 2-year results in three randomized clinical trials: treatment of age-related macular degeneration with photodynamic therapy and verteporfin in photodynamic therapy study report no. 4. Retina 2004, 24:1-11.
28. Heier JS, Boyer DS, Ciulla TA et al. Ranibizumab Combined With Verteporfin Photodynamic Therapy in Neovascular Age-Related Macular Degeneration: Year 1 Results of the FOCUS Study. Arch Ophthalmol 2006, 124(11):1532-1542.
29. Schmidt-Erfurth U, Wolf S. Same-day administration of verteporfin and ranibizumab 0.5 mg in patients with choroidal neovascularisation due to age-related macular degeneration. Brit J Ophthalmol 2008, 92(12):1628-1635.
30. Challa JK, Gillies MC, Penfold PL. Exsudative degeneration and itravitreal triamcinolone: 18 month follow up. Aust N Z J Ophthalmol 1998, 26:277-281.
31. Lee J, Freeman WR, Azen SP, Chung EJ, Koh HJ. Prospective, randomized clinical trial of intravitreal triamcinolone treatment of neovascular age-related macular degeneration: one-year results. Prospective, randomized clinical trial of intravitreal triamcinolone treatment of neovascular age-related macular degeneration: one-year results. Retina 2007, 27(9):1205-1213.
32. Spaide RF, Sorenson JA, Maranan L. Combined photodynamic therapy with verteporfin and intravitreal triamcinolone acetonide for choroidal neovascularization. Ophthalmology 2003, 110:1517-1525.
33. Macular Photocoagulation Study G. Persistent and recurrent neovascularization after krypton laser photocoagulation for neovascular lesions of age-related macular degeneration. Arch Ophthalmol 1990, 108:825-831.
34. Macular Photocoagulation Study G. Argon laser photocoagulation for senile macular degeneration. Arch Ophthalmol 1982, 100:912-918.
35. Macular Photocoagulation Study G. Argon laser photocoagulation for neovascular maculopathy. Arch Ophthalmol 1986, 104:694-701.
36. Macular Photocoagulation Study G. Krypton laser photocoagultion for neovascular lesions of age-related macular degeneration. Arch Ophthalmol 1990, 108:816-824.
37. Macular Photocoagulation Study G. Five-year follow-up of fellow eyes of patients with age-related macular degeneration and unilateral extrafoveal choroidal neovascularization. Arch Ophthalmol 1993, 111:1189-1199.
38. Macular Photocoagulation Study G. Laser Photocoagulation for juxtafoveal choroidal neovascularization. Arch Ophthalmol 1994, 112:500-509.
39. Macular Photocoagulation Study G. Visual outcome after laser photocoagulation for subfoveal choroidal neovascularization secondary to age-related macular degeneration. The influence of initial lesion size and initial visual acuity. Arch Ophthalmol 1994, 112(4):480-488.
40. Submacular surgery trials randomized pilot trial of laser photocoagulation versus surgery for recurrent choroidal neovascularization secondary to age-related macular degeneration: I. Ophthalmic outcomes submacular surgery trials pilot study report number 1. Am J Ophthalmol 2000, 130(4):387-407.

Table 1. Summary of SVRG recommendations for the treatment of neovascular AMD

Therapy and Notes/Recommendations
Anti-VEGF therapies *Ranibizumab* First-line therapy for neovascular AMD. Monthly injections ideal; if PRN dosing is used, monthly monitoring is essential. *Pegaptanib* An option for treatment of neovascular AMD when ranibizumab is not an option. Magnitude of response likely to be less than ranibizumab. *Bevacizumab (off-label)* Not recommended due to insufficient clinical evidence and off-label status.
Photodynamic therapy *Verteporfin* An option for treatment of patients with predominantly classic or occult with no classic subfoveal CNV. Magnitude of response likely to be less than ranibizumab.
Corticosteroids *Triamcinolone (off-label)* Not recommended due to poor efficacy in clinical studies and off-label status. Increased risk of elevated intraocular pressure and progression of cataract.
Non-pharmacological techniques *Photocoagulation* An option for the treatment of lesions outside the avascular zone of the fovea. Magnitude of response not likely to reach that of verteporfin or anti-VEGF therapies. *Submacular surgery* Not recommended due to insufficient clinical evidence and poor efficacy in clinical studies. *Ionising radiation* Not recommended due to insufficient clinical evidence and poor efficacy in clinical studies.
Combination therapy *Anti-VEGF / verteporfin* Not currently recommended due to insufficient clinical evidence. May be indicated in combination with ranibizumab when need for reduced number of treatments outweighs the potential for reduced efficacy. *Verteporfin / triamcinolone (off-label)* Not recommended due to off-label status. Benefits not likely to be as great as those with anti-VEGF or anti-VEGF / verteporfin therapy.