Ranibizumab (Lucentis®)

Ranibizumab is a Fab fragment of a recombinant humanized monoclonal antibody with high affinity for VEGF-A (the ranibizumab binding site has an affinity for binding VEGF-A 140-fold higher than that displayed by the bevacizumab binding site) specifically studied for the treatment of AMD[(39,40,41)].

Ranibizumab has a solid clinical development program for this therapeutic indication, involving over 7,000 patients.

Ranibizumab binds to an amino acid chain common to all VEGF-A isoforms, thus rendering them inactive, reducing retinal and choroidal angiogenesis and halting the increase in capillary permeability.

It has been shown in animal models that ranibizumab effectively penetrates the retina and the subretinal space after intravitreal injection.

Its systemic half-life is short (2-3 hours, following intravitreal administration) and systemic clearance is fast, which makes its administration safe.

The average vitreous elimination half-life is approximately10 days[(42,43)]. Ranibizumab has been approved for all types of exudative/neovascular AMD lesions: classic, predominantly classic, minimally classic and occult lesions with no classic component, up to 12 disc areas (DA), where the neovascular component is ≥ 50% of the entire lesion.

The recommended dose is 0.5 mg.

Treatment includes a loading phase, consisting of 3 monthly injections, in the first 3 months, and a maintenance phase, where retreatment is decided according to disease progression, mostly evaluated in monthly visits through VA and OCT criteria, at least during the initial stage or recent neovascularization activity[(44)].

Phase III clinical trials MARINA and ANCHOR, which supported ranibizumab approval for the treatment of AMD, demonstrated that treatment with monthly intravitreal injections for a 12 months period was associated with a significant increase in visual acuity, compared to photodynamic therapy and placebo[(45)].

After 12 months, 25-40% of patients treated with ranibizumab showed gains of ≥ 15 letters (ETDRS), compared to 5-6% of the control group patients ($p<0.001$).

Similar results were confirmed after 2 years.

Both these studies have established ranibizumab as the first therapy not only capable of preventing loss of vision but also of improving vision in a substantial percentage of

patients: 33% of the patients treated with ranibizumab in the MARINA study and 41% in the ANCHOR study showed visual gains of at least 15 letters[45, 46,47,48, 49].

Subsequent studies (PIER, SUSTAIN, EXCITE) were aimed at defining flexible and individual dose regimes for the maintenance stage of treatment with ranibizumab, allowing an effective approach to maintaining visual gains, practical in terms of hospital follow-up and with maximum systemic and ocular safety[50,51,52].

These visual gains translate into real benefits for patients.

This effect was evaluated through 3 VFQ-25 sub-scales (near vision, distance vision and vision-related dependency); in fact, patients treated with ranibizumab showed improvements in these 3 sub-scales (MARINA and ANCHOR endpoints).

Specifically regarding dependency, ranibizumab allowed patients to become more independent in their daily activities.

Overall average VFQ scores increased by 4.6 points in the Lucentis® 0.5 group, compared to a 4.4-point decrease observed in the placebo group[53].

The PIER study evaluated an alternative therapeutic regime consisting of monthly injections, in the first 3 months, followed by quarterly injections, corresponding to a total of 6 injections within a year.

After an initial gain of 4.8 letters at month 3, patients treated with ranibizumab had lost an average of 0.2 letters at month 12, whereas patients in the control group lost 16.3 letters.

These results indicate that individual treatment criteria should be adopted during the maintenance stage, allowing an effective approach to maintaining visual gains, as well as allowing follow-up in clinical practice, with maximum systemic and ocular safety.

Vision is expected to be maintained in 90-95% of patients; a minimum gain of 3 lines should be observed in 30-40% of patients treated with ranibizumab[50].

In the EXCITE study, the quarterly treatment regime used in the PIER study (0.3 mg and 0.5 mg) was directly compared with a monthly regime (0.3 mg).

An average increase in VA was observed in all treatment groups during the 12 months of study duration. At month 12, compared to month 3, VA gains had decreased slightly with the quarterly regime (by -2.2 and -3.1 letters with ranibizumab 0.3 mg and 0.5 mg, respectively), having slightly increased (by +0.9 letters) with monthly administration of 0.3 mg of ranibizumab[52].

PrONTO, a small prospective, unicentric, open-label, non-randomized study sponsored by the investigator, evaluated the efficacy of 3 consecutive monthly injections, followed by individual retreatment based on OCT results (at intervals ≥ 1 month).

Retreatment criteria were: loss of 5 letters in VA, presence of fluid in the macula detected by OCT; increase ≥ 100 µm in central retinal thickness (CRT); de novo classic choroidal neovascularization; de novo macular haemorrhage; or persistent macular fluid detected by OCT.

Despite similar VA outcomes to those observed in the MARINA and ANCHOR studies having been observed with a smaller number of intravitreal injections, comparisons are limited by substantial differences in study design.

Although being a small, open-label trial, this study suggests that individual retreatment based on OCT results allows visual gains to be maintained with a smaller number of injections[45,54] .

The SAILOR-cohort 1 study evaluated the efficacy and safety of 3 consecutive monthly injections followed by quarterly monitoring visits, injections according to VA criteria (loss of > 5 letters from the maximum previous VA score) and OCT, if available (increase > 100 µm in CRT from the lowest previous measurement).

Additional visits/injections would take place if required.

Average VA increased from baseline after the first 3 injections, having subsequently decreased to an average gain of 2.3 letters for both ranibizumab doses, a better outcome than that observed for the PIER study, albeit suboptimal compared to those observed in the ANCHOR and MARINA studies.

These results indicate that quarterly visits are not sufficient to monitor and evaluate disease progression[45,55].

The objective of the SUSTAIN study was to evaluate the efficacy of 3 consecutive monthly injections followed by monthly monitoring and treatment according to the following criteria: loss of > 5 letters from the maximum previous VA score, in the first 3 months; or increase > 100 µm in CRT from the lowest previous measurement, in the first 3 months.

It was observed at month 12 that the majority of visual gains achieved in the first 3 months had been maintained.

Although this study consisted only of an interim analysis of 69 patients, the corresponding results suggest that efficacy outcomes may be maintained by a flexible regime with a smaller number of intravitreal injections and monthly monitoring.

However, some VA loss occurred after month 3, whereas fixed monthly injections led to additional VA gains during the maintenance stage[51,56].

In summary, the best VA outcomes were achieved with the monthly regime.

The poorest, albeit variable, efficacy outcomes were observed in studies with < 5 intravitreal injections.

The PrONTO and SUSTAIN studies demonstrated that monthly monitoring is required to maintain efficacy benefits, when compared to the SAILOR-cohort 1 study, which included compulsory quarterly monitoring visits, although more frequent follow-up was performed in many patients.

Therefore, ranibizumab emerges as the first approved neovascular AMD therapy (FDA approval in June 2006) able to improve visual acuity, having thus been recommended as first line therapy by many Ophthalmological Societies (e.g., the Royal College of Ophthalmologists, the German Ophthalmologists Association, etc.) and NICE (National Institute for Health and Clinical Excellence)[(57)].

Extension study HORIZON was performed in order to evaluate efficacy and safety after the first 2 years.

This study was designed as a post-marketing surveillance to monitor the safety and tolerability of Lucentis®, with a follow-up period of up to 3 years.

HORIZON enrolled 853 patients who had already completed one of the 2-year randomized Lucentis® trials, ANCHOR, MARINA or FOCUS[(58,59)].

While participating in the ANCHOR, MARINA or FOCUS studies, patients received monthly injections (active treatment with Lucentis® or Visudyne®, or sham).

During the HORIZON study, patients attended fixed quarterly visits; however, visit frequency could be increased by the investigator if they deemed it necessary to see the patient more often.

Lucentis® 0.5 mg injections were given on an as-needed basis, when the investigator felt that the patient would benefit from Lucentis® treatment.

The interval between injections was at least 30 days.

After 2 years (preliminary results), 69% of the 600 initial Lucentis®-treated patients received their injections.

Visual Acuity was available for 384/600 patients.

Among these 384 patients, median Snellen VA had increased by 3 lines, from 20/100 to 20/50, during the initial 2-year trial, having subsequently decreased by 2 lines from the HORIZON baseline to 20/80, at year 2 of the HORIZON study.

Overall, the safety profile of Lucentis® was very good and consistent with previous pivotal clinical trials of Lucentis®.

In general, better VA and anatomical outcomes after the first 2 years delayed the need for subsequent retreatment.

Additionally, the need for early AMD treatment was somewhat confirmed.

ome loss of previously achieved VA gains occurred, eventually related to sub-treatment during the extension period.

Loss of visual acuity and the need for retreatment during the HORIZON study shows that the disease remains active after the first two years of monthly injections, evidencing the need for careful patient monitoring, as well as timely retreatment.

In clinical trials, the benefits of ranibizumab regarding visual acuity were independent of the type of CNV lesion.

Additionally, these benefits were associated with a low rate (< 0.1%) of severe adverse events (endophthalmitis, retinal detachment, traumatic cataract).

Less severe ocular adverse events occurred in less than 2% of patients, including intraocular inflammation and increase in intraocular pressure. In all clinical trials, Lucentis® revealed to be a well-tolerated drug, with no statistically significant differences observed in ocular adverse events between treatment arms.

The results of the SAILOR study suggest a possible increase in the risk of de novo cardio vascular adverse events (CVA) in patients treated with ranibizumab with previous history of CVA or its risk factors (e.g., cardiac arrhythmias), although the differences observed were not statistically significant.

Safety monitoring during the post-marketing period has confirmed the good ocular and systemic safety profile of ranibizumab, whose risk management plan has been strictly implemented.

Other clinical trials are in course for other therapeutic indications, namely Diabetic Macular Oedema, Central Retinal Vein Occlusion and other ocular pathologies involving choroidal neovascularization, whose preliminary results have revealed to be promising.

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