• Clinical Research •

Impact of switching from ranibizumab to aflibercept on the number of intravitreous injection and follow up visit in wet AMD: results of real life ELU study

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Abstract

● **AIM:** To study if one of the two molecules could lead to a lower number of follow up visits and intra-vitreous injection (IVI) with the same efficacy.

● **METHODS:** ELU (or "elected" in French) study is a retrospective study conducted in real life in patients presenting suboptimal response after ranibizumab IVI (phase 1) and secondary switched to aflibercept (phase 2). The number of follow up visits and IVI were compared in both phases. Visual acuity (VA) evolution and "switching" reasons were secondary analyzed.

● **RESULTS:** We retrospectively included data of 33 patients (38 eyes) with age-related macular degeneration (AMD; mean age: 77±7.7y). The number of monthly follow up visits [median (Q1; Q3)]: was significantly lower with aflibercept (phase 2), respectively 1.0 (0.81; 1.49) visits in phase 1, versus 0.79 (0.67; 0.86) visits in phase 2. The median number of monthly IVI also significantly decreased in phase 2, respectively 0.67 (0.55; 0.90) IVI in phase 1, versus 0.55 (0.45; 0.67) IVI in phase 2. The mean VA evolution (VA final-VA initial) was similar in both phases, (P>0.05). Whatever the reason for "switching" (loss of efficacy, tachyphylaxis, tolerance problems), there was no incidence on VA evolution over the time.

● **CONCLUSION:** Our results show that switching from ranibizumab to aflibercept in "suboptimal" patients significantly reduce the number of follow up visits and IVI, with a comparable efficacy. This decrease in visit number could improve patients' quality of life and reduce surgical risk by reducing the number of injections.

● **KEYWORDS:** wet age-related macular degeneration; anti-VEGF; aflibercept; ranibizumab; follow up visit; intravitreal injection; visual acuity
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INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of legal blindness in industrialized countries[1-2]. Vascular endothelial growth factor (VEGF) have modified the prognosis of patients with exudative AMD, offering for the first time, the possibility to improve visual acuity (VA)[3-4].

Two products with marketing authorization for this indication are currently used in France: ranibizumab and aflibercept. To date, no study has clearly shown the superiority of either product in terms of safety or efficacy[5-6].

It is therefore difficult to rationally justify the use of either of these two first-line drugs in terms of efficacy. If we can demonstrate that one of the two molecules produces the same efficacy with a lower number of follow up visits and intra-vitreous injection (IVI), then this molecule could will be the "ELU" (or "elected" in French means "a better person than others, with special gift"). In fact, the "ELU" molecule, could be used as first intention and possibly improve the quality of life for the patients and their families.

Because pivotal studies on ranibizumab and aflibercept have already clearly demonstrated the comparable efficacy of the two products [by optical coherence tomography (OCT) analysis], we decided in this study to focus on the number of follow up visits and the number of IVI to compare the two molecules.

The main objective of the "ELU" study was analyzing the number of follow up visits and IVI for patients switching from

ranibizumab to aflibercept because of suboptimal response. Anatomical parameters (measured by OCT) were not analyzed. The secondary objectives were to assess VA evolution and switching reasons.

SUBJECTS AND METHODS

Ethical Approval ELU is a retrospective, observational, mono-centric study, performed in the Ophthalmology Department of the Saint Joseph Hospital in Marseille. The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the IRB. All retrospective data was obtained from the electronic hospital's medical record system.

Elderly patients with exudative AMD, regardless of the type of subretinal neo-vessels (NV) determined by fluorescein angiography and OCT at the time of diagnosis [5 types classification adapted from Freund *et al*[7] as: 1) visible NV; 2) occult NV; 3) mixed NV with visible predominance; 4) mixed NV with occult predominance; 5) neo-vascularized retinal pigment epithelium detachment (PED)], treated with anti-VEGF IVI for the first time (naïve patients) and followed in the ophthalmologic department from Mar. 2013 to Nov. 2015 were included. All patients received ranibizumab as first line (phase 1), and were switched to aflibercept because of suboptimal response (phase 2).

Patients with the following criteria were included in the study: patients with exudative AMD, treated by IVI of ranibizumab for the first time (naïve patients) and with suboptimal response to ranibizumab and then "switched" to aflibercept. A suboptimal response was defined as a primary favorable response to treatment (with lesion drying measured by OCT), followed by a therapeutic escape, objectivized during 3 consecutive monthly follow up visits, as a loss of treatment efficacy (persistence of intra-retinal fluid by OCT).

Patients with pathology other than AMD and IVI other than ranibizumab then aflibercept in this sequence of treatment were not included in the study.

All patients were followed by pro re nata (PRN) monitoring, with a monthly follow up visit conducted by the same practitioner as part of a specific consultation dedicated to maculopathies (AMD, diabetic maculopathy, macular edema due to central retinal vein occlusion and so on).

During the entire study period (2013-2015) follow up visits were systematically based on: VA scores measured with ETDRS charts (performed by an orthoptist under the same conditions), slit-lamp examination with fundus and intraocular pressure analysis, macular OCT (model: NIDEK RS3000 Advance) with radial anatomical cuts and a perifoveal central mapping.

At the end of each consultation, a treatment plan was established based on the analysis of the following parameter: visual loss or subretinal hemorrhage persistence in the fundus, change in subretinal NV (sub-or intra-retinal edema), NV thickening, PED persistence, and central retinal thickness increase). When a treatment with IVI was necessary, a new visit was programmed within the same week. In case of suboptimal response after IVI with ranibizumab, the patients benefited from a "switch" to aflibercept. A "suboptimal response" was defined as a primary favorable response to treatment (with lesion drying measured by OCT), followed by a therapeutic escape, objectivized during 3 consecutive monthly follow up visits, as a loss of treatment efficacy (persistence of intra-retinal fluid by OCT).

VA evolution in both groups was assessed by comparing VA at the beginning of the follow-up (initial VA) with VA at the end of the follow up (final VA). The reasons for "switching" and their incidence on VA were also analyzed.

Statistical Analyses Quantitative variables are expressed as mean and standard deviation (SD), or median (Q1; Q3), as appropriate. Non-parametric Wilcoxon and Brown Mood tests were used to compare the means and medians for each phase. All statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

We retrospectively included 33 patients (38 eyes) with AMD and mean age 77±7.7y [median (Q1; Q3): 78.1 (72.3; 82.9)y], with a male/female ratio of 10/23. The NV type distribution of in this population was, 7.9% (3/38) of type 1 NV, 42.1% (16/38) of type 2 NV, 10.5% (4/38) of type 3 NV, 2.6% (1/38) of type 4 NV and 36.8% (14/38) of type 5 NV. The mean follow-up duration in months was 20.13±14.92mo in phase 1, versus 19.28±6.28mo in phase 2.

Number of Follow-up Visits and IVI Analysis The number of monthly follow up visits [median (Q1; Q3)]: was significantly lower with aflibercept (phase 2); respectively 1.0 (0.81; 1.49) visits in phase 1, versus 0.79 (0.67; 0.86) visits in phase 2. The median number of monthly IVI also significantly decreased in phase 2; respectively 0.67 (0.55; 0.90) IVI in phase 1, versus 0.55 (0.45; 0.67) IVI in phase 2. This decrease during the aflibercept treatment was statistically significant, for follow up visits and injections (Table 1), especially when comparing medians (P=0.0002 for follow up visits versus P=0.0041 for IVI; Brown Mood test).

Visual Acuity Evolution VA over time was therefore stable and comparable during each of the two phases. During phase 1 (ranibizumab), the initial and final VA were respectively 0.41±0.25 and 0.42±0.23 versus 0.42±0.23 and 0.45±0.29 during the phase 2 (aflibercept; Figure 1). The non-parametric tests did not show any statistically significant difference on VA evolution between the two phases (P=0.7886; Brown-Mood median test; Table 2).

Table 1 Monthly number of control follow up visits and injections for each phase mean±SD

Studied data	Phase 1: ranibizumab	Phase 2: aflibercept	*P* (Wilcoxon)	*P* (Brown-Mood)
The follow-up duration in months	20.13±14.92	19.28±6.28		
Monthly No. of follow up visits	1.33±1.07	0.99±1.15	0.0005	0.0002
Median (Q1; Q3)	1.00 (0.81; 1.49)	0.79 (0.67; 0.86)		
No. of monthly IVI	0.83±0.66	0.57±0.24	0.0049	0.0041
Median (Q1; Q3)	0.67 (0.55; 0.90)	0.55 (0.45; 0.67)		

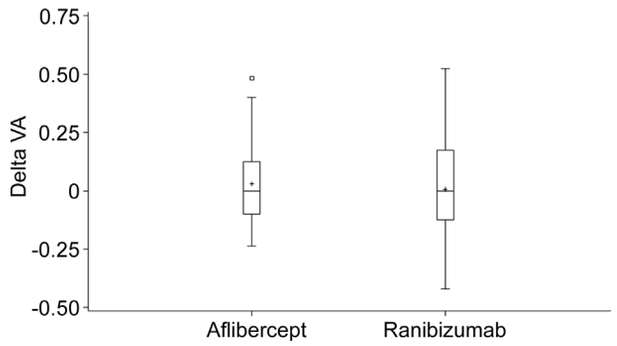

Figure 1 Comparison of VA evolution (delta VA=VA final-VA initial), measured by ETDRS for each phase.

Table 2 Comparison of VA delta (VA final-VA initial)

Studied data	Phase 1: ranibizumab	Phase 2: aflibercept
Mean±SD	0.0066±0.2377	0.0305±0.1792
Median (Q1; Q3)	0.000 (-0.125; 0.175)	0.000 (-0.100; 0.125)
P (sign test)	0.8642	1.0000
P [signed rank test (W)]	0.8409	0.5752
P (Wilcoxon)	0.8113	
P (Brown-Mood)	0.7886	

VA: Visual acuity.

Switching Reasons Whatever the reason for "switching" (loss of efficacy, tachyphylaxis, tolerance problems), there was no incidence on VA evolution over the time.

DISCUSSION

Aflibercept is not a monoclonal antibody but an anti-VEGF. Its "multitarget" mechanism of action differs from that of ranibizumab with supplementary placental growth factor (PLGF) and VEGF-B inhibition (in addition to VEGF-A inhibition common in both products)[8]. The half-life of aflibercept is slightly greater than that of ranibizumab, suggesting that its clinical efficacy is prolonged over time. On the other hand, there is also an associated action on the PLGF[9].

Our study showed a statistically significant decrease in the number of follow up visits and IVI after switching from ranibizumab to aflibercept, regardless of initial NV type. No change in VA over time was observed. This study was a retrospective study with all the biases related to this type of study.

The cohort was also limited (38 eyes), including only patients "switched" from one treatment to another because of a suboptimal response. Because this population experienced a loss of efficacy during initial treatment, we expected an increase (due to the need to intensify the treatment) or rather a stability of IVI number after the switch. On the contrary, the results showed a slight decrease in the number of follow up visits and IVI after the witch, during the aflibercept treatment. Furthermore, in this "real life" population under treatment for several years, we would have rather expected an improvement of anatomical efficacy but not an improvement of VA.

Many results have been presented on this subject. They are difficult to compare because very different from a methodological point of view[10-30].

The results of the ELU study are consistent with those of retrospective studies[10-15,20,22,25-26,29,31] reporting a decrease in the number of IVI over time with VA stabilization associated anatomic improvement (especially in case of associated PED). The most significant study is the Fight Retinal Blindness study conducted in a large cohort of 384 patients[14].

The results of the main prospective studies[16-19,27,31] are mainly in favor of a stable number of IVI, with a VA improvement associated with anatomic improvement (always greater in the case of PED). It seems then, that in prospective studies, the results are different. This confirms the results of real-life studies conducted over the last years, with always lower results than those of pivotal studies. It would therefore seem that keeping a high injection rate for these "suboptimal" patients, would improve the positive effect of the switch.

In addition, the decrease in the number of follow up visits and IVI, although statistically significant, is quite low: usually less than one visit and one IVI per year.

Some studies also showed that this improvement after a switch was temporary[19,32]. After 12mo, it would indeed seem necessary either to intensify the treatment again (by increasing again the number of follow up visits and IVI), or to achieve switch again (also called "switch back"). The temporary effect of this improvement suggested it secondary to the switch itself, that is to say, related to the change of molecule in patients with a loss of efficiency over time (drug tolerance or tachyphylaxis effect), and not on the molecule itself. The prospective study of Mantel *et al*[19] in 2016, as the only control study, seemed to be the most interesting methodologically, comparing switched patients, with a control arm including patients continuing ranibizumab. No statistically significant difference between

the two groups was found. It was however a small cohort[17], but the switch seemed not beneficial for all patients. Moreover, study of Georges *et al*[33], ARVO congress 2015, comparing two naïve arms on a PRN follow-up, showed that there was no difference in efficacy and IVI number between the two products (aflibercept and ranibizumab) after 18mo of follow-up. However, this is again a retrospective study conducted on a limited cohort.

Regarding Meta-analysis (prospective and retrospective)[21,23-24], we can notice their overall results in favor of VA stabilization (or even improvement) associated with anatomic improvement. It is nowadays accepted that the persistence of intra-retinal fluid is deleterious for the patients, causing a photoreceptors alteration and a VA decrease with retinal atrophy progression[32,34-35]. Switches or even switches-back[12,36] seem a good option for these suboptimal patients with compromised functional results. For these patients, the objective is to intensify the treatment in order to improve the clinical situation and to best protect the photoreceptors, and therefore the vision and autonomy of the patient.

The ELU study did not allow finding the "ELU" molecule. Today, the choice of the best molecule in our department remains difficult. The difference observed between the two products seemed rather to be due to a "switch effect" than to a better efficacy of one molecule versus the other (cf. switch and switch back). Since their market authorization we are routinely using both products in our ophthalmological department.

In conclusion, the ELU study did not allow finding the "ELU" molecule. Our results showed that switching from ranibizumab to aflibercept in "suboptimal" patients, significantly reduced the number of follow up visits and IVI, with a comparable efficacy. This decrease in visit number could improve patients' quality of life and reduce surgical risk by reducing the number of injections. Despite its small population, the study confirmed therefore the interest of the switch for patients with a suboptimal response over time, in order to limit photoreceptor involvement and progression to atrophy and fibrosis.

Because the switch effect might be more related to the change of molecule than to the effectiveness of the molecule itself, this hypothesis should be confirmed by further prospective and controlled studies. It seems also necessary to study whether the switch from ranibizumab to aflibercept is as effective as the switch from aflibercept to ranibizumab.

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