Inject and Extend Dosing versus Dosing As Needed

A Comparative Retrospective Study of Ranibizumab in Exudative Age-Related Macular Degeneration

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Purpose: The purpose of this study was to compare two strategies for retreatment with ranibizumab in exudative age-related macular degeneration.

Method: Two series of consecutive patients treated with ranibizumab in a hospital-based department of ophthalmology were analyzed retrospectively: the first series (n = 52), after as-needed reinjections (PRN group) and the second (n = 38) after reinjections according to the Inject and Extend dosing method (IaE group). Patients’ baseline characteristics, type of choroidal neovascularization, and Early Treatment Diabetic Retinopathy Study initial and final visual acuity (at 52 ± 4 weeks) were recorded in each group. Groups were compared by the Mann–Whitney U test or Fisher’s exact test.

Results: Groups were well balanced at baseline for age (P = 0.58), sex (P = 0.66), laterality (P > 0.99), and initial visual acuity (P = 0.33). At 1 year, the mean gain in visual acuity was greater in the IaE group than in the PRN group (+10.8 ± 8.8 vs. +2.3 ± 17.4 letters, P = 0.036), but eyes in the IaE group were given significantly more injections (7.8 ± 1.3 vs. 5.2 ± 1.9 injections, P < 0.001). The number of follow-up visits attended was similar (8.5 ± 1.1 vs. 8.8 ± 1.5, P = 0.2085).

Conclusion: Patients reinjected by the IaE dosing method had a far better visual outcome but after more injections.

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Antivascular endothelial growth factor therapy is the current standard treatment for exudative age-related macular degeneration. The initial clinical trials of ranibizumab showed that it was effective for the treatment of this condition. The MARINA study included patients with subfoveal occult choroidal neovascularization (CNV) and showed a 1-year mean improvement of 7.2 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart in the visual acuity of eyes treated with ranibizumab. The 1-year results of the ANCHOR study, which included patients with subfoveal classic CNV, showed a major improvement in visual acuity with a gain of 11.3 letters in eyes treated by monthly injections of 0.5 mg ranibizumab. In both the MARINA and ANCHOR trials, ranibizumab was injected according to a fixed monthly dosage regimen, whatever the course of the disease. In a subsequent clinical trial called the PIER study, the initial treatment, consisting of 3 monthly intravitreal injections of ranibizumab, was followed by a 3-month fixed-dose regimen. Mean visual acuity stabilized but did not improve significantly compared with baseline. The PrONTA study was an open-label, prospective, single-center, nonrandomized clinical study. Its protocol comprised three initial monthly injections followed by an as-needed (PRN) decision.
to retreat or not to retreat based on the evolution of visual acuity and the presence or absence of subfoveal fluid as observed by optical coherence tomography (OCT). The 1-year results showed a mean visual acuity improvement of 9.3 letters.\textsuperscript{5} During the 2 years of the study, great interpatient variability was observed in the number of injections needed, which ranged from 3 to 23.\textsuperscript{5,6} However, in the PrONTOS study, patients had to be monitored on a monthly basis with at least measurement of visual acuity and OCT examination at each visit. Monthly visits are sometimes problematic because traveling to specialized centers may be difficult, and most elderly patients need to be accompanied. Furthermore, the monthly management of a large number of patients constitutes a burden for both ophthalmologists and technicians. In the case of elderly patients who find it difficult to travel to a center for periodic follow-up, it is very tempting to see them less frequently once the macular fluid has disappeared and to ask them to phone in case of visual loss. However, in such cases, visual results may be disappointing. Thus, studies in which a monthly follow-up was achieved indeed reproduced the visual results of the PrONTOS study.\textsuperscript{7,8} On the contrary, a study in which follow-up visits were gradually spaced out gave less satisfactory results with a mean visual acuity improvement of only 0.7 letters at 1 year.\textsuperscript{9} To lengthen the period between follow-up examinations, Spaide\textsuperscript{10} recently suggested that eyes be re injected without macular fluid. This method\textsuperscript{10,11} has been called Inject and Extend (IaE) or Treat and Extend and consists of extending the interval between re injection without macular fluid and the next follow-up visit. However, to date, no results for this procedure are available, except for a limited series of 11 eyes with type 3 neovascularization, a particular form of CNV.\textsuperscript{12}

We report the visual results of 2 series of consecutive patients initially treated with 3 monthly consecutive injections of ranibizumab. For the first series, retreatments were decided on a PRN basis with intent to follow-up monthly and for the second, according to the IaE dosing method.

**Methods**

We retrospectively analyzed the consecutive charts and angiograms of patients with naïve subfoveal CNV who had been treated with ranibizumab in 2007 or 2008 for the first time, in 1 or both eyes, in a hospital-based department of ophthalmology in Orleans, France.

For the first series (the PRN group), we recorded patients’ data after retreatment by 3 monthly intravitreal injections of ranibizumab during the period from April to July 2007. Subsequent reinjections were given as needed according to the changes in patients’ visual acuity and/or the exudation shown by OCT. Four to 5 weeks after the third and last injection, all patients in the PRN group underwent an examination, including ETDRS visual acuity, fundus photography, and OCT. In case of persistent subfoveal or perifoveal fluid, macular intraretinal edema, visual loss of >5 letters, or the occurrence of a new hemorrhage, patients were retreated. The persistence of hemorrhage without evidence of fluid was not considered a criterion for retreatment. In the absence of retreatment criteria, no further injections were given and another examination was proposed usually 5 weeks later. Patients were also asked to call for an appointment immediately if they experienced any visual loss and/or worsening of metamorphopsia. In all follow-up examinations, ETDRS visual acuity, fundus ophthalmoscopy and photography, and OCT were performed.

For the second series (IaE dosing group), we recorded patients’ data from a different 4-month period. For this retrospective study, we considered including patients if they received the third injection of ranibizumab between December 2007 and March 2008. Patients who agreed to be retreated by the IaE method were recruited at that time. Patients who gave informed consent to its use were examined 6 weeks after the third injection, with ETDRS visual acuity testing, fundus ophthalmoscopy and photography, and OCT, and treated on the same day regardless of the results of OCT. Their next visit was scheduled 8 weeks later provided that OCT and fundus examination did not show either exudative manifestations (subfoveal or perifoveal fluid or macular intraretinal edema) or new macular hemorrhage or 4 weeks later in case of such manifestations or hemorrhage. The persistence of pigment epithelium detachment was not considered a condition that justified shortening the interval between injections. Patients who had no sign of active CNV at week 8 were examined and retreated 10 weeks later and in the absence of active CNV at week 10, 12 weeks after that. However, the follow-up was not extended beyond 12 weeks, because this time limit corresponded to the maximal length of this interval without injection. Patients who presented with active CNV at week 6 were treated; their next visit was scheduled 4 weeks later for examination and retreatment. Their next visit was scheduled 4 weeks later if CNV was still active or 6 weeks later if CNV was active. All patients were also asked to call for an appointment immediately if they experienced any visual loss and/or worsening of metamorphopsia between two visits. They were encouraged not to hesitate to call and be examined quickly.
All OCTs were performed with the Zeiss stratus OCT (Carl Zeiss, Jena, Germany). All intravitreal injections were performed according to the usual procedure, including topical anesthesia and surface disinfection with 5% povidone–iodine.

Baseline patient characteristics were recorded, i.e., age, sex, laterality of the treated eye, type of CNV (classic, including minimally classic; occult, including vascularized pigment epithelium detachment; retinal angiomatosus proliferation). Initial visual acuity and final visual acuity (at 52 ± 4 weeks) were measured as the number of letters by an independent observer on an ETDRS chart. Final visual acuity was the visual acuity measured at the time closest to 52 weeks.

Results are represented in mean ± standard deviation. Mann–Whitney’s nonparametric test was used to compare statistical distributions and the Fisher’s r-to-z transformation to explore correlations. The chi-square or Fisher’s exact test was used for categorical variables. The number of intravitreal injections given and of follow-up examinations attended were recorded and compared between the PRN and IaE groups.

Patients excluded were those with conditions other than age-related macular degeneration such as pathologic myopia or suspected idiopathic polypoidal choroidal vasculopathy and those who had not been examined at 52 ± 4 weeks from baseline even if they were examined later.

The study was performed in accordance with Health Insurance Portability and Accountability Act guidelines. According to French law, retrospective studies do not require Institutional Review Board agreement. Nevertheless, the study was approved by the Institutional Review Board and Ethics Committee of the Société Française d’Ophtalmologie (French Society of Ophthalmology).

Results

Fifty-two eyes were included in the PRN group and 38 in the IaE group. The PRN group of patients comprised 34 women and 18 men, aged from 63 to 87 years (mean, 79.8 ± 5.1 years). The right eye was studied in 24 cases and the left eye in 28 cases. Choroidal neovascularization was occult in 33 eyes (63.5%), classic in 14, and retinal angiomatosus proliferation in 5. Initial visual acuity ranged from 27 to 80 letters with a mean of 59.4 (Snellen equivalent: 20/64+). Final visual acuity ranged from 20 to 85 letters with a mean of 62.1 (Snellen equivalent: 20/64+). The number of injections performed ranged from 3 to 10 (mean, 5.3) and the number of visits from 6 to 13 (mean, 8.8 ± 1.5). Two patients developed a significant subretinal hemorrhage during follow-up.

The IaE group comprised 23 women and 15 men aged 58 to 87 years (mean, 79.1 ± 5.8). The right eye was studied in 18 cases and the left eye in 20 cases. Choroidal neovascularization was occult in 32 eyes (84.2%) and classic in 6. Initial visual acuity ranged from 20 to 81 letters with a mean of 61.2 (Snellen equivalent: 20/64+). Final visual acuity ranged from 33 to 85 letters with a mean of 72.0 (Snellen equivalent: 20/32+). The number of injections performed ranged from 6 to 11 (mean, 7.8) and the number of visits from 7 to 12 (mean, 8.5). No patient presented any complication such as a subretinal hemorrhage during the follow-up.

Comparison of baseline characteristics showed that groups were well balanced at baseline for age (P = 0.58), sex (P = 0.66), laterality (P > 0.99), and initial ETDRS visual acuity (P = 0.33). For types of CNV, there was a slight difference (P = 0.045) with more occult CNV in the IaE group (84.2 vs. 63.5%; Table 1). At 1 year, the eyes in the IaE group had a higher mean visual acuity gain than those in the PRN group (+10.8 ± 8.8 vs. +2.3 ± 17.4 letters, P = 0.036) and had been given significantly more injections (7.8 ± 1.3 vs. 5.2 ± 1.9, P < 0.001). The number of visits was similar (8.8 ± 1.5 vs. 8.5 ± 1.1 visits, P = 0.2085; Table 2).

We tested the hypothesis that the between-group difference in visual results was because of the different distribution of CNV subtypes with more cases of occult CNV in the IaE group. However, when only occult CNV, the most frequent subtype, was considered, the gain in visual acuity in the IaE group versus

<table>
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<tr>
<th>Table 1. Baseline Characteristics of the Patients and Eyes Studied</th>
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<td>PRN Group</td>
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<tr>
<td>Age</td>
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<tr>
<td>Sex (male/female)</td>
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<td>Percent of right eyes</td>
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<tr>
<td>Percent occult CNV</td>
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<tr>
<td>Initial VA (ETDRS letters)</td>
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</tbody>
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VA, visual acuity; NS, not significant.
the PRN group was significant (+9.5 ± 7.1 letters vs. −0.1 ± 18.5, \( P = 0.0452 \), Mann–Whitney U test).

We also tested the hypothesis that the between-group difference in visual results was a result of a difference between the risk of loss of vision, i.e., the loss of ≥1 letter, and there was indeed a significant reduction in the risk of visual acuity loss in the IaE group compared with the PRN group (2.6 vs. 34.6%, \( P = 0.002 \), Fisher’s exact test).

**Discussion**

This study shows the results of 1 year’s treatment with ranibizumab in a hospital-based department of ophthalmology in France, a country where ranibizumab is fully covered by third party buyers. In hospital-based departments, all the costs of consultations, imaging, and injections are also similarly covered. Consequently, there are no economic limitations on the retreatment of patients. As already stated, our aim was to compare two methods of retreatment: the PRN method, as proposed in the PrONTO study,\(^5\) and the IaE method, as proposed by Spaide.\(^10\)

However, our study was not designed as a randomized clinical trial but as a retrospective nonrandomized case series. Because it involved a single center and was retrospective, its results are difficult to compare with those of randomized trials or even open-label prospective studies. However, the purpose was to analyze the results for ranibizumab in the “real world,” i.e., in a hospital-based clinical setting with two different methods of retreatment.

The results showed that in our PRN group, monthly follow-up was not possible. In this group, as observed in another series,\(^9\) the results were disappointing with a mean improvement of only 2.3 letters. Patients were only examined 8.8 times a year instead of the 12 times initially expected. This was probably because of the difficulty of traveling to our department, especially for elderly patients living far from the hospital. These results are below expectations, because for all the published series of patients retreated on a PRN basis who could be followed-up more frequently than the present PRN group, the visual results were an improvement of 7 to 9 letters,\(^5,8\) i.e., similar to the improvement of 7 to 11 letters obtained in the initial randomized trials.\(^2,3\) We did not try to analyze the reasons for the disappointing visual acuity results in this group, but it is likely that there was a great delay in diagnosis and treatment of recurrences, thus leading to irreversible foveal damage as suggested in another retrospective study.\(^9\)

The patients in the present IaE group were given significantly more injections than those in the PRN group. In fact, the main drawback of the IaE method is that it may lead to unnecessary injections. For example, the results of the PrONTO study showed that 3 patients out of 40 did not require any additional treatment during their 2-year follow-up.\(^6\) If they had been retreated according to the IaE method, they would have been injected seven times during the first year of treatment and another four times during the second. Nevertheless, this number of injections is still far below the 24 recommended by the authors of the initial randomized clinical trials.\(^2,3\) In our IaE group, the risk of visual loss was reduced to 2.6%, a low risk for eyes with subfoveal CNV.

Table 2. Comparison of Visual Results at 12 Months With the Number of Injections Given and of Follow-Up Visits Attended*

<table>
<thead>
<tr>
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<th>PRN Group</th>
<th>IaE Group</th>
<th>Difference</th>
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<tbody>
<tr>
<td>VA gain</td>
<td>+2.3 ± 17.4</td>
<td>+10.8 ± 8.8</td>
<td>( P = 0.03 )</td>
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<tr>
<td>Mean number of injections</td>
<td>5.2 ± 1.9</td>
<td>7.8 ± 1.3</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Mean number of visits</td>
<td>8.8 ± 1.5</td>
<td>8.5 ± 1.1</td>
<td>( P = 0.20 )</td>
</tr>
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*The significance level was set at \( P < 0.05 \).

VA, visual acuity.
CNV, i.e., retinal angiomatous proliferation. The present “real-life” retrospective study showed that, in our department, patients reinjected by the IaE method had a far better visual outcome than those reinjected by the PRN method, although the latter were given more injections. Furthermore, the monthly follow-up originally proposed did not prove possible for our PRN group, and the mean number of visits by the patients in this group was only 8.8 instead of the 12 as initially planned.

Overall, the IaE method seemed more effective than the PRN method in preventing visual loss in patients treated with ranibizumab, at least when PRN dosing with monthly follow-up is not obtained, because visual results were far better in the IaE group with a similar number of follow-up visits as that for the PRN group. Randomized prospective studies comparing the two methods are now needed to establish the best reinjection strategy for patients treated with ranibizumab.

**Key words:** age-related macular degeneration, antivascular endothelial growth factor, choroidal neovascularization, ranibizumab.

**References**