A Treat and Extend Regimen Using Ranibizumab for Neovascular Age-Related Macular Degeneration

Clinical and Economic Impact

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 Purpose: To evaluate the visual outcome, number of injections, and direct medical cost of a “treat and extend” regimen (TER) in managing neovascular age-related macular degeneration (nAMD) with intravitreal ranibizumab.

 Design: Retrospective, interventional, consecutive case series.

 Participants: Ninety-two eyes of 92 patients met the entry criteria from May 2006 to May 2008.

 Methods: All patients with treatment-naïve nAMD were treated monthly until no intraretinal or subretinal fluid was observed on optical coherence tomography (OCT). The treatment intervals were then sequentially lengthened by 2 weeks until signs of exudation recurred. The interval was individualized for each patient in an attempt to maintain an exudation-free macula.

 Main Outcome Measures: Change from baseline visual acuity, proportion of eyes losing <3 lines and gaining ≥3 lines at 1 year of follow-up, annual mean number of injections, change from baseline OCT central retinal thickness (CRT), maximum period of extension, and adverse ocular and systemic events.

 Results: The mean follow-up was 1.52 years. Mean Snellen visual acuity improved from 20/135 at baseline to 20/77 at 1 year follow-up (P<0.001) and 20/83 at 2 years follow-up (P = 0.002). The proportion of eyes that lost <3 Snellen visual acuity lines at final follow-up was 96% and the proportion that gained ≥3 Snellen visual acuity lines was 32%. The mean OCT CRT decreased from 303 μm at baseline to 238 μm at 1 year follow-up (P<0.001). The mean number of injections over the first year and between years 1 and 2 was 8.36 and 7.45, respectively. The mean maximum period of extension was 79.9 days. No adverse ocular or systemic events were reported during the follow-up period. The direct annual medical cost per patient was $16 114.52 for the TER. The direct annual medical cost per patient ranged from $15 880.07 to $28 314.16 based on previous clinical trial protocols.

 Conclusions: Eyes with nAMD experienced significant visual improvement when managed with intravitreal ranibizumab using a TER. This treatment approach also was associated with significantly fewer patient visits, injections, and direct annual medical cost compared with monthly injections such as in the phase III clinical trials.

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 Neovascular age-related macular degeneration (nAMD) is a leading cause of irreversible blindness in people ≥50 years old in the developed world. By 2030, AMD will be the cause of more blindness in the United States than diabetic retinopathy and glaucoma combined. Outcomes of patients with choroidal neovascularization (CNV) secondary to AMD have improved dramatically since the introduction of anti-vascular endothelial growth factor agents in 2004.

 The Minimally Classic/Occult Trial of Anti-vascular Endothelial Growth Factor Antibody Ranibizumab in the Treatment of Neovascular Age-related Macular Degeneration (MARINA) and Anti-vascular Endothelial Growth Factor Antibody for the Treatment of Predominantly Classic CNV in Age-related Macular Degeneration (ANCHOR) trials demonstrated that visual acuity outcomes in treating nAMD with intravitreal ranibizumab were far superior to any prospective, randomized, large-scale clinical trial of nAMD treatment previously published. In these trials, ranibizumab was injected intravitreally on a fixed, monthly basis over 2 years and resulted in a significant improvement in mean visual acuity.

 Alternative, fewer, fixed scheduled injections have not resulted in visual outcomes that were as favorable in some previous studies. In the Phase IIIb, multicenter, randomized, double-masked, sham injection-controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to AMD (PIER), patients with new-onset nAMD were treated with...
intravitreal ranibizumab on a monthly basis for the first 3 injections and then treated every 3 months thereafter. At 1 year, visual outcomes were statistically better than the control group but, unlike the MARINA and ANCHOR trials, the mean visual acuity improvement observed at month 3 was lost by month 12.

Individualized dosing regimens tailored to each patient using intravitreal ranibizumab to treat nAMD have been explored in an attempt to maximize visual acuity gains to a degree comparable to the ranibizumab pivotal MARINA and ANCHOR studies, but at the same time minimize the total number of intravitreal injections and patient visits.6–10 In the 2008 American Society of Retina Specialists Preferences and Trends (ASRS PAT) annual survey, nearly 88% of retina specialists reported treating nAMD patients in an individualized fashion (Mitra RA, Pollack JS. ASRS PAT Survey, 2008). The only prospective trial published to date using an individualized approach to treat nAMD was with ranibizumab in the Prospective Optical Coherence Tomography imaging of patients with Neovascular AMD Treated with Intra-ocular Ranibizumab (PrONTO) study. Favorable outcomes have been reported in this small, open-label trial as well as other retrospective studies with ranibizumab using similar pro re nata (PRN) regimens. Close follow-up with frequent office visits are typically needed to monitor the response to treatment in such PRN protocols. Because eyes are only retreated for recurrent exudation, multiple recurrences over time may potentially compromise long-term visual outcomes.11

In an attempt to minimize the number of intravitreal injections, office visits, and ancillary testing, a “treat and extend” regimen (TER) was first put forth by Bailey Freund, MD (Regillo CD, personal communication, February 2006) and then adopted by others. A typical TER starts with monthly injections until the signs of exudation have resolved with confirmation by optical coherence tomography (OCT). The treatment interval is then sequentially lengthened by 1 to 2 weeks as long as there are no signs of recurrent exudation. When recurrent exudation is detected on a follow-up visit, the treatment interval is reduced to the prior interval. Treatment is rendered at every visit but the time between visits is individualized based on a given patient’s response to treatment. As with traditional PRN regimens, the goal is to maintain an exudation-free macula with the fewest number of injections. This approach also may allow for a significant reduction in office visits and tests. However, to our knowledge, using ranibizumab in a TER has never been published. Therefore, this study analyzes the visual outcome, number of injections, and direct medical cost of managing treatment-naïve nAMD with intravitreal ranibizumab using a TER approach.

Methods

Institutional review board approval at Wills Eye Institute was obtained to review patient data for this retrospective, interventional, consecutive case series from 2 treating physicians (CDR and RSK) in a single clinical practice. Informed consent was not required for this deidentified review.

Patient Selection

All patient records were identified by the diagnosis of nAMD (International Classification of Diseases-9 code: 362.52) from May 2006 to May 2008. Patient medical records were reviewed and the following data were collected: Age, gender, date of nAMD diagnosis, best-corrected visual acuity at each visit, evaluation of fluorescein angiography at initial visit, and OCT evaluation for central retinal thickness (CRT), intraretinal or subretinal fluid, or pigment epithelial detachment.

The inclusion criteria consisted of patients with new-onset (treatment-naïve), subfoveal CNV associated with AMD who were managed using a TER with a minimum of 6 months of follow-up. All fluorescein angiographic CNV lesion subtypes and lesion sizes were eligible. Occult with no classic CNV eyes had to have signs of presumed disease progression with recent decreased visual acuity, known CNV enlargement, or signs of hemorrhage in the macula.

The exclusion criteria included eyes with any prior treatment for nAMD including laser photocoagulation, verteporfin photodynamic therapy, or intravitreal pegaptanib sodium. Other exclusion criteria included previous participation in a clinical trial for either eye for nAMD or prior vitrectomy surgery in the study eye. This cohort was defined as patients who received only intravitreal ranibizumab during the entire follow-up period. However, because in clinical practice the use of ranibizumab was not always authorized by a patient’s insurance at the initial visit, a single bevacizumab injection sometimes occurred as the patient’s first treatment. For the purpose of this study, these patients were allowed in this group if all subsequent injections were ranibizumab. Pretreatment fluorescein angiograms were analyzed for the CNV lesion size (in disc areas) and type (predominantly classic, minimally classic, and occult with no classic). The percentage of the lesion complex composed of hemorrhage was also determined.

Optical Coherence Tomography Analysis

The Stratus OCT (Carl Zeiss Meditec, Dublin, CA) or RTVue-100 OCT (Optovue Corporation, Freemont, CA) was used for all evaluations. For the initial visit, examination, and follow-up visits, each patient was managed with only the Stratus or RTVue-100 OCT machines. The internal limiting membrane, the retinal pigment epithelium, and Bruch’s membrane were identified on all scans centered through the fovea as determined by the red-free image on the OCT scanner. The macular thickness map and radial line scan protocols were used on all Stratus OCT scans. This consisted of 6 radial line scans of 6-mm length with high resolution 512 A-scans per line in 7.68 seconds of scanning. The MM5 and MM6/radial slicer scan protocols were used on all RTVue-100 OCT scans. The MM5 scan protocol consisted of 13 horizontal and vertical lines of 5-mm length with 807 A-scans per line and 8 horizontal and vertical lines of 4-mm length with 512 A-scans per line in 0.78 seconds of scanning. The MM6/radial slicer protocol consisted of 12 radial line scans 6-mm in length with 1024 A-scans per line in 0.27 seconds of scanning. All OCT images were examined qualitatively for the presence or absence of intra- and subretinal fluid. The CRT was obtained from the center subfield of the macular thickness map.

Treat and Extend Regimen

All patients were initially evaluated with slit lamp biomicroscopy, fluorescein angiography, and OCT. Patients were then treated monthly (every 4–5 weeks) with intravitreal ranibizumab (Lucentis, Genentech Inc, San Francisco, CA) until no signs of macular hemorrhage on slit lamp biomicroscopic examination and no intra- or subretinal fluid was observed on OCT. The treatment intervals were
Clinical outcome measures included mean and median logarithm of the minimum angle of resolution score for statistical analysis. Their most up-to-date distance correction and converted into a logarithm of the minimum angle of resolution score for statistical analysis. A Student t test analysis with P<0.05 was considered significant. Clinical outcome measures included mean and median Snellen visual acuities and gaining ≥3 Snellen visual acuity lines of visual acuity at 1 year follow-up from baseline, annual mean number of injections, OCT mean and median CRT change from baseline, mean maximum period of extension, and adverse ocular and systemic events.

### Economic Analysis

A third-party insurer cost perspective employing only direct medical costs was used for this analysis. The health care cost arising from provider services were according to the 2009 Current Procedural Terminology data payments by the Centers for Medicare and Medicaid Services (Table 1).

Direct medical costs of patients treated with TER were compared with those treated with intravitreal ranibizumab on a monthly basis for 1 year as performed in the MARINA and ANCHOR studies. These studies included an ophthalmic examination, fluorescein angiography, OCT, and intravitreal ranibizumab at the initial evaluation. Subsequent monthly visits included an ophthalmic examination and intravitreal ranibizumab injection. The direct medical cost of the PrONTO study was also determined per protocol. Ophthalmic examinations and OCT was obtained at the initial visit, followed by monthly visits thereafter. Fluorescein angiograms were obtained at the initial visit followed by at month 1, 2, 3, and every 3 months thereafter. Intravitreal ranibizumab injections were calculated based on the average of 5.6 injections over the 12 months followed. The cost of the protocol refraction was not included. It was assumed that the additional visits at day 14 and day 45 as well as additional OCTs at day 2, 4, 7, and 14 were for study purposes as outlined in the PrONTO protocol and were not necessary for routine care in clinical practice and therefore not included in the cost analysis.

### Results

#### Baseline Characteristics

Ninety-two eyes from 92 patients met the inclusion and exclusion criteria. The mean age was 80.6 years (range, 61–94; standard deviation 7.2).

### Table 1. Medical Costs (Medicare Average Allowable 2009 Rates in United States Dollars), Current Procedural Terminology (CPT) Codes, and J Codes for Interventions Associated with the Treatment of Neovascular Age-related Macular Degeneration

<table>
<thead>
<tr>
<th>Service</th>
<th>CPT or J Code</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmic examination and evaluation; intermediate</td>
<td>92012</td>
<td>75.23</td>
</tr>
<tr>
<td>Fluorescein angiography, fundus photographs, both eyes</td>
<td>92235</td>
<td>253.92</td>
</tr>
<tr>
<td>OCT evaluation, including technical and professional fees, 1 eye</td>
<td>92135</td>
<td>45.64</td>
</tr>
<tr>
<td>Intravitreal injection procedure</td>
<td>67028</td>
<td>192.32</td>
</tr>
<tr>
<td>Cost of ranibizumab injection</td>
<td>J2778</td>
<td>2067.00</td>
</tr>
</tbody>
</table>

OCT = optical coherence tomography.

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### Table 2. Comparison of Baseline Characteristics between Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR), Minimally Classic/Occult Trial of Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA), Prospective Optical Coherence Tomography imaging of patients with Neovascular AMD Treated with Intra-ocular Ranibizumab (PrONTO), and Treat and Extend Regimen (TER)

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>MARINA (0.5 mg arm)</th>
<th>ANCHOR (0.5 mg arm)</th>
<th>PrONTO</th>
<th>TER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>63.3</td>
<td>46.4</td>
<td>65</td>
<td>66.3</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>96.7</td>
<td>97.1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>77±8</td>
<td>76±8.6</td>
<td>83.5±7.2</td>
<td>82.6±6.6</td>
</tr>
<tr>
<td>VA, mean (median)</td>
<td>Not available</td>
<td>Not available</td>
<td>20/80 (20/80^1)</td>
<td>20/135 (20/100)</td>
</tr>
<tr>
<td>VA ≤20/200 (%)</td>
<td>12.9</td>
<td>23.0</td>
<td>Not available</td>
<td>22.8</td>
</tr>
<tr>
<td>20/200 &gt; VA &gt; 20/40</td>
<td>72.1</td>
<td>72.7</td>
<td>Not available</td>
<td>67.4</td>
</tr>
<tr>
<td>VA ≥20/40</td>
<td>15.0</td>
<td>4.3</td>
<td>Not available</td>
<td>9.8</td>
</tr>
<tr>
<td>Predominately classic CNV lesion (%)</td>
<td>0</td>
<td>96.4</td>
<td>17.5</td>
<td>19.6</td>
</tr>
<tr>
<td>Minimally classic CNV lesion (%)</td>
<td>37.9</td>
<td>3.6</td>
<td>57.5</td>
<td>28.7</td>
</tr>
<tr>
<td>Occult with no classic CNV lesion (%)</td>
<td>62.1</td>
<td>0</td>
<td>25</td>
<td>52.5</td>
</tr>
<tr>
<td>Size of lesion (disc areas)</td>
<td>4.5</td>
<td>1.79</td>
<td>3.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

CNV = choroidal neovascularization; SD = standard deviation; VA = visual acuity; VEGF = vascular endothelial growth factor.
deviation, 6.6), 61 were female (66.3%), and all participants were Caucasian. There were 48 right eyes (52%) and 50 pseudophakic eyes (54%). These baseline characteristics were comparable to the MARINA, ANCHOR, and PrONTO trials (Table 2). The mean duration of visual symptoms before treatment was 74.8 days (median, 30; range, 1–365). Forty-six eyes (50%) were treated within 1 month of symptom onset. Intravitreal ranibizumab was used for 975 of the 1053 total injections (93%) in the study group. The mean follow-up period was 1.52 years (range, 0.5–2.5). The mean CNV lesion size was 2.66 disc areas (range, 0.5–10) with 12.8% (range, 0–100%) of the lesion consisting of macular hemorrhage. The CNV subtype was categorized by fluorescein angiography as occult with no classic lesion in 48 eyes (52.2%), minimally classic in 48 eyes (28.7%), and predominantly classic in 18 eyes (19.6%). No adverse ocular or systemic events were reported over the course of the study.

The mean initial Snellen visual acuity at baseline was 20/135 (median 20/100; range, 20/25 to counting fingers at face; Table 3). The mean visual acuity improved significantly to 20/85 (median 20/60) at 3 months (P < 0.001), 20/77 (median 20/60) at 6 months (P < 0.001), 20/75 (median 20/54) at 9 months (P < 0.001), 20/77 (median 20/60) at 12 months (P < 0.001), 20/87 (median 20/60) at 18 months (P = 0.01), and 20/83 (median 20/70) at 24 months follow-up (P = 0.002; Fig 1). At the 1 year follow-up visit, 96% of patients lost <3 lines of Snellen visual acuity and 32% improved ≥3 lines of Snellen visual acuity. The mean OCT CRT improved from 303 μm (median, 286; range, 190–558) to a mean minimum thickness of 208 μm (median, 204; range, 182–390; P < 0.001) at 1 year of follow-up. The mean longest period of extension was 79.9 days with a mean of 8.36 injections over the first year (median, 8) and 7.45 injections between years 1 and 2 (median, 7).

After an exudation-free macula was achieved, 42 eyes (45.7%) demonstrated no exudative recurrence, 28 eyes (30.4%) demonstrated 1 exudative recurrence, 8 eyes (8.7%) demonstrated 2 exudative recurrences, 5 eyes (5.4%) demonstrated 3 exudative recurrences, 2 eyes (2.2%) demonstrated 4 exudative recurrences, and 7 eyes (7.6%) demonstrated persistent signs of exudation at each visit during the follow-up period (Table 4; Figs 2 and 3). In those eyes with exudative recurrence, the mean duration was 296 days (range, 112–631) after the start of treatment.

**Economic Impact**

The direct medical costs of the TER were calculated for each patient. The mean cost per patient using TER at year 1 was $13 164.52 (range, $13 710.48–$23 747.53) and the mean cost per patient years 1 and 2 was $13 971.44 (range, $11 191.42–$21 098.18). The direct medical cost over 1 year of treatment in a fixed, monthly fashion comes to $28 314.16 and $15 880.07, respectively.

**Discussion**

The TER used in this study demonstrated favorable visual acuity results in patients with nAMD with significantly fewer visits and intravitreal injections compared with treatment in a fixed, monthly fashion such as in the MARINA and ANCHOR trials. Compared with the PrONTO study, there were a lower mean number of office visits and tests with a higher total annual mean number of treatments. The direct medical costs between the PrONTO and TER were similar.

Owing to the patient, physician, and economic burden of the MARINA and ANCHOR protocol with monthly visits and treatments, alternative dosing strategies were explored. Initial published reports of individualized treatment were documented with intravitreal bevacizumab.13–15 The PrONTO study was the first attempt to study individualized ranibizumab treatment.8 It was a 2-year, prospective trial that enrolled nAMD patients with subfoveal CNV with a visual acuity between 20/40 and 20/400 and a CRT of ≥300 μm. Patients received 3 consecutive monthly intravitreal injections of ranibizumab and were retreated based on 1 of 5 criteria: 5-letter visual loss associated with macular fluid noted on OCT, an increase in OCT CRT of ≥100 μm, new-onset classic CNV, new macular hemorrhage, or persistent macular fluid detected by OCT after the last injection. At the 1 year follow-up, there was mean visual acuity improvement

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**Table 3. Visual Acuity (VA) Outcomes for the Treatment of Neovascular Age-related Macular Degeneration Using a Treat and Extend Regimen with Ranibizumab**

<table>
<thead>
<tr>
<th>Follow-up Interval (no. of patients)</th>
<th>Mean Snellen VA</th>
<th>Median Snellen VA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (92)</td>
<td>20/135</td>
<td>20/100</td>
<td></td>
</tr>
<tr>
<td>3 months (92)</td>
<td>20/85</td>
<td>20/60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 months (92)</td>
<td>20/77</td>
<td>20/60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9 months (84)</td>
<td>20/75</td>
<td>20/54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 months (76)</td>
<td>20/77</td>
<td>20/50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18 months (53)</td>
<td>20/87</td>
<td>20/60</td>
<td>0.001</td>
</tr>
<tr>
<td>24 months (28)</td>
<td>20/83</td>
<td>20/70</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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**Table 4. Exudative Recurrences in Eyes during the Extension Phase of the Treat and Extend Regimen with Ranibizumab**

<table>
<thead>
<tr>
<th>Exudative Recurrence Frequency</th>
<th>Eyes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42 (45.7)</td>
</tr>
<tr>
<td>1</td>
<td>28 (30.4)</td>
</tr>
<tr>
<td>2</td>
<td>8 (8.7)</td>
</tr>
<tr>
<td>3</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>4</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Persistent exudation</td>
<td>7 (7.6)</td>
</tr>
</tbody>
</table>
Figure 2. Representative case of 62-year-old man with neovascular age-related macular degeneration in the right eye (A). Baseline color fundus images with early (B) and late phase (C) fluorescein angiographic images demonstrate subfoveal, occult choroidal neovascularization with intraretinal hemorrhage.

Figure 3. Optical coherence tomography (OCT) images of the representative case. The baseline OCT demonstrates intraretinal fluid, subretinal fluid, and a pigment epithelial detachment with a Snellen visual acuity of 20/100 (A). The patient was injected every month with intravitreal ranibizumab until no signs of exudation were observed. After 3 intravitreal injections the visual acuity improved to 20/40 (B). The follow-up, retreatment period was initially extended to 6 weeks and the visual acuity improved to 20/25 (C). The follow-up, retreatment period was then extended to 8 weeks and the visual acuity was 20/30 (D). The follow-up, retreatment period was then extended to 10 weeks, the visual acuity decreased to 20/60, and signs of exudation recurred (E). The follow-up, retreatment period was then shortened to the previous interval of 8 weeks and the visual acuity was 20/30 (F). The follow-up, retreatment period was then reextended because signs of exudation resolved. The follow-up, retreatment period was then extended to 10 weeks and the visual acuity remained stable at 20/30 (G). All OCTs included in this figure were representative of the entire study and obtained from approximately the same orientation.
by 9.3 letters with 95% of patients losing <15 letters and 35% of patients improving by ≥15 letters. These visual outcomes were similar to the ranibizumab arms of the MARINA and ANCHOR trials, but with an average of 5.6 injections over 12 months.\textsuperscript{8,11} However, exudative recurrence was noted in 37 (92.5%) of the 40 eyes in the PrONT study. In comparison to the present study, 62 eyes (42.7%) did not demonstrate any exudative recurrence during the follow-up period. These exudative recurrences have the potential to limit the final visual acuity achieved over the long term.\textsuperscript{11}

To test the PrONT style of PRN treatment with ranibizumab in a larger scale clinical trial, the Safety Assessment of Intravitreal Lucentis for Age-Related Macular Degeneration (SAILOR) trial was initiated.\textsuperscript{16} The SAILOR trial was a prospective, randomized, open-label, Phase IIIb trial that modeled the retreatment criteria after the PrONT study with >2000 patients treated with either 0.3 or 0.5 mg of ranibizumab. The retreatment criteria were based on >5 Early Treatment Diabetic Retinopathy Study (ETDRS) letter visual loss from the best VA at prior visits or >100 μm increase in CRT from the lowest measurement on prior visits. In contrast with the PrONT protocol, new-onset macular hemorrhage, new classic CNV, and persistent fluid after the last injection were not included in the retreatment criteria. In the SAILOR trial, patients were treated with 3 monthly injections and PRN thereafter. The mandated follow-up visits decreased from a monthly schedule to quarterly from months 3 to 12, although investigators were allowed to evaluate patients more frequently if needed. After the first 3 injections, the mean VA improved 5.8 to 7.0 ETDRS letters from baseline in treatment-naïve patients. However at month 12, the mean visual acuity gain was 0.5 to 2.3 ETDRS letters compared with baseline. The proportion of patients gaining ≥15 letters in the treatment-naïve arm was 14.6% to 19.3% at month 12. The mean number of treatments was 3.9 to 4.6 treatments administered over a mean of 8.8 visits at the 1-year end point. Less favorable visual outcomes in the SAILOR trial may be explained by more conservative management with fewer retreatments and less frequent follow-up compared with the PrONT study.

The TER also attempts to individualize treatment of nAMD patients with the goal of maintaining an exudation-free macula. Patient visits and physician time are utilized more efficiently. Compared with the MARINA and ANCHOR trials, significant direct medical cost savings resulted from fewer treatments and office visits. Compared with the PrONT study, direct medical cost savings were similar compared with TER-treated patients in our study. In addition, the TER resulted in fewer patient visits, OCTs, and fluorescein angiograms. Patient visits also increase the indirect medical cost associated with caretakers. This was not assessed in the present study, but also favors the TER.

The mean number of injections in the present study was higher than the PrONT study. In particular, the patients in our TER study received nearly 3 more injections in the first year compared with the PrONT study first year. With both types of PRN approaches, the mean number of injections is likely to decrease with longer follow-up when patients are in the maintenance phase of therapy, and this trend is evident in the current study with a lower mean and median number of injections between 12 and 24 months. In general, more frequent treatments should help to minimize anatomic damage from recurrent fluid, and minimizing exudative recurrences is a logical approach to maximizing visual acuity results.\textsuperscript{11}

The PrONT study not only showed that individualized treatment of nAMD can be very effective, but also helped to establish the role of OCT in evaluating the effect of treatment. Visual acuity and clinical examination are important in evaluating patients with nAMD, but alone are probably not sufficient with a PRN treatment strategy. Visual acuity can be variable in the setting of nAMD and not reflective of disease activity.\textsuperscript{11} Changes on OCT may precede visual acuity deterioration.\textsuperscript{8,11} The favorable visual acuity outcomes of the present study can be partially attributed to the reliance on OCT findings in guiding management decisions.

This study has several limitations. First, the study is relatively small, especially compared with the ranibizumab prospective clinical trials such as ANCHOR, MARINA, PIER, and SAILOR. Second, the study is retrospective, with all its inherent limitations, and there is no monthly treatment or traditional PRN control groups. Third, Snellen visual acuity was utilized in contrast with the prospective studies that used the standardized, refracted ETDRS protocol. Lastly, lack of a strict entry visual acuity range or lesion size limits our ability to make comparisons between studies. Furthermore, the use of 2 different OCT machines introduces inherent variation in the cohort analysis. Nonetheless, this study does reflect real-world clinical practice with a TER for managing AMD-related new-onset, subfoveal CNV and shows relatively good clinical outcomes that have yet to be demonstrated consistently utilizing ranibizumab in a patient-individualized fashion.

In conclusion, patients with nAMD can have significant visual improvement when managed with intravitreal ranibizumab using a TER. Given the limitations of a retrospective study design of unmasked participants and nonprotocol visions, the TER showed favorable visual outcomes with fewer patient visits, fewer treatments, and lower associated direct medical costs compared with the phase III pivotal trials.

References


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