Interferon Alfa-2a Is Ineffective for Patients With Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

Results of a Prospective Randomized Placebo-Controlled Clinical Trial

Pharmacological Therapy for Macular Degeneration Study Group

**Background:** Interferon alfa-2a has been shown to be effective as an antiangiogenic agent for several systemic human angiogenic disorders and has shown antiangiogenic activity in the laboratory.

**Objective:** To evaluate the safety and efficacy of interferon alfa-2a for the treatment of choroidal neovascularization secondary to age-related macular degeneration.

**Methods:** A randomized, placebo-controlled, parallel, multicenter double-blind trial was performed at 45 ophthalmic centers worldwide. Four hundred eighty-one patients were randomly assigned to 4 treatment groups: placebo or interferon alfa-2a (Roferon-A), 1.5, 3.0, or 6.0 million international units (MIU). Visual acuity testing, clinical examination, fluorescein angiography, and indocyanine green angiography were evaluated, with the primary end point being a comparison of the number of patients who experienced a loss of 3 lines or more of vision at 1 year.

**Results:** At 52 weeks, 40 (38%; 95% confidence interval, 29%-48%) of 105 placebo-treated patients had lost at least 3 lines of vision (with 12% unavailable for follow-up), compared with 142 (50%; 95% confidence interval, 44%-55%) of 286 in the 3 active treatment groups combined. The difference in proportions was not statistically significant. However, a pairwise comparison of these proportions for the placebo group vs the group that received interferon alfa-2a, 6 MIU (with 26% unavailable for follow-up), showed a statistically significant difference in favor of the placebo group (P=0.02) and a nearly significant difference for the placebo vs the 1.5-MIU group (P=0.05) (with 16% unavailable for follow-up), again favoring the placebo group. The 3-MIU group (with 22% unavailable for follow-up) did not show a statistically significant difference in pairwise comparison (P=0.8), suggesting that a dose-response relationship was not evident.

**Conclusion:** Interferon alfa-2a provides no benefit as a treatment for choroidal neovascularization secondary to age-related macular degeneration and may be associated with a poorer visual outcome when given at a dose of 6 MIU. However, the absence of a clear dose-response relationship suggests the possibility that the observed differences result from chance.

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Aging-related macular degeneration is the leading cause of irreversible vision loss in the elderly in the Western world. Although laser photocoagulation has been shown to be beneficial in treating patients with classic or well-defined choroidal neovascularization (CNV), the great majority of patients with exudative maculopathy have poorly defined or occult disease that is not amenable to laser therapy. Using fluorescein imaging and conventional laser photocoagulation, studies have shown that only approximately 15% of patients are actually eligible for laser treatment, and that 50% will experience recurrences; thus, only about 7.5% of patients can be successfully treated at present.

Recent innovations with the use of indocyanine green (ICG) angiography in the imaging of CNV may increase our ability to treat this condition, but most patients will still remain ineligible for laser treatment because of either our inability to accurately image the blood vessels or their proximity to the foveal region. In addition, the high recurrence rate after laser treatment suggests that new treatment options for this condition be explored.

**For editorial comment see page 915**

Pharmacological therapy with antiangiogenic drugs is an attractive theoretical approach. However, the results of this study suggest that interferon alfa-2a is not effective for the treatment of choroidal neovascularization secondary to age-related macular degeneration.
SUBJECTS AND METHODS

The protocol for this study was approved by an internal review board at each participating institution. Forty-five centers from around the world enrolled patients in this study.

INCLUSION CRITERIA

Patients with clinical signs of exudative age-related macular degeneration with subfoveal involvement were enrolled. Fellow eyes either had signs of nonexudative age-related macular degeneration (drusen and/or retinal pigment epithelial changes) or also had exudative macular degeneration. Choroidal neovascularization in the study eye was classified into 1 of 4 subgroups by the investigators: (1) primary (no previous laser treatment) classic subfoveal CNV; (2) primary poorly defined or occult CNV with local involvement; this group consisted of eyes with occult CNV only without classic components, hemorrhage through the fovea, or a history of laser treatments; (3) recurrent classic or recurrent poorly defined subfoveal CNV; and (4) any of the above with blood encompassing the fovea.

The best-corrected visual acuity in the study eye had to be 20/320 or better (Snellen equivalent) with the use of the modified Early Treatment of Diabetic Retinopathy Study protocol and Early Treatment of Diabetic Retinopathy Study charts, measured within 14 days before the start of treatment. The patients had to be 50 years of age or older, have an Eastern Cooperative Oncology Group performance status of 0 or 1, and be willing to provide written informed consent.

EXCLUSION CRITERIA

Patients were not eligible if they had any of the following: CNV greater than 12 Macular Photocoagulation Study disc areas in size by fluorescein angiography; additional eye disease(s) that could compromise visual acuity in the study eye; a history of class III or IV cardiovascular disease (New York Heart Association functional status criteria); significant hepatic disease; significant renal disease; significant rheumatologic disease; a major allergic disease; significant central nervous system disease; autoimmune thyroid disease or systemic lupus erythematosus; relevant laboratory studies outside a specified range; a history of depression or suicidal tendencies; current use of other investigational new drugs, cytokines, or systemic corticosteroids (within 4 weeks before the start of the study treatment); and/or diabetes with poor glycemic control or diabetic retinopathy.

EVALUATIONS

Visual acuity testing performed by the Early Treatment of Diabetic Retinopathy Study protocol with Early Treatment of Diabetic Retinopathy Study charts, and contrast sensitivity testing with Pelli-Robson charts, were performed at baseline and at weeks 4, 12, 24, 36, and 52. Complete ophthalmic examinations were conducted at baseline and at weeks 4, 12, 24, 36, and 52. Hematologic and serum chemistry evaluations were conducted before enrollment and then weekly for the first month and monthly thereafter. Fluorescein angiography was performed at baseline and at 3, 6, 9, and 12 months. Optional ICG angiography was performed at baseline and at 6 and 12 months.

In addition, each patient had measurement of vital signs, physical examination, and an electrocardiogram before enrollment.

RANDOMIZATION PROCEDURE

An independent biostatistical center in Brussels, Belgium (International Institute for Drug Development), established a centralized randomization system for all of the centers. Randomization was performed by means of a computer program that used a minimization algorithm that took into account the center and the lesion type so that these variables would be evenly distributed across the 4 treatment groups.

TRIAL MEDICATION

Patients were randomized into 4 treatment groups: placebo and interferon alfa-2a, 1.5, 3, and 6 million international units the natural course of CNV resulted in our undertaking this large-scale controlled trial.

We report the 1-year results of a randomized, placebo-controlled, parallel, multicenter, double-blind study testing the efficacy of interferon alfa-2a in 481 patients with conventionally untreatable forms of CNV.

RESULTS

RECRUITMENT AND RANDOMIZATION

The results that follow are derived from an intent-to-treat analysis, which includes all patients randomized into the study. Four hundred eighty-one patients were enrolled by 45 centers during a 9-month period. The randomization procedure resulted in treatment groups being well balanced with respect to center and type of lesion.
(MIU), given 3 times a week for 1 year. The test medication was supplied in vials as either a 1-ML sterile solution (provided by Hoffmann-La Roche Inc, Nutley, NJ) or lyophilized powder together with ampules containing 1 mL of sterile water for reconstituting the medication (provided by Hoffmann-La Roche Ag, Basel, Switzerland). In both cases the matching placebos were identical in appearance to the vials of interferon alfa-2a. All patients received 0.5 mL of test solution (half-dose) for the first 3 injections (days 1, 3, and 5) and 1 mL (full dose) thereafter. Dose reductions (half-dose) for drug intolerance were permitted, and patients could discontinue treatment for a maximum of 4 weeks, but if they were unable to tolerate 50% of their assigned dose after this time, treatment was discontinued. No further dose reductions were permitted.

DATA MANAGEMENT

Data were transcribed at the centers onto standard case report forms and sent via mail or fax to a centralized data entry center. Data were entered twice and validated by the data manager. Consistency of efficacy, safety, and end-of-study information was checked with SAS-based programs. No masked patient data were provided by the International Institute for Drug Development until the end of the study.

ANGIOGRAPHIC EVALUATION

An independent fluorescein angiogram reading center was established at the Wilmer Reading Center in Baltimore, Md. The ICG angiograms were read by the ICG Reading Center in New York, NY. All angiograms were read by reviewers masked to treatment assignments.

EFFICACY EVALUATION

The primary efficacy measure was visual acuity change measured at the end of 52 weeks. The primary end point of the trial was the proportion of patients who had lost 3 or more lines of vision at the end of 52 weeks. Patients could receive credit for a maximum of 17 lines. Credit was given for the smallest line read with 1 or no errors. The number of lines of change from the baseline measurement was then determined. Visual acuity scores were also computed on the basis of the exact number of letters read for a maximum score of 85. A second categorical variable for visual acuity based on the proportion of patients who lost 15 or more letters at week 52 was also considered. Secondary criteria included other visual measures as well as fluorescein and ICG angiographic findings.

SAFETY EVALUATION

The safety and tolerability of the treatments were assessed from reports by the patients every month. Serious or life-threatening adverse events required immediate notification of the study chairman, safety committee chairman, and clinical leader from Hoffmann-La Roche so that the necessity for reporting to the Food and Drug Administration could be determined. A safety monitoring committee reported serious and/or life-threatening adverse events directly to Hoffmann-La Roche and the International Institute for Drug Development in parallel.

METHODS OF ANALYSIS

All tests of significance were 2 tailed. P values were considered statistically significant if they were less than .05. Confidence intervals were calculated with a coverage probability of 95%.

Treatment effect was tested by comparison of the control group with the 3 treatment groups combined as well as each individually in pairwise comparisons.

In the analysis of safety, the proportion of patients who experienced adverse events was calculated overall and by body system, severity, and relationship to trial medication and compared between the 4 treatment groups.

DEMOGRAPHIC FEATURES

The treatment groups also appeared well balanced with respect to demographic features and baseline visual acuity (Table 1). Overall, 61% of the patients were female and 39% male. The median age of the patients in the study was 73.1 years (range, 50.2-89.3 years). Ninety-nine percent of the patients were white.

UNAVAILABILITY FOR FOLLOW-UP

Overall, 18.8% of the patients were unavailable for follow-up visual acuity assessment at week 52; the breakdown by subgroups was as follows: control group, 12%; 1.5-MIU group, 16%; 3-MIU group, 22%; and 6-MIU group, 26%.

Patients were considered ophthalmologically ineligible if the Reading Center determined that the patient did not meet the clinical criteria as described above for inclusion in the study. Ophthalmologically ineligible patients (n=25) were not followed up beyond the point at which they were withdrawn from treatment.

EFFICACY EVALUATION

Lines of Vision Lost at 52 Weeks

The proportion of patients who had lost at least 3 lines of vision at 52 weeks was 40 of 105 (38%; 95% confidence interval, 29%-48%) in the control group and 142 of 286 (50%; 95% confidence interval, 44%-55%) in the 3 treatment groups combined (Table 2). This difference was not statistically significant (P=.06).

Pairwise comparisons of each treatment group vs the placebo group are shown in Table 2. A statistically significant difference was found only for the 6-MIU group in favor of the placebo (P=.02).
Table 1. Baseline Characteristics by Treatment Group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=119)</th>
<th>1.5 MIU* (n=122)</th>
<th>3 MIU (n=119)</th>
<th>6 MIU (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>73 (61)</td>
<td>78 (64)</td>
<td>68 (57)</td>
<td>73 (60)</td>
</tr>
<tr>
<td>M</td>
<td>46 (39)</td>
<td>44 (36)</td>
<td>51 (43)</td>
<td>48 (40)</td>
</tr>
<tr>
<td>Mean (±SD) age, y</td>
<td>73.0±7.0</td>
<td>73.3±7.4</td>
<td>73.1±7.1</td>
<td>72.9±7.2</td>
</tr>
<tr>
<td>Lesion type, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occult</td>
<td>46 (39)</td>
<td>46 (38)</td>
<td>45 (38)</td>
<td>47 (39)</td>
</tr>
<tr>
<td>Classic</td>
<td>41 (34)</td>
<td>41 (34)</td>
<td>40 (34)</td>
<td>41 (34)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>19 (16)</td>
<td>22 (18)</td>
<td>22 (18)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>13 (11)</td>
<td>13 (11)</td>
<td>12 (10)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Mean baseline visual acuity score</td>
<td>55.3±15.0</td>
<td>53.4±14.7</td>
<td>56.2±14.4</td>
<td>54.8±14.8</td>
</tr>
<tr>
<td>No. of letters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* MIU indicates million international units.

Table 2. Visual Acuity Findings at 52 Weeks: Pairwise Comparisons

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Losing ≥3 Lines</th>
<th>% Unavailable for Follow-up</th>
<th>95% Confidence Interval, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>38</td>
<td>12</td>
<td>29-48</td>
<td>. .</td>
</tr>
<tr>
<td>Interferon alfa-2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 MIU*</td>
<td>51</td>
<td>16</td>
<td>41-61</td>
<td>.05</td>
</tr>
<tr>
<td>3.0 MIU</td>
<td>43</td>
<td>22</td>
<td>33-54</td>
<td>.48</td>
</tr>
<tr>
<td>6.0 MIU</td>
<td>54</td>
<td>26</td>
<td>44-65</td>
<td>.02</td>
</tr>
<tr>
<td>All treatment groups</td>
<td>50</td>
<td></td>
<td>44-55</td>
<td>.06</td>
</tr>
</tbody>
</table>

* MIU indicates million international units. †Statistically significant.

Letters of Vision Lost at 52 Weeks

When loss of 15 letters or more was used as an outcome criterion, pairwise comparisons showed a statistically significant relationship only for the 1.5-MIU group in favor of the placebo (P = .04). There was no statistically significant finding with regard to the 3-MIU group or the 6-MIU group in this comparison.

Lines of Vision Lost at Earlier Time Points

In comparing the proportion of patients who lost at least 3 lines of vision at earlier time points (Table 3), we found a significant difference for the placebo group vs all treatment group patients at week 24, but not at weeks 12 or 36. In pairwise comparisons, significant differences were observed only for the 6-MIU group at weeks 12 and 36, again in favor of the control group.

Mean Visual Acuity Over Time

Because of the possible loss of information when a continuous scale variable is categorized, the mean visual acuity score (number of letters) was also examined for treatment and time effect. The mean visual acuity over time was analyzed by means of a repeated-measures analysis of variance. The tests showed a significant time effect, ie, vision decreased over time in all groups (illustrated in the Figure), but no significant treatment effect and no significant interaction between time and treatment were found.

OTHER SUBGROUP ANALYSES

No significant differences were seen in any of the subgroup analyses controlling for lesion type (classic, occult, recurrent, or hemorrhage).

A subgroup analysis of US centers vs European and other non-US centers (including Canada, Israel, and Australia) was performed. Although no evidence of treatment effect was observed in the US centers as a group, a significant difference (P = .03) favoring the control group was seen when the analysis was limited to only the patients entered in the non-US centers.
Table 4. Adverse Events by Treatment Group

<table>
<thead>
<tr>
<th>Body System</th>
<th>Placebo (n=119)</th>
<th>1.5 MIU (n=122)</th>
<th>3 MIU (n=119)</th>
<th>6 MIU (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site disorders</td>
<td>2 (2)</td>
<td>5 (4)</td>
<td>3 (3)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Autonomic nervous system disorders</td>
<td>8 (7)</td>
<td>12 (10)</td>
<td>12 (10)</td>
<td>20 (17)</td>
</tr>
<tr>
<td>Body as a whole—general disorders</td>
<td>62 (52)</td>
<td>80 (66)</td>
<td>90 (76)</td>
<td>100 (83)</td>
</tr>
<tr>
<td>Cardiovascular disorders, general</td>
<td>7 (6)</td>
<td>11 (9)</td>
<td>5 (4)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Central and peripheral nervous system</td>
<td>44 (37)</td>
<td>47 (39)</td>
<td>54 (45)</td>
<td>60 (50)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>4 (3)</td>
<td>8 (7)</td>
<td>4 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>ENT disorders</td>
<td>15 (13)</td>
<td>28 (23)</td>
<td>25 (21)</td>
<td>16 (13)</td>
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<tr>
<td>Gastrointestinal system disorders</td>
<td>43 (36)</td>
<td>54 (44)</td>
<td>58 (49)</td>
<td>67 (53)</td>
</tr>
<tr>
<td>Hearing and vestibular disorders</td>
<td>4 (3)</td>
<td>5 (4)</td>
<td>5 (4)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Heart rate and rhythm disorders</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0 (0)</td>
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<tr>
<td>Liver and biliary system disorders</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td>13 (11)</td>
<td>12 (10)</td>
<td>11 (9)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Musculoskeletal system disorders</td>
<td>34 (29)</td>
<td>54 (44)</td>
<td>45 (38)</td>
<td>49 (40)</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>2 (2)</td>
<td>6 (5)</td>
<td>4 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Platelet, bleeding, and clotting disorders</td>
<td>2 (2)</td>
<td>4 (3)</td>
<td>2 (2)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>27 (23)</td>
<td>29 (24)</td>
<td>28 (24)</td>
<td>51 (42)</td>
</tr>
<tr>
<td>Red blood cell disorders</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>3 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Reproductive disorders, female</td>
<td>2 (2)</td>
<td>6 (5)</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Reproductive disorders, male</td>
<td>1 (1)</td>
<td>4 (3)</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Resistance mechanism disorders</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Respiratory system disorders</td>
<td>16 (13)</td>
<td>20 (16)</td>
<td>27 (23)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Skin and appendage disorders</td>
<td>32 (27)</td>
<td>47 (39)</td>
<td>42 (35)</td>
<td>52 (43)</td>
</tr>
<tr>
<td>Special senses, other disorders</td>
<td>5 (4)</td>
<td>3 (2)</td>
<td>6 (5)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Urinary system disorders</td>
<td>8 (7)</td>
<td>8 (7)</td>
<td>13 (11)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Vascular (extracardiac) disorders</td>
<td>2 (2)</td>
<td>6 (5)</td>
<td>2 (2)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Vision disorders</td>
<td>19 (16)</td>
<td>14 (11)</td>
<td>29 (24)</td>
<td>20 (17)</td>
</tr>
<tr>
<td>White blood cell and RES disorders</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Others</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>No. of patients with ≥1 adverse event</td>
<td>102 (86)</td>
<td>113 (93)</td>
<td>112 (94)</td>
<td>118 (98)</td>
</tr>
</tbody>
</table>

*MIU indicates million international units; ENT, ear, nose, and throat; and RES, reticuloendothelial system.

No significant differences were seen with the data stratified to adjust for visual acuity at baseline (20/64 or better vs worse than 20/64).

No statistically significant differences were noted when adjustment was made for age of the CNV at the time of treatment (onset of 4 months or more vs onset of less than 4 months). These data were not available for all subjects.

SAFETY EVALUATION

The total number of adverse events was 498 for the control group, 644 for the 1.5-MIU group, 688 for the 3-MIU group, and 813 for the 6-MIU group.

The frequency of adverse events is shown by body system in Table 4. For the 4 treatment groups, most of the adverse events were observed in the following body systems: body as a whole—general disorders (especially fatigue and influenza-like symptoms), gastrointestinal system disorders (especially nausea, diarrhea, and appetite loss), and central and peripheral nervous system disorders (especially headache, dizziness, and chills). The percentages of patients who experienced at least 1 adverse event were high in all treatment groups (see column totals, Table 4) and increased with dose. It is noteworthy that 86% of all patients taking placebo reported at least 1 adverse event.

OPHTHALMIC SIDE EFFECTS

Signs of interferon-associated retinopathy (retinal hemorrhage and/or cotton-wool spots) were noted with increased frequency in the highest-dose group. Retinal hemorrhages were noted in 1 patient (1%) taking placebo, 2 patients (2%) taking interferon alfa-2a, 1.5 MIU, 2 patients (2%) taking 3 MIU, and 6 patients (5%) taking 6 MIU. Cotton-wool spots were noted in 0 controls (0%), 1 patient (1%) taking 1.5 MIU, 3 patients (3%) taking 3 MIU, and 6 patients (5%) taking 6 MIU.

SEVERITY OF ADVERSE EVENTS

Most adverse events were mild to moderate, but there was a tendency for the group receiving 6 MIU of interferon alfa-2a to report a greater number of severe adverse events (33 severe or life-threatening adverse events in the control group, 34 in the 1.5-MIU group, 42 in the 3-MIU group, and 66 in the 6-MIU group).

SERIOUS ADVERSE EVENTS

None of the serious adverse events thought to be possibly or probably related to study treatment was considered unexpected by the study physicians or Hoffmann-La Roche.
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personnel, so that no expedited reports to the Food and Drug Administration were required.

**COMMENT**

We report the findings of a phase 3 dose ranging safety and efficacy study that compared 3-times-weekly treatment with each of 3 doses of interferon alfa-2a (1.5, 3, and 6 MIU) with placebo for 1 year in patients with neovascularized age-related macular degeneration with foveal involvement. The study was designed as a double-masked, placebo-controlled, randomized, parallel group trial. A total of 481 patients were enrolled at 45 centers to achieve a target of 111 evaluable patients per group. Patients were stratified at randomization according to lesion category determined by the investigator at baseline.

The results of our study indicate that interferon should not be used for the treatment of CNV secondary to age-related macular degeneration. No benefit of interferon was seen in any subgroup analysis. In fact, pairwise comparisons of each treatment group vs the placebo group suggest the possibility of a detrimental effect of interferon at the 6-MIU and 1.5-MIU dosage levels.

The results of this study regarding the potential efficacy of interferon suggest that interferon is not effective as a treatment for exudative age-related macular degeneration. The controlled nature and large sample size of our trial give us confidence to make this statement. More difficult to evaluate from the study is whether the drug had any potentially detrimental effects on visual acuity at 52 weeks.

Pairwise subgroup analysis showed statistically significant findings in favor of the control group compared with the interferon-6 MIU group, with 3 lines of vision (P=.02) used as the outcome criteria, and com-
pared with the interferon alfa-2a, 1.5 MIU, group with 15 letters of vision used as the outcome (P=.04). No subgroup analysis, however, showed any statistically significant differences in visual acuity for the intermediate group (3 MIU), which suggests the absence of a dose-response effect. This raises the possibility that the differences observed at the 6- and 1.5-MIU levels are caused by chance.

A scientific explanation for a potential retinal toxic reaction with interferon does exist. A number of reports have described an interferon-associated retinopathy consisting of cotton-wool spots and retinal hemorrhages. While these findings were seen only in a minority of patients in this study (up to 5% in the 6-MIU group) and were not associated with decreased visual acuity, it is possible that more subtle retinal ischemia may occur with the use of this medication.

In summary, the results of this prospective, randomized, controlled clinical trial suggests that there is no benefit to interferon alfa-2a therapy for CNV secondary to age-related macular degeneration. Two of 3 treatment groups showed a worsening of visual acuity at 52 weeks in comparison with the control group.

This study represents the first large, randomized, placebo-controlled clinical trial of a drug to treat CNV secondary to age-related macular degeneration. Although the findings in this study are discouraging, pharmacological antiangiogenic intervention holds great promise for treating this devastating condition in the near future. Effective drug therapies would enable us to avoid or minimize laser-induced damage and to treat patients with vessels that cannot be well imaged. In addition, a safe, effective drug still holds great promise as a prophylactic agent for this disease. For all of these reasons, there is now widespread interest in developing antiangiogenic drugs that may combat this devastating disease in the near future.

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