Oral Tyrosine Kinase Inhibitor for Neovascular Age-Related Macular Degeneration
A Phase 1 Dose-Escalation Study

Timothy L. Jackson, PhD, FRCOphth; David Boyer, MD; David M. Brown, MD; Nauman Chaudhry, MD; Michael Elman, MD; Chris Liang, PhD; Denis O’Shaughnessy, PhD; Edward C. Parsons, PhD; Sunil Patel, MD, PhD; Jason S. Slakter, MD; Philip J. Rosenfeld, MD, PhD

IMPORTANCE An oral treatment for neovascular age-related macular degeneration would be less burdensome than repeated intravitreous injections. X-82 is an oral tyrosine kinase inhibitor active against vascular endothelial growth factor (VEGF) and platelet-derived growth factor.

OBJECTIVE To undertake safety testing of oral X-82 administered for the treatment of neovascular AMD.

DESIGN, SETTING, AND PARTICIPANTS Phase 1, open-label, uncontrolled, dose-escalation study at 5 US retinal clinics between November 2012 and March 2015 (Retina-Vitreous Associates Medical Group, Beverly Hills, California; Blanton Eye Institute, Houston Methodist Hospital, Retina Consultants of Houston, Houston, Texas; New England Retina Associates, Guilford, Connecticut; Elman Retina Group, Baltimore, Maryland; and Retina Research Institute of Texas, Abilene). Thirty-five participants with neovascular age-related macular degeneration, 7 of whom were treatment naive.

INTERVENTIONS Participants received oral X-82 for 24 weeks at 50 mg alternate days (n = 3), 50 mg daily (n = 8), 100 mg alternate days (n = 4), 100 mg daily (n = 10), 200 mg daily (n = 7), and 300 mg daily (n = 3), with intravitreous anti-VEGF therapy using predefined retreatment criteria. Every 4 weeks, participants underwent best-corrected visual acuity measurement, fundus examination, and spectral-domain optical coherence tomography.

MAIN OUTCOMES AND MEASURES The main outcome was adverse events. Other outcomes included visual acuity, central subfield retinal thickness, and number of anti-VEGF injections.

RESULTS Of the 35 participants, the mean age was 76.8 years, 16 were men and 19 were women, and 33 were white and 2 were nonwhite. Of 25 participants (71%) who completed the 24 weeks of X-82 treatment, all except 1 maintained or improved their visual acuity (mean [SD], +3.8 [9.6] letters). Fifteen participants (60%) required no anti-VEGF injections (mean, 0.68). Mean [SD] central subfield thickness reduced by −50 [97] μm, with 8 participants (all receiving at least 100 mg daily) demonstrating sustained reductions despite no anti-VEGF injections. The most common adverse events attributed to X-82 were diarrhea (n = 6), nausea (n = 5), fatigue (n = 5), and transaminase elevation (n = 4). A dose relationship to the transaminase elevations was not identified; all normalized when X-82 was discontinued. All but 1 were asymptomatic. Ten participants withdrew consent or discontinued prematurely, 6 owing to adverse events attributed to X-82 including leg cramps (n = 2), elevated alanine aminotransferase (n = 2), diarrhea (n = 1), and nausea/anorexia (n = 1).

CONCLUSIONS AND RELEVANCE X-82 can be associated with reversible, elevated liver enzymes; hence, liver function testing is needed to identify those unsuited to treatment. Although 17% of participants discontinued X-82 owing to AEs, those who completed the study had lower than expected anti-VEGF injection rates. Further studies appear justified, with a phase 2 randomized clinical study under way.

Published online June 1, 2017.

© 2017 American Medical Association. All rights reserved.
Tyrosine kinase is an enzyme that transfers a phosphate group to the amino acid tyrosine on proteins. In doing so, it can alter the protein’s structure and function and thereby facilitate signal transduction between macromolecules. In the eye, both vascular endothelial growth factor (VEGF) and platelet-derived growth factor bind to cell-surface receptors that rely on a tyrosine kinase to propagate signal transduction into the cell.

Many malignancies are caused by aberrant tyrosine kinase function, which initiates unchecked cell proliferation. Consequently, tyrosine kinase inhibitors are used to treat cancer. Sunitinib is one such tyrosine-kinase inhibitor and is licensed for the treatment of metastatic renal cell carcinoma, gastrointestinal stromal tumors, and pancreatic neuroendocrine cancers. Sunitinib is also a potent inhibitor of angiogenesis, with a rabbit model of corneal neovascularization suggesting topical sunitinib is almost 3 times as effective as bevacizumab.

X-82 is a novel, potent, oral, multikinase, VEGF-receptor and platelet-derived growth factor–receptor inhibitor that is structurally similar to sunitinib. X-82 has been designed to have a smaller volume of distribution than sunitinib, with limited tissue accumulation to minimize adverse effects. Because X-82 inhibits both the VEGF-receptor and platelet-derived growth-receptor kinases, it is intended as an oral treatment of pathologic angiogenesis in diseases such as neovascular age-related macular degeneration (AMD), von Hippel-Lindau disease, and solid tumors.

To our knowledge, the first human study of X-82 was as a treatment for solid tumors. Sixteen patients with colorectal, renal, carcinoid, and other tumors enrolled in a dose-escalation study, with daily doses from 20 mg to 400 mg. Half the patients showed either stable disease, reduced tumor size, or complete remission. None experienced dose-limiting toxicity (DLT). The most common adverse events (AEs) were fatigue (n = 6), nausea (n = 4), diarrhea (n = 3), hypertension (n = 2), and vomiting (n = 2). Ongoing oncology studies are exploring doses up to 800 mg daily (clinicaltrials.gov: NCT02146222).

Oral X-82 was found to inhibit Matrigel-induced choroidal neovascularization in a rat model. An oxygen-induced ischemic retinopathy mouse model also showed potent inhibition of retinal neovascularization, with cell culture studies suggesting similar antiangiogenic activity to sunitinib.

We hypothesized that oral X-82 may have therapeutic potential as a treatment for neovascular AMD given the known importance of VEGF in the pathogenesis and clinical course of neovascular AMD and the potential importance of platelet-derived growth factor in neovascular AMD. Neovascular AMD is the leading cause of vision loss in most developed nations. Treatment usually involves repeated intravitreous injections of anti-VEGF agents, but these impose a substantial burden on patients and eye clinics. An oral treatment for neovascular AMD would have several obvious advantages. Most importantly, it might reduce or eliminate the need for intravitreous injections. It could treat bilateral disease and may reduce the likelihood of second eye involvement. We therefore aimed to undertake preliminary safety testing of oral X-82 to determine whether larger, randomized clinical trials are justified.

### Key Points

**Question** X-82 is an oral tyrosine kinase inhibitor that blocks the action of vascular endothelial growth factor and platelet-derived growth factor; might it treat neovascular age-related macular degeneration?

**Findings** In this phase 1 dose-escalation study of 35 participants, the most common adverse events attributed to oral X-82 were diarrhea (n = 6), nausea (n = 5), fatigue (n = 5), and transaminase elevation (n = 4). The 71% of participants who tolerated X-82 and completed 6 months of treatment averaged 0.68 intravitreous anti-vascular endothelial growth factor rescue injections, with 60% requiring none.

**Meaning** These results justify further study, and a phase 2 trial has completed recruitment.

### Methods

**Study Design**

This phase 1, open-label, dose-escalation study received institutional review board approval from all 5 US study sites (Retina-Vitreous Associates Medical Group, Beverly Hills, California; Blanton Eye Institute, Houston Methodist Hospital, Retina Consultants of Houston, Houston, Texas; New England Retina Associates, Guilford, Connecticut; Elman Retina Group, Baltimore, Maryland; and Retina Research Institute of Texas, Abilene). It was conducted in accordance with the tenets of the Declaration of Helsinki. All participants provided written informed consent.

**Participants**

The study enrolled 35 male and female participants 50 years and older with active neovascular AMD and ran from November 2012 to March 2015. Eligibility criteria are provided in the Appendix 1 in the Supplement. Participants could be anti-VEGF naive or have received prior anti-VEGF therapy.

**Study Visits**

Participants attended for screening, day 14, and then monthly for 7 months (210 days). The schedule of procedures is shown in eAppendix 2 in the Supplement.

**Study Treatment**

Groups of participants were assigned to 1 of 7 X-82 doses over 24 weeks, with an additional 4 weeks for follow-up. The dose escalated from one level to the next in the absence of any DLT. Dose-limiting toxicity was defined as a drug-related safety event during the first 2 weeks of treatment that was severe enough to require removal of the participant from the study. If a DLT occurred in a given dose group, then the initial allocation of 3 participants was expanded to at least 6. The maximum tolerated dose was the maximum dose at which no DLT occurred in a group of 3 participants or no more than 1 DLT in a group of 6. The planned escalating dose regimens were 50 mg alternate days, 50 mg daily, 100 mg alternate days, 100 mg daily, 200 mg daily, and 300 mg daily.

**Study Treatment**

Groups of participants were assigned to 1 of 7 X-82 doses over 24 weeks, with an additional 4 weeks for follow-up. The dose escalated from one level to the next in the absence of any DLT. Dose-limiting toxicity was defined as a drug-related safety event during the first 2 weeks of treatment that was severe enough to require removal of the participant from the study. If a DLT occurred in a given dose group, then the initial allocation of 3 participants was expanded to at least 6. The maximum tolerated dose was the maximum dose at which no DLT occurred in a group of 3 participants or no more than 1 DLT in a group of 6. The planned escalating dose regimens were 50 mg alternate days, 50 mg daily, 100 mg alternate days, 100 mg daily, 200 mg daily, and 300 mg daily.

**Study Treatment**

Groups of participants were assigned to 1 of 7 X-82 doses over 24 weeks, with an additional 4 weeks for follow-up. The dose escalated from one level to the next in the absence of any DLT. Dose-limiting toxicity was defined as a drug-related safety event during the first 2 weeks of treatment that was severe enough to require removal of the participant from the study. If a DLT occurred in a given dose group, then the initial allocation of 3 participants was expanded to at least 6. The maximum tolerated dose was the maximum dose at which no DLT occurred in a group of 3 participants or no more than 1 DLT in a group of 6. The planned escalating dose regimens were 50 mg alternate days, 50 mg daily, 100 mg alternate days, 100 mg daily, 200 mg daily, and 300 mg daily.

**Study Treatment**

Groups of participants were assigned to 1 of 7 X-82 doses over 24 weeks, with an additional 4 weeks for follow-up. The dose escalated from one level to the next in the absence of any DLT. Dose-limiting toxicity was defined as a drug-related safety event during the first 2 weeks of treatment that was severe enough to require removal of the participant from the study. If a DLT occurred in a given dose group, then the initial allocation of 3 participants was expanded to at least 6. The maximum tolerated dose was the maximum dose at which no DLT occurred in a group of 3 participants or no more than 1 DLT in a group of 6. The planned escalating dose regimens were 50 mg alternate days, 50 mg daily, 100 mg alternate days, 100 mg daily, 200 mg daily, and 300 mg daily.
Other Permitted Treatments
Intravitreous anti-VEGF rescue therapy with 0.5-mg ranibizumab (Genentech), off-label 1.25-mg bevacizumab (Genentech), or 2-mg aflibercept (Regeneron) was permitted if predefined re-treatment criteria were met (eAppendix 3 in the Supplement).

Safety Outcomes
The safety outcomes comprised findings on ophthalmic examination, incidence of systemic and ocular AEs and serious AEs (SAEs), DLT, discontinuation for drug-related AEs, and laboratory values. Adverse events were coded using the Medical Dictionary for Regulatory Activities’ Preferred Terms, version 17.1. Relatedness of the AE or SAE to X-82 treatment was determined by the reporting principal investigator.

Efficacy Outcomes
The predefined efficacy outcomes were change from baseline in mean best-corrected visual acuity, choroidal neovascularization (CNV) size, central retinal thickness, proportion who developed CNV in the unaffected fellow eye, time to intravitreal anti-VEGF rescue therapy, and number of anti-VEGF injections.

Image Analysis
Fundus photographs and fluorescein angiography were acquired at baseline, month 3, and month 6 to monitor safety and CNV size. Monthly optical coherence tomography (OCT) helped determine whether anti-VEGF rescue therapy was needed. The automated measurement of central subfield thickness was prospectively collected by the investigator at each visit.

A post hoc, central, masked assessment of the baseline and last available OCT for each participant was conducted using experienced, reading center-certified graders. The following were determined as present or absent: subretinal fluid (and the extent of any fluid present), retinal cystoid changes, pigment epithelial detachment (and the extent, if present), subretinal fibrosis, and other retinal findings. The response to treatment was thereby categorized as marked improvement, mild improvement, no change, mild worsening, or marked worsening.

Statistical Analysis
No formal hypothesis testing was performed. Continuous variables are summarized by descriptive statistics. Discrete variables are summarized by frequencies and percentages. Two participants had bilateral disease (in both, the right eye was the study eye). The safety population comprised all participants who received at least 1 dose of X-82. The efficacy population comprised all those who completed the course of X-82 treatment. Mean (SD) values are presented unless noted otherwise.

Results
Patient Demographics and Disposition
Of 35 participants, 28 had already commenced anti-VEGF therapy, and 7 were treatment naive. eTable 1 in the Supplement shows the baseline characteristics. Figure 1 shows the disposition of participants and their dosing. Twenty-eight participants completed 3 months, and 25 completed 6 months.

Safety Outcomes
Adverse Events
There were 4 ocular AEs in 4 of 35 participants (11.4%) comprising dry eye, meibomian gland dysfunction, retinal scar, and vitreous floaters. Twenty-eight participants (80%) had at least

CONSORT flow diagram showing disposition of participants. Relatedness determined by site clinician. All participants included in safety analysis. AE indicates adverse event.

Figure 1. CONSORT Flow Diagram

CONSORT flow diagram showing disposition of participants. Relatedness determined by site clinician. All participants included in safety analysis. AE indicates adverse event.
1 systemic AE (eTable 2 in the Supplement). Most were considered mild or moderate. Three AEs (8.6%) were considered severe: 1 case of multiple myeloma, 1 of pulmonary hypertension, and 1 with an isolated, 5-fold increase in serum transaminase, which was reversible and not associated with other abnormalities (hence, not considered an SAE). Of 94 systemic AEs, 32 were considered related to X-82 (Table).

### Serious AEs

There no deaths and 4 SAEs in 3 participants (8.6%), none attributed to X-82. One 73-year-old participant was hospitalized with mild chest pain. He was prescribed clopidogrel, but results of cardiac enzyme testing were negative, and he was discharged after angiography revealed no significant stenosis. A 95-year-old participant took of X-82 for 1 day, then elected to discontinue treatment. Two weeks later, she developed acute renal failure, and 4 days after that was admitted with congestive heart failure, from which she recovered. A 73-year-old participant discontinued X-82 owing to leg cramps. Two weeks later she was diagnosed as having multiple myeloma and commenced chemotherapy.

### Dose-Limiting Toxicity and Discontinuation for Drug-Related AEs

Of 35 participants, 25 completed 24 weeks of treatment. Six discontinued X-82 owing to AEs potentially related to X-82 (2 in the 50 mg daily group, 1 each in the 100 mg daily and 200 mg groups, and 2 in the 300 mg group). Four discontinued owing to unrelated events (eTable 3 in the Supplement). Although no participants met our definition of DLT, 2 of 3 participants in the 300 mg group withdrew owing to AEs attributed to X-82; 1 had mild anorexia, nausea, and weight loss, and the other had diarrhea.

### Laboratory Investigations

Liver enzyme elevations were reported as AEs 10 times across 5 participants. An 80-year-old woman experienced AEs of fatigue, leg cramps, nausea, and faintness and withdrew from the study, having taken 50 mg of X-82 daily for 10 weeks. Two weeks later, her alanine transaminase (ALT) level was 6 times the upper limit of normal (ULN), with an aspartate transaminase (AST) level 1.9 times the ULN. Both normalized over 6 weeks.

An asymptomatic 56-year-old man receiving 100 mg alternate days had an ALT level 3.3 times the ULN and an AST level 1.6 times the ULN at 3 months. By month 6, both had normalized despite continuing X-82.

An asymptomatic 71-year-old woman receiving 100-mg daily had an ALT level 3.1 times the ULN and an AST level 2.7 times the ULN at month 3. X-82 was withheld, and both normalized within 3 weeks. After rechallenging with 100 mg daily, the ALT level rose to 1.6 times the ULN, and the AST level to 1.5 times the ULN. X-82 was discontinued and transaminases normalized.

An asymptomatic 69-year-old woman receiving 200 mg daily had an ALT level 8.4 times the ULN and an AST level 2.9 times the ULN at month 2. X-82 and atorvastatin were withheld. By month 3, the ALT level was 1.6 times the ULN and the AST level 1.1 times the ULN, and she was rechallenged with 100 mg of X-82 daily. The ALT level rose to 3.6 times the ULN and the ALT level to 1.6 times the ULN within 1 week. X-82 was discontinued, and both values normalized.

An 82-year-old woman receiving 300 mg daily had an ALT level 1.5 times the ULN at month 2. Values normalized when she discontinued X-82 owing to diarrhea.

No other laboratory abnormalities were noted.

### Efficacy Outcomes

#### Visual Acuity

In the 25 participants who completed 24 weeks of treatment, the mean (SEM) best-corrected visual acuity change from baseline was +3.8 (9.6) letters (Figure 2; eTable 4 and eTable 5 in the Supplement). The mean (SEM) best-corrected visual acuity change across all 35 participants was +3.5 (9.7) letters. The

<table>
<thead>
<tr>
<th>System Organ Classa</th>
<th>Event (Preferred Term)a</th>
<th>Grade of Severity (No. of Occurrences)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal discomfort</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>General disorders</td>
<td>Fatigue</td>
<td>4</td>
</tr>
<tr>
<td>Investigations</td>
<td>Alanine aminotransferase increased</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Aspartate aminotransferase increased</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Liver function test abnormal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Weight decreased</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>Muscle spasms</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Dyseusia</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>1</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Pollakiuria</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Accelerated hypertension</td>
<td>0</td>
</tr>
</tbody>
</table>

*a As defined by the Medical Dictionary for Regulatory Activities, version 17.10.*
28 participants dosed at least daily gained +4.3 (9.2) letters. Three participants (8.6%), dosed with 100 mg alternatedays, 200 mg daily, and 300 mg daily, had worsening of at least 5 letters. One participant completing 24 weekstreatment lost at least 5 letters.

Anti-VEGF Rescue Therapy
The mean number of anti-VEGF injections in the 25 participants who completed 24 weeks of treatment was 0.68 (median, 0; range, 0-4; interquartile range, 0-1), with 15 (60%) not requiring any anti-VEGF rescue injections. The mean time to the first rescue injection was 130 days in the 10 participants who completed the study and required an injection. All doses except for 50 mg alternate days showed very low injection rates (Figure 3). The mean number of anti-VEGF injections in those who received at least 50 mg daily for 24 weeks was 0.4 (median, 0; range, 0-2; interquartile range, 0-1). None of those assigned to 300 mg daily required intravitreous injections while receiving X-82. Previously treated participants who completed 24 weeks of X-82 treatment had a mean (SD) of 9.0 (4.1) injections yearly prior to enrollment.

Central Retinal Thickness
There was little change in OCT central subfield thickness at doses from 50 mg alternate days up to 100 mg daily, except for 1 participant in the 100 mg daily group who showed a “marked improvement.” Five of 7 participants receiving 200 mg had a reduction in thickness, as did 2 of 3 receiving 300 mg. None of these participants required anti-VEGF therapy. Reduced central subfield thickness was usually associated with improved vision (eFigure in the Supplement). The mean (SEM) OCT central subfield thickness in those who completed 24 weeks of treatment reduced by ~50 (97) μm (Figure 4). The greatest response occurred in treatment-naive participants (eTable 5 in the Supplement). No participants showed increased macular fluid while receiving X-82, 27 showed “no change,” 2 showed “mild improvement,” and 6 showed “marked improvement.”

Angiography
In the study eyes with baseline and final visit angiographic measurements (n = 27), there was minimal change in the investigator-determined CNV area (mean [SD], ±0.24 [3.1] disc areas). No participants developed new neovascular AMD in the fellow eye, but 1 (receiving 50 mg daily) developed new exudation from a previously treated fellow eye CNV.

Post Hoc Analyses
There was no significant change in mean (SD) systolic (+0.5 [15.3] mm Hg, P = .84) or diastolic (~2.6 [10.9] mm Hg, P = .19) blood pressure (n = 35).

To investigate whether anti-VEGF injections drove the visual acuity and OCT improvements, we analyzed the 15 participants who received no anti-VEGF injections. The VA and OCT improvements were slightly better than the entire efficacy

Discussion

Early-phase studies, such as ours, are not sufficient to confirm the therapeutic benefit of X-82, but the results suggest it warrants further investigation. The main downside of treatment was elevated liver enzymes and gastrointestinal symptoms, which occurred in 11% and 14% of participants, respectively. Of 35 participants, 6 (17%) did not tolerate X-82, and an additional 4 failed to complete the study. Thus, X-82 may not be suitable for all patients, but in those who tolerated X-82, there was the suggestion of reduced demand for anti-VEGF therapy, averaging only 0.68 injections over 6 months.

Of the 25 participants who completed the 24 weeks of X-82 treatment, 60% required no anti-VEGF injections, increasing to 72% if the lowest dose is excluded. Despite low retreatment rates, best-corrected visual acuity was maintained to within 4 letters of baseline at the 24-week end point or improved in all except 1 participant. It seems unlikely that the vision gains are attributed mainly to anti-VEGF injections, given how few injections were given and because the greatest vision gains occurred in those not receiving injections. Further, most participants in the 200 mg and 300 mg groups showed substantial OCT improvements in the absence of anti-VEGF therapy. Taken together, these results suggest that X-82 has biological activity and reduces intravitreal anti-VEGF therapy. A drug that reduces anti-VEGF therapy without sacrificing vision would have considerable clinical utility.

The most common AEs were fatigue, nausea, and diarrhea, consistent with the early-phase study of X-82 for cancer and the known adverse effects of sunitinib.2,3 The AEs were generally mild or moderate and resolved with time or when X-82 was discontinued, as did the mostly asymptomatic transaminase elevations, but larger studies are needed to confirm these preliminary observations. The transaminase elevations did not appear to be dose related, and thus, it is important to monitor liver function in all patients receiving X-82 regardless of dose. If X-82 was adopted, then the transaminase elevations and AEs may mean some patients need to discontinue X-82 therapy, but it appears most patients would tolerate treatment.

Considering both safety and efficacy, 200 mg daily may be the best dose. At this dose, there were no SAEs and a good visual acuity and OCT response in the absence of anti-VEGF injections. Given the relatively short half-life of X-82 (<9 hours), twice-daily 100-mg dosing might also be appropriate.

A phase 1 dose-escalation trial of another oral tyrosine kinase inhibitor, pazopanib, was conducted in healthy volunteers and reported alongside a fixed-dose pilot study of 15 treatment-naive participants with neovascular AMD (clinicaltrials.gov identifiers: NCT01051700 and NCT01154062). The authors reported that pazopanib was well tolerated, with no withdrawals owing to AEs.5 Two of 72 healthy volunteers (3%) and none of those with AMD developed elevated transaminases, fewer than in this study (11%) but during a much shorter follow-up (1 month vs 6 months). Six participants (40%) with AMD required anti-VEGF rescue therapy before the day 29 end point. If we had reported our injection rate during the same interval, then only 6% of participants required rescue injections. If we consider only the treatment-naive participants (as with the pazopanib study), none required an injection in the first month. None of the participants in our study had elevated liver enzymes in the first month.

Limitations

Strengths of our study include its prospective design and longer follow-up than other studies investigating oral tyrosine kinase inhibitors for neovascular AMD. The main weaknesses, inherent to most open-label phase 1 studies, are a small sample size and lack of both masking and a control group. Accordingly, the safety and efficacy results should be considered preliminary, and both require confirmatory studies prior to clinical adoption of X-82. For example, our study may be too small to detect rare thromboembolic events associated with anti-VEGF suppression. This study cannot determine the level of patient compliance with X-82 in a clinical setting. Wet AMD is often symptomatic and this might be expected to improve compliance, whereas any AEs might reduce compliance. Because 80% of the participants were already receiving anti-VEGF therapy at enrollment, this may reduce the potential for clinical improvement.

Conclusions

In summary, 29% of participants failed to complete the study, and while not all withdrawals were owing to AEs, many were. Therefore, the potential benefits of X-82 need to be carefully weighed against the risks. However, in the 71% of participants who tolerated X-82 and completed the study, particularly those taking daily doses, there were far fewer than expected anti-VEGF injections. If it was established that X-82 offers an almost three-quarters chance of far fewer intravitreal injections, then it may yet be acceptable to many patients; however, larger studies are needed to confirm the balance of safety and efficacy. A phase 2, randomized, double-masked, placebo-controlled trial of X-82 for neovascular AMD completed enrollment of 157 patients in January 2017 (NCT02348359).
Advanced age-related macular degeneration (AMD) is the leading cause of blindness in individuals older than 50 years in the industrialized world. It presents in 2 forms: a dry (nonneovascular) form characterized by atrophy of retinal pigment epithelial cells and subsequent death of the overlying photoreceptor neurons, and a wet (neovascular) form characterized by the development of abnormal blood vessels called choroidal neovascularization. Neovascular AMD is responsible for 90% of severe vision loss in AMD and is caused by release of vascular endothelial growth factor (VEGF) in response to localized tissue stress. Anti-VEGF therapies have revolutionized treatment of this devastating disease. Despite these advances, a significant proportion of patients are underresponsive to anti-VEGF monotherapy, creating an urgent need for multitarget, synergistic therapeutic approaches. In addition, anti-VEGF therapies require frequent, intravitreal injections that create significant patient and caregiver burden and can be associated with the rare but potentially devastating complication of endophthalmitis. As such, novel therapeutic strategies that either complement or improve on current VEGF-directed approaches are highly desirable. Examples of such therapies would be those that do not require intraocular injections, are longer lasting, and have a favorable safety profile. Systemically delivered agents have an added advantage of treating bilateral disease, which must be carefully weighed against adverse reactions.

In this issue, Jackson et al report phase 1 clinical trial results of X-82, an oral tyrosine kinase inhibitor (TKI) that is thought to target both VEGF and platelet-derived growth factor receptor-activated pathways. Tyrosine kinases are ubiquitous signaling molecules that regulate key biological processes within diverse cell types. They play a critical role both in maintaining cellular homeostasis and in pathobiology of disease. Numerous TKIs are being investigated in clinical trials, and some have been approved for the treatment of diverse cancers. Ocular toxicity has been associated with