ABSTRACT

Like all pharmacologic- and laser-based treatments, verteporfin therapy and pegaptanib injections are associated with adverse events. Some, such as infusion-site events and infusion-related back pain with verteporfin, are generally transient and mild in nature, but others, although uncommon, are serious. This article reviews clinical trial data on the overall safety of verteporfin and pegaptanib in the treatment of age-related macular degeneration and the most serious therapy-related risks associated with each: acute severe visual acuity loss with verteporfin and photodynamic therapy and endophthalmitis with pegaptanib injections. The article also includes a side-by-side comparison of the benefits and risks associated with verteporfin therapy and pegaptanib injections.


SAFETY AND EFFICACY ARE THE MAJOR DETERMINANTS OF WHETHER A DRUG OR OTHER TREATMENT MODALITY IS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION (FDA). HOWEVER, SAFETY AND EFFICACY ALSO ARE IMPORTANT IN CLINICAL PRACTICE. THIS IS PARTICULARLY TRUE IN THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (AMD) AND OTHER DISEASES OF THE EYE BECAUSE VISION IS AT STAKE.

AS WITH ALL THERAPIES FOR ANY MEDICAL CONDITION, AND BECAUSE NO PHARMACOLOGIC- OR LASER-BASED THERAPY USED TO TREAT AMD IS WITHOUT SIDE EFFECTS OR RISK, THE BENEFITS OF TREATMENT MUST BE CAREFULLY WEIGHED AGAINST THE RISKS.

This article reviews the adverse events observed in clinical trials evaluating 2 recently approved therapies for AMD: (1) photodynamic therapy (PDT) with verteporfin (Visudyne; Novartis Pharma AG; Basel, Switzerland) infusion, also referred to as verteporfin therapy; and (2) intravitreal pegaptanib (Macugen; Eyetech Pharmaceuticals, Inc. and Pfizer Inc; New York, NY) injections. It also presents a side-by-side comparison of the benefits and risks of each therapy if differences in visual acuity outcome cannot be determined.

VERTEPORFIN THERAPY

The most frequently reported systemic adverse events in clinical trials evaluating verteporfin therapy were, in descending order: transient visual loss or disturbance, injection-site reactions (of all types, including major ones, such as extravasation), photosensitivity reactions, and infusion-related back pain. In the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigation, the incidence of transient visual loss during months 0 to 24 in 402 patients originally assigned to verteporfin therapy was 22%, whereas
the incidence of injection-site events during the same time frame in the same patients was 16%.\(^1\) Photosensitivity reactions and infusion-related back pain were less common, affecting 3.5% and 2.5% of patients, respectively. In other studies evaluating verteporfin therapy for 0 to 60 months in a total of 320 patients originally assigned to that therapy, the incidence of adverse events was 30% for transient visual loss, 19% for injection-site events, and 3% each for photosensitivity reactions and infusion-related back pain.\(^2\) There is some additive risk for these relatively benign events with repeated PDT.

Although less commonly reported than transient visual disturbances and injection-site reactions, the adverse event that causes the most concern is acute severe visual acuity decrease, defined by the TAP and Verteporfin in Photodynamic Therapy (VIP) study groups as a severe decrease in visual acuity of 20 or more letters within 7 days of PDT with verteporfin.\(^3\) In a combined report from the TAP and VIP study groups, the incidence of acute severe visual acuity decrease was 0.7% (3 of 402 patients) in the TAP investigation and 4.4% (10 of 225 patients) in the VIP study.\(^3\) Several other studies evaluating verteporfin therapy have shown similar rates, ranging from 0.3% to 5%.\(^2\) The Verteporfin Therapy in Age-Related Macular Degeneration\(^4\) (VAM) and Visudyne in Minimally Classic Choroidal Neovascularization\(^5\) (VIM) studies fit into this range, with an incidence of 0.6% in the VAM study and 1.3% in the VIM study. In total, there were 53 cases of acute severe visual acuity decrease in 5586 patients receiving verteporfin therapy in 7 studies, for an overall incidence of 0.9%.\(^2,4\) In most cases, acute severe visual acuity decrease occurred after the first treatment, suggesting that it may be an idiosyncratic reaction. Causes of acute severe visual acuity decrease included subretinal hemorrhage, retinal pigment epithelial tear, serous retinal detachment with slow choroidal perfusion, and unexplained factors.

With respect to lesion composition at baseline, 8 (62%) of 13 patients with acute severe visual acuity decrease described in the TAP and VIP report had occult with no classic lesions, 3 patients (23%) had minimally classic lesions, and 2 patients (15%) had predominantly classic lesions.\(^3\) In terms of pretreatment lesion size, acute severe visual acuity decrease occurred in lesions with greatest linear diameter (GLD) from 3000 to 3999 µm in 6 patients (46%), from 4000 to 6000 µm in 6 patients (46%), and at 6200 µm in 1 patient (8%). The median GLD was 4000 µm, or approximately 5 Macular Photocoagulation Study (MPS) disc areas. Specifically for occult with no classic lesions, the pretreatment lesion size in these 8 patients who experienced acute severe visual acuity decrease was more than 4 MPS disc areas in 6 patients (75%) and 4 or less MPS disc areas in 2 patients (25%), indicating a predominance of larger lesions.\(^2,3\)

Interestingly, most patients with acute severe visual acuity decrease had better visual acuity at baseline (visual acuity of 20/50 or better) than patients who did not experience acute severe visual acuity decrease.\(^2,3\) One explanation for this is that occult with no classic lesions, which often have better pretreatment visual acuity, are more prone to acute severe visual acuity decrease than other lesions. Other explanations are that these eyes with better vision at baseline had the greatest amount of vision to lose, and patients with better baseline visual acuity were more likely to notice acute severe visual acuity decrease than patients with worse baseline visual acuity.

![Figure: Visual Acuity Loss and Recovery at Next 3-Month Follow-up Examination](image)

10 of 13 patients experienced full/partial recovery (>70%). VA = visual acuity.
*These 2 events occurred in the same patient.
Data from Arnold et al.\(^3\)
The average amount of visual acuity lost was fewer than 4 lines. However, by the next follow-up visit (3 months later), 10 of 13 patients had fully or partially recovered the visual acuity lost (Figure). Three patients, including 1 who lost visual acuity in both eyes, continued to lose vision.

At 1 year, visual acuity in eyes that had developed acute severe visual acuity decrease was similar to the overall visual acuity in the control group, demonstrating that verteporfin therapy was not more harmful than no treatment.

PEGAPTANIB INJECTIONS

The most frequently reported adverse events in 890 patients receiving pegaptanib injections in the Vascular Endothelial Growth Factor (VEGF) Inhibition Study in Ocular Neovascularization (VISION) were ocular and related to the injection procedure rather than to the drug itself. In the first year of the trial, there were 12 cases of endophthalmitis (1.3%), 6 retinal detachments (0.7%), and 5 instances of traumatic injury to the lens (0.9%) in phakic patients.

However, because pegaptanib injections are repeated every 6 weeks, and because the risk is cumulative to some extent, it is more meaningful clinically to consider the incidence of each adverse event on a per-injection basis rather than over time. Event rates per injection were 0.16% for endophthalmitis, 0.08% for retinal detachment, and 0.007% for traumatic injury to the lens.

Severe loss of visual acuity, defined in VISION as loss of 30 or more letters—occurred in 1 patient who developed endophthalmitis and in 1 patient with traumatic injury to the lens. Five of the 6 patients with retinal detachment did not experience severe visual acuity loss; visual acuity measurements were not available for the remaining patient.

Most of the visual acuity loss in patients with endophthalmitis occurred during the first 12 weeks. However, at 54 weeks mean visual acuity was better in these eyes than visual acuity in sham-treated eyes.

Endophthalmitis is the adverse event of greatest concern with intravitreal injections. As previously noted, 12 patients treated with pegaptanib developed endophthalmitis in the first year of VISION, for a per-injection incidence of 0.16%. However, the condition was associated with deviations in injection protocol in 8 patients, leading to a change in protocol for the second year of the study and for other studies evaluating intravitreal pegaptanib injections.

More meticulous attention to administration of the injection and adoption of proper aseptic technique (ie, use of a lid speculum, sterile drape, povidone-iodine, and a topical broad-spectrum antibiotic) in the second year of VISION, which included 9 of 12 patients who developed endophthalmitis in the first year, reduced

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**Table 1. Benefits of Verteporfin Therapy and Pegaptanib Injections**

<table>
<thead>
<tr>
<th>Verteporfin Therapy</th>
<th>Pegaptanib Injections</th>
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<tbody>
<tr>
<td>For classic-containing lesions (predominantly classic and minimally classic) without recent disease progression, reduced risk of ≥15-letter loss by approximately 15%</td>
<td>For predominantly classic lesions and lesions with recent disease progression that are minimally classic or occult with no classic lesions, pegaptanib injections reduced risk of ≥15-letter loss by approximately 15%</td>
</tr>
<tr>
<td>Lesions &gt;9 MPS disc areas</td>
<td>Lesions &gt;12 MPS disc areas</td>
</tr>
<tr>
<td>Benefits shown through 2 years</td>
<td>Benefits shown through 1 year; some 2-year data are available, but trials not designed to provide efficacy data for same primary outcome at 2 years as for 1 year</td>
</tr>
<tr>
<td>Totality of data suggests benefits in all predominantly classic lesions and smaller minimally classic and occult with no classic lesions with recent disease progression</td>
<td>Subgroup analyses are insufficient to conclude if there are benefits for large lesions, especially minimally classic or occult with no classic lesions with recent disease progression</td>
</tr>
</tbody>
</table>

MPS = Macular Photocoagulation Study.

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**Table 2. Risks of Verteporfin Therapy and Pegaptanib Injections**

<table>
<thead>
<tr>
<th>Verteporfin Therapy</th>
<th>Pegaptanib Injections</th>
</tr>
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<tbody>
<tr>
<td>Small risk of acute severe visual acuity decrease (1%–4%), photosensitivity* (approximately 3%), infusion-related back pain (approximately 2%) Intravenous and laser setup Done as often as every 3 months</td>
<td>Small risk of traumatic cataract, endophthalmitis, vitreous hemorrhage, retinal tears or detachment (1%–4%) Intravitreal injection setup Injections given every 6 weeks</td>
</tr>
</tbody>
</table>

*Institute photosensitivity precautions for 2 days.
the number of patients who developed endophthalmitis from 12 to 4.7

Combined pre- and postprotocol-change results from VISION and a phase II study of pegaptanib in patients with diabetic macular edema (in which 1 patient developed endophthalmitis) have shown that the overall incidence of endophthalmitis was 17 per 12,488 injections, or 0.14% per injection. Before the protocol change in May 2003, the incidence of endophthalmitis was 15 per 8169 injections, or 0.18% per injection. Between May 2003 and July 2004, the incidence was 2 per 4317 injections, or 0.05% per injection, a statistically significant difference (P < .05). This finding strongly suggests that the lower incidence of endophthalmitis was the result of the protocol change.

SIDE-BY-SIDE COMPARISON

A side-by-side comparison of the benefits and risks of different therapies is helpful in making treatment decisions, particularly when differences in visual acuity outcome are not readily apparent or cannot be determined.

Data on the benefits and advantages of verteporfin therapy and pegaptanib injections are summarized in Table 1, and the risks and drawbacks of these therapies are summarized in Table 2. FDA on-label approval covers subfoveal predominantly classic lesions for verteporfin therapy and all lesion types for pegaptanib injections. In addition, the agency governing Medicare reimburses for the treatment of minimally classic and occult with no classic lesions that are 4 or less MPS disc areas in size with recent disease progression with verteporfin.

CONCLUSIONS

The most frequently reported adverse events in clinical trials evaluating verteporfin therapy were injection-site reactions, transient visual disturbances, photosensitivity reactions, and infusion-related back pain. All were generally transient and mild in nature.

The most serious adverse event was acute severe decrease in visual acuity, which occurred in 53 (0.9%) of 5586 patients treated with verteporfin. Of the 13 patients with acute severe visual acuity loss in the TAP and VIP studies, 10 patients experienced full or total recovery of visual acuity by the next 3-month follow-up examination.

Most adverse events reported in clinical trials evaluating intravitreal pegaptanib injections were ocular and related to the injection procedure rather than to the drug itself. These events included endophthalmitis, retinal detachment, and traumatic injury to the lens in phakic patients. The most serious—and frequent—adverse event was endophthalmitis, which occurred in 12 (1.3%) of 890 patients in the first year of VISION. In the second year of the study, after a change in the injection protocol that required the use of a lid speculum, a sterile drape, povidone-iodine, and a topical broad-spectrum antibiotic, the occurrence of endophthalmitis was reduced from 0.18% to 0.05%.

Visual benefits, such as reducing the risk of moderate or severe visual acuity loss, have been proven for both treatment modalities. Clinicians should weigh these benefits against the therapy-related risks when choosing the treatment approach for their patients.

DISCUSSION

RISK OF ACUTE VISUAL ACUITY LOSS WITH PHOTODYNAMIC THERAPY AND VERTEPORFIN

Dr Bressler: I often hear from my colleagues that they are very concerned about this 4% risk of acute severe visual acuity decrease. I think that that statistic does not necessarily reflect what's in the literature. The way I look at what's in the literature, we have a 1% risk in the TAP investigations, a 1% risk in the VIP study, and a 1% risk in the Verteporfin in Early Retreatment (VER) study. All 3 studies had very careful coordinators calling patients for follow-up examinations. All 3 were done over different periods of time. Then we have a 4% risk of acute severe visual acuity decrease in the VIP study. The 4 studies differ in their lesion composition: the VIP study is mainly occult with no classic lesions, the VER study is all predominantly classic lesions, the TAP investigation is predominantly classic and minimally classic lesions, and the VIP study is smaller minimally classic lesions.

I become concerned about this 4% risk when I'm talking about occult with no classic lesions. The data suggest that acute severe visual acuity decrease may be more common in these larger occult with no classic lesions, the very lesions we may want to avoid treating with verteporfin and PDT in most cases. I don't think of the risk as 4%, but as somewhere between 1% and 4%. That is what I tell most of my patients. But in my mind, when I'm weighing the risks, I really think of it as 1% unless it's an occult with no classic lesion.

Dr MacCumber's comment that most patients with acute severe visual acuity decrease in the VIP
study had better visual acuity to begin with is important; patients are more likely to notice a loss of acuity when their vision is good. Yet patients with pretty good visual acuity were included in the VER and VIM studies. So, I’m not worried about treating those patients with good visual acuity when their lesions are minimally classic and relatively small or when they are predominantly classic.

**Risk of Infection with Pegaptanib**

**Dr Bressler:** I’m heartened that the only risks with pegaptanib so far appear to be associated with the injection itself. However, we’re going to need more data to ascertain whether there is any systemic absorption of the drug. Hopefully, this will not prove to be the case, so that pegaptanib will have significant concentrations only in retinal and choroidal tissue.

As for the risk of endophthalmitis events in the second year, you have to multiply 0.05% by 9 because that is what the data suggest: 9 injections the first year and 9 injections the second year. That’s approximately 0.5%, or roughly 1 in 200 patients. That’s something a patient will want to know. Even though I tell my patients that the benefits outweigh the risks, it’s reasonable to tell them that 1 in 200 patients will develop endophthalmitis.

**Dr Klein:** I come up with a figure of 1% risk. The 0.05% risk per injection should be multiplied by 18 over 2 years. You end up with 1%, not 0.5%.

**Dr Bressler:** You are right. I was only thinking about the first year. The overall risk for endophthalmitis is 1%, or 1 in 100 patients over 2 years if 18 injections are given. We also have to add the risk of a retinal tear or detachment, which may approach 1% when you have 18 injections. Of course, we don’t know what the actual utilization will be in the real world. Will we stop treating if a great deal of vision has been lost? After how many treatments will we stop?

**Dr Klein:** In fairness, the number of people who end up with really severe vision loss is very, very small. We’ve done well in managing the cases of endophthalmitis that have occurred and the other complications from the injections. They rarely lead to a permanent loss.

**Dr Bressler:** That’s why I think it’s fair to tell patients that the benefits outweigh the risks. It’s distressing for a patient to hear that 1 in 100 patients will need a tap and intraocular antibiotics because of an eye infection over 2 years of treatment, but it is reassuring to hear that the infection is not likely to affect the overall outcome.

**REFERENCES**


