In the nearly two decades following the publication of the Branch Retinal Vein Occlusion Study (BVOS) and Central Retinal Vein Occlusion Study (CVOS), pharmacologic therapy for retinal vein occlusion (RVO) was almost nonexistent. However, the introduction of intravitreal therapy — namely corticosteroids and anti-VEGF agents — has provided a host of new pharmacologic options to clinicians. As evidenced by several large-scale clinical trials, intravitreal monotherapy is effective for the vast majority of patients with RVO and has thus become the predominant therapeutic approach.\(^5\)

Unfortunately, a small minority of patients display recalcitrant macular edema despite frequent intravitreal monotherapy dosing. In the SCORE trials, 11.6% to 12.0% of patients treated with repeated intravitreal triamcinolone lost at least 15 letters, and more than 20% had central point thicknesses greater than 500 µm at 12-month follow-up.\(^1,2\) Although the rate of refractory edema was lower in the BRAVO/CRUISE trial (0.7% to 3.8% lost at least 15 letters, and 6.7% to 15.9% had central foveal thickness greater than 400 µm at 12 months), frequent ranibizumab monotherapy was not universally successful.\(^3,4\) Such recalcitrant cases have prompted the search for therapeutic alternatives, most notably combination pharmacologic and pharmaco-laser treatments.

Rationale for combination therapy

Mechanism of action, pharmacokinetics, and side effect profiles (Table 1) must be considered in discussing the rationale for combination therapy. An additional consideration is whether...
Combination therapy is intended as an alternative in monotherapy-responsive patients — to reduce dosing frequency and intensity, avoid cumulative dose-limiting side effects, or minimize reductions in efficacy due to tachyphylaxis — or as an escalation strategy in monotherapy-resistant cases. In either scenario, the ideal combination regimen would employ agents with activity targeted to disparate components of RVO pathophysiology and possess complementary pharmacokinetic profiles. Such a combination should in theory allow for greater therapeutic efficacy and/or higher trough activity.

As seen in Table 1, there is significant diversity in the mechanism of action of the various candidate combination agents, providing an opportunity for synergistic treatment effects. For example, combination therapy with corticosteroids and anti-VEGF agents target both the inflammatory (via decreased leukotriene/prostaglandin production and ICAM-1 expression) and ischemic (via robust VEGF inhibition) drivers of RVO-related macular edema. And from a pharmacokinetic standpoint, combining agents with differing intravitreal half-lives may allow for a prolonged treatment effect of rapid, short-acting agents (eg, corticosteroids and anti-VEGF agents) and/or a shortening of effect latency for delayed, longer-acting therapies (eg, laser). Moreover, early intervention with a rapid, short-acting agent such as intravitreal triamcinolone (IVTA), bevacizumab (IVB), or ranibizumab (IVR) — which, unlike laser, can be administered regardless of the extent of associated macular hemorrhage or edema — may allow for earlier adjunctive laser therapy.

In monotherapy-responsive patients, combination therapy may also be applied to limit the burdens of frequent treatments visits and/or adverse effects related to cumulative exposure. Some investigators have suggested that repeated intravitreal therapy, in addition to the psychosocial and financial burden associated with frequent re-treatment, can lead to diminishing anatomic and functional improvement due to tachyphylaxis, which appears to be mediated by upregulation of VEGF receptors. Additionally, repeated monotherapy may also increase the incidence of certain adverse effects due to increased cumulative toxicity. This may be particularly problematic with intravitreal steroid therapy in which rates of cataract and possibly ocular hypertension or glaucoma have been linked with more frequent administration. There appear to be fewer safety concerns regarding repetitive anti-VEGF dosing, but there remain theoretical concerns related to the potential for increased rates of arteriothrombotic events and glaucoma with frequent dosing.

Evidence to date
In light of the many potential pitfalls of repeated monotherapy detailed above, clinicians are increasingly exploring combination therapy. Unfortunately, the currently available data have lagged somewhat...

### TABLE 1
Characteristics of Candidate Combination Therapy Agents

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Anti-VEGF</th>
<th>Macular Grid Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>VEGF inhibition</td>
<td>↓ retinal O&lt;sub&gt;2&lt;/sub&gt; consumption</td>
</tr>
<tr>
<td>↓ leukotriene/prostaglandin production</td>
<td>↓ vascular permeability</td>
<td>↑ inner retinal oxygenation</td>
</tr>
<tr>
<td>↓ inflammatory markers (ICAM-1)</td>
<td>↓ permeability of RPE barrier</td>
<td>↓ permeability of RPE barrier</td>
</tr>
<tr>
<td>↓ vascular permeability, ↑ permeability of RPE barrier</td>
<td>↑ permeability of RPE barrier</td>
<td>↓ hydrostatic pressure in capillaries/venule</td>
</tr>
<tr>
<td>↓ permeability of RPE barrier</td>
<td>↓ VEGF production</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elimination Half-Life</th>
<th>18.6d</th>
<th>IVR: 7.19d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency to Peak Effect</td>
<td>Minimal</td>
<td>IVB: 9.92d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Cataract</th>
<th>Glaucoma</th>
<th>↑ macular ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td></td>
<td>Cardiovascular events</td>
<td></td>
</tr>
<tr>
<td>Paracentral scotoma</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

VEGF = vascular endothelial growth factor; RPE = retinal pigment epithelium.
behind clinical practice. Of the handful of studies published to date, many are small, short-term, and retrospective, limiting the ability to draw firm conclusions. For the sake of brevity, noncomparative retrospective studies will not be included in the following review.

Combined anti-VEGF, corticosteroid therapy

Primary corticosteroid and anti-VEGF combination therapy was compared to anti-VEGF monotherapy in two prospective studies with mixed results. In the first study, combination of IVB and IVTA (2 mg) was not superior to IVB alone in terms of visual outcome, macular edema reduction, frequency of re-treatment, or IOP-related adverse effects in patients with CRVO. In contrast, posterior sub-Tenon’s kenalog (40 mg) plus IVB was found to result in significantly greater visual acuity improvement and macular edema reduction with significantly fewer injections in BRVO patients when compared to IVB alone.9

The use of the longer-acting dexamethasone implant (Ozurdex; Allergan, Irvine, CA) in conjunction with anti-VEGF therapy was recently examined in a small prospective, noncomparative trial. In this study, robust visual acuity gains were achieved up to 6 months (12.3 to 16.8 letters gained), with infrequent re-treatment (mean time to re-treatment: 125.9 ± 25.5 days).10 Anatomic improvement was excellent through 3 months but waned in the final 3 months of the study.

Combined anti-VEGF, laser therapy

Two prospective studies looked at combined anti-VEGF and laser therapy and compared it to either IVB alone11 or macular grid laser (MGL) alone12 in patients with BRVO-related macular edema. Interestingly, anti-VEGF plus MGL combination therapy was found to result in significantly greater visual and anatomic improvement compared to IVB alone, although no such superiority was found when this combination was compared to MGL alone.12 Combined therapy was also associated with significantly fewer injections over the study period when compared to IVB alone.

In an effort to reduce the source of VEGF production, investigators have explored the use of pan-retinal photocoagulation (PRP) in conjunction with anti-VEGF therapy. In CRVO patients, IVB plus subsequent (7 to 14 days) PRP was found to result in a significant reduction in the need for re-treatment, although no functional or anatomical difference was found.13 In contrast, a follow-up study found no difference in injection frequency after PRP in 10 CRVO patients with peripheral nonperfusion who received PRP plus as-needed IVR treatment after 6 months of IVR monotherapy.14

Combined corticosteroid, laser therapy

In a prospective, noncomparative analysis, significant functional and anatomic improvements were noted in patients with BRVO-related macular edema

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**TABLE 2**

**Pros and Cons of Pharmacologic and Pharmaco-Laser Therapies**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Allows for synergist effects based on differential mechanism of action of component therapies  
  - May overcome tachyphylaxis  
  - May allow for reduced effective dosages  
  - May allow for reduced dosing frequency  
  Takes advantage of different pharmacokinetic profiles of component therapies  
  - May allow for reduced dosing frequency  
  No added technical difficulty in administration  
  Component therapies are well-studied in large prospective clinical trials  
  Alternative for monotherapy-resistant patients  
  Alternative for patients with dose-limiting adverse effect or practical limitations on dosing frequency | Large-scale prospective clinical trial data not available  
Guidelines regarding re-treatment intervals not established  
Volume of injected agents limited if concurrent administration desired (unless combined with aqueous removal)  
Non-concurrent administration requires two closely spaced office visits |

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undergoing MGL within 3 weeks of IVTA. This occurred after a mean of 1.13 IVTA injections over 6 months.

The use of the dexamethasone implant in combination with MGL was prospectively examined in two abstracts presented in 2012. Both reported significant improvement in retinal thickness at all analyzed time points, but only one study found similar improvements in visual acuity. No data were available regarding the impact of combining therapies on injection frequency.

In the sole prospective, comparative study to date, the combination of a single IVTA injection and subthreshold micropulse grid laser was found to result in significantly greater visual gains as compared to micropulse grid laser alone in patients with BRVO-related macular edema. Both groups achieved significant improvement in foveal thickness, without intergroup differences detected. IOP higher than 21 mm Hg requiring medical therapy occurred in 55% of IVTA-treated patients; the rate of IOP elevation in the micropulse grid laser–alone cohort was not given.

Conclusions

There appears to be no compelling evidence to date to support the use of combination pharmacologic and pharmaco-laser therapy as a primary treatment in RVO. The well-established efficacy of intravitreal monotherapy, particularly with anti-VEGF agents, warrants at the very minimum a trial of either anti-VEGF or corticosteroid monotherapy. Such an approach will continue to be standard of care until a large-scale randomized clinical trial demonstrates clear superiority of combination therapy over intravitreal monotherapy.

There is, however, enough evidence to recommend combination therapy in patients in whom monotherapy is failing as well as in patients for whom frequent re-treatments have become an overwhelming social or financial burden or in whom dose-limiting adverse effects are a significant concern. Currently, specific recommendations regarding the ideal combination approach fall largely to individual providers, who are tasked with creating treatments customized for individual patients based on available clinical data, with particular attention paid to previously documented responses to component agents, preexisting adverse effects or predisposition to adverse effects, and angiographic data documenting extent of ischemia (Table 2). Of note, the addition of PRP to treat patients with documented nonperfusion on wide-field angiography appears to be a promising approach to reducing the frequency of intravitreal anti-VEGF administration.

In the future, intravitreal cytokine profiling in treatment-naive RVO patients may provide a greater level of customization of RVO therapy and allow for identification of candidates for initial combination therapy based on a particularly unfavorable intravitreal cytokine milieu.

REFERENCES


