UPDATE ON SICKLE CELL RETINOPATHY MANAGEMENT

Here's where we are–and where my research shows we could be going.

BY JENNIFER I. LIM, MD, FARVO, FASRS

Ischemia and infarction inherent in sickle cell disease result in myriad ocular manifestations, the most important of which are the retinal manifestations.[1] Sickle cell retinopathy (SCR) findings can be divided into five stages.[2] Nonproliferative SCR is comprised of stage 1, characterized by arteriolar narrowing, and stage 2, characterized by arteriovenous anastomosis. Proliferative sickle cell retinopathy (PSR) is comprised of stage 3, characterized by peripheral retinal neovascularization (in a classic seafan configuration); stage 4, characterized by vitreous hemorrhage; and stage 5, characterized by retinal detachment (RD).

SCR SIGNS AND SYMPTOMS

The progression of SCR from nonproliferative to proliferative has been closely studied. In one study, only 10% of the eyes of patients with sickle cell disease experienced a VA loss of 20/60 or worse.[3] The proliferative stage is responsible for the majority of vision loss from SCR, with an incidence of vision loss of 31 per 1,000 eye-years of observation among eyes affected by PSR compared with 1.4 per 1,000 eye-years among eyes experiencing nonproliferative changes.[4]

In addition to the well-defined clinical spectrum, there are also subclinical findings of SCR. My research team has shown that patients without visual symptoms with good visual acuity can have significant thinning on macular OCT imaging.[5,6] Moreover, this macular thinning has been associated with decreased sensitivity on microperimetry testing.[7] OCT angiography (OCTA) reveals flow voids associated with macular thinning in both pediatric and adult patients.[8] In addition, AI analysis of OCTA images can be used to classify the stage of PSR.[9,10]

MANAGEMENT OF SCR

Patients with sickle cell disease should receive a screening examination at least yearly.[11] Typically, this should start at 8 to 10 years of age. Unfortunately, most patients with sickle cell disease are not screened.[12] Although there is no treatment for nonproliferative SCR, my research team has shown hydroxyurea is associated with lower rates of macular thinning.[13]

Stage 3

Management for stage 3 SCR includes observation, laser photocoagulation, and intravitreal anti-VEGF injections. With a 30% rate of spontaneous regression of retinal neovascularization, some question whether treatment is necessary.[3] A prospective laser trial showed the efficacy of laser treatment, which was well-tolerated. Laser resulted in a lower rate of prolonged visual acuity loss (1% vs 6.7%) and a lower incidence of vitreous hemorrhage (11% vs 18.7%) compared with observation.[14] The laser treatment included laser application to an area extending one disc diameter beyond the anterior and posterior seafan borders and one clock hour to each side of the seafan. However, the rates of complete seafan closure and new seafan formation were the same for the treated and observation arms.[14]

Subsequently, postmortem studies have shown increased VEGF and HIF-1α staining in the 2 mm area around the retinal neovascularization. The authors suggest that a more generous application of laser surrounding the seafan of two disc diameters could ablate the regions that contribute to HIF-1α and VEGF production and result in better, more successful outcomes.[15]

More recently, anti-VEGF treatment has been used in the management of both stage 3 and stage 4 PSR.[16-19] Isolated case reports have shown regression of seafans soon after intravitreal anti-VEGF injection. In most cases, laser photocoagulation is applied, so there are no data using anti-VEGF alone for the management of stage 3 PSR.

To compare anti-VEGF therapy with laser for stage 3 or 4 PSR, I created the Anti-VEGF vs. Laser Photocoagulation for PSR Study (ALPS). In preparation for this prospective study, the ALPS collaborators performed a retrospective study to collect preliminary evidence of efficacy

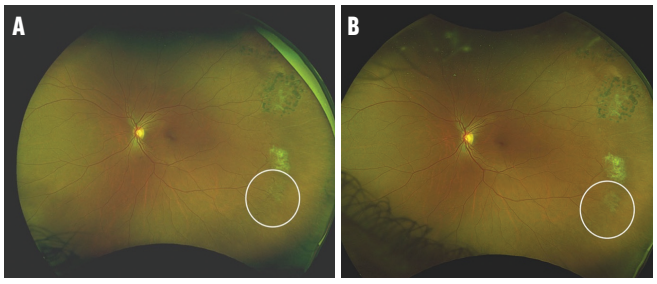

Figure. Color fundus photography of the left eye of a patient with stage 3 PSR shows an active seafan (A, white circle). Five weeks after treatment with an anti-VEGF agent, the seafan is inactive (B, white circle).

for the use of intravitreal anti-VEGF injections for stage 3 and 4 PSR. We found that anti-VEGF therapy for stage 3 eyes may result in seafan regression (Figure). We did not encounter any cases of endophthalmitis. However, seafans recurred in one-third of patients with complete regression. In addition, some of the treating physicians combined anti-VEGF with laser photocoagulation after seafan regression occurred. The ALPS study will help refine the treatment and determine the efficacy and safety of anti-VEGF for PSR.[19,20]

Stage 4

For stage 4 PSR, treatment options include observation and pars plana vitrectomy (PPV). If the vitreous hemorrhage is mild and there is no associated tractional RD, consider using laser photocoagulation or anti-VEGF injection.[16-19] Otherwise, for more significant vitreous hemorrhage, perform either anti-VEGF injection or PPV for non-clearing vitreous hemorrhage. In the retrospective anti-VEGF study by the ALPS investigators, anti-VEGF injections for stage 4 resulted in three or more lines of visual acuity improvement in all eyes with vitreous hemorrhage; this improvement usually occurred within 1 month of treatment.[19] Some investigators added laser photocoagulation after the hemorrhage cleared, and others used additional anti-VEGF injections as needed. The prospective ALPS study will determine whether intravitreal anti-VEGF injections can result in a significantly lowered rate of PPV versus observation.

Stage 5

Treatment for eyes with stage 5 PSR typically requires PPV, although consideration can be given to pneumatic retinopexy for rhegmatogenous RD without tractional RD and scleral buckling procedures with or without PPV. Concerns related to PPV in patients with sickle cell disease include the risk of inducing a sickle cell crisis, iatrogenic retinal breaks, optic and retinal ischemia, and postoperative anterior segment ischemia. As such, it is important to avoid systemic hypotension and keep the patient well-hydrated and warm during surgery.

In the first report of surgery for PSR in 1971, scleral buckling was used to repair RDs, which led to high rates of postoperative anterior segment ischemia.[21] Consequently, to mitigate the risk of this complication, preoperative exchange blood transfusion, local anesthesia without epinephrine, and supplemental oxygen were recommended. The authors strongly recommended avoiding compression of the long posterior ciliary vessels, meticulously controlling IOP, and using cryopexy sparingly. These recommendations reflected the prevalent surgical techniques of that era before the widespread adoption of PPV. In general, I agree that scleral buckling, particularly high buckles, should be avoided.

In 1982, Jampol et al introduced PPV with or without scleral buckling for treating PSR complications.[22] The series had a 30% rate of iatrogenic retinal tears. The rate of reattachment was low at 60%, and only 50% of eyes had improved postoperative visual acuity. Since then, with improvements in PPV techniques and instrumentation, better anatomic and visual outcomes have been achieved. However, the rates of recurrent RD remain high at 29% to 50%, as compared with non-PSR-related RDs.[23-27]

At my institution, modified techniques using delamination over segmentation and careful vitreous base shaving with release of all anterior-posterior traction and circumferential traction have resulted in improved anatomic and visual acuity outcomes. I often use a lighted pick and internal limiting membrane forceps to segment the seafans free of the vitreous adhesions and adjacent retinal tissue. To avoid bleeding and retinal tear formation, I do not attempt to delaminate adherent seafans. In addition, I ensure the IOP is kept at a low, normal range to avoid optic nerve infarction.

Using this modified 25-gauge technique, my colleagues and I achieved a 100% reattachment rate for PSR-related RDs.[28] Over a median follow-up of 42 months, BCVA stabilized or improved by 3 or more lines in 96% of eyes. Median VA improved from 20/400 preoperatively to 20/40 postoperatively.[28] Our study highlights the importance of early intervention in macula-on RD cases to maximize the postoperative visual outcomes.

MANAGEMENT QUICK HITS

When managing stage 3 PSR, consider intravitreal anti-VEGF injection with close follow-up versus laser photocoagulation. Use more generous laser photocoagulation (two disc diameters around the seafan).

For stage 4 PSR, use anti-VEGF injection with or without laser versus PPV with laser.

For stage 5, small-gauge PPV with modified techniques may achieve anatomic reattachment while minimizing risks of intraoperative complications.

The ALPS prospective study will help decipher the efficacy and safety of anti-VEGF therapy for PSR. Overall,

long-term stability of visual and anatomic outcomes after surgical intervention in PSR cases is possible with continued monitoring and treatment of ischemic-related complications and management of postoperative cataracts that occur with time. ■

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