Clinical Update

Ocular Graft-vs.-Host Disease
The Downside of Success

BY PEGGY DENNY, SENIOR EDITOR
INTERVIEWING REZA DANA, MD, MPH, MARTINE J. JAGER, MD, PHD, AND STELLA K. KIM, MD

Hematopoietic stem cell transplantation (HSCT) has contributed substantially to survival among patients with severe hematologic disorders, including leukemias and lymphomas, since the first successful bone marrow transplant was performed in 1968. More recently, the development of new immunosuppressive regimens, preconditioning protocols, and better HLA typing has continued to improve posttransplant survival rates.

Although anything that increases survival among patients with these life-threatening diseases is great news, the downside is that physicians are also seeing a rise in the rates of chronic complications of HSCT, especially graft-vs.-host disease (GVHD), as patients are living longer, according to Martine J. Jager, MD, PhD, at Leiden University Medical Center in the Netherlands. Because GVHD has a multitude of systemic manifestations—which may involve the skin, gastrointestinal tract, liver, musculoskeletal system, and more—its ocular manifestations are too often overlooked, both at cancer treatment centers and in eye clinics.

Yet ocular GVHD is not uncommon. “More than a third of the survivors who get allogeneic HSCT develop significant eye disease,” said Reza Dana, MD, MPH, at Harvard Medical School. “That’s a very considerable disease burden. Patients survive due to bone marrow engraftment, but the ‘price’ is that these cells can attack the tissues of the recipient.”

Ocular GVHD most often presents as severe dry eye and ocular surface disease, which can have a profound impact on the quality of life in survivors. Unfortunately, ocular GVHD is often misdiagnosed. Helping these patients involves both raising awareness of the condition at large and tailoring the ophthalmic treatment approach to each affected individual.

An HSCT Primer
Stem cells used for transplantation may be derived from donor bone marrow, peripheral stem cells, or cord blood. HSCT is known as autologous when the cells are harvested from the patient; syngeneic when taken from an identical twin; and allogeneic (allo-SCT) when the donor cells are from either a related or an unrelated individual. HSCT can be used to treat a variety of diseases, but over 80 percent is performed in the setting of cancers such as leukemia or lymphoma. Patients receive either autologous or allogeneic transplantation depending on the type and status of their cancer.

Immunological warfare. Before HSCT is administered, the patient undergoes a preconditioning regimen, in which the patient’s own bone marrow—and, accordingly, immune system—is depleted through intensive chemotherapy, with or without radiation therapy. The transplanted donor cells repopulate the recipient’s marrow and reconstitute the patient’s hematologic profile, including the immune system. GVHD occurs when the donor-derived graft cells, often T cells, react to the recipient’s autoantigens.

Stella K. Kim, MD, at the M.D. Anderson Cancer Center, said, “Patients are cured of their cancers, but often the cure can result in GVHD, which is essentially an autoimmune disease,” with a variety of clinical manifestations, often with a protracted course.

Prophylactically curtailing the activity of the donor immune cells could reduce the incidence of GVHD. However, the anticancer efficacy of HCST requires a vigorous graft-vs.-tumor response; thus, one of the greatest chal-
The Spectrum of Ocular GVHD

GVHD can occur in acute (Fig. 1) and chronic (Fig. 2) patterns. Dr. Kim said, “Acute forms of ocular GVHD can be quite severe, resembling toxic epidermal necrolysis, requiring immediate evaluation and early intervention. These patients are typically in their early course post-HSCT and are often being treated in the inpatient setting. On the opposite end of the clinical spectrum are patients who are years out from their HSCT and doing well systemically but are dealing with severe ocular surface disease, such as cicatricial keratoconjunctivitis, from chronic ocular GVHD.” Chronic ocular GVHD is more commonly seen in ophthalmology outpatient clinical practice than is the acute form.

Principal manifestation: dry eye.

Although chronic ocular GVHD spans a range of ocular surface disorders, the published literature and the specialists interviewed agree that severe dry eye is by far its chief clinical manifestation.

In her clinic, Dr. Jager said, “Ocular GVHD patients are like very severe dry eye patients. They usually have both lack of aqueous tear formation and lack of oil secretion as a result of meibomian gland dysfunction. Some just don’t make tears anymore; they’re absolutely dry.”

Other ocular surface problems.

At the worst, Dr. Jager continued, patients go on to develop other forms of corneal and ocular surface disease, including limbal deficiencies, scarring, and symblepharon formation. Eyelid inflammation and scarring may cause cicatricial entropion and trichiasis, further irritating the cornea.

Treatment Guidance

According to Drs. Dana, Jager, and Kim, the treatment approach for chronic ocular GVHD is essentially the same as for other types of severe dry eye, but understanding the status of the patient’s systemic GVHD can influence the ocular treatment strategy. For example, all three doctors consider the use of topical steroids earlier for ocular GVHD than they would for ordinary dry eye.

Basic principles of therapy. The seminal 2006 NIH consensus guidelines listed the four major supportive care goals for ocular GVHD as lubrication, control of tear evaporation, control of tear drainage, and decreasing ocular surface inflammation.

The 2013 major review coauthored by Dr. Dana had a similar list of treatment goals: lubrication and tear preservation, reduction of inflammation, prevention of tear evaporation, and epithelial support.

Both sources agree that the treatment needs to be matched to each patient’s particular mix of symptoms; the individual’s systemic medications should be taken into account. Ideally, said Dr. Dana, “Treatment regimens should be realistic, starting with readily available things such as topical steroids and punctal plugs. If there’s no response, then you step it up to another level.” It’s important to note that a patient’s clinical presentation may require managing some or all of the following problems simultaneously.

Inflammation. Randomized clinical trials have shown that topical steroids remain the most useful treatment overall for chronic ocular GVHD. However, because of their side effects, including increased risk of infections, cataract, and increased IOP, research is continuing on other immunosuppressive agents such as anakinra, tacrolimus, and ultra-low-dose interleukin-2.

Dr. Jager said that her patients have had excellent results with topical cyclosporine drops. “It does not have side effects, and it’s one of the nicest drugs for chronic GVHD.” However, it is not commercially available in Europe and must be compounded, taking it out of the price range for many patients, she said, adding that U.S. patients are fortunate to have a commercially available form (Restasis).

However, Dr. Kim noted, “Depending on the severity of chronic ocular GVHD, topical cyclosporine can have varying degrees of efficacy. More clinical research is needed in this area.”

Decreased tears. The first steps in reducing the symptoms of decreased tearing are the old standbys of dry eye therapy: preservative-free artificial tears and punctual occlusion with silicone plugs or cautery.

Although oral agents to increase tear secretion, such as pilocarpine or cevimeline, have been tried, there is little clinical or trial evidence to support this therapy in GVHD.

Tear evaporation/dysfunction. Tear evaporation and break-up can be reduced through the use of warm eyelid compresses to improve meibomian gland function. Patients may also benefit from increasing humidity in their home and workplace, using moisture goggles, or trying nutritional supplements such as flaxseed oil or fish oil.

Oral doxycycline or minocycline may be useful in meibomian gland dysfunction for their anti-inflammatory as well as antibiotic effects. Given that GVHD patients are often on a multitude of drugs, Dr. Dana cautioned that adding any systemic therapy, including the tetracyclines, should be coordinated with patient’s hematologist-oncologist.

Epithelial damage. Autologous serum eyedrops contain many growth factors and vitamins that support the healing and integrity of the ocular surface. These drops have proved beneficial in clinical studies and anecdotally. Dr. Jager said that she finds them very helpful in patients with epithelial problems. Her patients say that...
the drops “make their eyes feel much, much better, and if they have been off for a few weeks, they beg me for them.”

The limitation of this therapy is that it may be difficult to obtain except at specialized medical centers. Dr. Dana said, “There are a lot of issues in terms of obtaining or compounding autologous serum tears,” in part because, as a blood product, they require specific testing and handling regimens.

Scleral contact lenses, including the PROSE device, have been shown to improve vision and comfort in patients with epithelial damage. “Providing scleral contact lenses can completely change patients’ lives,” said Dr. Jager. These devices are more effective in reducing patient symptoms than improving epitheliopathy, however.2

**Long-Term Management**

Drs. Dana, Jager, and Kim agreed that ocular GVHD should be considered a lifetime condition. Even after the need for intensive intervention has passed, patients should be examined routinely—not just to follow their dry eye but also to monitor for complications such as infections, cataract, or increased intraocular pressure. (See “More Online,” below.)

Dr. Dana added: “Like any chronic disease—from hypertension and cardiac disease to MS or diabetes—ocular GVHD comes in a wide range of flavors. Patients who respond well to treatment can be followed by their local ophthalmologist. It’s only the severe or nonresponsive cases that continue to require specialized attention.”

**Late Diagnosis and Misdiagnosis**

Despite the availability of treatments, in many cases, the patient’s symptoms may be far advanced before the diagnosis of ocular GVHD is established. Such treatment delays cause unnecessary suffering and, in some cases, permanent ocular damage.

Dr. Jager recounted the story of her worst patient, who had received HSCT for leukemia: “She was admitted to intensive care, and for six weeks nobody looked at her eyes. By the time she had survived intensive care, her corneas looked like completely dried-out pieces of leather. Now, three years later, she is doing fine in terms of her leukemia, but she comes to my clinic every week for eye problems. If someone had paid attention to her eyes when she was in intensive care, she wouldn’t be in the state she is now.”

Why is the timely and accurate diagnosis of ocular GVHD so difficult?

**Overshadowed by bigger issues.** These patients and their doctors have been dealing with a life-threatening hematologic disease requiring intensive treatment; and after HSCT, they may be coping with multisystem GVHD. Dr. Dana noted that eye disease is a relatively late complication of GVHD, with other forms, such as skin and oral, typically occurring first. Thus, eye conditions do not top the list of medical concerns.

Dr. Jager said, “I recently spoke to a hematologist, and he said, ‘Eye problems? What are you talking about? I never see any eye problems in my leukemia patients.’ But I think he never asked.” She added that doctors may be “so thrilled by the survival that everything else seems trivial.” By the time patients come to her eye clinic, their ocular disease is severe.

**Condition is not widely known; thus misdiagnosed.** According to Dr. Dana, “A lot of GVHD patients end up getting misdiagnosed when they see their eye doctor. They’re told they have ‘an eye infection’ or conjunctivitis. Then they mention it to their hematologist, who says, ‘No, that’s eye GVHD,’ and they eventually end up going to the cornea specialist.”

**Solutions: Education and Awareness**

“From a public health standpoint, there’s a critical need to educate both optometrists and ophthalmologists about ocular GVHD manifesting as severe dry eye,” said Dr. Dana. Distinguishing between GVHD and garden-variety dry eye “is primarily based on the history of the patient’s condition”; thus, clinicians need to be aware of a patient’s prior HSCT and its ocular implications.

**More visibility.** Dr. Jager noted that there has been an upswing in conference presentations on ocular GVHD in recent years, and she is hopeful that this increased visibility will continue to raise awareness.

**Communication between transplant and ophthalmology teams.** Dr. Kim said that “awareness by the primary team and having readily accessible ophthalmology teams can facilitate earlier evaluation of patients.” For example, she continued, “because the M.D. Anderson Cancer Center ophthalmology clinic is within the hospital, we are able to treat patients both in the early and late course of their GVHD.” She noted that other centers that have an ophthalmology presence or designated individuals with interest in GVHD are also highly successful in treating HSCT patients with ocular GVHD.

---

**References**


**Reza Dana, MD, MPH, is the Claes Dohlman Professor of Ophthalmology at Harvard Medical School; Senior Scientist at Schepens Eye Research Institute; and Director of Cornea and Refractive Surgery at Massachusetts Eye and Ear Infirmary. Financial disclosure: Consults for Alcon/Novartis, Allergan, Bausch + Lomb, Eleven Biotherapeutics, Genentech, Novabay, and Novalig.**

**Martine J. Jager, MD, PhD, is senior medical specialist at Leiden University Medical Center, Leiden, the Netherlands, and guest faculty professor at Peking University Health Center in Beijing. Financial disclosure: None.**

**Stella K. Kim, MD, is associate professor and Director of Clinical Research in Ophthalmology, Ophthalmology Section, University of Texas, M.D. Anderson Cancer Center. Financial disclosure: Consults for Bayer, Eli Lilly, Sanofi Aventis, and Seattle Genetics.**

---

**MORE ONLINE. For a discussion of other eye conditions associated with GVHD, see this article at www.eyeenet.org.**

---