A COORDINATED team approach by a variety of medical specialists allied to a carefully calibrated programme of systemic immunosuppression is helping to deliver higher success rates for stem cell transplantation in patients with ocular surface disease, according to Edward J Holland MD.

“We advocate and practise a careful pre-operative and postoperative team approach to stem cell transplantation in our institution, drawing on the expertise of corneal surgeons, ocular plastic surgeons, glaucoma specialists and transplant immunologists to give our patients the best chance of visual recovery over the long term. As a result, we can now rehabilitate some of the most severely injured eyes that were impossible to treat a few decades ago. Our experience has also shown that systemic immunosuppression is vital to success rates with our procedures and we think it is very safe in our group of patients,” he said.

Addressing delegates at the joint meeting of the European Society of Ophthalmology (SOE) and the American Academy of Ophthalmology (AAO), Dr Holland, director of cornea at the Cincinnati Eye Institute and professor of ophthalmology at the University of Cincinnati in Ohio, said that careful sequential staging of the procedures involved in treating ocular surface disease delivers better outcomes for his patients.

“About 50 per cent of our patients have significant glaucoma, so we try to reduce the amount of topical glaucoma medications that we use the stem cells to. On patients’ initial presentation to our clinic, they are evaluated by the glaucoma service and a significant number will get tube shunts prior to any other procedure in order to lower their intraocular pressure,” he said.

The next step taken by Dr Holland’s team is to evaluate the status of the eyelid and lashes before performing ocular surface transplantation, as significant eyelid abnormalities can cause a breakdown of the epithelium and secondary microbial infection in patients with ocular surface disease.

“Many of the patients, especially the trauma and chemical injuries patients, will have associated lid abnormalities and about half of the patients will get lid surgery prior to the stem cell transplant procedure,” said Dr Holland.

**Getting to grips with inflammation**

Once any lid abnormalities have been tackled, the next phase is to deal with any inflammation, since limbal allografts transplanted to an inflamed ocular surface have a significantly poorer prognosis than those in which the inflammation has been reduced.

“Significant conjunctival inflammation is present, topical and systemic immunosuppression should begin weeks to months before transplantation to improve the overall success rate of the procedure,” he said.

Once these measures have been taken – stabilising IOP, restoration of lid anatomy and function, and ocular inflammation quietening – the way is clear for ocular surface transplantation to be performed, said Dr Holland. This is often followed several months later by a penetrating or lamellar keratoplasty for visual reconstruction once the ocular surface is stabilised.

He noted that the selection of transplantation technique is based on several factors. For patients with unilateral disease, a conjunctival limbal autograft is the procedure of choice because it does not run the risk of failure secondary to immune rejection.

For patients with bilateral disease, the most common choices of donor tissue are the cadaveric procedure, known as keratolimbal allograft, or the living-related conjunctival limbal allograft.

“In our practice, the majority of patients undergo a keratolimbal allograft procedure because of the readily available tissue that we have from cadaver donors and the increased amount of stem cells that we can obtain. However, in cases of significant conjunctival disease, such as Stevens-Johnson syndrome, we will use the living-related conjunctival allograft procedure, which provides healthy conjunctival cells in addition to limbal tissue,” he said.

A combination approach, using keratolimbal allograft with living-related conjunctival allograft, has also been tried in patients with very severe ocular surface disease. This combination maximises the advantages inherent to each procedure, said Dr Holland. He added that the future trend seems to be heading towards greater use of ex-vivo expanded limbal cells, in which limbal tissue from a donor is expanded in culture before transplantation. Cils can come from a normal fellow eye, a living relative, or a cadaver.

“The advantages of ex-vivo expansion include reduced risk to any donor eye, it allows for HLA typing of the donor, and you can grow large sheets of cells, thereby paving the way for cultured conjunctiva, which is really what we need.”

The disadvantages include the fact that it is technically difficult, much more expensive than our present procedures and currently, we get a small number of stem cells with these procedures,” he said.

To illustrate the benefits of a typical keratolimbal allograft procedure, Dr Holland presented the case of a young male patient with severe alkali injury and high IOP. After firstly having a tube shunt placed to lower his IOP, followed by induction of immunosuppression, three months later he underwent a keratolimbal allograft, followed another three months later by a penetrating keratoplasty.

“This patient has been able to sustain visual function in the 20/30 range for more than a decade now,” said Dr Holland.

**The keys to success**

To put the results of the Cincinnati Eye Clinic into a wider perspective, Dr Holland said that a meta-analysis of the published scientific literature over the past decade showed a success rate of about 57 per cent for ocular surface treatments, most of which involved patients with Stevens-Johnson syndrome, ocular cicatricial pemphigoid and chemical injuries. A closer examination of the use of autoimmune suppression in these cases revealed that patients with a shorter duration of immunosuppression recorded a higher failure rate than those with a longer duration, a finding echoed by Dr Holland’s own clinical case experience.

“If we look at our outcomes at the Cincinnati Eye Institute, we have a total of 132 cases, primarily aniridia, chemical injury, and Stevens-Johnson syndrome, with an average follow-up of 3.2 years, and our success rate is about 78 per cent with a significant improvement in visual acuity. We firmly believe that our success rate is based on our approach to immunosuppression,” he said.

Dr Holland’s immunosuppression protocol involves three agents: corticosteroids, tacrolimus, and mycophenolate. He noted that the necessary duration of immunosuppression depends on a patient’s pre-operative diagnosis, postoperative course, and whether the rejection of a transplant has occurred.

“After two years, about 20 per cent of our patients are completely off all oral immunosuppression, and half of the patients are on a low dose taper with no prednisolone orally taken in this group. In terms of side effects, there has been no associated mortality or organ failure for these patients. Some transient problems of renal impairment were encountered that were effectively managed with reduced intake of the oral immunosuppressants,” he said.

Dr Holland added that a study of 32 patients over a two-year period carried out by immunologists at the University of Cincinnati confirmed that ocular surface patients experienced a much lower rate of side effects than renal transplant patients in terms of hypertension, blood cholesterol and bone marrow complications.