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# Protecting Insulin-Producing ß-cells After Transplantation: Immunosuppression and Encapsulation

**Announcer:**
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

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**Dr. Bellin:**
Hello, I'm Dr. Melena Bellin from the University of Minnesota. I'm a professor of pediatric endocrinology and surgery. I will be speaking today on protecting insulin producing beta cells after transplantation, talking specifically about anti-rejection medications, to other strategies including tolerance, induction and encapsulation to avoid chronic immunosuppression.

I'd like to start by giving you a little bit of background about the current state of eyelet transplantation. Most eyelet transplants have been cadaveric donor eyelets obtained from a deceased donor and then transplanted into a patient with Type 1 diabetes. This is done largely under clinical trials, under FDA regulation in the US, but it is available as a clinical procedure in certain areas of Europe and Canada. The goal here is to restore endogenous insulin production. In this procedure, the pancreas is resected from the deceased donor and transplanted into the recipient. The eyelets are isolated specifically and transplanted into the portal vein of the liver.

This is done either by a small incision, a mini laparotomy with infusion of the eyelets into the portal vein, or through a interventional radiology guided approach. The eyelets then ingraft in the liver sinusoids and start to function over a period of weeks to months. But in order to protect and maintain function of those eyelets, patients must be on immunosuppression to prevent a recurrence of autoimmunity and alloimmune rejection. And largely because of that immunosuppression, eyelet transplants have been restricted to patients who have high risk Type 1 diabetes, and that is specifically in most cases defined by either patients who are having very labile blood glucoses, or a brittle form of diabetes complicated by severe hypoglycemia, or they have had a kidney transplant and already require immunosuppression. And typically they're insulin sensitive non-obese individuals so that you can get enough eyelets to function and provide the body's insulin needs.

Now, under those circumstances, eyelet transplants are very successful. The majority of patients have resolution of liability and severe hypoglycemia. And at experienced centers, 80% or more may come off insulin, although sometimes it requires two eyelet infusions to get enough eyelets.

Again, all patients are placed on immunosuppression currently, with our current therapy, and this consists of two components, an induction immunosuppression component and maintenance. Induction is typically with a T-cell depleting agent like ATG or Alemtuzumab, or sometimes with an IL-2 receptor antagonist like Bevacizumab. And often a TNF alpha inhibitor is given at the same time to block innate immunity. This is short term in the peri transplant period. But then patients must also be kept on maintenance therapy for as long as the eyelets continue to function. And that usually consists of tacrolimus or sometimes cyclosporine, combined with an anti-proliferative agent like mycophenolate or sirolimus.

The choice of immunosuppression does matter in outcomes and particularly so in long-term outcomes. So the figure on the right here

shows data from whole organ pancreas transplant in the red, and two groups of eyelet transplant recipients in the purple who received T-cell depleting agents and TNF alpha inhibition for their induction immunosuppression compared to patients who received only IL-1 receptor antagonists for induction in the blue bars. Showing insulin independence is better long term when a more ideal induction regimen is used. More recent results have also shown better long-term outcomes when Sirolimus and calcineurin inhibitor maintenance like tacrolimus is used in combination.

Unfortunately, the problem with long-term immunosuppression is that it has a risk of side effects and complications. So this immunosuppression is fairly equivalent to what someone would get if they were getting a whole organ pancreas or other solid organ transplant. So patients must be monitored very closely with routine labs and clinical examinations, looking particularly for serious side effects like bone marrow suppression, particularly leukopenia, infection risk, including monitoring for EBV and CMV viruses that can have significant complications in transplant recipients, monitoring kidney function, particularly in those on tacrolimus and monitoring for skin cancers and other malignancy. In addition, patients oftentimes have minor but bothersome side effects like GI symptoms or mouth ulcers that must be managed.

So while this immunosuppression risk is justifiable for those patients who have complicated forms of Type 1 diabetes and are having hypoglycemia, in order to bring this to a larger transplant audience, a larger group of patients with Type 1 diabetes, we need to be able to minimize or get rid of that immunosuppression. So well, that's not available in the clinic right now. There's many strategies being developed. Those include work on tolerance where we'd actually retrain the immune system to recognize the eyelets as part of self. This might include using T-regulatory cells or sort of a negative vaccine approach to retrain the immune system. Gene editing of donor cells. Now this becomes particularly an option when you have stem cell derived eyelets like are being translated it now into the Type 1 diabetes setting that you might be able to gene edit these cells to make them less responsive to the immune system or encapsulation strategies.

Now, encapsulation strategies are under clinical trial right now and can take a few different approaches. So a macro encapsulation strategy puts multiple eyelets in one capsule. These are retrievable, which is appealing and protective, but there's a very thick diffusion barrier. Micro and nano encapsulation encapsulate a single eyelet at a time and are a little bit thinner, but still there is a challenge in terms of the thickness between the eyelets and the blood vessels that can lead to hypoxia or problems with fusion of glucose or insulin across to the cells. Another concept is to apply an open bio scaffold where local immunosuppression or trophic factors could be placed to protect the eyelets. These are all in development, but will be really important to bringing stem cell derived eyelet therapy and renewable cell sources to a larger patient population with Type 1 diabetes or other forms of diabetes.

So what do you need to know for your patients with Type 1 diabetes right now in the clinic? Cell therapy for diabetes is limited currently to patients who have type one diabetes complicated by severe hypoglycemia or who need immunosuppression for a kidney transplant. And this might be a clinical procedure or clinical trial, depending on your setting. However, approaches to reduce the immunosuppression are currently under development, including encapsulation, tolerance induction and gene editing, and these would greatly improve safe access to eyelet therapies including stem cell derived eyelet transplants for more patients with Type 1 diabetes. Thank you for your attention.

**Announcer:**
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