Immune Antibody Monitoring Predicts Outcome in Islet Transplantation

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With over 40 years of intense collaborative research in the making, has clinical islet transplantation finally come of age? This cellular replacement tool has been tried and tested in over 1,000 patients undergoing various forms of islet transplantation since 2000, and it is becoming increasingly safe, effective, and durable in stabilizing glycemic control, HbA_{1c}, and lowering the risk of secondary complications in refractory type 1 diabetes (1–4). Evanescent rates of insulin independence observed by 3 years in previous protocols were multifactorial in origin, but driven predominantly by an innate and adaptive immunologic response to transplanted cells (5). The good news is that more effective control of inflammation, auto- and alloimmunity with rationally targeted induction, and maintenance therapeutics have recently led to marked improvement in 5-year insulin independence rates exceeding 50% in six independent transplant centers (1,6–8). This milestone places islet transplantation, albeit in highly selected centers, on a par with whole pancreas–alone transplantation, while avoiding surgery and attendant risk (6). While this pace of progress is indeed impressive, major challenges remain, and include *1*) the current need for intense induction and maintenance immunosuppression; *2*) limited access and funding for islet processing and transplant facilities; and *3*) low single-donor engraftment rates in the absence of strategic donor and recipient selection, exacerbating an already limited human islet donor supply.

Effective control of both auto- and alloimmunity is a perquisite for the sustained success of islet transplantation, but monitoring by direct tissue biopsy is impractical for a widely dispersed, low-volume endocrine graft (9,10). Cellular and antibody-based assays have therefore been developed for surrogate islet monitoring in peripheral blood to help unravel the relative contributions of auto- and alloreactivity. Immune profiling could optimize donor and recipient matching, better predict outcome, and most importantly allow preemptive selection and titration of immunosuppressive agents to maximize islet graft longevity while minimizing the risk of side effects, opportunistic infection, or malignancy (Fig. 1).

On the cellular side, Bart Roep's immunology group at Leiden University found that markers of T-cell autoreactivity against insulinoma-associated protein 2 (IA-2A) and glutamic acid decarboxylase (GADA) correlate strongly with clinical outcome (11,12). Cytotoxic T lymphocyte precursor frequencies (CTLp) for HLA Class I alloreactivity and donor-specific interleukin-10 cytokine profiling in mixed lymphocyte culture for Class II alloreactivity also strongly correlated with outcome, and tapering of immunosuppression led to high-avidity allospecific CTLp responses (13,14). Furthermore, Han et al. (15) found that elevations in granzyme B and other cytotoxic lymphocyte genes preceded islet loss.

The humoral side of the equation has been even more complicated to resolve. Previous interpretation of alloantibody responses was perhaps clouded by the presence of disparate HLA mismatched antigens from multiple islet donors. Furthermore, the impact of islet autoantibodies had been largely overlooked in several previous studies, largely because the presence of preexisting autoantibodies did not seem to reflect risk of failure. The article by Piemonti et al. (16) in this issue of *Diabetes* is therefore enlightening and provides the most comprehensive assessment to date of the potential negative impact of rising auto- and alloantibody titers upon islet transplant survival. Application of an array of autoantibody markers including zinc transporter 8 antigen (ZnT8A), which has previously been shown to be of importance in recurrent autoimmunity after pancreas transplantation (17), IA-2A and GADA, and high-resolution single-bead antigen alloantibody monitoring with intensive serial monitoring over time, were essential to the analysis. Perturbations in titer rather than absolute values now appear to be the keys to understanding how to better protect islets posttransplant. Piemonti et al. analyzed the outcomes of 59 islet recipients in this manner and found a surprisingly high presence of donor-specific antibody (DSA) pretransplant in almost half of the cases. The finding of improved islet survival in cases with pretransplant DSA seems anomalous. Autoantibody rise—especially epitopic spreading to additional autoantigens—was a poor prognostic marker and occurred early posttransplant (detectable by day 16 posttransplant, and almost 70% of the subjects developed autoantibodies within 3 months). Rising autoantibodies were associated with a 5.2 times increased risk of graft failure, which occurred at a median of 304 days posttransplant. A rise of both DSA and autoantibody was an especially poor prognostic marker of graft endurance. The finding by Piemonti et al. that antithymocyte globulin (ATG) induction was associated with the greater risk of antibody formation and poorer long-term graft survival is inconsistent with the finding by Bellin et al. (6) of 50% islet transplant success with T-cell depletional induction. One may surmise that the omission of tumor necrosis factor-α blockade at induction and the omission of therapeutic calcineurin inhibition in the maintenance regimen of Piemonti et al. may have contributed to this finding rather than the specific use of ATG per se.

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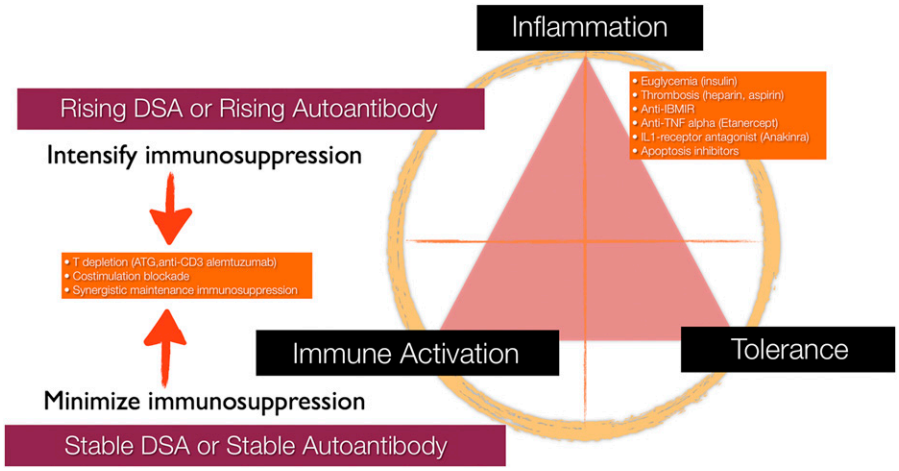

FIG. 1. Interrelational balance between immune activation, inflammation, and tolerance and current favored approaches to modify inflammatory response in clinical islet transplantation. Perturbations in DSA or type 1 diabetes autoantibodies can potentially direct intensity of immunosuppression in a more precise manner than current empiric approaches, thereby lowering risk to patients. IBMIR, instant blood-mediated inflammatory reaction.

Drawbacks to this study include the fact that it was conducted over an 8-year period with evolving collagenase enzymes and islet isolation techniques and with changing induction and maintenance approaches over this time. The data were collected prospectively, but analyzed retrospectively. Patients were not managed based on their antibody responses, so it remains to be seen whether rising antibody responses would be reversible with more intensified, preemptive immunosuppression, and thus whether this would indeed be protective to the graft. A future study now begs for a prospective, controlled intervention arm based upon simultaneous state-of-the-art antibody and T-cell–based assays to direct immunotherapy. The contributions by Piemonti et al. have certainly laid the foundation for such a study. If immunosuppression could be tailored to meet these immunological perturbations, and especially be minimized in patients with optimal profiles, islet transplantation could be more broadly and safely applied to a much greater cohort of patients with type 1 diabetes.

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