FDA BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE
SUMMARY MINUTES
Meeting #26, March 20-21, 2000

The 26th meeting of the Biological Response Modifiers Advisory Committee was held at the Holiday Inn, Bethesda, Maryland on March 20-21, 2000. Four topics were included on the agenda: 1) Islet Transplantation; 2) Chairman's Summary Report of the January 13, 2000 meeting of the Xenotransplantation Subcommittee of the BRMAC, 3) administrative update, 4) update of CBER research programs in the Division of Cellular and Gene Therapies and the Division of Therapeutic Proteins. A closed session was held on March 21. This portion of the meeting was closed to permit discussion and review of trade secret and/or confidential information, 5 U.S.C. 552b (c) (4). The public meeting was attended by approximately 75 persons.

On March 20, the meeting, was opened to the public and called to order at 9:10 a.m. by Daniel Salomon, M.D., Committee Chair. A conflict of interest statement was read into the public record which stated that members with the appearance of a conflict of interest based on their work with products which could be affected in the future were given waivers to participate. Copies of the waivers are available from the FDA Freedom of Information Office. A copy of the agenda and roster are attached.

The FDA provided a brief introduction to the islet transplantation issues proposed for discussion on day 1 of the meeting.

The committee heard presentations from several experts in the field of islet transplantation. These presentations addressed islet transplantation as an alternative to whole organ pancreas transplantation; methods and techniques employed in recent islet transplant protocols; and quality standards for islet preparations.

The committee also heard presentations from two major funding organizations of islet transplantation research, the National Institutes of Health and the Juvenile Diabetes Foundation International. The FDA provided a regulatory perspective for the manufacture of islets for transplantation.

The chair then commenced the open public hearing. There were no requests for public comment. At this time the committee began deliberations of questions posed to the committee by FDA regarding issues related to the manufacture of pancreatic islets.

Pancreatic Islet Product Questions

1. Organ Quality - Source Material for Islets.

The committee was asked to discuss recommendations for pancreata exclusion criteria including restrictions on minimum and maximum donor age; diseases or other conditions. The committee was also asked to discuss appropriate serum markers in addition to, or as an alternative to serum lipase.

The committee discussed issues related the use of pancreata from donors <14 years of age. There was no consensus by the committee on the use of younger donors. While younger donors may provide a larger source of organs, some problems could exist with this use of islets from younger donors, including decreased cell number, difference in secretory capacity and difference in the time necessary for younger islets to increase insulin production. The committee stated that at this time there are no data to support rigid age criteria but if the age limits are expanded there could be the need to modify guidelines and adjust laboratory techniques.

There was no consensus by the committee on exclusion criteria for malignancy, prior diabetes history or acute pancreatitis. While the committee discussed the importance of using the best criteria to produce safe and effective islets, in general there are no data to exclude pancreata from pancreatitis donors, cancer donors or donors with a prior history of type II diabetes. The committee suggested that the same criteria used for normal pancreatic organ donation be adopted for early clinical islet trials.

The committee agreed on the need for a safe product and that efforts should be made to obtain the highest quality islets available. There was a concern expressed that islet transplant programs not adversely affect the ability of patients to obtain high quality whole pancreata. The committee stated for the public record that the FDA should join with islet purification centers and UNOS to address whole organ vs islet programs.

2. Appropriate Types of Identity and Potency Testing

The committee included issues related to identity testing and potency in the same discussion. The committee discussed 3 separate levels of testing. The committee stated that the following criteria for islets should be measured: within 2 hours of purification there should be a determination of sterility (gram stain and endotoxin negative), islet integrity (determined by diphenylthiocarbazone positive staining) and islet number (at least 5000 IE/kg). There should also be a reasonable volume to contain the islet mass obtained (e.g. less than 10ml) and viability should be greater than 95% as determined by vital dye exclusion.

Within 24 to 48 hours of transplantation, follow-up testing should include a measure of insulin content and a dynamic test of insulin release. These assays could include glucose stimulated insulin release, and insulin biosynthesis assays.

The committee also discussed additional assays that could be performed for further research purposes, including gene expression arrays; expression of apoptosis markers and confocal microscopy for stimulated Ca++ fluxes.

The committee also discussed the value of a true in vivo potency assay, for instance, transplantation in a diabetic SCID mouse model.

3. Viability, Number and Size of Islet Preparations

The committee discussed lot release specifications for islet viability and recommendations for appropriate measures of viability. There was some consensus among the committee that while it is hard to set absolute criteria for viability, 70% viability as determined by fluorescent dye exclusion would be acceptable. An islet preparation of 50% viability would not be recommended for transplant.

In further comments the committee stated there are insufficient data available to recommend a maximum volume/dose that may safely be transplanted. As the maximum tolerated dose is unknown the committee recommended monitoring hepatic portal pressure during transplantation or keeping the volume under 10ml.

4. Purity-Composition of Islet Preparations

There was a brief discussion by the committee about the effect of exocrine tissue which might be present in islet preparation. The committee stated that there is no evidence that exocrine tissue associated with islets is associated with immunogenicity problems. On the other hand, the significant post transplant death of many cells in the nonislet pancreatic tissue associated with the islets might well result in inflammatory cytokine release and other immune effects that should be the subject of further research. Moreover, it is also known that animals and human patients can be chimeric with donor-derived cells in tissue compartments distant from the transplant site after islet transplantation, which might also have effects on the immune response, positive or negative.

5. Demonstration of Control in Islet Processing

The committee agreed new investigators/islet transplantation centers will need to obtain training and to demonstrate proficiency in procurement and processing. New investigators/islet transplantation centers will ultimately need to demonstrate (possibly by an independent assessment) they can reproducibly meet purification standards for at least 10 consecutive preparations with at least 90% sterility after processing and 70% viability from sterile, non-clinical grade pancreata.

This completed the discussion of islet manufacturing issues.

The committee began a discussion of the Chairman's Summary Report of the January 13, 2000 meeting of the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee.

The report of the FDA Xenotransplantation Subcommittee was presented to the committee by the subcommittee chair. The report outlined the recommendations of the subcommittee regarding FDA policy on blood donor deferral and the risks posed by different types of xenotransplantation products.

The committee received an update from the FDA regarding further recommendations made by the Blood Products Advisory Committee on the issue of additional questions to be included in the current blood donor questionnaire. Members of the Xenotransplantation Subcommittee present voiced concerns regarding a recommendation by the BPAC on questions pertaining to close contacts of xenotransplant recipients that did not agree with the recommendation of the Xenotransplantation Subcommittee.

Following a brief discussion of the report the committee voted unanimously 10 yes, 0 no to approve the report as written.

At this time, the meeting was adjourned at approximately 6:15 p.m., March 20, 2000.

The meeting was reconvened at 8:00 a.m., March 21, 2000. The committee received information on the proposed future direction of the Biological Response Modifiers Advisory Committee. It was proposed by FDA that future committee discussions focus on early product development issues. Committee members expressed a concern that as these types of discussions are less focused than product approval discussions the committee might lose some enthusiasm for the topics brought before them. It was emphasized by the FDA that the direction of the BRMAC would be expanded and the committee would continue to be involved in future product approval issues but also would have a major role in early development policy discussions.

Following this discussion, the committee was provided updates of several CBER research programs in the Division of Cellular and Gene Therapies and the Division of Therapeutic Proteins. Individual research programs from the Laboratory of Cytokine Research and the Laboratory of Chemistry were briefly summarized for the committee.

At this time the committee held a brief closed session. The meeting was closed to allow for discussion of confidential issues as warranted under 5 USC 552b(c) (6).

The meeting was then reopened to the public. The topic for day two was Preclinical and Clinical Issues in Allogeneic Islet Therapy. A brief introduction by FDA to the topic was followed by an open public hearing. There were no requests for public comment.

The FDA perspective on animal models of islet therapy was provided and the committee heard two expert presentations on non-human primate and other animal models of islet transplantation. The last presentation provided the FDA perspective of clinical issues concerning islet therapy.

At this time the committee began deliberations of questions posed to the committee by FDA regarding issues related to preclinical and clinical issues in allogeneic islet therapy.

1. Immunosuppression

The committee was asked to consider what additional animal studies should be done to optimize the immunosuppressive regimens.

The committee stated at the current time, there are insufficient data from preclinical studies to justify a particular immunosuppressive regimen in clinical trials. Some committee members suggested there are current clinical data from which to base future clinical trials, others suggested that non-human models be recommended for new immunomodulatory agents or combined regimens which have never been used in humans. It was generally agreed that a justification of any given immunosuppressive or tolerance inducing strategy should be based on multiple preclinical models including but not limited to specific islet transplantation models and at least some nonhuman primate work.

Some members recommended, if possible, data be obtained from an autoimmune animal model of diabetes along with more clinically analogous models such as pigs or monkeys that have been rendered diabetic. However, some on the committee were not convinced that autoimmunity had any major role in the success or failure of allogeneic human islet transplants, particularly under immunosuppression.

The committee was asked which patients would be most appropriate to include in studies of islet-only therapy.

There was no consensus from the committee on the question of patient selection. Some eligibility criteria suggested by the committee included hypoglycemia unawareness, metabolic instability, and early secondary diabetic complications with a creatinine cut-off. Psycho-social factors should be considered and it would be important for patient eligibility to be assessed by an independent diabetologist. Reference was made to standards employed for selecting patients for pancreas transplant but some felt that islet administration is less risky and could potentially be employed more broadly.

Some of the committee stated that the risk/benefit ratio will be different for each individual, therefore, the only recommended required standard eligibility criteria should be the patient's informed consent. Others stated that an informed consent was an imperfect document and subject to real or perceived bias introduced by the investigators. Therefore, some felt that it was critical to have independent members on a selection committee to make sure that protocols were well based on the science and medicine. The potential positive role of the FDA IND process in this issue was acknowledged by some.

2. Donor-recipient matching

The committee was asked to discuss preclinical or clinical data which address the immunogenicity of islet preparations, the minimum criteria (HLA disparity, etc) to be used for donor-recipient matching and the collection of data on donor-recipient matching.

The committee stated HLA matching should not be required but data on HLA typing should be collected from clinical trials. There was no consensus among the committee on the need for cross-matching of blood groups. The committee stated that animal models, other than non-human primates, could provide preclinical immunogenicity (e.g. relative to whole pancreas transplant) data, however there are no data at this time that indicate that HLA antibodies adversely affect the outcome in islet transplantation.

3. Route/Site of Islet Product Administration

The committee was asked to discuss direct contact of islet preparations with portal circulation, safety considerations of intraportal injection of islets, other routes of administration (immunoprivileged sites) and animal models to evaluate route/site of administration of islet preparations.

There was consensus by the committee that current preclinical and clinical data suggest portal infusion of islets, employing the current best islet preparations and recently improved methods of infusion, is safe. There was a suggestion that alternative sites of administration be considered that would allow insulin to be released into the portal vein and not directly into the liver or systemic circulation.

The committee stated that preclinical data need to be obtained to evaluate other routes/sites of administration.

4. Outcome Measures

The committee was asked to discuss issues related to activity measures in early clinical studies including the appropriateness of specific measures (C-peptide, Hemaglobin A1c, glucose tolerance, insulin usage, hypoglycemic episodes and patient diaries); other potential endpoints, and criteria to determine loss of graft function. The committee also discussed issues related to efficacy endpoints in phase 3 trials.

The committee discussed activity measures that would evaluate function. Recommendations were made for all centers to perform daily glucose monitoring, as well as measure glucose disappearance and insulin release. Periodic activity measures of Hb1Ac and C-peptide were recommended.

The committee stated there are not sufficient current data to set criteria for determining loss of graft function, particularly in partial function transplants, therefore, it is important to obtain information on as many activity measures as possible in early trials.

There was no consensus by the committee on potential endpoints for phase 3 trials of allogeneic islet products. The committee stated there is not sufficient available information to recommend which patients should go into Phase III trials. Some areas of concern include patients with severe hypoglycemia and ketoacidosis. Cardio-vascular complications are significant risk factors in allogeneic transplants and there need to be parameters in this regard also. Additionally, while there are some data from current

clinical trials there are no preclinical or clinical data on the long term consequences of the immunosuppressive regimens used in these early clinical trials.

This completed the discussion of issues related to allogeneic islet therapy for the treatment of diabetes. The meeting was adjourned by the chair at 4:00 p.m., March 21, 2000.

For more detailed information concerning the open session presentations and committee discussions summarized above, please refer to the meeting transcripts. Transcripts may be obtained through the FDA Freedom of Information Office or accessed through the Internet (http:www.fda.gov)

Attachments