Cellular Therapy Products and Immune Rejection: Clinical Perspective

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Immunosuppression in Clinical Trials:
Questions, Considerations, and Current Practices

- **Is immunosuppression needed for a specific cellular product?**
- Considerations
  - Type of product
    - Immunosuppressants have been administered for allogeneic cells (both embryonic stem cell-derived products and differentiated cells).
    - Immunosuppressants do not appear to be necessary for autologous cellular products or for mesenchymal stem cells.
  - Site of administration
    - Immunosuppressants may not be necessary for 'immune privileged' sites (e.g., the retina)
  - Clinical (and preclinical?) experience with related products

Immunosuppression in Clinical Trials:
Questions, Considerations, and Current Practices

- **What immunosuppressants have been used?**

(from Collaborative Islet Transplant Registry (CITR))

Category	Medications Included
Polyclonal T-cell depleting antibodies	Rabbit-anti-human anti-thymocyte globulin (rATG) Horse-anti-human anti-thymocyte globulin (hATG) Anti-lymphocyte globulin (ALG)
Monoclonal T-cell depleting antibodies	Alemtuzumab (Campath)
Monoclonal Anti-IL2R antibodies	Daclizumab, Basiliximab
Monoclonal Anti-CD3 antibodies	hOKT3g1 (Ala-Ala)
TNF-α antagonists	Infliximab, Etanercept
Anti-inflammatory	Deoxyspergualin
Calcineurin inhibitors	Tacrolimus, Cyclosporine
mTOR Inhibitors	Sirolimus, Everolimus
Inosine monophosphate dehydrogenase inhibitors	MMF, Mycophenolate Sodium
Corticosteroids	Prednisone, Methylprednisolone, others

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- **When has immunosuppression been administered, relative to the time of administration of the cellular product?**
  - Immunosuppression started at:

    Day -7 to Day 0 (i.e., at one week prior to, or on the day of, administration of the cell product)
  - Immunosuppression stopped at:
    - 6 weeks, 3 months, 6 months, 9 months, lifetime, or individualized for each study subject
    - Consider projected duration of cell survival, and occurrence of adverse reactions to the immunosuppressant

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- **Adverse reactions associated with immunosuppressants, from CITR:**
  - 29% of 592 serious adverse events have been related to immunosuppression
  - One death attributed to viral meningitis, possibly related to immunosuppression

Immunosuppression in Clinical Trials:
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- **How is subject safety ensured when administering immunosuppressants?**
  - Use “standard” dose and regimen of each immunosuppressant
  - Monitoring:

    Blood levels of immunosuppressant(s); electrolytes, glucose, CBC, renal function, hepatic function
  - Data Safety Monitoring Board (DSMB)
  - Rules for stopping the immunosuppressant
    - For signs of infection
    - For toxicity previously associated with the immunosuppressant

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- **Example of rules for stopping tacrolimus:**
  - Occurrence of atypical (e.g., fungal) infection
  - Fever unresponsive to antibiotics
  - Elevated liver function tests or bilirubin
  - Elevated creatinine
  - Seizure
  - Thrombotic thrombocytopenic purpura (TTP)

Immunosuppression in Clinical Trials:
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- **Regulatory recommendations**
  - For first-in-human study of a cellular therapy:
    - Sponsor should propose and justify (based on preclinical, clinical, or other scientific data) whether or not to administer immunosuppressant(s) in the clinical trial.
    - If administering an immunosuppressant, specify and justify the choice of immunosuppressant, the dose, the duration of administration, monitoring procedures for toxicity, and stopping rules for the immunosuppressant.

OCTGT Regulatory Resources

- OCTGT Learn Webinar Series:

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- General information for OCTGT and related regulatory references

  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

Thank You…

- Regulatory Questions
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