Treatment of Cellular Primary Immune Deficiencies: Innate and Adaptive

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Session 1206 PID: What do I do with my patient?
Disclosures

I have a financial relationship or interest related to the content of this CME program with the following entities:

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- Grifols – advisory Board, speaker
- Green Cross – Data Safety Monitoring Board
- Kedrion - Data Safety Monitoring Board
Innate Immune Deficiencies

Chronic Granulomatous Disease
Therapy for CGD

- Prophylaxis –
  - Antibacterial – trimethoprim-sulfamethoxazole
    - 5mg/kg/day up to 320 mg in 2 divided doses
  - Antifungal – Itraconazole
    - 100 mg/day <13 y or <50 kg
    - 200 mg/day >13 y or >50 kg
  - Immunomodulatory – Interferon gamma
    - 50 mcg/m2 SQ three times per week
DHR Assay to Diagnose CGD

Normal

AR deficient CGD

Phox$^{91}$ deficient CGD (X-linked)

X-linked CGD carrier

Residual NADPH Oxidase and Survival in Chronic Granulomatous Disease

Douglas B. Kuhns, Ph.D., W. Gregory Alvord, Ph.D., Theo Heller, M.B., Ch.B., Jordan J. Feld, M.D., M.P.H., Kristen M. Pike, M.S., Beatriz E. Marciano, M.D., Gulbu Uzel, M.D., Suk See DeRavin, M.D., Ph.D., Debra A. Long Priel, M.S., Benjamin P. Soule, M.D., Kol A. Zarember, Ph.D., Harry L. Malech, M.D., Steven M. Holland, M.D., and John I. Gallin, M.D.
B

\[ O_2^- \geq 2.3, \text{ MFI} \geq 225 \text{ AU} \]

\[ O_2^- < 2.3, \text{ MFI} < 225 \text{ AU} \]

\[ P = 0.002 \]

Proportion Surviving (%)

Years

Kuhns et al New Eng J Med 2010
CGD and Hematopoietic Stem Cell Transplantation

- Over 99 transplantations (Dec 2010) with over half in the past 10 years
  - More often offered in Europe than North America
  - Candidates – low NADPH oxidase, increase in alkaline phosphatase, liver abscess, decrease in platelet counts (portal hypertension)

- Advances in BM transplantation
  - Non-myeloablative regimens; high resolution sequence based tissue HLA matching
    - Busulfan and fludarabine based regimens
    - ATG or alemtuzumab with mycophenolate for GVH prophylaxis
  - Europe consortium - 96% survival
  - NIH experience – 91% survival

Kang et al JACI 2011
CGD and Gene Therapy

- Advances in vector technology

- Early NIH experience#
  - Autologous CD34 stem cells transduced ex vivo with an amphotrophic pseudotyped retroviral vector encoding gp 91phox
  - Busulfan conditioning
  - Early cell marking was 4.26%, decreased to 0.03-1.1% with partial resolution of infections in 2/3 patients

- Other clinical trials have seen myeloplasia

- Good news - to achieve a significant functional correction, only need about a 10% of marked neutrophils

Kang et al Blood 2010
CGD and Gene Therapy

- CGD remains a difficult target for gene therapy
  - expansion of wild type gene does not provide any survival advantage to the transduced stem cells
    - need for myeloablative conditioning
  - Unlike T-cells, circulating neutrophils have a short half life
    - larger number of transduced HCS needed
  - Inflammatory environment of the disease can exert a negative effect on the success of engraftment of transduced Cd34+ cells

Mukherjee et al Gene 2013
TLR 5/10/1

TLR 2

TLR 1/6

MD2

CD14

IRAK4

New gene transcription

Nucleus

Cytoplasm

MyD88

MyD88

TIRAP

TIRAP

Activation of NF-κB plus other transcription factors

Ligand = dsRNA

Ligands = ss RNA, CpG motifs

Flagellin

Lipooligosaccharides

Lipopolysaccharide (LPS)

Endosom

e

TLR 7/8/9

Cell membrane

TLR 3

Endosom

e

Ligand = dsRNA
Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency

Science 299:2076-2079, 2003

IRAK (1-4, M) = IL-1 Receptor Associated Kinase

AR defect in IRAK4 results in defective TLR, IL-1, and IL-18 signaling.

Clinical history of recurrent bacterial infections that usually decrease following adolescence
Patients/families with herpes simplex encephalitis – defects in Toll-Like Receptor pathway

- Defects in TLR3 and UNC93B (an endoplasmic reticulum protein required for normal TLR3, 7, 8 and 9 signaling)
- HSV-1 signaling via TLR3 (involving UNC93B) with the generation of (type 1) IFN-α, β, is crucial for the normal host defense against HSV-1 in the CNS
- Interferon-alpha may prove to be an important adjunctive agent added to anti-viral (acyclovir) therapy for treating HSE
Mutations in only 10 genes account for >95% of SCID

Table 1
Ten abnormal genes in human SCID

Cytokine-receptor genes
IL-2RG
JAK3
IL-7Rα

Antigen-receptor genes
RAG1
RAG2
Artemis
CD3δ
CD3ε

Other genes
ADA
CD45

IMMUNOLOGICAL RECONSTITUTION OF SEX-LINKED LYMPHOPENIC IMMUNOLOGICAL DEFICIENCY

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Treatment Modalities for T-cell Immune Deficiency Diseases

- Bone marrow transplantation
  - HLA/MLC matched sibling
  - HLA haploidentical donor (parent/sibling)
  - unrelated HLA/DR match
  - cord blood stem cell
BM Transplantation for the Treatment of SCID

- 89 patients with SCID
- T-cell depleted, HLA-haploidentical parental marrow (77), or HLA-identical sibling marrow (12)
- 89 infants (81%) still alive 3 mos to 16.5 yrs after transplant
  - 100% of HLA matched
  - 78% haploidentical
- No pre-transplant conditioning regimen
  - 36% had peripheral B-cells
  - 63% required IVIG replacement therapy

Buckley et al NEJM ’99
Buckley JACI 2010
BM Transplantation of SCID

- No conditioning or prophylaxis against GVHD
  - 40% developed GVHD, but mild not requiring treatment

- T-cell function after transplant
  - 2 weeks in HLA identical
  - 3-4 months in haploidentical transplants

- B-cell function - abnormal in haploidentical transplants ($\gamma_c$ chain/Jak 3 deficiency)
  - Need IVIG

- Early BM transplantation by 3-4 months of age, and before infection develops critical!

Buckley et al. NEJM '99
Buckley JACI 2010
BM Transplantation of SCID

- European experience:
  - 26% of their SCID patients had absent T and B-cells with normal NK cells
  - rates of survival and engraftment after HLA-haploidentical BM low
    - host NK cells accounts for poor engraftment
    - myeloablative conditioning needed in these patients
    - risk of GVHD and infection

Haddad et al, Blood'98
RGI – HLA identical sibling; RPI – HLA matched non-sibling family donors
URD – HLA matched, unrelated; MMR – mismatched related
Gennery et al JACI 2010
Cellular Reconstitution in SCID

- HLA matched family donor BMT is the optimal therapy for SCID

- Haploidentical BMT using a parental donor and T cell depletion is a common approach (Buckley)

- Matched unrelated donor, peripheral blood and cord blood stem cell transplantation have been used successfully
  - High resolution molecular typing

- Outcome studies support early intervention with >90% success when BMT performed in SCID pts <28 days of age (Myers L, et al, NEJM 2002)
Gene Therapy of Human Severe Combined Immunodeficiency (SCID)–X1 Disease

Marina Cavazzana-Calvo,∗1,2,3 Salima Hacein-Bey,∗1,2,3 Geneviève de Saint Basile,1 Fabian Gross,2 Eric Yvon,3 Patrick Nusbaum,2 Françoise Selz,1 Christophe Hue,1,2 Stéphanie Certain,1 Jean-Laurent Casanova,1,4 Philippe Bousso,5 Françoise Le Deist,1 Alain Fischer1,2,4†

www.sciencemag.org  SCIENCE  VOL 288  28 APRIL 2000
Gene Therapy for XSCID: NEJM Report in 2002

- 5 XSCID patients treated
  - Ages: 1, 3, 6, 8, 11 mos
  - 3 severe infections, 2 maternal engraftment
- Target: Bone Marrow CD34+ Cells
- Outcome
  - T cell and NK cell reconstitution
  - Stable correction of immune deficiency for more than one year
Complications Related to the SCID-X Gene (γc deficiency) Therapy

- Five of 20 patients developed leukemia 2-5.5 years after gene therapy
  - following chemotherapy 4 patients survived

- provirus integrations within a proto-oncogene locus
  - clinical trials discontinued
  - retroviruses preferentially integrate within actively transcribed genes
    - LMO2 locus in hematopoietic progenitors favor local integration
      - vector viral LTRs' enhancer activity can permanently turn on transcription of the target gene and trigger the leukemic process
      - not seen in gene therapy for ADA, but has for WAS

Fischer A Gene 2013
<table>
<thead>
<tr>
<th>Trial period</th>
<th>No.</th>
<th>Results</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID-X1 (Paris)</td>
<td>10</td>
<td>Eight alive, 4 SAEs</td>
<td>Closed</td>
</tr>
<tr>
<td>SCID-X1 (London)</td>
<td>10</td>
<td>Ten alive, 1 SAE</td>
<td>Closed</td>
</tr>
<tr>
<td>SCID-X1 (France/ UK/US)</td>
<td>3</td>
<td>Three alive</td>
<td>Open</td>
</tr>
<tr>
<td>SCID-ADA (Milan)</td>
<td>15</td>
<td>Fifteen alive, 13 off ERT</td>
<td>Open</td>
</tr>
<tr>
<td>SCID-ADA (London)</td>
<td>7</td>
<td>Seven alive, 3 off ERT</td>
<td>Open</td>
</tr>
<tr>
<td>SCID-ADA (US: 2 trials)</td>
<td>9</td>
<td>Nine alive, 5 off ERT</td>
<td>Open</td>
</tr>
<tr>
<td>WAS (Hanover)</td>
<td>10</td>
<td>Ten alive, 1 SAE</td>
<td>Closed</td>
</tr>
<tr>
<td>WAS (Milan)</td>
<td>2</td>
<td>Alive</td>
<td>Open</td>
</tr>
<tr>
<td>WAS (France/ UK/US)</td>
<td>2</td>
<td>Alive</td>
<td>Open</td>
</tr>
</tbody>
</table>

*ERT, Enzyme replacement therapy; SCID-X1, X-linked severe combined immunodeficiency; UK, United Kingdom; US, United States.*

Fischer A et al JACI 2011
Status of Gene Therapy in PIDD

- Efficacy in SCID-X1, ADA deficiency and WAS provides proof of concept

- Construct safer vectors:
  - enhancer deleted LTR -SIN(self-inactivating) vector containing an internal promoter
    - less likely to initiate transcriptional activity of adjacent proto-oncogenes
  - HIV-derived lentiviral vectors
    - reduced probability of insertional mutagenesis
    - can transduce non-dividing cells
      - eliminate the need for a cytokine cocktail to induce cell division
      - maintain stem-cell like function for long term engraftment
      - allows for inclusion of larger and more sophisticated transgene expression cassettes

- Engineered endonucleases and homologous recombination

- Genomic safe harbors
  - regions of the human genome where newly integrated transgenes can be expressed stably without adverse effects

Mukherjee and Thrasher Gene 2013
Pessach and Notarangelo JACI 2011
Status of Gene Therapy in PIDD
Primary Immune Deficiency Treatment Consortium

- Network of 33 centers in North America

- Objectives
  - Study the natural history and treatment of rare and severe PIDD
    - Comprehensive database
  - Prospective treatment studies to determine the optimal therapy
    - B-cell reconstitution in SCID following stem cell Tx
      - ? Pre-HCT conditioning
        - None vs minimal intensity regimens
        - Type of SCID, e.g. NK cell+, B+ SCID
    - GVH prophylaxis

Griffith LM et al JACI 2013 in press
Shearer WT et al JACI 2013 in press
Primary Immune Deficiency Treatment Consortium

- Prospective treatment studies to determine the optimal therapy
  - Late effects of HCT
    - Neurocognitive, growth and development
    - Chronic GVHD
    - Development of autoimmune and inflammatory complications
  - Effects of conditioning regimens in young children (infants)
    - Non-toxic regimens
  - Need for additional HCT “boosts”
- Gene therapy
  - What degree of transduction necessary
  - Better and safer vectors
“...the greatest teachers of modern immunology: patients with immunodeficiency diseases.”

Robert A. Good, M.D., D.Sc., Ph.D.