Immune Reconstitution Inflammatory Syndrome

Joseph R. Berger, M.D.
University of Kentucky

For Session 3: Treatment of drug-induced PML
Transatlantic Workshop: Drug-related PML
IRIS Definition

- There is no widely accepted standard definition of IRIS
- “Paradoxical deterioration in clinical status attributable to recovery of the immune system”¹
- First recognized with HIV infection after the introduction of highly active antiretroviral therapy
  - ↓HIV load → ↑CD4 (and CD8)² → recovery of T cell specific immune response
  - 90% ↓HIV within 2 weeks of HAART
  - IRIS develops with 2-3 months of HAART (1-104 weeks)

Categories of IRIS in HIV Infection

<table>
<thead>
<tr>
<th>Table I. Categories of immune reconstitution inflammatory syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>Infectious – unmasking</td>
</tr>
<tr>
<td>Infectious – paradoxical</td>
</tr>
<tr>
<td>Autoimmune</td>
</tr>
<tr>
<td>Malignancies</td>
</tr>
<tr>
<td>Other inflammatory conditions</td>
</tr>
</tbody>
</table>

- Conditions reported with IRIS in HIV
  - MAI, M. Tb, B. henselae, C. neoformans, PCP, CMV, HSV, VZV, Hepatitis C, Hepatitis B, PML
  - Kaposis sarcoma, sarcoidosis, Graves disease
- Increased risk with greater severity of illness
- PML-IRIS may occur in up to 23% of HIV-associated PML
- Survival in HIV-associated PML unaffected by IRIS

Pathogenesis of IRIS

• The pathogenesis of IRIS is poorly understood.
  – Reconstitution of the immune cell numbers and function
  – Redistribution of lymphocytes
  – Defects in regulatory function
  – Changes in Th₁ v Th₂ profile
  – Genetic susceptibility
  – Antigenic load

• Accounts for clinical and pathological heterogeneity

Features of PML IRIS in HIV

• Clinical worsening
• MRI progression
  – Extension of lesion on T2WI and FLAIR
  – Contrast enhancement (may be transient)
  – Brain edema

Initial MRI July 2004
Follow-up MRI Oct 2004

Martinez JV et al: Neurology 2006; 67:1692-4
PML-IRIS with Natalizumab
Representative Case

- 21 year old woman
- RRMS x 15 years
- PML after 29 months of natalizumab
- Heralded by seizures
- Rx with PLEX, mirtazapine and mefloquine
- Worsening 1 week after PLEX
- IVMP 500 mg/d x 5 d and mannitol

Pathology of PML

Demyelination

Bizarre astrocytes

Enlarged oligodendroglial nuclei
Pathology of PML-IRIS

Acute perivenular demyelination and inflammation

Intense perivascular inflammation with CD8+ cells


Treatment of PML-IRIS in HIV Infection

• Common therapeutic intervention is high dose corticosteroids
  – Typically dramatic clinical improvement
  – No increase in adverse events\(^1\)
  – Trend but no statistically significant difference in survival with steroid treatment of PML-IRIS in HIV\(^2\)
    • Early corticosteroid introduction
    • High doses
    • Prolonged administration

PML-IRIS with Natalizumab

- Review of 28 confirmed natalizumab-associated PML between July 2006-November 2009\(^1\)
- IRIS occurred in almost all cases
- Characterized by
  - Subacute progression and exacerbation of earlier symptoms
  - Enlarging MRI lesions or contrast enhancement
- IRIS occurred even in absence of PLEX
- Mortality 28.5% (8/28)
- JCV may persist in CSF even months after IRIS\(^2\)

Tysabri-treated PML Cases

Frequency of IRIS is Similar in Patients With or Without PLEX/IA

- As of 28-Jan-2011 with 93 confirmed PML cases, the majority of patients (84/93, 90%) underwent accelerated removal of Tysabri from the circulation by PLEX and/or IA

- 2 patients (2/84, 2%) did not develop IRIS and the occurrence of IRIS was either not reported or unknown for 26 patients (26/84, 31%)

- IRIS usually occurred days to several weeks after PLEX/IA
- Without PLEX/IA, IRIS usually occurred ~3 months after the last dose of Tysabri
- Most patients were treated with corticosteroids for IRIS (or IRIS prophylaxis) 73/93, 78%; 7 patients were not treated with corticosteroids and it was unknown if corticosteroids were prescribed in 13 patients.

<table>
<thead>
<tr>
<th>Treatment Received (PLEX and/or IA)</th>
<th>Number of Confirmed PML patients (N=93)</th>
<th>Number/percent of patients who developed IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLEX alone</td>
<td>76</td>
<td>56/84 (67%)*</td>
</tr>
<tr>
<td>IA alone</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>PLEX and IA</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>NO PLEX or IA</td>
<td>4</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Unknown status</td>
<td>5</td>
<td>4/5 (80%)</td>
</tr>
</tbody>
</table>

* 2 patients (2/84, 2%) did not develop IRIS and the occurrence of IRIS was either not reported or unknown for 26 patients (26/84, 31%)

BiogenIdec communication July 22, 2011
Recommended Treatment for PML-IRIS

• No controlled trials to date

• Suggested therapies
  – 1 g IVMP for 3-5 days followed by oral taper over 6-8 weeks\(^1\)
  – 1 g IVMP for 5 days followed by oral taper over 2 weeks\(^2\)
    • If symptoms during or after taper worsen, retreatment with the same dose or IVMP 2 g for 5 days with subsequent taper

Medicine is a science of uncertainty and an art of probability.

Sir William Osler
1849-1919