Therapies for Moderate to Severe Psoriasis

Mark Lebwohl, MD

Sol and Clara Kest Professor
And Chairman
Department of Dermatology
The Mount Sinai School of Medicine
Impact of Psoriasis vs. Other Diseases on Patient-reported Physical Outcomes

Lower scores reflect worse patient-reported outcomes

Impact of Psoriasis vs Other Diseases on Patient-Reported Physical Outcomes

GenenUser, 8/13/2003
Impact of Psoriasis vs. Other Diseases on Patient-Reported Mental Outcomes

Lower scores reflect worse patient-reported outcomes
Title: Impact of Psoriasis vs Other Diseases on Patient-Reported Mental Outcomes

Rank: 1

Keywords: search words

QCname: Person's Name

QCdate: mm/dd/yy

GenenUser, 8/13/2003
Patients Dissatisfied with Current Psoriasis Therapy


- Frustrated with treatment: 78%
- Treatment not aggressive enough: 32%
Patients Dissatisfied with Current Psoriasis Therapy

GenenUser, 8/13/2003
Prevalence of Psoriasis

- 5 – 7 million adults
- ~10% severe
- ~15% psoriatic arthritis
Light Therapy Unit
Limitations of PUVA

♦ Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment (Stern et al., *J Invest Dermatol*, 1988)

Limitations of Methotrexate
Accidental kidney biopsies in psoriasis.


15 cases 1981-1991

contributing fx:
• ↑BUN, creatinine
• ↑MCV
• ↑age
• trimethoprim-sulfamethoxazole
Limitations of Cyclosporine A

- Renal biopsy findings in long-term cyclosporin treatment of psoriasis (Zachariae et al., *Br J Dermatol* 1997)
  - 30 psoriatics, 6 months - 8 years, 2.5 - 6 mg/kg/d
  - after 2 years, all showed features of CsA nephropathy
  - arteriolar hyalinosis, focal interstitial fibrosis, sclerotic glomeruli
Retinoid Side Effects
Retinoid Side Effects
Retinoid Side Effects
Retinoid Side Effects
Retinoid Side Effects
# Drawbacks of Current Psoriasis Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>UVB</td>
<td>Frequent visits</td>
</tr>
<tr>
<td>PUVA</td>
<td>Frequent visits, skin carcinoma, melanoma</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Teratogenic, inadequate as monotherapy</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Bone marrow toxicity, hepatotoxicity</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>Alefacept</td>
<td>Weekly office visits, slow onset</td>
</tr>
</tbody>
</table>
<Title> Drawbacks of Current Psoriasis Therapies <Title>

QCdate mm/dd/yy

GenenUser, 8/13/2003
MARKET OVERVIEW - TRx’s
Adalimumab, Alefacept, Efalizumab, Etanercept and Infliximab

- Not hepatotoxic
- Not nephrotoxic
- Not toxic to marrow
- Not teratogenic
- Their main side effect is...
POVERTY
Clinical Results With 1st Course of IV Alefacept

Patient A

Baseline (Course 1) PASI 14.2

2 Weeks After Last Dose PASI 9.5

12 Weeks After Last Dose PASI 4.8
### Alefacept IM Phase 3 Study

**Overall Response Rate After 1 Course**

<table>
<thead>
<tr>
<th>Proportion Responding (%)</th>
<th>Alefacept 10 mg</th>
<th>Alefacept 15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% Reduction in PASI</td>
<td>53%</td>
<td>57%</td>
</tr>
<tr>
<td>≥75% Reduction in PASI</td>
<td>28%</td>
<td>33%</td>
</tr>
<tr>
<td>PGA “Almost Clear” or “Clear”</td>
<td>22%</td>
<td>24%</td>
</tr>
</tbody>
</table>

* P<0.001
† P = 0.002
Will we see complications of immune suppression in patients treated with biologics?

- Lymphoproliferative diseases
- Infections
Disseminated sporotrichosis associated with treatment with immuno-suppressants and tumor necrosis factor-alpha antagonists.

Gottlieb GS, et al.


- 49 yo ♂
- ETN, IFX, & other immunosuppressives
Cerebral toxoplasmosis following etanercept treatment for idiopathic pneumonia syndrome after autologous peripheral blood progenitor cell transplantation (PBPCT).

Gonzalez-Vicent M, et al.

Disseminated cryptococcal infection in rheumatoid arthritis treated with methotrexate and infliximab.

True DG, et al.

Invasive pulmonary aspergillosis associated with infliximab therapy.

Warris A, et al.

Disseminated cytomegalovirus infection in Crohn's disease following anti-tumour necrosis factor therapy.

Helbling D, et al.

Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents.

Slifman NR, et al.


FDA Adverse Event Reporting System

- 14 - infliximab; 1 - etanercept; all on other immunosuppressives.
Most opportunistic infections occur in patients on other immunosuppressives - 6MP, MTX, Steroids, CsA - along with biologics.
Tuberculosis associated with infliximab, a tumor necrosis factor $\alpha$-neutralizing agent.

Keane J, et al.  

70/147,000

48 $\leq$ 3 infusions

Test for TB!
Tuberculosis (TB)

• TNF necessary for granuloma development\(^1\)
• Cases of TB have been seen in patients treated with all the TNF antagonists\(^2\)
  – Often extrapulmonary
  – Reactivation
  – Risk factors: concomitant corticosteroids and diabetes
  – Screen for TB prior to beginning TNF-antagonist therapy\(^3\)

Infliximab
SERIOUS INFECTIONS, INCLUDING SEPSIS HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.

Adalimumab
SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF BLOCKING AGENTS INCLUDING HUMIRA. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.

Etanercept
IN POST-MARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ENBREL®. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS.
WARNING
RISK OF INFECTIONS TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST. ¹ TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.
WARNING
RISK OF INFECTIONS
Cases of tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) have been observed in patients receiving HUMIRA. Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infection should be initiated prior to therapy with HUMIRA.
Are psoriasis therapies associated with an increase in lymphoproliferative diseases?

Baird RD, et al.

Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration.

Brown SL, et al.


- 18 – etanercept; 8 – infliximab
- 81% non-Hodgkin’s lymphoma
- Lymphoma regression after d/c in 2 (1 etanercept, 1 infliximab)
## Malignancy and Lymphoma in RA Clinical Trials

<table>
<thead>
<tr>
<th>Number of RA patients</th>
<th>SIR for cancer</th>
<th>SIR for lymphomas (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baecklund</strong>(^1) 1998</td>
<td>11,683</td>
<td>–</td>
</tr>
<tr>
<td><strong>Adalimumab</strong>(^2)</td>
<td>8,730</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Etanercept</strong>(^3,4)</td>
<td>3,389</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Infliximab</strong>(^3,4)</td>
<td>1,298</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Malignancies
Lymphomas have been observed in patients treated with TNF blocking agents including HUMIRA. In clinical trials, patients treated with HUMIRA had a higher incidence of lymphoma than the expected rate in the general population (see ADVERSE REACTIONS - Malignancies). While patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the role of TNF blockers in the development of malignancy is not known.
Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides.
Mohan N, et al.

- 17 – etanercept, 2 – infliximab
- partial or complete resolution on d/c
- 1 positive rechallenge
Drawbacks of Biologics

• Administered by injection
• ? Heart failure - TNF blockers
• ? Connective tissue disease – TNF blockers
• Rebound – Raptiva