Biologic agents in Psoriasis

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So many choices
Treatment options

**BIOLOGIC AGENTS**

- Alefacept [Amevive®]
- Efalizumab [Raptiva®]
- Etanercept [Enbrel®]
- Infliximab [Remicade®]
- Adalimumab [Humira®]
- Ustekinumab [Stelara®]
Biological Therapies: Targets

• Cells (anti-T-cell agents)
  – Alefacept
  – Efalizumab

• Anti-TNF agents
  – Etanercept
  – Infliximab
  – Adalimumab

• Anti-IL12/23 p40
  – Ustekinumab
Nomenclature of biologic therapies

- Suffix indicates class of biologic therapy\textsuperscript{1}
  - \textbf{cept} = human receptor fusion protein
e.g. etanercept, alefacept
  - \textbf{ximab} = chimaeric monoclonal antibody
e.g. infliximab
  - \textbf{zumab} = humanized monoclonal antibody
e.g. efalizumab
  - \textbf{umab} = fully human monoclonal antibody
e.g. adalimumab, ustekinumab

\textsuperscript{1}Johnston SL. J Clin Pathol. 2007;60(1):8-17.
ENBREL WORKS DIFFERENTLY

<table>
<thead>
<tr>
<th></th>
<th>ENBREL</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Fully human soluble tumour necrosis factor (TNF) receptor</td>
<td>Chimeric monoclonal antibody</td>
<td>Human monoclonal antibody</td>
<td>Recombinant human IgG1k monoclonal antibody</td>
</tr>
<tr>
<td><strong>Presence of neutralising antibodies</strong></td>
<td>No</td>
<td>Human antichimeric antibodies (HACAs) Detected</td>
<td>Patients receiving adalimumab may develop antibodies that are neutralising in vitro</td>
<td>~5% of patients developed antibodies to ustekinumab, which were generally low-titre. Antibody positivity does not preclude a clinical response</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>2.9 days</td>
<td>8–9.5 days</td>
<td>14 days</td>
<td>~21 days</td>
</tr>
</tbody>
</table>

This table is not intended to imply a comparison of efficacy or safety. Please refer to the Product information for further information.

Adapted from Boehnke W et al.\(^\#\) Adapted from Stelara Product Information.\(^\#\#\)
Etanercept

• **Structure**
  - Human fusion protein composed of TNF receptor type II (TNF-R p75) and human IgG1 Fc fragment

• **Target**
  - TNF-α and TNF-β (lymphotoxin-α)

• **Presumed mechanism of action**
  - Attenuates inflammatory action of TNF by interfering with binding to cell-surface receptors

Etanercept
Mechanism of action\(^1\)

Infliximab

• Structure
  - Chimeric monoclonal antibody with mouse variable region and human IgG1 region

• Target
  - TNF-α

• Presumed mechanism of action
  - Attenuates inflammatory action of TNF-α by interfering with binding to cell-surface receptors
  - Apoptosis of TNF-α-positive macrophages and T cells

Infliximab
Mechanism of action

Adalimumab

• Structure
  – Human monoclonal antibody

• Target
  – TNF-α

• Presumed mechanism of action
  – Attenuates inflammatory action of TNF-α by interfering with binding to cell-surface receptors
  – Apoptosis of TNF-α-positive macrophages and T cells

Adalimumab
Mechanism of action

1

Ustekinumab

• **Structure**
  - Human monoclonal antibody

• **Target**
  - p40 subunit of IL-12 and IL-23

• **Presumed mechanism of action**
  - Prevents binding of IL-12 and IL-23 to IL-12Rß1 receptors on the surface of immune cells
  - Prevents IL-12- and IL-23-mediated activation and differentiation of CD4⁺ T-cells, interrupting signaling and cytokine cascades relevant to psoriasis pathology

Human anti-p40

Human IgG₁

IL-12 and IL-23 neutralization

IL-12Rβ1

IL-12Rβ2

IL-23R

IL-12Rβ1

NK or T cell membrane

No signal
Mechanism of action\textsuperscript{1-4}

Antibody binds to the p40 subunit of IL-12 and IL-23, preventing binding to their cell surface receptors

Differentiation and clonal expansion of Th1 and Th17 subsets is prevented

Down-regulation of inflammatory cytokines

## Approved biologic therapies for plaque psoriasis

### Comparison of structure and function

<table>
<thead>
<tr>
<th></th>
<th><strong>Ustekinumab</strong>&lt;sup&gt;1&lt;/sup&gt;</th>
<th><strong>Etanercept</strong>&lt;sup&gt;2&lt;/sup&gt;</th>
<th><strong>Infliximab</strong>&lt;sup&gt;3&lt;/sup&gt;</th>
<th><strong>Adalimumab</strong>&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of biologic</strong></td>
<td>Fully human monoclonal antibody</td>
<td>Human TNFR2/p75 Fc fusion protein</td>
<td>Chimaeric monoclonal antibody</td>
<td>Fully human monoclonal antibody</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>IL-12/23 p40</td>
<td>TNF-a</td>
<td>TNF-a</td>
<td>TNF-a</td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>Blocks IL-12 and IL-23 activity</td>
<td>Blocks TNF activity</td>
<td>Blocks TNF-a activity</td>
<td>Blocks TNF-a activity</td>
</tr>
</tbody>
</table>

## Approved biologic therapies for plaque psoriasis

### Comparison of dosing and administration

<table>
<thead>
<tr>
<th>Method of administration</th>
<th>Ustekinumab&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Etanercept&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Infliximab&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adalimumab&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction dose</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>45/90 mg every 12 weeks</td>
<td>25/50 mg once or twice weekly (up to 24 weeks)</td>
<td>5 mg/kg every 8 weeks</td>
<td>40 mg every other week</td>
</tr>
<tr>
<td>Self-administered</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Weight-based dosing</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

## Biologic therapies

### Comparison of tolerability and safety

<table>
<thead>
<tr>
<th></th>
<th>Ustekinumab(^1)</th>
<th>Etanercept(^2)</th>
<th>Infliximab(^3)</th>
<th>Adalimumab(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion/injection/allergic reactions</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Malignancies/lymphoma/HSTL</td>
<td>✓, - , -</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-drug antibodies</td>
<td>5%</td>
<td>9%</td>
<td>28%</td>
<td>8%</td>
</tr>
<tr>
<td>Neurological events</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Haematologic disorders</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HBV reactivation</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatobiliary events/jaundice</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Based on Contraindications (section 4.3) and Warnings and Precautions (section 4.4) of the SmPCs

Anti-TNF therapies for plaque psoriasis: Etanercept, infliximab, adalimumab
Anti-TNF therapy in the pathophysiology model

Etanercept
**Etanercept**

PASI 75 responses at week 12 in the pivotal studies

- **US study**
  - Placebo: 4 patients
  - Etanercept 25 mg BIW: 34% (p<0.0001 vs placebo)
  - Etanercept 50 mg BIW: 49%

- **Global study**
  - Placebo: 3 patients
  - Etanercept 25 mg BIW: 34%
  - Etanercept 50 mg BIW: 49%

*References:

*Copyright

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*p<0.0001 vs placebo
Clearing of Skin Lesions Through 6 Months

Patient was treated with Etanercept 25 mg once weekly.

PASI 75 Responders
24 Week Data

van de Kerkhof PC. Br J Dermatol 2008; 159: 1177-85
Mean PASI Scores
% Improvement

van de Kerkhof PC. Br J Dermatol 2008; 159: 1177-85
WHEN YOU CHOOSE ENBREL YOUR PATIENTS BENEFIT FROM A WEALTH OF EXPERIENCE

- 18 years and over 2.25 million patient-years* of collective clinical experience⁵
  * Worldwide commercial exposure was estimated using available unit sales distribution data.

Plus, you have the reassurance of an established long-term safety profile

- Incidence of serious adverse events⁶ and infections² were similar to controls in psoriasis trials

- Long-term safety profile demonstrated over 2 years in plaque psoriasis² and 8 years in rheumatoid arthritis⁷
Etanercept

PASI 75 response through 96 weeks

*Duration of open-label treatment was extended to 132 weeks.

Etanercept

DLQI response through 54 weeks

Meaningful improvement in DLQI Total Score†

* p<0.05 difference between the continuous and paused groups at 6 of 11 observed post-baseline visits

†Patients in continuous or paused etanercept group showing ≥5 point improvement

Etanercept in children and adolescents

Efficacy at Week 12

PASI 75 (Primary endpoint)

Physician’s Global Assessment clear or almost clear

* p<0.001 vs placebo

Note: Data from patients who entered the escape group were imputed as nonresponses.

Etanercept in children and adolescents

Efficacy through Week 36

Note: Up to week 12, data from patients who entered the escape group were not imputed as nonresponses.

Etanercept

DLQI responses up to 4 years

DLQI responders*

*Responders were defined as patients with DLQI score of 0 or decrease from baseline of at least 5, based on as-treated analysis

Infliximab
Infliximab

PASI 75 responses: 10 week data

*\(p<0.001\) vs placebo; †\(p<0.0001\) vs placebo

Percent of Subjects with 75% Improvement in PASI at Week 10

- Placebo: 5.9%
- 3 mg/kg: 71.7%*
- 5 mg/kg: 87.9%*

*P-value vs. placebo < 0.001

PASI 90: 57.6%
PASI 50: 97.0%

Percent of Subjects with 75% Improvement in PASI at Week 10

- Placebo: 5.9%
- 3 mg/kg: 71.7%
- 5 mg/kg: 87.9%

*p-value vs. placebo < 0.001

Infliximab Patient Results

Week 0

Week 10
Infliximab

PASI 75 responses through 50 weeks

**EXPRESS**¹ (week 50)
Infliximab 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks

**EXPRESS II**² (week 50)
Infliximab 5 mg/kg every 8 weeks (randomised at week 14)

Infliximab vs methotrexate

PASI 75 responses at Weeks 16 and 26


*p<0.001 vs placebo

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Quality of life (DLQI) at 10 weeks and 24 weeks

- Mean change from baseline DLQI score:
  - Week 10: -0.4
  - Week 24: -0.2

* p<0.001 vs placebo
† Mean baseline DLQI values: placebo 11.8; infliximab 12.7

Adalimumab
Adalimumab

PASI 75 responses in the REVEAL study


*P<0.001, adalimumab vs placebo

Example from REVEAL

Week 0

PASI = 25.2

Week 16

PASI = 1.2
Adalimumab vs methotrexate

PASI 75 responses through Week 16

* p<0.001 vs placebo
† p<0.001 vs MTX
‡ p=0.001 vs placebo

Adalimumab

Quality of life (DLQI) at 16 weeks

Placebo (n=53)
-3.4

Methotrexate 7.5-25 mg (n=108)
-5.7

Adalimumab 40 mg EOW (n=103)
-9.1*,†

Clinically meaningful improvement

* p<0.001 vs placebo; † p<0.001 vs methotrexate
Mean baseline DLQI scores: placebo 11.7; methotrexate 9.8; adalimumab 11.8.

Adalimumab

PASI response rates in PASI 75 responders through Week 150

*Weeks from REVEAL baseline for patients who completed 52 weeks in REVEAL
Ustekinumab
Position of anti-IL-12/23 therapy in the current pathophysiology model
PHOENIX 1

PASI 75 response through Week 12


*p<0.0001 vs. placebo at 4 weeks
**p<0.0001 vs. placebo at 12 weeks

Ustekinumab

Placebo

Patients (%)

Week

0 4 8 12

Ustekinumab 90 mg
Ustekinumab 45 mg
Placebo injections

67%**
66%**
3%
PHOENIX 1

Efficacy after three injections

PASI 75 through Week 28
(injections at weeks 0, 4 and 16)

Full efficacy generally seen around Week 24 after three injections

Efficacy maintained with every 12 week dosing

PASI 75 through Week 40
(injections at weeks 0, 4, 16 and 28)

Full efficacy generally seen around Week 24

Ustekinumab

Effective maintenance therapy for plaque psoriasis

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 12</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI =23.7</td>
<td>PASI =1</td>
<td>PASI =1.6</td>
</tr>
<tr>
<td>PGA =3</td>
<td>PGA =1</td>
<td>PGA =1</td>
</tr>
</tbody>
</table>

Images courtesy of the PHOENIX 2 Investigators.
PHOENIX 1

Long-term efficacy through Year 3

Median† percent improvement in PASI score through Year 3‡

<table>
<thead>
<tr>
<th>Week</th>
<th>Ustekinumab 45 mg (n)</th>
<th>Ustekinumab 90 mg (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>024</td>
<td>255 255 255 255 254 250 251 249* 248* 246*</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>255 253 249 251 248 248 246 243 241* 238* 238*</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>286 309 328 332 332 330 320</td>
<td></td>
</tr>
<tr>
<td>112</td>
<td>251 278 304 315 312 313 295</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td>286 309 328 332 332 330 320</td>
<td></td>
</tr>
<tr>
<td>136</td>
<td>251 278 304 315 312 313 295</td>
<td></td>
</tr>
<tr>
<td>148</td>
<td>286 309 328 332 332 330 320</td>
<td></td>
</tr>
</tbody>
</table>

†Median and interquartile range.
‡Patients randomised at Week 0. Placebo crossover patients included after crossover to ustekinumab.
*Patients randomised at Week 0. For Week 28 nonresponders, Week 28 values were carried forward to Weeks 32-40.

Why treat psoriasis?

- Symptoms
- Signs
- QOL
- Productivity
- Co-morbidities
- Life expectancy
Treatment goals

• Define severity
  – BSA
  – PASI
  – DLQI
  – Sites
  – Pruritus

• Treatment goals
  – PASI 75
  – DLQI \leq 5
Psoriasis Manifestation and Treatment Decision

Visible indicators

Primary basis of treatment decision

Influences treatment decision

Skin

Quality of life

Joints

Nails

Should influence treatment decision?

Co-morbidities

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## European Guideline
**Treatment Goals in Psoriasis**

<table>
<thead>
<tr>
<th>Treatment goals (assessment after 10 to 16 weeks, and every 8 weeks thereafter)</th>
<th>Skin symptoms</th>
<th>Health-related quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75 response or PGA ‘clear’ or ‘almost clear’ (0/1)</td>
<td>DLQI 0 or 1</td>
<td></td>
</tr>
</tbody>
</table>

**Minimum efficiency: ‘lowest hurdle’ for switching**

<table>
<thead>
<tr>
<th>Skin symptoms</th>
<th>Health-related quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 50 response</td>
<td>DLQI &lt;5 or DLQI improvement ≥5</td>
</tr>
</tbody>
</table>

DLQI, dermatology life quality index; PASI, psoriasis area and severity index; PGA, physician global assessment.

Note: Additional treatment goals may be required in individual patients, such as those with joint or nail involvement or with other psoriasis-related co-morbidities.

Treatment goal algorithm

\[ \Delta \text{PASI} < 50 \]
\[ \Delta \text{PASI} > 50 < 75 \]
\[ \Delta \text{PASI} > 75 \]

Modify Treatment Regimen

\[ \Delta \text{DLQI} > 5 \]
\[ \Delta \text{DLQI} \leq 5 \]

Continue Treatment Regimen

\[ \Delta = \text{in comparison to baseline}! \]
Treatment goal algorithm

\[ \Delta \text{PASI} < 50 \quad \Delta \text{PASI} \geq 50 < 75 \quad \Delta \text{PASI} \geq 75 \]

**Modification strategies:**
- Increasing the dose
- Reducing dose intervals
- Adding a topical
- Adding another systemic
- Changing the drug!

\[ \Delta = \text{in comparison to baseline!} \]

Continue Treatment Regimen
Current treatment algorithm for psoriasis

Patient Diagnosed with

Treat with topical

Continue to treat with topical

Patient meets treatment goal

Patient does not meet treatment goal

Treat with phototherapy, cyclosporin, MTX or acitretin

Patient meets treatment goal

Continue photo or systemic therapy

Patient does not meet treatment goal or becomes contraindicated due to toxicity or has PASI ≤15

Treat with biologics (anti-TNF or anti-IL)

Patient has failed at least 3 therapies and has PASI >15

Continue biologic therapy

Patient meets treatment goal (PASI 75)

Patient does not meet treatment goal (PASI 75) or becomes contraindicated due to toxicity

Treat with an alternative biologic (maximum of 2)

Patient meets treatment goal (PASI 75)

Continue biologic therapy

Patient does not meet treatment goal (PASI 75) or becomes contraindicated due to toxicity

Failure of 3 biologic therapies

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PROPOSED TREATMENT ALGORITHM

Figure 1.

Psoriasis diagnosed and initial assessment

- Mild
  - PASI ≤ 10
    - Topicals
      - Remains mild
        - Continue topicals
      - Worsens
        - Continue systemic therapy and/or phototherapy

- Moderate/severe
  - PASI > 10
    - Non-biologic systemic therapy and/or phototherapy
      - Partial Response
        - Δ PASI ≥ 50 and < 75
          - DLQI ≤ 5
            - Continue systemic therapy and/or phototherapy
          - DLQI > 5
            - Modify/change therapy
              - Failed Response
                - Δ PASI < 50

- At least 2 of 4 therapies trialled or contraindicated
  - PASI and/or DLQI remain > 10
    - Biologic therapy (anti-TNF or anti-IL)
      - Assessment of response as for non-biologic systemic therapy and phototherapy

Notes:
1. In absence of modifying features such as visible site, genital, palmoplantar, nails involvement, pruritus with excoriation (see text).
2. Appropriate time to review varies with each treatment and range is 6-24 wks.
3. Non-biologic therapies include methotrexate, cyclosporin, acitretin.
4. Psoriasis area severity index (Δ PASI) ≥ 75 but dermatological quality of life index (DLQI) ≥ 5 may occur if modifying features such as the visible site, genital, palmoplantar, nail involvement or pruritus are present or the response is discordant with patient’s expectations. Physician assessment whether to continue, modify or change therapy.
5. Continuation/discontinuation is modulated by toxicity and contraindication
6. Treatment change to take into account patient wishes
7. In addition to change of treatment, modify may include add topicals, add other systemic, increase dose or frequency, or hospital admission.
8. The Australian consensus group propose 2 of 4 therapies as reasonable and best practice. The current requirement of the Australian reimbursement body, the Pharmaceutical Benefits Scheme, is three of four therapies.
The decision making process

• Drug factors
• Type of psoriasis
• Patient factors
• Psoriatic arthritis
• Other disease states
• Comorbidities
Drug factors

- Efficacy
- Mode of delivery
- Safety
- Onset of action
- Rebound
Convenience

Collectively considering dosing frequency, route of administration, accessibility, ability to administer as monotherapy and long-term, biological therapies provide advantages over current systemic therapies with respect to convenience.

<table>
<thead>
<tr>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/kg at W 0, 2 and 6 IV infusion over 2 hours Then 8 weekly</td>
<td>25 mg SC twice weekly or 50mg SC weekly for 12 weeks After demonstrating proficiency, patients can self-administer at home</td>
<td>80 mg SC W0, 40 mg SC W1 then 40 mg EOW After demonstrating proficiency, patients can self-administer at home</td>
<td>45 mg or 90 mg SC initial conditioning dose at W0 and W4 then 45 mg or 90 mg SC 12 wkly After demonstrating proficiency, patients can self-administer at home</td>
</tr>
</tbody>
</table>
When To Expect A Clinically Significant Response?

- **Infliximab:** 1–2 weeks
- **Phototherapy:** 1–2 weeks
- **Adalimumab:** 4 weeks
- **Cyclosporin:** 4 weeks
- **Ustekinumab:** 4-8 weeks
- **Retinoids:** 4–8 weeks
- **Etanercept:** 6–8 weeks
- **MTX:** 4–12 weeks
- **(Alefacept:** 2–6 weeks following 12-week course)
Adverse event profile

- Infection
- Malignancy
- Injection site reactions
- Infusion reactions
- Neurological
- LE-like
- Heart failure/cardiovascular events
Type of psoriasis

• Extent of disease
• Stability of disease
Patient factors

- Weight
- Reliability/compliance
- Travel
- Family planning
- Patience/onset of action
Other disease states

- Psoriatic arthritis
- Multiple sclerosis/demyelinating disorders
- Lupus erythematosus
- Heart failure
- Skin cancer
- Other malignancy
- Hepatitis B
- Hepatitis C
- HIV
Heart failure and TNF antagonists

- New onset or exacerbation of CHF
- Avoid TNF antagonists in patients with NYHA Class III or IV heart failure
- Avoid TNF antagonists in patients with decreased ejection fraction
17.41 Hepatitis C

• TNF plays a role in hepatitis C-induced hepatocyte injury and treatment resistance to interferon alfa-2b.
• The role of TNF blockade has therefore been investigated in a phase II, randomized, placebo-controlled study, where etanercept (24 weeks, n = 19) was used as adjuvant therapy to ribavirin and interferon in treatment-naive patients.
• Etanercept improved viral clearance rates with no significant increase in adverse events.
• Data from small case series and case reports also report successful use of TNF antagonist therapy for rheumatological disease in hepatitis C virus-positive patients, with no increased rate of hepatotoxicity or viral replication.
Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study

- Etanercept given for 24 weeks as adjuvant therapy to interferon and ribavirin significantly improved virologic response at the end of the etanercept randomization period among patients with HCV, and was associated with decreased incidence of most adverse effects associated with interferon and ribavirin.
17.42 Hepatitis B

• In contrast to hepatitis C, TNF may play a role in clearing and controlling hepatitis B virus.

• Cases of severe (and sometimes fatal) reactivation of occult hepatitis B infections have been reported (summarized Domm & Mrowietz).
  
17.43 Human immunodeficiency virus

• The safety of biologic therapy in the context of HIV infection is unknown but particular caution should be exercised in this group given the risks of infection.

• There are several case reports of successful use of TNF antagonist therapy for rheumatological indications in patients who are HIV positive.

17.43 Human immunodeficiency virus

- Paradoxically, perhaps, TNF has been implicated in HIV disease progression in HIV-associated tuberculosis, and therefore the benefit of etanercept as adjunctive therapy for this indication has been investigated in a phase I study (25 mg twice weekly for 4 weeks, n = 16).

- There was a tendency towards improved outcome in the etanercept arm and, more importantly, no increased toxicity compared with standard antituberculous therapy (n = 47).
Adverse event profile

- Infection
- Malignancy
- Injection site reactions
- Infusion reactions
- Neurological
- LE-like
- Heart failure/cardiovascular events
Adverse Events – Overview

- Injection site reactions
  - (etanercept > adalimumab >> ustekinumab)
- Infusion reactions (infliximab)
- Neurological (anti-TNF)
  - Multiple sclerosis, demyelinating disorders
- Lupus erythematosus-like (anti-TNF)
- Congestive heart failure (anti-TNF)
  - New onset or exacerbation
- MACE (Major Adverse Cardiovascular Events)
- Psoriasis (anti-TNF)
- Drug-related skin eruptions (e.g., vasculitis)
Etanercept

Safety and tolerability

• Injection-site reactions were the most common adverse events
  – 14% vs placebo 6% \(^1\)
  – Diminished with ongoing therapy

• Other common adverse events included:
  – Headache
  – Upper respiratory tract infection
  – Pruritus
  – Fever \(^1\)

• Infection
  – Serious infection (0.4%) rare and comparable with placebo rates

• Other serious AEs occurred with frequency comparable to placebo:
  – Malignancies
  – Asthma
  – Pancytopenia and aplastic anaemia
  – Interstitial lung disease \(^1\)

• Lupus-like syndrome with positive antibodies: reported, but rare

• Etanercept has received a black box warning for risk of reactivation of TB \(^2\)

---

Etanercept

Formation of antibodies

– Formation of antibodies to etanercept observed in some patients:
  • Non-neutralising
    – Observed in 18% of patients
    – No apparent effect on efficacy or safety
  • Generally transient

– No apparent correlation between antibody development, clinical response or adverse effects

Infliximab

Safety and tolerability

• Infusion-related reactions are most common AEs (20% vs 10% placebo)¹
• Other common AEs include:
  – Upper respiratory tract infection
  – Headache
  – Increased liver enzymes
  – Infections
• Malignancies and lymphoproliferative disorders
  – No increased risk
  – Comparable to controls
• Hepatotoxicity
  – Autoimmune hepatitis
• Antinuclear antibody formation:
  – Seen in ~50% infliximab-treated patients (~20% controls)
  – Lupus and lupus-like syndromes are uncommon¹
• FDA has issued a black-box warning following reports of tuberculosis and other serious opportunistic infections associated with infliximab use²

Infliximab

Antibody formation

• Formation of antibodies to infliximab
  – Reported in ~28% of patients studied\(^1-^3\)

• Antibody development is weakly correlated to reduced duration of response \(^1,^2\)

• Patients who develop antibodies are more likely to develop infusion-related reactions\(^3\)

Adalimumab

Safety and Tolerability

• Analysis of data from 3010 psoriasis patients with >4800 patient-years of exposure to adalimumab:
  – Treatment emergent AE incidence rates were:
    • Generally low
    • Stable over time
  – Low rates of treatment for:
    • Emergent SAEs
    • Serious infections
    • Malignancies
  – Most SAE rates decreased with increased duration of exposure

• FDA black box warning for:
  – Risk of tuberculosis and other infections (some of which have been fatal)
  – Hepatitis B reactivation
  – Allergic reactions
  – Immunosuppression
  – Malignancies
  – Lymphoproliferative disorders
Adalimumab

Neutralising antibodies

• Development of antibodies:
  – Seen in 8% of psoriasis patients studied\(^1\)

• Antibody formation to adalimumab results in:
  – Reduction in efficacy
  – No apparent correlation between the presence of antibodies and adverse effects\(^1,2\)

## Integrated safety analysis

### Adverse events in placebo-controlled phase

<table>
<thead>
<tr>
<th>AEs, %</th>
<th>Placebo (n=732)</th>
<th>Ustekinumab 45 mg (n=790)</th>
<th>Ustekinumab 90 mg (n=792)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>50.4</td>
<td>57.6</td>
<td>51.6</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7.9</td>
<td>8.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Headache</td>
<td>4.5</td>
<td>5.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4.4</td>
<td>5.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.9</td>
<td>3.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.0</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.6</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.1</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.4</td>
<td>2.2</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*A ≥2% of combined ustekinumab treatment group*
Cutaneous adverse effects of TNF antagonists

- Infusion reactions
  - Infliximab only
- Injection site reactions
  - Etanercept and adalimumab
- Infections
  - Fungal
  - Bacterial
  - Viral
- Malignancies
- PSORIASIS
- Eczema
- Drug-related skin eruptions
  - Exanthema
  - Urticaria
  - Purpura
  - Lichenoid
- Vasculitis
- Lupus-like syndrome
- Dermatomyositis
- Lymphomatoid-papulosis-like eruption

Adverse effects of TNF antagonists

- **Infusion reactions**
  - Infliximab only

- **Tuberculosis reactivation**
  - CXR, PPD, quantiferon gold

- **Infections**
  - Potentially serious including sepsis

- **Malignancies**
  - Possibly lymphomas

- **Demyelination events**
  - MS

- **Pancytopenia**
  - Rare, monitor FBE

- **Congestive heart failure**
  - Worsening of pre-existing severe disease

- **Hepatitis**
  - Monitor LFT esp infliximab patients

- **Auto-antibodies – lupus-like syndrome**
  - Rare

- **Cutaneous adverse effects**
  - Skin infections, Eczema, Drug-related skin eruptions
  - Vasculitis, Lymphomatoid-papulosis-like eruption, Dermatomyositis

- **Weight gain**
Adalimumab, etanercept, infliximab

Serious infection risk vs DMARDs in RA

7664 anti-TNF-treated and 1354 DMARD-treated patients with severe RA


* IRR=Incidence Rate Ratio.
### Adalimumab, etanercept, infliximab

**Serious infection risk in RA**

<table>
<thead>
<tr>
<th>Serious infections</th>
<th>Patients: 3.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls: 1.7%</td>
</tr>
<tr>
<td></td>
<td>NNH: 59</td>
</tr>
<tr>
<td><strong>Meta-analysis of infliximab and adalimumab clinical trials</strong></td>
<td></td>
</tr>
<tr>
<td><strong>UK registry</strong></td>
<td>Infliximab: 5.2/100 PY</td>
</tr>
<tr>
<td></td>
<td>Etanercept: 5.3/100 PY</td>
</tr>
<tr>
<td></td>
<td>Adalimumab: 6.3/100 PY</td>
</tr>
<tr>
<td><strong>German registry</strong></td>
<td>Infliximab: 6.2/100 PY</td>
</tr>
<tr>
<td></td>
<td>Etanercept: 6.4/100 PY</td>
</tr>
<tr>
<td></td>
<td>Controls: 2.3/100 PY</td>
</tr>
</tbody>
</table>

**PY:** Patient Years. **NNH:** Numbers Needed to Harm. **RR:** Relative Risk

Ustekinumab pooled safety analysis

Serious infections*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ustekinumab 45 mg</th>
<th>Ustekinumab 90 mg</th>
<th>Ustekinumab combined</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controlled Period</strong></td>
<td>1.70 (0.35, 4.96)</td>
<td>1.97 (0.54, 5.03)</td>
<td>1.23 (0.40, 2.87)</td>
<td>0.49 (0.01, 2.74)</td>
</tr>
<tr>
<td><strong>1.5 Years</strong></td>
<td>1.08 (0.56, 1.88)</td>
<td>1.05 (0.54, 1.84)</td>
<td>1.07 (0.68, 1.59)</td>
<td>1.70 (1.07, 2.05)</td>
</tr>
<tr>
<td><strong>3 Years</strong></td>
<td>1.05 (0.56, 1.88)</td>
<td>1.07 (0.54, 1.84)</td>
<td>1.08 (0.68, 1.59)</td>
<td>1.50 (1.07, 2.05)</td>
</tr>
</tbody>
</table>

Incidence per 100 PY (95%CI)

<table>
<thead>
<tr>
<th>n=</th>
<th>Placebo</th>
<th>Ustekinumab 45 mg</th>
<th>Ustekinumab 90 mg</th>
<th>Ustekinumab combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Period</td>
<td>732</td>
<td>790</td>
<td>792</td>
<td>1582</td>
</tr>
<tr>
<td>1.5 Years</td>
<td>1110</td>
<td>1156</td>
<td>2266</td>
<td>2266</td>
</tr>
<tr>
<td>3 Years</td>
<td>1319</td>
<td>1906</td>
<td>3117</td>
<td>3117</td>
</tr>
<tr>
<td>Patient years</td>
<td>177</td>
<td>203</td>
<td>203</td>
<td>406</td>
</tr>
<tr>
<td># of events</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*Serious adverse events caused by infection

Adalimumab, etanercept, infliximab

Management of tuberculosis risk in patients with rheumatic diseases

BIOBADASER National Registry (Spain): Impact of Implementing Local TB Recommendation

<table>
<thead>
<tr>
<th>Treatment initiation</th>
<th>Patient-years exposure</th>
<th>No. Cases</th>
<th>IR / 100000</th>
<th>IRR vs general population</th>
<th>IRR vs EMECAR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 1Q2002</td>
<td>8671</td>
<td>41</td>
<td>472</td>
<td>19</td>
<td>5.8</td>
</tr>
<tr>
<td>After 1Q2002</td>
<td>8717</td>
<td>15</td>
<td>172</td>
<td>7</td>
<td>2.4</td>
</tr>
<tr>
<td>- 100% compliant</td>
<td>4546</td>
<td>2</td>
<td>43</td>
<td>1.8</td>
<td>nd</td>
</tr>
<tr>
<td>- &lt;100% compliant</td>
<td>4170</td>
<td>13</td>
<td>311</td>
<td>13</td>
<td>4.8</td>
</tr>
<tr>
<td>Since Sept 03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Infliximab</td>
<td>1303</td>
<td>5</td>
<td>383</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>- Etanercept</td>
<td>1740</td>
<td>2</td>
<td>114</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>- Adalimumab</td>
<td>565</td>
<td>1</td>
<td>176</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

IR: incidence rate; IRR: incidence rate ratio
*EMECAR: RA-Patients, not treated with biologics

Adalimumab, etanercept, infliximab
Management of tuberculosis risk

- Anti-TNF therapies are associated with an increased risk of tuberculosis necessitating TB screening and monitoring\(^1\)\(^-\)\(^4\)
- Risk higher with antibodies as compared to etanercept
- Guidelines for the diagnosis and treatment of latent and active tuberculosis in patients treated with TNF blockers are available\(^5\)\(^-\)\(^8\)
- Strategies to treat latent TB infection that are tailored to the at-risk population reduce the risk of active TB in patients treated with TNF antagonists\(^9\)

Adalimumab, etanercept, infliximab

Malignancy risk in RA

The LORHEN registry: SIRs of cancer in RA patients (n=1064) treated with anti-TNF biologics compared with expected rates in a general population in the same geographical region

- General cancer risk not increased, but risk of lymphoma and haematological cancer significantly higher
- Risk factors for cancer development were male gender and age >65 years

Long term malignancy risk in RA, PsA, AS*

4322 subjects with active rheumatic diseases enrolled in 24 clinical trials

* RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis

Ustekinumab pooled safety analysis

Non-melanoma skin cancer (NMSC)

**Incidence per 100 PY (95%CI)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ustekinumab 45 mg</th>
<th>Ustekinumab 90 mg</th>
<th>Ustekinumab combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Period</td>
<td>1.13 (0.14, 4.09)</td>
<td>0.98 (0.12, 3.55)</td>
<td>0.74 (0.15, 2.16)</td>
<td></td>
</tr>
<tr>
<td>1.5 Years</td>
<td>0.63 (0.25, 1.30)</td>
<td>0.97 (0.48, 1.74)</td>
<td>0.80 (0.48, 1.27)</td>
<td></td>
</tr>
<tr>
<td>3 Years</td>
<td>0.64 (0.35, 1.08)</td>
<td>0.77 (0.47, 1.19)</td>
<td>0.71 (0.49, 1.00)</td>
<td></td>
</tr>
</tbody>
</table>

**BCC:SCC ratio of 3.1 to 1** is consistent with the ratio reported in immunocompetent patients in the general population, and is not suggestive of immunosuppression.

Ustekinumab pooled safety analysis

Non-NMSC malignancies

Rate of other malignancies compared with the SEER Database*

*SEER = Surveillance, Epidemiology, and End Results (2004) Number expected in age, race, gender-matched general population.

Copyright
Ustekinumab pooled safety analysis

Major adverse cardiovascular events*

* Sudden cardiac death, serious myocardial infarction events, and serious stroke events

Adverse Events Of Interest In Clinical Trials Of TNF Antagonists In Psoriasis

Adapted from:
1. Tyring S, et al. WCD 2007, #1587; ADA 40 mg EOW dosing; 2. Gordon K, et al. AAD 2007, P1817; results from 6 trials, except non-melanoma skin cancer (3 trials); 25 mg twice weekly, 50 mg once weekly, and 50 mg twice weekly dosing included.
3. Gordon K, et al. WCD 2007, #5158; Patient-years calculated from mean exposure per patient and number of patients receiving at least 1 dose of IFX; 3 mg/kg and 5 mg/kg dosing; no rates provided for serious infections or CHF; original analysis included 200 pts from IMPACT 2 PsA trial. These have been excluded from the results presented here; 4. Bala M, et al. J Investigative Dermatol 2007;127(Suppl 1)S61; data from EXPRESS, EXPRESS II & SPIRIT trials (n=1,373); 5. Menter A, et al. J Am Acad Dermatol 10.1016/j.jaad.2006.07.017.)

Serious infections
Non-melanoma skin cancer
Lymphoma
Demyelination
CHF
SLE-like
Malignancies*

Etanercept
Adalimumab
Infliximab

N/A, not available; *excluding nonmelanoma skin cancers and lymphoma
The decision making process

- Drug factors
- Type of psoriasis
- Patient factors
- Psoriatic arthritis
- Other disease states
- Comorbidities
Working Up a Patient with Psoriasis for Biologic Therapy – Safety Screening and Monitoring
Patient Workup: History

- Consider risk factors for infection:
  - History of blood transfusions, IV drug use
  - Past or current chronic infection
  - Consider risk factors for TB
- Malignancy
  - Past or current malignancy
  - Hx of cervical dysplasia
  - Strong family Hx of malignancy
- Neurological disease
  - Hx of demyelinating disease
- Cardiovascular disease
  - Past Hx
  - Active disease
  - Risk factors
Patient Workup: Vaccinations

- Vaccinations
  - Patient’s vaccination history should be taken and vaccinations given as appropriate, preferably before commencing biologic therapy.
    - Little evidence on whether prior vaccination is effective or not in patients taking biologics
    - Since patients are potentially taking biologics, long-term consideration to vaccination may be given
  - Live and live-attenuated vaccines should be avoided once biologic therapy has commenced
  - Particular vaccines to consider include:
    - Varicella (a live vaccine)
    - HPV
    - Hep B/A
    - Influenza (inactivated form if already on biologic)
    - Pneumococcal
    - Consider booster for tetanus, diphtheria, pertussis
  - Close contacts of those with altered immune competence can safely receive all age-appropriate vaccines

Patient Workup: Screening

- Complete the Psoriasis Area Severity (PASI) Index
  - Measures psoriasis severity for Medicare reimbursement
  - Repeated periodically each time new biologic script needed
- Examine for NMSC/MM/Lymphadenopathy
- Investigations (baseline)
  - FBE
  - UEC/LFTs
  - Fasting lipids
  - CRP
  - ANA
  - β-HCG (females of child-bearing age)
  - CXR
  - Quantiferon Gold and/or Mantoux/TST/PPD
  - Hep BsAg, Hep BsAb, Hep BcAb, HepC, HI, varicella
- Ensure age appropriate screening up to date e.g., PSA, mammogram, Pap smear, faecal occult blood
Patient workup

Screening for skin cancer

• Patients should be screened for skin cancer before commencing biologics and re-evaluated once psoriasis has sufficiently cleared

• Biologics are not contraindicated for those with a history of skin cancer but caution is advised and patients should be monitored closely for the development of skin cancer

• The decision to continue biologics treatment in patients who develop skin cancer should be made on a case by case basis following lengthy discussion with the patient
Patient Workup: Tuberculosis

• Screening for tuberculosis
  – All patients selected for biologic treatment, should be screened for tuberculosis using both a chest X-Ray and the Quantiferon Gold test
  – Screening dramatically reduces risk of activating latent TB
  – Quantiferon Gold is more sensitive than Mantoux:
    • not affected by prior BCG vaccination
    • reliable in immunosuppressed patients on methotrexate or cyclosporin
  – Mantoux can be used if QFN-Gold not available
  – TB-positive patients should be referred to infectious diseases specialist

• Cellestis. Quantiferon-TB Gold clinical studies information, January 2005.
New patient

Administer appropriate TB screening test
(Prior exposure to TB + chest X-ray + QFG or Mantoux)

Evaluate test results

Test negative

QFG or Mantoux test positive and normal chest X-ray

QFG or Mantoux positive and active TB

Initiate latent TB treatment

Initiate biologic therapy

Initiate biologic therapy

Initiate biologic therapy

Treat active TB to resolution

Patient monitoring

• Investigations
  – 3 monthly
    • PASI
    • FBE
    • UEC
    • LFT (consider monitoring of LFT pre and post infliximab infusions)
  – 6 monthly
    • Examine for NMSC/MM/Lymphadenopathy
  – Annually
    • Ensure age appropriate screening up to date e.g., PSA, mammogram, Pap smear, faecal occult blood
  – Consider repeat Quantiferon Gold based on risk factors
Patient Monitoring

- **Serious infections**
  - Signs/symptoms of infection
  - Ask patients to be vigilant for infection
    - Establish when they should seek treatment from HCP
  - Withhold treatment if infection is serious
  - Treat infection and recommence biologic once the infection is cleared, if appropriate

- **Malignancy**
  - Look for signs/symptoms of malignancy

- **Autoantibodies**
  - Only check levels if patient becomes symptomatic
  - Stop treatment if clinical symptoms/signs consistent with lupus-like syndrome develop
QUESTIONS?
Patient factors

• Weight
• Reliability/compliance
• Travel
• Family planning
• Patience/onset of action
Consequences of limited knowledge

• Decision to cease a specific immunosuppressive drug during pregnancy because of lack of data on its safety can have serious consequences for both mother and foetus
  o Disease flare in the mother
  o Risk of maternal allergic reactions on recommencement post-delivery
  o Fetal complications such as premature delivery and low birth weight

• Concerns about reduced vaccine responses or safety prompt intentional delay in the administration of routine vaccinations and subsequent risk of vaccine preventable disease in the infant
Current data on safe use of adalimumab in pregnancy are limited, although there are a few case reports of successful pregnancy outcomes following adalimumab use during pregnancy.

Available data does not seem to indicate an increased risk of adverse fetal outcomes.

Theoretical concerns that adalimumab inhibition of TNF during pregnancy could affect normal immune responses in the newborn.
Infliximab

- Chimeric monoclonal IgG1 antibody to human tumour necrosis factor (TNF) alpha
- Most pregnancy experience in women with IBD
- Not tested in animal reproductive models as it does not react with non-human TNFα but categorised as B
- Minimal transfer of IgG across palcenta in 1st trimester with increasing transfer throughout gestation
- Based on limited current data infliximab does not appear to increase risk of congenital malformations
Etanercept-human data

- OTIS study of women exposed to etanercept during pregnancy and also a few case reports

- None of these studies suggest a particular pattern of defects or increased rate of malformations or adverse outcomes although data obviously quite limited

- One study surveyed US rheumatologists and reported no increase in birth defects or miscarriage rates in 417 women exposed to etanercept in pregnancy and about 1/3 of these women continued to take the medication throughout pregnancy
TNF antagonists and VATER association

- Reported data from FDA database described 61 congenital anomalies in 41 children born to mothers taking a TNF antagonist
  - Etanercept N = 22
  - Infliximab N = 19
- Authors concluded that 24 cases had 1 or more anomalies that are part of VACTERL association with a rate higher than historical controls
  - Vertebral anomalies
  - Anal atresia
  - Cardiac defects
  - TracheoEsophageal
  - Renal
  - Limb abnormalities
TNF antagonists and VATER association

However accompanying editorial concluded that the evidence for teratogenicity or with the VACTERL association was lacking.

Many of the anomalies reported occur commonly, such as ventricular septal defects.

In addition, such databases have selection bias (only cases with adverse outcomes are reported) and emphasis is placed on exposures to new drugs.

- Carter et al J Rheumatol 2009;36:635–41
Biologica ls and breastfeeding—summary

• Limited data but reassuring and biologically reasonable given
  – Low amounts in milk
  – Large MW
  – Poor oral bioavailability

• General recommendations are caution in
  – Infants <1 month of age
  – Premature infants
  – Consider using alternative drug for infants in above categories
Neonatal immune responses

- Unknown effects on infant immune system but concern that normal maturation may be modified
  - Predispose to increased infection
  - Reduced response to immunisation

- Studies have shown that infliximab detectable in neonate at up to 6 months of age
  - normal T and B cell development
  - normal levels IgG IgM and IgA
  - Normal response to vaccination (HiB, tetanus, strep pneumoniae)