Systemic non-biologic therapies
Dr Oriol Yélamos

Barcelona, July 9th-10th, 2013
Non-biologic systemic therapies for moderate to severe psoriasis

PASI 75 responses at primary endpoints

Patients achieving PASI 75 (%)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Percentage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin¹</td>
<td>52</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Mean dose 0.54 mg/kg/day (n=127)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fumaric acid ester²</td>
<td>56</td>
<td>16 weeks</td>
</tr>
<tr>
<td>105-1290 mg/day (n=100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate³</td>
<td>60</td>
<td>16 weeks</td>
</tr>
<tr>
<td>15-22.5 mg/wk (n=43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PUVA⁴</td>
<td>63</td>
<td>12 weeks</td>
</tr>
<tr>
<td>3 times weekly (n=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclosporin³</td>
<td>71</td>
<td>16 weeks</td>
</tr>
<tr>
<td>3-5 mg/kg/d (n=42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB-UVB⁵</td>
<td>70</td>
<td>Up to 24 weeks</td>
</tr>
</tbody>
</table>

Indications for systemic therapy

- Failure of adequate trial of topical therapy
- Repeated hospital admissions for topical therapy
- Extensive chronic plaque psoriasis in the elderly or infirm
- Generalised pustular or erythrodermic psoriasis
- Severe psoriatic arthropathy

Rule of tens
- Body surface area affected (BSA) >10%, or
- PASI score >10, or
- DLQI >10

Oral systemic therapies

- **Methotrexate** – a folic acid antagonist that interferes with purine synthesis and thus inhibits DNA synthesis and cell replication; it also has specific T-cell suppressive activities

- **Ciclosporin** – an immunosuppressant that inhibits the activation of T cells and may also exert a direct effect on epidermal keratinocytes

- **Oral retinoids** – vitamin A analogues (acitretin is the principal licensed product in this class) which reduce epidermal proliferation and differentiation

- **Fumaric acid esters** – non-specific T cell inhibitors producing changes in cytokine production that are beneficial in psoriasis (used mainly in Germany, for severe psoriasis)

Menter A, Griffiths CEM. Lancet. 2007; 370:272-84.
<table>
<thead>
<tr>
<th></th>
<th>CSA</th>
<th>MTX</th>
<th>Acitretin</th>
<th>Fumarates</th>
<th>PUVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Teratogenicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin cancer (EBV-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma (RA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid carcinomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Skin cancer (RA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carcinogenicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin cancer (EBV-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma (RA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid carcinomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin cancer (RA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immune suppression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBC, others</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Organ toxicity/comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney, hypertension</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other contraindications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipids, diabetes mellitus, drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM, lung, drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous, lipids, MSK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI, lymphopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis (improvement)</td>
<td>+/-</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Probability of response (short-term)

### Probability of response [95% CI]

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose/Regimen</th>
<th>Probability of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>5 mg/kg</td>
<td>0% - 30%</td>
</tr>
<tr>
<td>Etanercept</td>
<td>50 mg BIW</td>
<td>20% - 40%</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg EOW</td>
<td>30% - 50%</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>3 mg/kg/day</td>
<td>40% - 60%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>15-22.5 mg/w</td>
<td>50% - 70%</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>45 mg</td>
<td>60% - 80%</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>90 mg</td>
<td>70% - 90%</td>
</tr>
</tbody>
</table>

131 studies on monotherapy or combination therapy:
  - 56 of good quality

Phototherapy is safe and effective for moderate-to-severe psoriasis:
  - PASI75 in ~75% of patients
  - clearance frequent

PUVA:
  - Had never been evaluated using PASI in a randomized, double-blind, placebo (UVA)-controlled trial
  - PASI75 in 63% (18/30) vs 0% (0/10)

Evaluation of PUVA using PASI in a randomized, double-blind, placebo (UVA)-controlled trial

- PASI 75 response:
  - PUVA: 63%
  - UVA + placebo: 0%
  - p<0.0001

Cost: 16,017 (~€12,000)

*ITT LOCF analysis

• Proportion of patients achieving PASI response (n=86)

Phototherapy

- Broadband and narrowband UVB phototherapy
  - Effective treatments for guttate or plaque psoriasis resistant to topical therapy
  - Requirement to visit clinic may limit use for some patients
  - Combination with other anti-psoriasis treatments (tars, topical calcipotriol, oral retinoids) have proved effective

- Photochemotherapy (PUVA)
  - Combination with other anti-psoriasis treatments (vitamin D analogue preparations, retinoids) have proved effective.
  - Potential adverse effects include itch, burning, risk of cataracts (eye protection required for 24 hours post therapy) and risk of skin cancer with chronic UV exposure

- Phototherapy requires good metering, equipment monitoring and maintenance of patient records to track UV exposure
Acitretin

• Initial dose 0.3–0.5 mg/kg/day for 4 wks, then 0.5–0.8 mg/kg; individual maintenance dosage dependent on response and tolerance

• Response rate widely variable and dose-dependent: PASI 75 in 34–52% (30–50 mg/d) (LE3: non randomised or low quality)

• Important contraindications
  – Teratogenicity, comorbidities (dyslipidemia and liver disease)

• Common adverse events eg mucocutaneous AEs (dose-limiting)

**Acitretin**

- **BAD guidelines**
- Monotherapy is recommended in the treatment of severe psoriasis, or psoriasis with severe effects on quality of life, meriting systemic therapy, which is resistant to topical therapy, phototherapy or is unsuitable for these treatments (A, 1+).

- **Combination therapy:**
  - Acitretin is recommended as a combination with PUVA therapy or narrowband phototherapy (A, 1+), or in combination with calcipotriol ointment (A, 1+).

- **Not recommended:**
  - Acitretin with cyclosporin: no evidence of additive efficacy (D, 3).
  - Acitretin with methotrexate: potential for severe hepatic toxicity (D, 3).

- **Combination and maintenance rather than induction therapy**
- Treatment option in case of contraindications for immunosuppression, such as patients with infections or cancer-prone patients

Acitretin

Long-term efficacy and safety

• Open-label study: optimal doses of acitretin (10-70 mg) administered to patients with severe psoriasis (n=63) for 12 months

• PASI reduced by 76% in patients reaching Week 52
  – Side-effects were common, including cheilitis (78%), hair loss (52%) and pruritis (51%)
  – 14 patients withdrew due to adverse reactions

PASI scores for patients who completed the study

• PUVA best for extensive and not very indurated lesions
• Retinoid adds effect on hyperkeratosis and acanthosis and reduces PUVA exposure
PUVA vs RePUVA systematic review

- Meta-analysis of association of retinoid with psoralen plus ultraviolet A (Re-PUVA)

<table>
<thead>
<tr>
<th>Study/subgroup</th>
<th>Re-PUVA</th>
<th></th>
<th>PUVA</th>
<th></th>
<th>Weight</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td>M-H, fixed, 95% CI</td>
</tr>
<tr>
<td>Parker 1984</td>
<td>14</td>
<td>15</td>
<td>9</td>
<td>13</td>
<td>15.2%</td>
<td>6.22 [0.60, 64.97]</td>
</tr>
<tr>
<td>Saurat 1988</td>
<td>33</td>
<td>38</td>
<td>16</td>
<td>20</td>
<td>65.1%</td>
<td>1.65 [0.39, 6.99]</td>
</tr>
<tr>
<td>Tanew 1991</td>
<td>22</td>
<td>23</td>
<td>20</td>
<td>25</td>
<td>19.7%</td>
<td>5.50 [0.59, 51.19]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>76</td>
<td>58</td>
<td></td>
<td></td>
<td>100%</td>
<td>3.10 [1.11, 8.66]</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Heterogeneity $\chi^2 = 1.33$, df = 2 ($P = 0.52$); $I^2 = 0\%$
- Test for overall effect: $Z = 2.16$ ($P = 0.03$)

- Qualitative results, M-H, Mantel-Haenszel; CI, confidence interval.

Cyclosporin

- Clinically significant response after 4 wks
- Response rate:
  - Dose-dependent,
  - After 8–16 weeks with 3 mg/kg, PASI 90 in 30–50%, PASI 75 in 50–70% (LE1)
- Comorbidities and contraindications
- Extensive monitoring required
  - Important drug interactions
  - Important and frequent side effects
Ciclosporin forms complex with cyclophilin (isomerase)

Complex inhibits calcineurin

Signal transduction from T cell receptor to cytokine promotors is blocked

Inhibition of IL-2, IL-3, IL-4, IL-5, GM-CSF and TNF-α

Efficacy of cyclosporin: systematic review

- PASI-75 response rates after 10-16 weeks of treatment with cyclosporin according to dosage in the different study groups of the systematic review

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meffert (1997)</td>
<td>44</td>
<td>2.5 mg/kg/d</td>
</tr>
<tr>
<td>Thaci (2002)</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Christophers (1992)</td>
<td>108</td>
<td>2.5 mg/kg/d</td>
</tr>
<tr>
<td>Laburte (1994)</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Mahrle (1995)</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Koo (1998)</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Ellis (1991)</td>
<td>25</td>
<td>3 mg/kg/d</td>
</tr>
<tr>
<td>Bigby (2003)</td>
<td>44</td>
<td>3 mg/kg/d</td>
</tr>
<tr>
<td>Ellis (1991)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>IMGSP (1993)</td>
<td>36</td>
<td>5 mg/kg/d</td>
</tr>
<tr>
<td>Laburte (1994)</td>
<td>132</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of patients (blue square) in the study group and its 95% confidence interval (lines)
N: number of patients enrolled in the study group
Ciclosporin

Intermittent therapy in patients non-responsive to topicals

Ciclosporin courses required during the study

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>400</td>
<td>259</td>
<td>117</td>
<td>26</td>
</tr>
</tbody>
</table>

Cumulative remission rates for each treatment period

Ciclosporin

Intermittent therapy in patients non-responsive to topicals - time to relapse

*Proportion of patients who have not relapsed.

PISCES study: Year 2 conclusions

- 60% of patients were managed with one to two 12-week courses of cyclosporin per year
- Mean percentage of time a patient received treatment: 43% (322 days)
- Median time to relapse: 115 days
- Percentage of time in remission
  - 56% for Group A (abrupt cessation)
  - 62% for Group B (tapered off)
- Tapering-off approach might be preferable

Cyclosporin in clinical practice

• A retrospective study was conducted on 193 patients treated in three Italian Psoriasis Units

• Cyclosporin A (CyA) was administered for a mean period of 14 months, the mean number of treatment courses was 1.6 (range 1-4), the mean dosage ranged from 1.5 to 3.1 mg/kg/day

• 90% of patients obtained complete therapeutic success or clinical remission

• Adverse events occurred in 36% of patients, with hypertension being the most commonly reported (17.6%)

Continuous vs intermittent

- 51 patients; mean PASI=10
- Initial dose 2.4 escalated to 5 mg/kg/day for 12 wks. If PASI 50 response achieved, during next 9 months:
  - Continuous Rx at lowest effective dose or
  - Intermittent 12 week courses on “agreed relapse” (approx PASI 60)
- At 12 months, better results in continuous treatment group:
  - PASI 75: 92% vs 62%
  - PASI 90: 58% vs 19%
- 39% higher cumulative dose in continuous therapy group
- Creatinine increase required dose adjustment in 10% of pts in each group

Step-up vs step-down

- 61 pts; mean PASI=20
- 12 weeks’ duration
  - 2.5–4–5 mg/kg (‘standard’) vs
  - 5–4–2.5 mg/kg (‘step-down’)
- Step-down:
  - better response rate (75% vs 51%)
  - shorter duration (6 vs 8 weeks)
  - higher cumulative dose (170 mg/kg vs 137)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Kidney/CV</th>
<th>Liver/GI tract</th>
<th>Nervous system/musculature</th>
<th>Metabolism/electrolytes</th>
<th>Skin</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very frequent &gt;10%</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Frequent &gt;1%, &lt;10%</td>
<td>Renal disturbances, irreversible kidney damage during long-term therapy</td>
<td>Gingival hyperplasia GI upset</td>
<td>Tremor, fatigue, headache, burning sensations on hand and feet</td>
<td>Increased lipids serum</td>
<td>Hypertrichosis</td>
<td>None</td>
</tr>
<tr>
<td>Sporadic &gt;0.1%, &lt;1%</td>
<td>None</td>
<td>Gastric ulcers</td>
<td>Convulsions</td>
<td>Weight gain, hyperglycemia, hyperuricemia, hypomagnesemia</td>
<td>Acne</td>
<td>Anemia</td>
</tr>
<tr>
<td>Rare &gt;0.001%, &lt;0.1%</td>
<td>Ischemic heart disease</td>
<td>Pancreatitis</td>
<td>Motor polyneuropathy, myopathy, visual, acoustic and central motor disturbances</td>
<td>None</td>
<td>Pruritus</td>
<td>Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Very rare &lt;0.01%</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Individual case reports</td>
<td>Colitis</td>
<td>Papilledema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Ciclosporin

#### Safety considerations

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th>Impaired renal function; uncontrolled hypertension; uncontrolled infections; malignant disease (current or previous, in particular haematologic diseases or cutaneous malignancies, with the exception of basal cell carcinoma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important side effects</td>
<td>Renal failure, hypertension, liver failure, nausea, anorexia, vomiting, diarrhoea, hypertrichosis, gingival hyperplasia, tremor, malaise, paresthesias</td>
</tr>
<tr>
<td>Important drug interactions</td>
<td>Many different interactions – the metabolism of ciclosporin is dependent on the hepatic enzyme cytochrome P450-3A4</td>
</tr>
<tr>
<td>Special issues</td>
<td>Increased risk of lymphoproliferative disease in transplant patients. Increased risk of squamous cell carcinoma in psoriasis patients following excessive photochemotherapy</td>
</tr>
</tbody>
</table>

"Ciclosporin can be considered for long-term therapy (up to 2 years) in individual cases, but patients should be monitored closely for signs of increasing toxicity, especially for decreases in renal function or the efficacy of treatment."
Cyclosporin: Tolerance

• Short-term regimen\(^1\)
  – Serum creatinine elevation 4 to 6.5%, returning to baseline following dosage reduction
  – Blood pressure stable in >85% of patients

• Long-term (median 55 months) maintenance treatment (3.5 mg/kg/day)\(^2\)
  – Renal impairment 71%: discontinuation 25%
  – New onset hypertension 9 to 45%

• Dose-related effect with lower doses (1-4 mg/kg/d) increasing mean BP by an average of 5 mmHg\(^3\)

• Comorbidities in psoriasis

Cyclosporin is associated with increased risk of skin malignancies

<table>
<thead>
<tr>
<th></th>
<th>Low exposure</th>
<th>High exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Any malignancy</td>
<td>1.8</td>
<td>1.2-2.6</td>
</tr>
<tr>
<td>Any skin malignancy</td>
<td>4.8</td>
<td>2.6-8.1</td>
</tr>
<tr>
<td>Non-melanoma skin malignancy</td>
<td>4.6</td>
<td>2.4-8.1</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>6.2</td>
<td>0.8-22.5</td>
</tr>
<tr>
<td>Any non-skin malignancy</td>
<td>1.2</td>
<td>0.7-1.9</td>
</tr>
</tbody>
</table>

- Effect of duration of exposure to cyclosporin on risk of malignancies in psoriasis (n=1252)
  - Low exposure: ≤2 yrs of cyclosporin
  - High exposure: >2 yrs of cyclosporin

Cyclosporin

- Cyclosporin is primarily suited for induction therapy
  - Start at 3-4 mg/kg: quick response – transition
  - Intermittent short courses (3–4 months); Cyclosporin can be used to treat suitable patients for up to 2 yrs maximum
  - Suitable for combination therapy with etanercept (50 mg OW and 200 mg/day)\(^1\)

- Potential for drug interactions and serious adverse effects, especially nephrotoxicity and risk of malignancies

Methotrexate

Proposed mechanisms of action

**Immunomodulatory effects**¹
- Inhibition of proliferating lymphoid tissue
- Inhibition of IL-1 activity and IL-6 production

**Anti-inflammatory effects**¹
- Reduced neutrophil and monocyte chemotaxis
- Inhibition of leucocyte accumulation at sites of inflammation

**Inhibition of epidermal proliferation**¹
- Interference with cell kinetics via temporary reduction on DNA synthesis

---

Methotrexate: RCTs in psoriasis

N=85; at wk 16 PASI75 60% vs 71% (CSA); PASI90 40% vs 33%

Methotrexate and ciclosporin
PASI 75 responses at Week 12


Methotrexate
7.5-15 mg/week (n=37)

Ciclosporin
3-5 mg/kg/day (n=31)

p=0.0094
Methotrexate and ciclosporin

PASI 75 responses at Week 16

Methotrexate: RCTs in psoriasis

- **Doses:**
  - MTX 7.5–15, CSA 3–5

- **Significant differences between groups at 4, 8 and 12 wks**
  - \( p=0.0161; p=0.0018; p=0.0028 \)

- **Successful treatment:**
  - PASI75 response:
    - 24% MTX vs 58% CSA \( p=0.0094 \) at Week 12
  - PASI90:
    - 11% vs 29% at Week 12

Methotrexate
Long-term treatment up to 26 years

- Majority of patients responded well to treatment
- No obvious relation between cumulative dose or duration of methotrexate therapy and frequency or severity of side effects
  - One or more side-effects were observed in 61% of patients
  - Therapy was discontinued in 20% of patients
- Patients should be regularly monitored in particular for liver and bone marrow toxicity.

Patients (%)

<table>
<thead>
<tr>
<th>Treatment response</th>
<th>Poor</th>
<th>Moderate</th>
<th>Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=157</td>
<td>6</td>
<td>18</td>
<td>76</td>
</tr>
</tbody>
</table>

MTX dose regimen: 15-20 mg/wk
Mean cumulative dose: 3394 mg
Mean treatment duration: 237 weeks

MTX dosing protocol in CHAMPION

<table>
<thead>
<tr>
<th>Week</th>
<th>MTX dosage (mg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.5, 7.5, 10, 10, 15, 15, 15, 15</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

≥ PASI 50 Group A

<table>
<thead>
<tr>
<th>Week</th>
<th>MTX dosage (mg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>15, 15, 15, 15, 15, 15, 15, 15</td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

≥ PASI 50 Group B

<table>
<thead>
<tr>
<th>Week</th>
<th>MTX dosage (mg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>20, 20, 20, 20</td>
</tr>
<tr>
<td>13</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

< PASI 50 Group C

<table>
<thead>
<tr>
<th>Week</th>
<th>MTX dosage (mg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>25, 25, 25, 25</td>
</tr>
<tr>
<td>13</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Reduction of MTX dosage was allowed for safety concerns

CHAMPION trial

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

Intention to treat (ITT), patients with missing PASI scores were considered non-responders.

CHAMPION: PASI 75, 90 and 100 at week 16

As-observed analysis

CHAMPION: Mean percentage change in PASI for MTX dosage groups

As observed analysis

RESTORE 1 study design

- Phase IIIb, randomised, parallel-group, multicentre, active-controlled, open-label study.
  - MTX included in the study as the active-control arm

Eligible patients were randomised (3:1) to either IFX or MTX.

Patients with <PASI 50 from weeks 0 to 16 or who were intolerant to treatment were discontinued from the initial treatment and permitted to switch treatment groups at Week 16.

---

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>2</th>
<th>6&lt;sup&gt;c&lt;/sup&gt;</th>
<th>10</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>22</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX 5 mg/kg&lt;sup&gt;a&lt;/sup&gt; (n=653)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX 15 mg/wk&lt;sup&gt;b&lt;/sup&gt; (n=215)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>a</sup>Patients randomised to IFX received infusions at Weeks 0, 2, 6, 14 and 22. Patients switching from IFX to MTX at Week 16 received 15 mg/wk from Week 16 through Week 22.

<sup>b</sup>Patients switching from MTX to IFX at Week 16 received infusions at Weeks 16, 18 and 22.

<sup>c</sup>At Week 6, MTX dose was increased to 20 mg/wk if PASI change from baseline was <25%. 55 patients received a dose of 20 mg for at least one visit between Week 6 and Week 16.

The 1° end point was PASI75 response at Week 16
Patients achieving <PASI 50 by Week 16 were permitted to switch treatment groups and were counted as non-responders

PASI75 was achieved by 78% of infliximab patients vs 42% of methotrexate patients: P < 0.001

RESTORE: PASI 75 responses over time

ITT-NRI; For all visits: p<0.001

Infliximab was well tolerated and demonstrated greater efficacy than methotrexate in moderate-to-severe psoriasis.

RESTORE: PASI 90 responses over time

Week 2: $P = 0.055$;
Weeks 6–26: $P < 0.001$

Patients randomised 1:1 to receive:
- Briakinumab: 200 mg subcutaneously at Weeks 0 and 4, and 100 mg every 4 weeks from Weeks 8 to 48 (n=154)
- Methotrexate: 5–25 mg/week from Weeks 0 to 51, per titration schedule, adjusted for safety and efficacy (n=163)
- Non-responding patients (patients with <PASI 75 and PGA ≥ 2 at Week 24 of <PASI 50 and PGA > 3 after Week 24) were discontinued from the study

Reich K, et al. WCD. 2011; Abstract 2578.
Briakinumab vs MTX: PASI 75 responses over time

*pp<0.001 vs. methotrexate

ITT with NRI for N=154 (briakinumab) and N=163 (methotrexate)

Reich K, et al. WCD. 2011; Abstract 2578.
PASI 75 response rates are greater at Weeks 24 and 52 for early responders and late responders compared with late non-responders.
Methotrexate
Safety considerations

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th>Severe infections, severe liver or kidney disorders, bone marrow dysfunction, pregnancy or breastfeeding, impaired lung function or pulmonary fibrosis, alcohol abuse, immunodeficiency, acute peptic ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important side effects</td>
<td>Bone marrow depression, liver toxicity, pneumonia, and alveolitis</td>
</tr>
<tr>
<td>Important drug interactions</td>
<td>Trimethoprim, probenecid, retinoids, NSAIDs</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Dosage only once weekly; overdose may lead to leucopenia/pancytopenia and thus be life-threatening</td>
</tr>
</tbody>
</table>

"Its clinical application is restricted by severe adverse drug reactions [...]. However, with precise patient selection, thorough patient information, strict monitoring, use of the lowest effective dose, and the additional administration of folic acid, an acceptable safety profile can also be attained for methotrexate therapy."
Methotrexate: Safety (mortality)

- PubMed review:
  - 125 deaths in 66 reports
    - Death rate: 1.2 per 100 000 psoriasis patients per year

- Major adverse drug reactions with MTX include:
  - Bone marrow suppression
  - Hepatotoxicity, nephrotoxicity
  - Stomatitis, GI & skin ulcers
  - Gastrointestinal ulcerations
  - Contraception ♀♂, olygospermia

<table>
<thead>
<tr>
<th>Fatal adverse event</th>
<th>Deaths, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>53 (42)*</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>22 (18)*</td>
</tr>
<tr>
<td>Infectious</td>
<td>13 (10)*</td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

*Acute toxicity – within 1 month of initiation: myelosuppression (8), pneumonitis (1), infectious (1).

Teratogenicity

• Methotrexate is absolutely contraindicated in pregnancy and breastfeeding, as well as in both men and women attempting conception. The washout period is 3 months for both sexes.

• Methotrexate is associated with miscarriage and a specific pattern of malformations, with head and limb abnormalities and developmental delays in infants.
  – Doses >10 mg/week appear to be necessary to produce this syndrome.
  – The critical exposure period is between 6 and 8 weeks post-conception.

• Data are insufficient to ascertain the exact threshold dose, the window of exposure, the effects of second and third trimester exposure and the possible protective effect of folate supplementation.
Liver fibrosis: systematic review

- Frequency of liver fibrosis in psoriasis patients treated with methotrexate

Robinson (1980)  n = 43
Malatjalian (1996)  n = 96
Themido (1992)  n = 22
Rosenberg (2007)\textsuperscript{a}  n = 71
Rosenberg (2007)\textsuperscript{b}  n = 71
Zachariae (2001)  n = 70

\textsuperscript{a} any stage of liver fibrosis
\textsuperscript{b} severe fibrosis

- Risk factors associated with an increased incidence of fibrosis:
  - alcohol (OR = 1.74),
  - obesity (OR = 2.44),
  - type 2 diabetes (OR = 7.65),
  - hepatitis B and C (OR = 5.61)

MTX liver toxicity: Increased risk in psoriasis?

- Studies on hepatotoxicity after long-term MTX therapy in patients with PsA found that the risk of developing cirrhosis may be as high as 25%\(^1\)

- Similar studies among RA patients reported substantially lower rates of liver cirrhosis of <2%\(^2,3\) as well as a low risk of mild liver fibrosis\(^4\) and abnormal liver tests\(^5\)

- Retrospective cohort (N=119 RA, 690 psoriasis)\(^6\):
  - Similar risk for hepatic enzyme elevation (but greater exposure in RA patients)
  - Higher risk: female gender and a higher cumulative dose of MTX (hazard ratios, 1.46 and 1.07, respectively, p<0.001)

Methotrexate: Liver toxicity

- Liver toxicity seems to be more frequent in psoriasis patients (comorbidities, alcoholic fatty liver - NAFLD)

- NAFLD (echographic) is more prevalent in psoriasis patients (47% vs. 28%; p < 0.0001), and is associated with metabolic syndrome, higher serum C-reactive protein concentrations and higher PASI score\(^1\)

- Abnormal glucose tolerance is a predictor of steatohepatitis and fibrosis in patients with NAFLD\(^2\)

---

Methotrexate: Liver toxicity and biopsy avoidance

- Monitoring for hepatic fibrosis using serial liver function tests and ACR guidelines (↑ALT, alcohol) alone as in RA appears safe in psoriasis and PsA1

- Liver biopsy ought to be considered to assess the liver if LFT are persistently elevated1

- PIIINP:
  - Liver biopsies can be avoided (cumulative dose <3–4 g, PIIINP normal levels)2,3
  - PIIINP is misleading in active PsA (↑)

- Fibroscan may be helpful4,5

- Correlation between FibroScan values and dose of MTX in 29 Crohn’s disease (CD) patients. FibroScan value of 8.7 kPa is the published cut-off for significant fibrosis

Methotrexate subcutaneous injection

- Multi-dose vial available
- More effective than oral MTX (in RA), similar tolerability and AE rate\(^1\)
- Safer? (better GI and liver tolerance because of enterohepatic bypass, pneumonitis?)
  - MTX lung toxicity: 10 cases reported in patients with psoriasis\(^2\)
- Patients (with psoriasis) now more familiar with self injection due to biologic therapy

Methotrexate: Folic acid supplementation

- Folic acid supplementation may reduce hematologic and GI toxicity; meta-analysis shows trend for reduced mucocutaneous and GI side effects
- Meta-analysis shows reduced hepatotoxicity

- **Debate** on decreased efficacy
  - Salim (2006) 5 mg/day decreases efficacy at 12 wks
  - Pinarbasi (2007) 5 mg 5/7 same efficacy
  - Chládek (2008) 10 mg BIW decreases efficacy at 16 weeks

- **Variable doses:**
  - 5 to 27.5 mg of folic acid per week [similar efficacy (Morgan 1994)], and 1 to 5 mg of folinic acid per week

CSA/MTX: Risk of pharmacologic interactions

- Ingenix (R) Impact National Managed Care Database (1999-2007 (USA):
  - Among 4,583 (57.6%) exposed and 3,372 (42.4%) nonexposed patients, nonsteroidal anti-inflammatory drugs and antibiotics were the most common drugs with potential interactions.
- The exposed patients had significantly greater risks of developing renal, gastrointestinal and pulmonary events
- and significantly greater health care resource utilization (e.g. OR for inpatient and emergency department visits: 1.47; p < 0.0001) and costs (adjusted incremental cost: USD 1,722; p < 0.0001).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Exposed, n/N (%)</th>
<th>Non-exposed, n/N (%)</th>
<th>Adjusted odds ratio Mean, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary event</td>
<td>433/3974 (10.9)</td>
<td>241/3104 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Renal event</td>
<td>38/4519 (0.8)</td>
<td>9/3352 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Hematologic event</td>
<td>228/4228 (5.4)</td>
<td>120/3195 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal event</td>
<td>206/4294 (4.8)</td>
<td>100/3245 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Hepatic event</td>
<td>96/4465 (2.2)</td>
<td>62/3317 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>

Fumaric acid esters (FAE)
Long-term safety in severe psoriasis

- Review of patients (n=66) with severe psoriasis receiving long-term FAE therapy (up to 14 years)
- Adverse events (73% of patients) were usually mild
  - Relative lymphocytopenia (76% of patients) led to permanent discontinuation of FAE therapy in four cases
  - A transient eosinophilia and moderate liver enzyme elevations were observed in 14% and 25% of patients, respectively

Traditional systemic treatments in the age of biologics

• In routine clinical practice, ≥30% patients require combined treatment with biologics and conventional systemics
  – To maximize therapeutic outcome
  – Overlapping when switching to a biologic
  – ‘Bridging’ when there is risk of rapid relapse or rebound after withdrawal
  – To hasten the start of improvement with ‘slow-onset’ biologics
  – To overcome stabilization of improvement or decrease in effectiveness
  – To decrease immunogenicity, clearance of incidence of infusion reactions (infliximab)

• Combined treatment with methotrexate, nbUVB and acitretin can be useful to optimize the therapeutic results and control transient flares of psoriasis

• Combination of biologics with traditional systemic therapies for psoriasis is off-label
Approved biologic therapies for plaque psoriasis:
Overview
Approved biologic therapies for plaque psoriasis

Indications for use in Europe

- **Adalimumab**
  Treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

- **Etanercept**
  Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA).

- **Infliximab**
  Treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

- **Ustekinumab**
  Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA.
Nomenclature of biologic therapies

- **Etanercept**
  - *cept = human receptor fusion protein

- **Infliximab**
  - *ximab = chimaeric monoclonal antibody

- **Adalimumab**

- **Ustekinumab**
  - *umab = fully human monoclonal antibody

Adapted from: Johnston SL. J Clin Pathol. 2007;60(1):8-17.
## Approved biologic therapies for plaque psoriasis

### Comparison of structure and function

<table>
<thead>
<tr>
<th></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><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-α</td>
<td>TNF-α</td>
<td>TNF-α</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNF-β (LYMPHOTOXIN)</td>
<td></td>
<td></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-α activity</td>
<td>Blocks TNF-α 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(^1)</th>
<th>Etanercept(^2)</th>
<th>Infliximab(^3)</th>
<th>Adalimumab(^4)</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>

# Approved biologic therapies for plaque psoriasis

## Comparison of tolerability and safety*

<table>
<thead>
<tr>
<th>Biologic Therapy</th>
<th>Contraindications:</th>
<th>Special warnings:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ustekinumab</strong></td>
<td>Hypersensitivity to the active substance or to any of the excipients.</td>
<td>Malignancies, hypersensitivity reactions, combinations with vaccines and immunosuppressant therapy.</td>
</tr>
<tr>
<td><strong>Etanercept</strong></td>
<td>Hypersensitivity to the active substance or to any of the excipients. Sepsis or risk of sepsis. Treatment should not be initiated in patients with active infections, including chronic or localised infections.</td>
<td>Infections, TB, hepatitis B reactivation, worsening of hepatitis C, concomitant use with anakinra and abatacept, malignancies and lymphoproliferative disorders, allergic reactions, immunosuppression, vaccines, haematological reactions, CNS disorders, combination therapy, congestive heart failure, alcoholic hepatitis, Wegener's granulomatosis, hypoglycaemia in patients treated for diabetes.</td>
</tr>
<tr>
<td><strong>Infliximab</strong></td>
<td>History of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients. TB or other severe infections such as sepsis, abscesses, and opportunistic infections. Patients with moderate or severe heart failure (NYHA class III/IV).</td>
<td>Infusion reactions and hypersensitivity, infections, hepatitis B reactivation, hepatobiliary events, concomitant use with anakinra and abatacept, autoimmune processes, vaccinations, neurological events, malignancies and lymphoproliferative disorders, heart failure, haematologic reactions and surgery.</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td>Hypersensitivity to the active substance or to any of the excipients. Active TB or other severe infections such as sepsis, opportunistic infections. Moderate to severe heart failure (NYHA class III/IV).</td>
<td>Infections including TB, Hepatitis B Reactivation, neurological events, allergic reactions, immunosuppression, malignancies and lymphoproliferative disorders, haematological disorders, vaccinations, congestive heart failure, autoimmune process, concomitant use with anakinra and abatacept, surgery, small bowel obstruction.</td>
</tr>
</tbody>
</table>

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

Biologic therapies
Comparison of tolerability and safety

<table>
<thead>
<tr>
<th></th>
<th>Ustekinumab&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Etanercept&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Inflixiamb&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adalimumab&lt;sup&gt;4&lt;/sup&gt;</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

## Biologic therapies

### Common adverse events*

<table>
<thead>
<tr>
<th>Biologic Therapy</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab¹</td>
<td>Cellulitis, viral upper respiratory tract infection, hypersensitivity reactions (including rash, urticaria), depression, dizziness, headache, pharyngolaryngeal pain, nasal congestion, diarrhoea, pruritus, back pain, myalgia, fatigue, injection site erythema</td>
</tr>
<tr>
<td>Etanercept²</td>
<td>Allergic reactions, autoantibody formation, pruritus, fever</td>
</tr>
<tr>
<td>Infliximab³</td>
<td>Viral infection (e.g. influenza, herpes virus infection), serum sickness-like reaction, headache, vertigo, dizziness, flushing, lower respiratory tract infection (e.g. bronchitis, pneumonia), upper respiratory tract infection, sinusitis, dyspnoea. abdominal pain, diarrhoea, nausea, dyspepsia. transaminases increased, urticaria, rash, pruritus, hyperhidrosis, dry skin, infusion-related reaction, chest pain, fatigue, fever</td>
</tr>
<tr>
<td>Adalimumab⁴</td>
<td>Systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), thrombocytopenia, leucocytosis, hypersensitivity, allergies (including seasonal allergy), hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia hyperglycemia, hypophosphotemia, blood potassium increased, mood alterations (including depression), anxiety, insomnia, paraesthesias (including hypoaesthesia), migraine, sciatica, visual impairment, conjunctivitis, vertigo, tachycardia, hypertension, flushing, haematoma, cough, asthma, dyspnoea, GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome, pruritus, urticaria, bruising (including purpura), dermatitis (including eczema), onycholysis, hyperhydrosis, muscle spasms (including blood creatine phosphokinase increased), haematuria, renal impairment, chest pain, oedema, coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased, impaired healing</td>
</tr>
</tbody>
</table>

---

¹ Ustekinumab - European Summary of Product Characteristics. Date: September 2010.
² Etanercept - European Summary of Product Characteristics. Date: June 2010.
³ Infliximab - European Summary of Product Characteristics. Date: May 2010.

*Common (≥1/100 to <1/10).
### Biologic therapies

#### Very common adverse events*

<table>
<thead>
<tr>
<th>Biologic Therapy</th>
<th>Common Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Upper respiratory tract infection, nasopharyngitis</td>
</tr>
<tr>
<td>Etanercept&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Infections (including upper respiratory tract infections, bronchitis, cystitis, skin infections), injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)</td>
</tr>
<tr>
<td>Infliximab&lt;sup&gt;3&lt;/sup&gt;</td>
<td>None listed</td>
</tr>
<tr>
<td>Adalimumab&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral), leucopaenia (including neutropenia and agranulocytosis), anaemia, lipids increased, headache, abdominal pain, nausea and vomiting, elevated liver enzymes, rash (including exfoliative rash), musculoskeletal pain, injection site reaction (including injection site erythema)</td>
</tr>
</tbody>
</table>

---


*Very common (≥1/10)*
Approved biologic therapies for plaque psoriasis
PASI 75 and PASI 90 responses

PASI 75 and PASI 90 responses for infliximab (week 10 data), etanercept, ustekinumab (week 12 data) and adalimumab (week 16 data)