Biologicals in the Treatment of Plaque Psoriasis: Drug Selection by Means of the SOJA Method

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Abstract

The treatment of plaque psoriasis is changing because of the introduction of new treatment options. The goal of this article is to allow a transparent and rational choice of medicines by means of the System of Objectified Judgement Analysis. The following selection criteria (relative weight) were applied: approved indications (40), drug interactions (60), clinical efficacy (400), safety (300), dosage frequency (100) and documentation (100). Acquisition cost was not taken into consideration to allow a preselection on quality aspects only. Adalimumab, etanercept, infliximab and ustekinumab were compared on these criteria. Infliximab and ustekinumab showed the highest scores and are the most suitable medicines for the treatment of severe plaque psoriasis. Of course, cost will play a key role in the final selection in individual hospitals.

Keywords: Approved indications; Drug interactions; Clinical efficacy; Safety; Dosage frequency

Introduction

The treatment of plaque psoriasis is changing because of the introduction of new treatment options. The goal of this SOJA is to allow a transparent and rational choice of medicines.

The SOJA method is a model for rational drug selection. The relevant selection criteria for a certain group of drugs are defined and judged (Table 1). The more important a selection criterion is considered, the higher the relative weight that is given to that criterion. The ideal properties for each selection criterion are determined and each drug is scored as a percentage of the relative weight for all selection criteria. The criteria, which were used in the present SOJA method and the weighting of the authors, are presented below. A Medline and Embase search was performed, as well as a search for studies in the Cochrane library. As well as these searches, the references of review articles on this subject were obtained and incorporated in the analysis when appropriate. All relevant data were included in the manuscript. The drugs with the highest total score are most suitable for formulary inclusion [1].

The following medicines were included:

- Adalimumab (Humira®)
- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Ustekinumab (Stelara®)

Alefacept, which is not available in the Netherlands, was not included in the analysis.

The evaluation of the criteria in the SOJA method is highly standardized in order to promote unbiased judgement of drugs from various pharmacotherapeutic categories based on clinically relevant criteria. There will of course always be room for debate whether or not the correct scoring system was used for each criterion and judgement may be arbitrary for most, if not all, criteria. This is the case with any method used to quantify properties of drugs. The SOJA method is intended as a tool for rational drug decision making, forcing clinicians and pharmacists to include all relevant aspects of a certain group of drugs, thereby preventing formulary decisions being based on only one or two criteria. Also, possible “hidden criteria” are excluded from the decision making process. The outcome of this study should be seen as the basis for discussions within formulary committees and not as the absolute truth.

Psoriasis

Psoriasis is a frequently occurring inflammatory condition of the skin. Its prevalence in the Netherlands is estimated at 2-3%. This review focuses on plaque psoriasis, which is by far the most frequent form of psoriasis [2-4]. Psoriatic arthritis occurs to a much more limited extent [5].

First line therapy consists of locally acting agents, such as calcitriol, calcipotriol or class 3 or 4 corticosteroids or dithranol [3,4]. When these drugs are not sufficient, rotation therapy using the above agents can be applied [6,7]. Local therapy can be combined with narrow spectrum UV-B or acute retin. PUVA therapy is an option in case of insufficient efficacy. As the next step methotrexate or ciclosporine can be used. Both treatments may have serious adverse effects [2,4,5,8]. Combinations may be used to optimise results [9]. The present analysis is limited to those patients in which all above agents are not effective or not tolerated [8,10,11].

| Criteria                        | Weight |
|--------------------------------|--------|
| Approved indications            | 40     |
| Drug Interactions               | 60     |
| Clinical efficacy               | 400    |
| Safety                          | 300    |
| Dosage frequency                | 100    |
| Documentation                   | 100    |
| Total                           | 1000   |

Table 1: Selection criteria and authors’ weighting.

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The treatment of moderate to severe, active rheumatoid arthritis

Twenty percent is deducted for iv infusion compared to sc.

The extent and the severity of adverse effects is another important selection criterion for drugs. A distinction was made between “minor” side effects, such as gastrointestinal disturbances or skin reactions, occurring in clinical trials and severe or even life-threatening adverse reactions observed with large scale use of the drugs. The evaluation of the “minor” adverse effects was based on results of double blind comparative studies.

Both the number of patients that has been treated on a worldwide basis and the period that a certain drug has been available are of importance, as it may take time until adverse reactions occur.

The number of years that a product has been marketed in any country in the world provides information on the clinical experience with the drug. If a product is on the market for more than 10 years it is very unlikely that serious adverse reactions will be observed that have not been seen in the first 10 years after its introduction. 10% of the relative weight for this sub criterion was awarded for every 10 years that the drug has been on the market.

The number of years that a product is on the market, also the number of patient days experience with the drug plays a role. 10% of the relative weight for this sub criterion was awarded for each year the product is available on the market.

The number of clinical studies, in which only a relatively small number of patients were included and most patients at risk for the development of adverse reactions (e.g. patients with diminished renal function) were excluded. The latter two criteria are indicative of the overall clinical documentation of the drugs in randomized controlled clinical studies. A large number of clinical studies and a large number of patients included in these studies leave no doubt about the clinical efficacy and safety of this drug in the studied population. The latter two criteria are indicative of the overall clinical experience with the drug. These sub criteria may introduce a bias to the advantage of older drugs, but this is done intentionally. The safety of a newly introduced drug cannot be guaranteed from the results of clinical studies, in which only a relatively small number of patients were included and most patients at risk for the development of adverse reactions (e.g. patients with diminished renal function) were excluded.

The number of randomized comparative studies

The number of randomized comparative clinical studies is an important determinant of the clinical documentation.

5% of the relative weight for this sub criterion was awarded for each randomized comparative study.

The number of patients that were treated with the drug in question must also be taken into consideration.

1% of the relative weight for this sub criterion was awarded for every 10 patients enrolled in randomised comparative studies.

The number of clinical studies

Besides the number of clinical studies, the number of patients that were treated with the drug in question must also be taken into consideration.

1% of the relative weight for this sub criterion was awarded for every 10 patients enrolled in randomised comparative studies.

The number of years marketed

Besides the number of years that a product is on the market, also the number of patient days experience with the drug plays a role. 10% of the relative weight for this sub criterion was awarded for every million patient days that the drug was on the market.

The number of patients treated worldwide

Besides the number of years that a product is on the market, also the number of patients treated worldwide with the drug plays a role. 10% of the relative weight for this sub criterion was awarded for every million patients treated with the drug in question worldwide.

Results

Approved indications

Adalimumab

Rheumatoid arthritis: Adalimumab in combination with methotrexate is indicated for:

- The treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- The treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab has been shown to reduce the rate of progression of
joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

**Polyarticular juvenile idiopathic arthritis**

Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents from the age of 2 years who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Humira has not been studied in children aged less than 2 years.

**Ankylosing spondylitis (AS)**

Adalimumab is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

**Axial spondyloarthritis without radiographic evidence of AS**

Adalimumab is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to Nonsteroidal anti-inflammatory drugs.

**Psoriatic arthritis**

Adalimumab is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

**Psoriasis**

Adalimumab is indicated for the 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 ciclosporine, methotrexate or PUVA.

**Crohn’s disease**

Adalimumab is indicated for treatment of moderately to severely active Crohn’s disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/ or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

**Pediatric Crohn's Disease**

Adalimumab is indicated for the treatment of severe active Crohn’s disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

**Ulcerative colitis**

Adalimumab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

**Etanercept**

**Rheumatoid arthritis**: Etanercept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Etanercept can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Etanercept is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Etanercept, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

**Juvenile idiopathic arthritis**: Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

**Psoriatic arthritis**: Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

**Enthesis-related arthritis**: Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy. Etanercept has not been studied in children aged less than 2 years.

**Psoriatic arthritis**: Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

**Ankylosing spondylitis**: Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

**Plaque psoriasis**: 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).

**Pediatric plaque psoriasis**: Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

**Infliximab**

**Rheumatoid arthritis**: Infliximab, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- Adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- Adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.
In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated

**Adult Crohn's disease:** Infliximab is indicated for:

- Treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

- Treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

**Pediatric Crohn's disease:** Infliximab is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies.

- Infliximab has been studied only in combination with conventional immuno-suppressive therapy.

**Ulcerative colitis:** Infliximab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

**Pediatric ulcerative colitis:** Infliximab is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or AZA, or who are intolerant to or have medical contraindications for such therapies.

**Ankylosing spondylitis:** Infliximab is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

**Psoriatic arthritis:** Infliximab is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.

- Infliximab should be administered
  - In combination with methotrexate
  - Or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated

- Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

**Psoriasis:** Infliximab is indicated for 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 therapies including cyclosporine, methotrexate or PUVA.

**Ustekinumab**

**Plaque psoriasis:** Ustekinumab is indicated for the 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 cyclosporine, methotrexate (MTX) and PUVA (psoralen and ultraviolet A).

**Psoriatic arthritis:** Ustekinumab, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

- Adalimumab and infliximab are approved for all indications and are awarded 100%. Etanercept is not approved for IBD and scores 90%. Ustekinumab is only approved for plaque psoriasis and psoriatic arthritis and scores 70%.

**Interactions:** Unless otherwise specified, all data are derived from the Summaries of Product Characteristics.

**Adalimumab**

Adalimumab has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking adalimumab as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when adalimumab was given together with methotrexate in comparison with use as monotherapy. Administration of adalimumab without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab. The combination of adalimumab and anakinra or abatacept is not recommended.

**Etanercept**

**Concurrent treatment with anakinra:** Adult patients treated with etanercept and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either etanercept or anakinra alone (historical data). In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with etanercept and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with etanercept. The combination etanercept and anakinra has not demonstrated increased clinical benefit, and is therefore not recommended.

**Concurrent treatment with abatacept:** In clinical studies, concurrent administration of abatacept and etanercept resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit, such use is not recommended.

**Concurrent treatment with sulfasalazine:** In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which etanercept was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with etanercept or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

**Non-interactions:** In clinical trials, no interactions have been observed when etanercept was administered with glucocorticoids, salicylates (except sulfasalazine), Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), analgesics, or methotrexate.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with warfarin [12], methotrexate [13] and digoxin [14].
Infliximab: No interaction studies have been performed.

In rheumatoid arthritis, psoriatic arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab.

Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent.

The combination of infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra and abatacept, is not recommended.

It is recommended that live vaccines not be given concurrently with infliximab.

Ustekinumab: Live vaccines should not be given concurrently with ustekinumab. No interaction studies have been performed in humans. In the population pharmacokinetic analyses of the phase III studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (>5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs and oral corticosteroids, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis.

The results of an in vitro study do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates.

In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab.

There are few, if any, drug interactions relevant for the treatment of plaque psoriasis. All medicines are awarded 90%.

Efficacy

Score for determination of efficacy: The PASI-score (Psoriasis Area and Severity Index) is the most common and most accepted score for the determination of efficacy for medicines in the treatment of plaque psoriasis. This score combines dexam symptoms: erythema, induration, desquamation (rated 0 to 4) and the percentage of the body surface area affected (rated 0 to 6). These are evaluated separately for head, trunk and the upper and lower extremities. PASI score ranges from 0 (no lesions) to 72 (most severe psoriasis). Psoriasis is considered severe when affects at least 20% of the body and/or in case of a PASI-score of at least 10.

A reduction of at least 75% in the PASI score (PASI-75) is the most usual primary endpoint in therapeutic studies in psoriasis. This reflects a clinically meaningful improvement of disease severity. Other endpoints include PASI-50 and PASI 90, as well as the percentage improvement in PASI [2]. The determination of PASI is labour intensive however, that is why other endpoints have been used in clinical trials, such as Overall Lesion Severity Scale (OLS) and Physician Global Assessment (PGA). Validated patient reported outcomes include Dermatology Life Quality Index (DLQI), visual analogue scale for the judgement of pruritis (VAS), Skindex-29 and the Psoriasis Symptom Assessment (PSA) [15-17]. A combined endpoint of effects on the skin, (PASI), joints (ACR) and quality of life (Euro EQ-50) has been proposed as well [18].

All biologicals have a limited indication in plaque psoriasis: "moderate to severe plaque psoriasis in adults who did not respond to other systemic therapies (methotrexate, ciclosporin or PUVA) or who have a contraindication to, or are intolerant for these drugs" and this limitation was assigned by the authorities. Most clinical studies with biologicals were however performed in another population. Only few studies were explicitly performed in patients who were pretreated with ciclosporin, methotrexate or PUVA and response to these agents was usually not described in the Materials and Methods sections of these studies. This makes it hard to judge the efficacy of biologicals in the correct population of patients (Table 3).

The most usual inclusion criteria were: plaque psoriasis patients of 18 years or older, stable plaque psoriasis during at least 6 months, minimal PASI of 10 or 12 and at least 10% of body surface area affected by plaque psoriasis. Use of biologicals in the last 4 weeks before randomization was not allowed.

Review double-blind studies and methodology

Efficacy Adalimumab: Several studies were performed with adalimumab [19-21]. One study [43] was not included in the analysis because of a low number of patients per treatment arm (n=23).

The first study compared adalimumab to placebo. Patients who completed the double-blind phase could continue adalimumab in an open setting. Patients randomized in the placebo arm received an 80 mg loading dose, followed by 40 mg every two weeks. Patients could be switched to a higher dose when PASI-50 was not achieved. No differences were observed in response rates of patients with moderate and with severe plaque psoriasis. PASI-75 was reached in 64% of patients treated with the higher dose and in 56% of patients treated every two weeks [19]. A sub analysis also showed an improvement of depressive symptoms compared to placebo [44]. Adalimumab was also better than placebo in patient-reported outcomes [45].

The double-blind phase of the second study lasted 15 weeks. Patients who reached PASI-75 could continue adalimumab once every two weeks for another 17 weeks in an open-label fashion. After this, patients who were originally treated with adalimumab were rerandomized to adalimumab (n=250) or placebo (n=240) for 19 weeks [20]. The primary endpoint "loss of adequate response" was not well specified, what makes it difficult to interpret the results (Table 4).

The third study compared adalimumab with oral methotrexate (7.5 mg titrated to 25 mg when well tolerated) and placebo during 16 weeks. Adalimumab was more effective than methotrexate on all endpoints [21] as well as quality of life [46].

Efficacy etanercept

The first study compared etanercept with placebo for 12 weeks. Patients in the etanercept group continued etanercept for another 12 weeks, whereas patients in the placebo group were changed to etanercept 25 mg twice per week in a blinded fashion [23].
| Medicine                  | Dosage                          | Allowed comedication          | Primary endpoint | Pretreatment | % BSA affected | Ref  |
|---------------------------|---------------------------------|-------------------------------|-----------------|-------------|----------------|------|
| Adalimumab                | 40 mg/week (+ load)             | Dermal corticoster.           | PASI-75         | No biological | 25%            | [19] |
| Adalimumab                | 40 mg/2 wk (+ load)             |                               | PASI-75         | 13%         | 26%            | [20] |
| Placebo                   |                                 |                               |                 | 28%         |                |      |
| Adalimumab                | 40 mg/2 wk (+load)              | Derma corticoster.            | PASI-75         | No biological or methotrexate | 34% | [21] |
| Methotrexaat              | 7.5 - 25 mg oral                |                               |                 |             | 28%            |      |
| Placebo                   |                                 |                               |                 |             |                |      |
| Adalimumab                | 40 mg/2 wk                      | Derma corticoster.            | PASI-75         | No biological | 43%            | [22] |
| Adalimumab                | 40 mg/2 wk (+ load)             |                               |                 | 48%         |                |      |
| Placebo                   |                                 |                               |                 | 46%         |                |      |
| Placebo                   |                                 | Derma corticoster.            | PASI-75         | 76% (systemic) | 28% | [23] |
| Placebo                   |                                 | Tar Dermal corticoster.       | PASI-75         | 39%         | 30%            | [24] |
| Placebo                   |                                 |                               |                 | 36% (MTX)   | 34%            |      |
| Etanercept                | 25 mg/wk                        | Emollients Tar Dermal corticoster. | PASI-75     | 35%         | 23%            | [25] |
| Placebo                   |                                 |                               |                 | 38%         | 25%            |      |
| Placebo                   |                                 |                               |                 | 39% (MTX)   | 20%            |      |
| Etanercept                | 50 mg 2x/wk                     | Emollients Tar Dermal corticoster. | PASI-75     | 33%         |                | [26] |
| Placebo                   |                                 |                               |                 | 33%         |                |      |
| Placebo                   |                                 | Emollients Tar                 | PASI-75         | 30%         |                | [27] |
| Placebo                   |                                 |                               |                 | 27%         |                |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 55%         | 20%            | [28] |
| Placebo                   |                                 |                               |                 | 59%         | 21%            |      |
| Placebo                   |                                 | Percentage improved PASI score |                 | 6.7% anti TNF | 16%            |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 14% biol    | 24%            | [30] |
| Placebo                   |                                 |                               |                 | 11% biol    | 24%            |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 15% biol    | 24%            | [31] |
| Placebo                   |                                 |                               |                 | 15% biol    | 24%            |      |
| Ustekinumab               | 45 mg at week 0 + 4             | Dermal corticoster.            | PASI-75         | 12% biol    | 27%            | [32] |
| Placebo                   |                                 |                               |                 | 12% biol    | 27%            |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 26%         |                | [33] |
| Placebo                   |                                 | Emollients Tar Salicylic acid |                 | 26%         |                |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 42%         | 19%            | [34] |
| Placebo                   |                                 |                               |                 | 46% (MTX)   | 18%            |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 33%         | 28%            | [35] |
| Placebo                   |                                 |                               |                 | 35%         | 29%            |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 34% (MTX)   | 28%            | [36] |
| Placebo                   |                                 |                               |                 | 34% (MTX)   | 28%            |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 51% biologicals | 27% | [37] |
| Placebo                   |                                 |                               |                 | 51% biologicals | 25% | [38] |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 28%         |                |      |
| Placebo                   |                                 |                               |                 | 28%         |                |      |
| Ustekinumab               | 45 mg                          | Dermal corticoster.            | PASI-75         | 26%         |                | [39] |
| Placebo                   |                                 |                               |                 | 27%         |                |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 26%         |                | [40] |
| Placebo                   |                                 |                               |                 | 27%         |                |      |
| Placebo                   |                                 | Dermal corticoster.            | PASI-75         | 26%         |                | [41] |
| Placebo                   |                                 |                               |                 | 26%         |                |      |

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PASI-75 was reached in 25%, 44% and 59% in the three etanercept groups, respectively at 24 weeks. PASI-90 was reached in 6%, 20% and 30%. Improvement in PASI scores varied from 50% to 71%. PASI-75 was achieved in 52% of patients treated with etanercept for 12 weeks after initial placebo treatment. The DLQI at 24 weeks was 54 to 74% in the etanercept groups [23]. Quality of life improved significantly in the etanercept groups compared to placebo [47].

In a follow-up study, treatment was discontinued in patients showing PASI-50 at 24 weeks. This study correlates well with the approved duration of treatment with etanercept. Once these patients relapsed (loss of at least 50% of initial improvement), they were retreated with the original dosage. Median time to relapse was 85 days in the group showing PASI-50 and 91 days in the group showing PASI-75. Time to loss of 50% of PASI-75 gain was 57 days. In the group originally showing PASI-50 83% reached PASI-50 again, whereas PASI-75 was again reached in 52% of patients originally showing PASI-75 response [48] (Table 5).

The third study compared etanercept and placebo for 12 weeks. After 12 weeks all patients received etanercept 25 mg twice weekly in an open label setting [23]. PASI-75 response in the groups originally randomized to 50 mg, 25 mg or placebo twice weekly at 24 weeks was 54%, 45% and 28%, respectively. Response rates at 24 weeks were at least as good as at 12 weeks. Of patients achieving PASI-75 at 12 weeks at the higher dose, 77% maintained PASI-75 at 24 weeks after 12 weeks of treatment with the lower dose; 32% of 88 patients who did not achieve PASI-75 at 12 weeks did so at 24 weeks [23]. DLQI remained constant at 12 and 24 weeks in patients originally treated with the higher dose [41].

The fourth study also investigated effect on tiredness and depressive complaints. Depression was seen in 33% and 3% for etanercept and placebo at baseline. After 12 weeks of treatment improvement was seen in 55% and 39%, respectively. Using the Hamilton rating scale, improvement was seen in 43% and 32% [28].

In a follow-up study all patients were changed to etanercept after 12 weeks in an open label setting. Results at 24 weeks were similar for patients originally treated with etanercept or with placebo. PASI-75 at 48 weeks was 62%, whereas this was 51% at 96 weeks [49].

Another study compared etanercept (50 mg 2 × per week) and placebo for 12 weeks. Then all patients received 50 mg once per week, still in a blinded manner for another 12 weeks. PASI-90, -75 and -50 were reached in 34%, 69% and 85% for etanercept, vs. 31%, 59% and 80% for placebo [30].

An analysis of studies 21 and 23 showed no major effects on PASI-75 regarding disease duration, previous treatment, presence or psoriatic arthritis and gender. A trend was observed of lower efficacy in European vs. American studies in patients with a baseline PASI of 16 or higher. A relatively poor effect was seen in patients with higher body weight (median>90 kg) [50].

Studies with etanercept included patients with moderate to severe plaque psoriasis, pretreated with systemic medicines or in whom such treatment was indicated. In the 3 studies judged by EMA [23-25], 83%

| Medicine      | Age (year) | Duration (year) | PASI baseline | Reference |
|---------------|------------|-----------------|---------------|-----------|
| Adalimumab    | 45 (66% M) | 19              | 16            | [19]      |
| Placebo       | 45 (66% M) | 18              | 19            | [20]      |
| Adalimumab    | 43.42 41  | 19              | 19            | [21]      |
| Methotrexate  | 45 (85% M)| 14              | 28            | [22]      |
| Placebo       | 45 (85% M)| 14              | 28            | [22]      |
| Etanercept    | 45 (67% M)| 19              | 18            | [23]      |
| Placebo       | 45 (67% M)| 19              | 18            | [23]      |
| Placebo       | 41 (85% M)| 14              | 15            | [24]      |
| Etanercept    | 45 (66% M)| 19              | 16            | [25]      |
| Placebo       | 44 (70% M)| 17              | 21            | [26]      |
| Elanercept    | 45 (58% M)| 198             | 21            | [27]      |
| Placebo       | 46 (67%)  | 20              | 18            | [28]      |
| Etanercept    | 13 (51% M)| 6               | 16            | [29]      |
| Placebo       | 41 (55% M)| 14              | 15            | [30]      |
| Etanercept    | 45 (70%)  | 17              | 19            | [30]      |
| Placebo       | 44 (69%)  | 16              | 18            | [31]      |
| Etanercept    | 47 (68% M)| 20              | 21            | [31]      |
| Placebo       | 45 (68% M)| 20              | 20            | [32]      |
| Ustekinumab   | 45 (72% M)| 20              | 20            | [32]      |
| Placebo       | 45 (72% M)| 20              | 20            | [32]      |
| Ustekinumab   | 45 (69%)  | 19              | 19            | [33]      |
| Placebo       | 47 (67%)  | 20              | 20            | [33]      |
| Placebo       | 49 (76%)  | 17              | 29            | [33]      |
| Placebo       | 50 (88%)  | 14              | 23            | [34]      |

Table 3: Double blind studies, methodology - part I

Table 4: Double blind studies, methodology - part II
of patients had received prior systemic therapy or light therapy. Of all patients 89% had used dermal corticosteroids, 46% UVB, 29% PUVA, 14% cyclosporine and 36% methotrexate. No relevant differences in treatment response were seen in subgroups with or without prior systemic therapy [2].

A more recent study compared etanercept and placebo in children and adolescents [49]. The double blind phase lasted for 12 weeks, after which all patients received weekly etanercept for 24 weeks. At 36 weeks patients were rerandomised to study the effects of treatment cessation. The results of the first double-blind phase are summarized in the Tables 4 and 5. The effects of etanercept remained constant during the 24 weeks open label phase, whereas PASI values in the original placebo group gradually approached those in the etanercept group during these 24 weeks. A gradual loss of efficacy was seen in the placebo group during the second double-blind phase, whereas PASI-75 was reached in 75% of patients in the etanercept group [29].

One study compared etanercept 50 mg once per week with placebo for 12 weeks. The results are summarized in the Table 6. After the double-blind phase all patients received 50 mg etanercept once per week. PASI at 24 weeks values were similar in both groups. PASI-90 in patients originally treated with etanercept increased from 14% to 42% in this period [27].

Other studies compared higher (100 mg per week) and lower

| Medicine        | OLS Minimal or clean | PGA Excellent or clean | DLQI Improved | VAS Improved | PSA Improved | Ref. |
|-----------------|----------------------|------------------------|---------------|-------------|-------------|------|
| Adalimumab      |                      | 76%                    |               |             |             | [19] |
| Adalimumab      |                      | 49%                    |               |             |             | [20] |
| Placebo         |                      | NR                     |               |             |             |      |
| Adalimumab      |                      | 60%                    |               |             |             | [22] |
| Placebo         |                      | 18%                    |               |             |             |      |
| Adalimumab      |                      | -4.6                   |               |             |             |      |
| Adalimumab      |                      | -5.5                   |               |             |             |      |
| Adalimumab      |                      | -7.0                   |               |             |             |      |
| Placebo         |                      | +1.3                   |               |             |             |      |
| Etanercept      |                      | 47%                    |               |             |             | [23] |
| Placebo         |                      | 69%                    |               |             |             |      |
| Placebo         |                      | 22%                    |               |             |             |      |
| Etanercept      |                      | 64%                    |               |             |             | [24] |
| Placebo         |                      | 7%                     |               |             |             |      |
| Etanercept      |                      | 37%                    | 72%           |             |             | [25] |
| Placebo         |                      | 54%                    | 77%           |             |             | [41] |
| Etanercept      |                      | 3%                     | 21%           |             |             |      |
| Placebo         |                      | 4%                     | 5%            |             |             | [27] |
| Etanercept      |                      | 38%                    | 54%           |             |             |      |
| Placebo         |                      | 2%                     | 21%           |             |             | [28] |
| Briakinumab     |                      | 71%                    | 36%           |             |             | [31] |
| Placebo         |                      | 3%                     | (score 0)     |             |             |      |
| Infliximab      |                      | 72%                    | 70%           |             |             | [33] |
| Infliximab      |                      | 90%                    | 80%           |             |             | [42] |
| Placebo         |                      | 10%                    | 16%           |             |             |      |
| Infliximab      |                      | 83%                    | 75%           |             |             | [34] |
| Placebo         |                      | 4%                     | 3%            |             |             |      |
| Infliximab      |                      | 73%                    | 67%           |             |             | [35] |
| Placebo         |                      | 75%                    | 70%           |             |             |      |
| Placebo         |                      | 0% (wk 10)             | 0% (wk 10)    |             |             |      |
| Infliximab      |                      | 57%                    |               |             |             | [36] |
| Infliximab      |                      | 10%                    |               |             |             |      |
| Placebo         |                      | 68%                    | 76%           |             |             | [37] |
| Ustekinumab     |                      | 74%                    | 70%           |             |             |      |
| Placebo         |                      | 0%                     | 4%            |             |             | [38] |
| Ustekinumab     |                      | 60%                    | 72%           |             |             |      |
| Placebo         |                      | 4%                     | 5%            |             |             |      |
| Ustekinumab     |                      | 71%                    | 70%           |             |             | [40] |
| Placebo         |                      | 8%                     | 7%            |             |             |      |

| Table 5: Double-blind studies, results at 12 weeks - part I |
| Medicine       | Dosage                        | N / N completed | PASI improvement | PASI-90 | PASI-75 | PASI-50 | Ref |
|----------------|-------------------------------|-----------------|------------------|---------|---------|---------|-----|
| Adalimumab     | 40 mg/wk                      | 50/47           | 48%              | 80%     | 88%     |         | [19]|
| Adalimumab     | 40 mg/2 wk                    | 46/43           | 24%              | 53%     | 76%     |         |     |
| Placebo        |                               | 52/50           | NR               | 4%      | NR      |         |     |
| Adalimumab     | 40 mg/2 wk (+ load)           | 814/783         | 76%              | 37%     | 68%     |         |     |
| Placebo        |                               | 398/355         | 15%              | 2%      | 5%      |         |     |
| Adalimumab     | 40 mg/2wk (+ load)            | 108/103         | 80%              | 52%     | 50%     | 88%     |     |
| Methotrexaat    | 7.5-25 mg                     | 110/105         | 54%              | 14%     | 35%     | 62%     |     |
| Placebo        |                               | 53/50           | 21%              | 11%     | 19%     | 30%     |     |
| Adalimumab     | 40 mg/2 wk                    | 50/47           | 53%              | 66%     | 74%     |         | [22]|
| Adalimumab     | 40 mg/2 wk + load             | 46/43           | 44%              | 69%     | 77%     |         |     |
| Placebo        |                               | 52/50           | 67%              | 81%     | 86%     |         |     |
| Placebo        |                               |                 | 4% (24 weeks)    | 13%     | 20%     |         |     |
| Etanercept     | 25 mg/wk                      | 160             | 41%              | 3%      | 14%     | 41%     | [23]|
| Etanercept     | 25 mg 2x/wk                   | 162             | 53%              | 12%     | 34%     | 58%     |     |
| Etanercept     | 50 mg 2x/wk                   | 164             | 64%              | 22%     | 49%     | 74%     |     |
| Placebo        |                               | 166             | 14%              | 1%      | 4%      | 14%     |     |
| Etanercept     | 25 mg 2x/wk                   | 57/53           | 67%              | 11%     | 30%     | 70%     |     |
| Placebo        |                               | 55/40           | 1%               | 0%      | 2%      | 11%     |     |
| Etanercept     | 25 mg 2x/wk                   | 196/191         | 11%              | 34%     | 64%     |         |     |
| Etanercept     | 50 mg 2x/wk                   | 194/190         | 21%              | 49%     | 77%     |         |     |
| Placebo        |                               | 193/178         | 1%               | 3%      | 9%      |         |     |
| Etanercept     | 50 mg 1x/wk                   | 137/127         | 11%              | 37%     | 88%     |         |     |
| Etanercept     | 50 mg 2x/wk                   | 136/124         | 29%              | 62%     | 68%     |         |     |
| Etanercept     | 50 mg 1x/wk                   | 96/90           | 55%              | 14%     | 38%     | 69%     |     |
| Placebo        |                               | 46/36           | -9%              | 2%      | 2%      | 7%      |     |
| Etanercept     | 50 mg 2x/wk                   | 311/305         | 21%              | 47%     | 74%     |         |     |
| Placebo        |                               | 307/292         | 1%               | 5%      | 14%     |         |     |
| Etanercept     | 0.8 mg/kg/wk                  | 106             | 68%              | 27%     | 57%     | 75%     | [29]|
| Placebo        |                               | 105             | 21%              | 7%      | 11%     | 23%     |     |
| Etanercept     | 50 mg 2 x pw/1x/wk            | 62/49           | 87%              | 25%     | 59%     | 85%     |     |
| Placebo        |                               | 62/49           | 26% (PSSI)       | 2%      | 5%      | 7%      |     |
| Etanercept     | 50 mg 2 x pw                  | 141             | 20%              | 56%     |         |         |     |
| Briakinumab    | 200 mg, weeks 0 and 4, 100 mg | 138             | 60%              | 82%     |         |         | [31]|
| Placebo        | at week 8                      | 68              | 2%               | 7%      |         |         |     |
| Etanercept     | 50 mg 2x/wk                   | 347             | 23%              | 57%     |         |         |     |
| Ustekinumab    | 45 mg at weeks 0 + 4          | 209             | 36%              | 68%     |         |         | [32]|
| Ustekinumab    | 90 mg at weeks 0 + 4          | 347             | 45%              | 74%     |         |         |     |
| Infliximab     | 3 mg/kg                       | 99/82           | 46%              | 72%     | 84%     |         | [33]|
| Infliximab     | 5 mg/kg (wks 0, 2 and 6)      | 99/78           | 58%              | 88%     | 97%     |         |     |
| Placebo        |                               | 51/16           | 2%               | 6%      | 22%     |         |     |
| Infliximab     | 5 mg/kg (wk 0, 2 and 6)       | 301/269         | 85%              | 57%     | 80%     | 91%     | [34]|
| Placebo        |                               | 77/68           | 6%               | 1%      | 3%      | 8%      |     |
| Infliximab     | 3 mg/kg                       | 313/296         | 37%              | 70%     |         |         | [35]|
| Infliximab     | 5 mg/kg (wk 0, 2 and 6)       | 344/299         | 45%              | 75%     |         |         |     |
| Placebo        |                               | 208/184         | 1%               | 2%      |         |         |     |
| Infliximab     | 5 mg/kg (wk 0, 2 and 6)       | 84/74           | 85%              | 57%     | 81%     | 94%     | [36]|
| Placebo        |                               | 45/40           | 6%               | 0%      | 2%      | 13%     |     |
| Ustekinumab    | 45 mg                         | 255             | 76%              | 42%     | 67%     | 84%     | [37]|
| Ustekinumab    | 90 mg                         | 256             | 77%              | 37%     | 66%     | 86%     |     |
| Placebo        |                               | 255             | 7%               | 2%      | 3%      | 10%     |     |
dosages (50 mg per week) of etanercept. The high dose was more effective (23x, 23B). One study with a mixed population of plaque psoriasis and psoriatic arthritis patients was not included in the analysis [51].

Etanercept 50 mg (n=347) twice per week was less effective than ustekinumab (45 mg (n=209) or 90 mg (n=347) at weeks 0 and 4) in a direct open-label comparative study. This study included patients with moderate to severe plaque psoriasis, 57% of patients received previous systemic therapy and 65% light therapy and 97% had used dermal treatment. Eleven percent had used previous biologics. Baseline PASI was 19. The mean age was 45 years. The mean weight (91 kg) was rather high. The primary endpoint was PASI-75. A secondary endpoint was the fraction of patients with a clear skin or minimal lesions, judged by the physician. Patients randomized to etanercept were switched to ustekinumab after 12 weeks. PASI-75 at 12 weeks was achieved in 68% and 74% of patients treated with 45 mg and 90 mg ustekinumab, respectively vs. 57% for etanercept, p<0.01 and p<0.001, respectively). Of all patients showing insufficient response to etanercept, 49% achieved PASI-75 after 12 weeks of treatment with ustekinumab 90 mg. A clear skin was seen in 65% and 71% for both dosages of ustekinumab vs. 49% for etanercept, p<0.001 [32] (Table 7).

Etanercept was also less effective than briakinumab in a double-blind, placebo controlled study [31].

**Efficacy Ustekinumab**

The most important results of the studies are summarized in the Table 8.

One study was too limited in size to be included and another study was excluded because it was a phase II study [52,53]. In the first study an induction therapy with three dosages of (3 mg/kg or 5 mg/kg at 0, 2 and 6 weeks) was compared to placebo. An additional dose could be given in patients with a recurrence after 26 weeks. The initial results at 10 weeks were favourable. The clinical response decreased with time after 10 weeks in the 3 mg/kg group and after 14 weeks in the 5 mg/kg group. PASI-75 was about 10% in the 3 mg/kg group and 25% in the 5 mg/kg group. In patients receiving retreatment after 26 weeks, 38% and 64% in the 3 mg/kg and 5 mg/kg infliximab groups reached a PGA of less than 3, compared to 18% with placebo [33].

The second study applied a 5 mg/kg dosage at 0, 2 and 6 weeks, which was repeated every 8 weeks afterwards. Patients in the placebo group switched to infliximab at 24 weeks. Despite continued treatment, the percentage of patients with PASI-75 decreased gradually from 80% at 10 weeks to 61% at 50 weeks. PASI-50 decreased from 91% to 69% at 10 and 50 weeks, respectively. Especially patients with non-detectable trough levels and patients with high concentrations of antibodies showed a low response rate [34]. This study also showed a significant effect on nail psoriasis: 56% improvement in the infliximab group versus -3% in the placebo group at 24 weeks. Quality of life was also favourably influenced by infliximab, expressed as DLQI or SF-36. The DLQI index decreased 87% in the infliximab group versus 3% for placebo. A significant improvement was seen in all 8 SF36 subscales for infliximab compared to placebo [54].

The third study randomized patients to induction treatment with infliximab 3 mg/kg, infliximab 5 mg/kg or placebo at weeks 0 and 2 and 6. Patients assigned to infliximab were rerandomised to continuous treatment (every 8 weeks) or intermittent treatment, based on complaints at 14 weeks. PASI-75 scores were 76% in the 5 mg/kg group and 70% in the 3 mg/kg group, compared to 2% for placebo at 10 weeks. PASI-90 was achieved in 45%, 37% and 0.5%, respectively. Continuous treatment was more effective than intermittent therapy, with PASI-75 of 25% and 38% for intermittent use of 3 mg/kg and 5 mg/kg and 44% (3 mg/kg) and 55% (5 mg/kg) for continued use (23B). Infliximab improved disease-related quality of life as well [35].

A Chinese study randomized patients to induction treatment with infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 14 and 22. The primary endpoint was PASI-75 at 10 weeks. The results at 10 weeks are summarized in the Tables. PASI-75 responses increased to 93% at week 26. Subjects in the placebo group received infliximab induction therapy at week 10; PASI-75 at 26 weeks was 80% in these patients [36].

One study was not included in the analysis, because the number of patients in the placebo arm was too low [56].

**Efficacy Ustekinumab**

The Phoenix studies compared ustekinumab 45 mg or 90 mg at time 0, at 4 weeks and every 12 weeks thereafter to placebo [37,38]. Patients in the placebo group were switched to ustekinumab 45 mg or 90 mg after 12 weeks treatment. The overall effects were judged after 28 weeks of treatment and treatment was stopped in all patients who had not achieved PASI-50 and dosage frequency was increased to every 8 weeks in all patients between PASI-50 and PASI-75. A randomized withdrawal phase started at 40 weeks.

The most important results of the studies at 12 weeks are summarized in the Table 8.

PASI-75 was reached in 71% and 79% of patients treated with 45 mg and 90 mg respectively. A difference in response between both dosages was seen between the two dosages in patients originally assigned to placebo. PASI-75 was reached in 66% for the 45 mg and in 85% for 90 mg. This was also reflected in a better PASI-90: 45% vs. 62% [37]. The effects were maintained during 3 years treatment [57].

The Phoenix 2 study randomized patients showing a response between -50 and PASSI-75 at 28 weeks to ustekinumab every 8 or 12 weeks. No advantage was seen for the shorter dosage interval for 45 mg, whereas a better efficacy was seen for 90 mg every 8 weeks [38].

| Ustekinumab | 45 mg | 409 | 77% | 42% | 67% | 84% |
|-------------|-------|-----|-----|-----|-----|-----|
| Ustekinumab | 90 mg | 411 | 82% | 51% | 76% | 89% |
| Placebo     |       | 410 | 5%  | 1%  | 4%  | 10% |
| Ustekinumab | 45 mg | 64/64| 73% | 33% | 59% | 83% |
| Ustekinumab | 90 mg | 62/58| 75% | 44% | 68% | 84% |
| Placebo     |       | 32/28| 11% | 3%  | 7%  | 13% |
| Ustekinumab | 45 mg | 61/57| 79% | 49% | 67% | 84% |
| Placebo     |       | 60/55| 3%  | 2%  | 5%  | 13% |

Table 6: Double-blind studies, results at 12 weeks-part II.
Ustekinumab 45 and/or 90 mg were more effective than placebo in studies with Asian patients [39,40]. In a Japanese study PASI-75 remained constant during in open label treatment of 1 year [39]. Etanercept 50 mg (n=347) twice per week was less effective than ustekinumab (45 mg (n=209) or 90 mg (n=347) at weeks 0 and 4) in a direct open-label comparative study. This study included patients with moderate to severe plaque psoriasis, 57% of patients received previous systemic therapy and 65% light therapy and 97% had used dermal treatment. Eleven percent had used previous biologicals. Baseline PASI was 19. The mean age was 45 years. The mean weight (91 kg) was rather high. The primary endpoint was PASI-75. A secondary endpoint was the fraction of patients with a clear skin or minimal lesions, judged by the physician. Patients randomized to etanercept were switched to ustekinumab after 12 weeks. PASI-75 at 12 weeks was achieved in 68% and 74% of patients treated with 45 mg and 90 mg ustekinumab, respectively vs. 57% for etanercept, p=0.01 and p<0.001, respectively). Of all patients showing insufficient response to etanercept, 49% achieved PASI-75 after 12 weeks of treatment with ustekinumab 90 mg. A clear skin was seen in 65% and 71% for both dosages of ustekinumab vs. 49% for etanercept, p<0.001 [32].

Discussion

It is difficult to draw conclusions concerning the relative clinical efficacy of the four drugs. Adalimumab has not been extensively studied in psoriasis, but appears to be effective. Etanercept showed a more limited effect concerning PASI-75 at 12 weeks. Most clinicians used PASI-50 more often in daily practice and no major differences between adalimumab and etanercept become apparent using this endpoint.

Infliximab was also more effective than etanercept, which was confirmed in two meta-analyses [58,59]. One of these analyses also showed superiority of adalimumab to etanercept [59]. One direct open-label comparative study between ustekinumab and etanercept showed superiority of ustekinumab regarding PASI-75 [32]. Other meta-analysis concluded that ustekinumab and infliximab were the most efficacious agents, followed by adalimumab and etanercept [60-62]. Because only one (open label) direct comparative study was performed, these results must be interpreted with caution.

Limited data are available concerning long-term efficacy of the drugs [61,62]. The efficacy of adalimumab and infliximab seems to decrease over time [19], while there are no data indicating a decreased efficacy over time for etanercept. It should however be noted that the maximal approved treatment period for etanercept is 24 weeks. One study compared drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. The drug survival rates were most favourable for infliximab, followed by adalimumab and etanercept [63].

Infliximab and ustekinumab are awarded the highest scores: 80%. Adalimumab scores 70% and etanercept 50%.

Sheets for the presentation

Safety: Safety data should be interpreted with caution, because plaque psoriasis has been linked to increased risk of the development of diabetes, cardiovascular diseases and cancer. One systematic review and meta-analysis found a pooled odds ratio for the development of diabetes of 1.53 for mild psoriasis and of 1.97 for severe psoriasis [64].

Two systematic reviews and meta-analysis investigated the association between psoriasis and adverse cardiovascular events. One study showed a significantly increased risk of myocardial infarction (RR 1.29) and stroke (RR 1.12) for mild psoriasis. For patients with severe psoriasis, an association was found with cardiovascular mortality (RR 1.39), myocardial infarction (RR 1.70) and stroke (RR 1.56) [65]. Another study was a meta-analyses of observational studies of psoriasis as study variable and cardiovascular disease and associated risk factors as outcome. The following odds ratios were found: ischaemic heart disease (1.5) and peripheral vascular disease (1.5). No significant effect on cerebrovascular disease and cardiovascular mortality was observed [66]. Another study combined plaque psoriasis and psoriatic arthritis. Increased odds ratios were found for coronary artery disease (1.19 for cross-sectional studies and 1.84 for case-control studies) [67]. So far, there are no indications that anti-TNF agents contribute to an increased cardiovascular risk in patients with plaque psoriasis [68].

Another meta-analysis found an increased risk of the development of various forms of cancer [69]. PUVA treatment increases the risk of cutaneous squamous cell carcinoma and malignant melanoma. Other treatments, methotrexate, cyclosporin and mycophenolate may be associated with increased risk of lymphoproliferative disorders. The situation is less clear concerning biologicals, but most studies suggest a slightly increased risk of non-melanoma skin cancer and lymphoma [70-72]. One study showed a higher incidence of lymphoma for adalimumab (SIR 4.1) and infliximab (SIR 3.6) than for etanercept (SIR 0.9) in patients with rheumatoid arthritis [73].

Antidrug antibodies may occur in patients treated with infliximab or adalimumab. The presence of antibodies reduce efficacy of infliximab and adalimumab in the treatment of rheumatoid arthritis. Etanercept does not give rise to the presence of anti-drug antibodies [74]. A meta-analysis of these studies showed a relationship between the presence of antibodies and infusion reactions on infliximab and hypersensitivity reactions on adalimumab [75]. Presence of antibodies is lower when combination is usual in the treatment of rheumatoid arthritis and inflammatory bowel disease, respectively, but much less so in the treatment of psoriasis.

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**Table 7: Etanercept vs placebo.**

| Study | Total incidence (%) | Withdrawal (%) | Headache (%) | Injection site reaction (%) | Resp tract infection (%) | Myalgia (%) | Nausea (%) |
|-------|---------------------|----------------|--------------|-----------------------------|-------------------------|------------|------------|
| 23    | 10/7                | 15/7           |              | 3/2                         | 2/1                     |            |            |
| 24    | 2/8                 | 16/13          | 11/9         | 35/20                       |                         |            |            |
| 25    | 1/1                 | 12/8           | 16/6         | 13/13                       |                         |            |            |
| 28    | ½                   | 6/6            | 6/4          | 4/5                         |                         |            |            |

**Table 8: Ustekinumab 45 and 90 mg vs placebo.**

| Study | Total incidence (%) | Serious (%) | Withdrawal (%) | Infections (%) | Cancer (%) |
|-------|---------------------|-------------|----------------|----------------|------------|
| 37    | 58/51/48            | 0.8/1.6/0.8 | 0.4/1.6/2.4    | 31/28/27       | 0/0/0      |
| 38    | 53/48/50            | 2.0/1.2/2.0 | 0.2/1.5/2.0    | 22/22/20       | 0/0/2.0/4 |
Limited data are available regarding safety of TNF-α blockers concerning patients with plaque psoriasis. The number of patients included in clinical studies is limited and the average duration was short compared to studies in rheumatology or inflammatory bowel disease.

**Adalimumab:** In a relatively large-scale placebo-controlled study, the incidence of serious adverse events was similar to placebo. One cases each of tuberculosis and opportunistic infections were observed in 540 patient years of treatment with adalimumab [20]. The incidence of malignancies was similar to placebo, although number of non-melanoma skin cancers (NMSC) (0.013 vs. 0.008) was numerically higher than for placebo. This should be related to the very low incidence (only one case in the placebo-group). No lupus-like disorders or demyelinating disorders were observed in this study [20] (Table 9).

An overview of all clinical studies with adalimumab was published in 2011. Total exposure was 370 patient years during the double-blind phases and 4844 patient years in overall adalimumab-treated patients. None of the serious adverse events, such as malignancies, opportunistic infections and congestive heart failure occurred significantly more frequent with adalimumab than with placebo. NMSC (1.35 vs. 0.58 per 100 patient years) occurred numerically higher than for placebo, but it was not stated whether this was statistically significantly different. In the overall database, the SIR for NMSC was 1.51 (1.04-2.11) for the largest dataset. Only one case of lymphoma (0.02 per 100 patient years) was observed in adalimumab-treated patients. There were no indications for an increased risk for heart failure, lupus-like syndrome and demyelinating disorders. Serious adverse events were seen to a similar extent as for placebo (8.6 vs. 7.5 per 100 patient years). There were no indications at all that adalimumab increased mortality rates [76].

Another, more recent, study evaluated all (25,000) patients involved in clinical trials with adalimumab, of which 3,000 patients with psoriasis (5061 patient years). The results were quite similar to the above study. The incidence of serious infections (1.7 per 100 years) was lower than that was expected for the overall database. Only one case of lymphoma (0.02 per 100 patient years) was observed in adalimumab-treated patients. There were no indications for an increased risk for heart failure, lupus-like syndrome and demyelinating disorders. Serious adverse events were seen to a similar extent as for placebo (8.6 vs. 7.5 per 100 patient years). There were no indications at all that adalimumab increased mortality rates [77].

**Etanercept:** One study provided an overview of reported adverse events in clinical trials with etanercept. Serious adverse events were reported at a rate of 7.9 reports per 100 patient years (total exposure 1305 patient years). Serious infections adverse events were uncommon: 0.9 per 100 patient years. No case of tuberculosis was reported. Malignancies were reported in 0.8 per 100 patient years. Cardiovascular events were reported in 1.3 per 100 patient years, mostly myocardial infarction (0.6 per 100 patient years). No data from the placebo groups were reported [78].

Another study compared pooled etanercept and placebo groups. Serious adverse events were seen in 6.2 to 6.7 cases per 100 treatment years for etanercept vs. 9.8 for placebo. The rate of serious infections was similar to that of placebo. The standardized incidence ratios for malignancies excluding NMSC were not significantly higher than expected. The incidence of NMSC was higher than expected in the etanercept groups [79] (Table 9).

One US database study consisting of 2511 patients taking etanercept for the treatment of psoriasis showed 290 adverse events in up to 5 years. Quantitatively the most important adverse events included cellulitis and pneumonia (17 cases each), myocardial infarction [13], coronary heart disease [9], osteoarthritis [7] and angina pectoris, atrial fibrillation, cholecystitis, diverticulitis, intervertebral disk protrusion, nephrolithiasis, staphylococcal infections and death (6 cases each). The incidence of cancer was not higher than that was expected for the database population [80]. Studies with etanercept in the treatment of psoriasis did not show an increased risk of serious infections compared to placebo [2].

**Infliximab:** No specific analysis of the safety profile of infliximab in patients with plaque psoriasis could be identified.

**Ustekinumab:** In the placebo-controlled studies of patients with psoriasis and/or psoriatic arthritis, serious infections occurred in 0.01 per patient-year of follow-up in ustekinumab-treated patients (5 serious infections in 616 patient-years of follow-up) and 0.01 in placebo-treated patients (4 serious infections in 287 patient-years of follow-up) (SPC Ustekinumab).

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis [81].

In the controlled and non-controlled periods of psoriasis and psoriatic arthritis clinical studies, representing 9,548 patient-years of exposure in 4,031 patients, the median follow up was 3.2 years for psoriasis studies. The rate of serious infections was 0.01 per patient-year of follow-up in ustekinumab-treated patients (104 serious infections in 9,548 patient-years of follow-up) and serious infections reported included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis and sepsis (SPC ustekinumab).

**Malignancies:** In the placebo-controlled period of the psoriasis and psoriatic arthritis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.16 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 615 patient-years of follow-up) compared with 0.35 for placebo-treated patients (1 patient in 287 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.65 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 615 patient-years of follow-up) compared to 0.70 for placebo-treated patients (2 patients in 287 patient-years of follow-up) (SPC ustekinumab).

In the controlled and non-controlled periods of psoriasis and psoriatic arthritis clinical studies, representing 9,548 patient-years of exposure in 4,031 patients, the median follow up was 1.0 year; 3.2 years for psoriasis studies and 0.5 year for psoriatic arthritis studies. Malignancies excluding non-melanoma skin cancers were reported in 54 patients in 9,530 patient-years of follow-up (incidence of 0.57 per 100 patient-years of follow-up for ustekinumab-treated patients). This incidence of malignancies reported in ustekinumab-treated patients

| Study | Total incidence (%) | Serious (%) | Severe infections | Infusion reaction | Antibodies |
|-------|---------------------|-------------|------------------|-----------------|------------|
| 33    | 75/63               | 8/0         | 1/0              | 22/2            | 20/0       |
| 34    | 82/71               | 6/3         |                  | 3/2             | 27/0       |
| 54    | 69/56               | 3/2         |                  | 3/2             |            |
| 36    |                     |             |                  |                 | 12/7       | (antinuclear) |

Table 9: Infliximab (5 mg/kg) vs placebo.
was comparable to the incidence expected in the general population (standardized incidence ratio=0.93 [95% confidence interval: 0.70, 1.22], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal and breast cancers. The incidence of non-melanoma skin cancer was 0.51 per 100 patient-years of follow-up for ustekinumab-treated patients (49 patients in 9,515 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (4:1) is comparable with the ratio expected in the general population.

### Hypersensitivity reactions

During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of ustekinumab, rash and urticaria have each been observed in<1% of patients.

**Immunogenicity**: Approximately 6% of ustekinumab-treated patients in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titer. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was observed. The majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies. Efficacy tended to be lower in patients positive for antibodies to ustekinumab; however, antibody positivity did not preclude a clinical response (SPC ustekinumab).

### Cardiovascular events Ustekinumab:

An analysis of controlled clinical trials with ustekinumab showed an incidence of major cardiovascular events (MACE) of 0.44 per 100 patient years [82]. An analysis also including another IL12/23 antagonist (briakinumab) showed a significantly increased incidence of MACE vs. placebo [83]. Patients with a history of cardiovascular disease should be treated with caution [84].

### Common, but non-serious adverse events

**Reactions at the Injection site**

**Adalimumab**: Local reactions at the injection site (erythema, itching, bleeding, pain or swelling) were seen in 20% of adalimumab-treated patients’ vs. 14% for placebo. A trend towards a lower incidence of local reactions was seen in patients also using methotrexate [85]. However, in one study in which 34% of patients also received methotrexate, injection site reactions were seen in 20% of adalimumab-treated patients vs. 12% in placebo [86]. Keystone [87] did not find a difference in the incidence of reactions in patients receiving methotrexate or not. A trend towards a gradual decrease of injection site reactions with time was observed in one study [19].

**Etanercept**: Local reactions at the injection site (erythema, itching, bleeding, pain or swelling) were seen in 14% of etanercept-treated patients vs. 6% for placebo [88].

### Other effects

**Adalimumab**: In a relatively large-scale placebo-controlled study, the incidence of adverse events was similar to placebo. Only infectious adverse events (28.9% vs. 22.4%) and upper respiratory tract infections (7.2% vs. 3.5%) occurred significantly more frequent with adalimumab. The overall incidence of adverse events (62% vs. 56%), serious adverse events (1.8% in both groups), withdrawal (1.7% vs. 2.0%), nasopharyngitis and headache occurred to a similar extent as placebo [20] (Table 10).

An overview of all clinical studies with adalimumab was published in 2011. Total exposure was 370 patient years during the double-blind phases and 4844 patient years in overall adalimumab-treated patients. The incidence of adverse events was 657 per 100 patient years for adalimumab vs. 557 for placebo (no data provided concerning statistical significance). Infectious adverse events were seen more often as well: 154 vs. 115 per 100 patient years [76].

**Etanercept**: One study provided an overview of reported adverse events in clinical trials with etanercept. Adverse events were reported at a rate of 243 reports per 100 patient years (total exposure 1305 patient years). Infectious adverse events had a major contribution: 97 per 100 patient years. Withdrawal due to adverse events occurred in 2.6% of patients [78].

Another study compared the incidence of adverse events in clinical trials with etanercept with placebo. The incidence of headache, injection site hemorrhage and infections was similar to placebo during short-term use. Arthralgia was observed more frequently for placebo (5.9-5.5 vs. 19 per 100 patient years) and fatigue was seen more often for etanercept (12-23 cases vs. 6 per 100 patient years). The total incidence of adverse events was between 550 and 650 cases per 100 patient years for all dosages of etanercept vs. 600 cases for placebo [79].

**Infliximab**: Infliximab was associated with an increased risk of doubling the upper normal aspartate amino transferase levels (OR 1.87) and alanine amino transferase levels (OR 1.74), whereas adalimumab and etanercept were not associated with increased liver enzyme levels. No significant effects on lipid levels or blood pressure were observed for any of the anti-TNF agents [89].

One study reported a higher incidence of fatigue (8% vs. 4%) and rhinitis (6% vs. 1%) compared to placebo [34].

Another study reported a higher incidence of headache (12% vs. 5%), sinusitis (6% vs. 1%) and rhinitis (3% vs. 0.5%) vs. placebo [35].

**Ustekinumab**: In the placebo-controlled studies of patients with psoriasis and/or psoriatic arthritis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo: 1.27 per patient-year of follow-up in ustekinumab-treated patients, and 1.17 in placebo-treated patients (SPC ustekinumab). The most frequently reported adverse events in patients treated with ustekinumab in clinical trials were nasopharyngitis (27%), upper respiratory tract infection (22%), headache (11%), arthralgia (7%), back pain (6%), influenza (6%) and sinusitis (5%). Treatment was discontinued because of adverse events in 3%. No difference in side-effect profile was observed between 45 and 90 mg ustekinumab. Analyses of three comparative studies with ustekinumab showed no difference in the incidence of adverse events compared to placebo or etanercept [90-92].

**Overview of adverse events in the treatment of psoriasis in placebo-controlled studies**

There are no clear indications of meaningful differences in the safety profile of the medicines. All are awarded an identical score of 80%.

**Dosage frequency**

**Documentation**: De documentation concerning randomized clinical trials is summarized below (Table 11-13):
SOJA score

The SOJA score is presented below

Infliximab and ustekinumab show the highest scores. The choice between these compounds mainly depends on the patient’s (physician’s) preference for iv or sc administration. Both medicines score better than adalimumab and etanercept concerning clinical efficacy and dosage frequency (Table 14).

Of course the final score depends on the relative weights assigned to the selection criteria and on the judgement of the medicines per criterion. The outcome of this analysis should certainly not been seen as the "truth", but much more as a starting point of a discussion on the pros and cons of the various treatment options.

Table 10: Adalimumab vs placebo.

| Medicine     | Studies | Patients | Years on the market | Patient days (million) | Score |
|--------------|---------|----------|---------------------|------------------------|-------|
| Adalimumab   | 3       |          | >1000               | >100                   | 79%   |
| Etanercept   | 10      |          | >1000               | >100                   | 88%   |
| Infliximab   | 4       |          | >1000               | >100                   | 80%   |
| Ustekinumab  | 5       |          | >1000               | >100                   | 68%   |

Table 11: Documentation concerning randomised clinical trials is summarised below.

| Dosage frequency | Score |
|------------------|-------|
| Adalimumab       | 60%   |
| Etanercept       | 20%   |
| Infliximab       | 80%   |
| Ustekinumab      | 100%  |

Table 12: Dosage frequency.

| Frequency          | Score |
|--------------------|-------|
| Once every 8-12 weeks | 100%  |
| Once every 4 weeks   | 80%   |
| Once every 2 weeks   | 60%   |
| Once per week        | 40%   |
| Twice per week       | 20%   |

Table 13: The dosage frequency was scored as follows.

| Weight | Adalimumab | Etanercept | Infliximab | Ustekinumab |
|--------|------------|------------|------------|-------------|
| 40     | 40         | 36         | 40         | 32          |
| 60     | 54         | 54         | 54         | 54          |
| 80     | 200        | 320        | 320        | 320         |
| 100    | 20         | 80         | 100        |             |

Table 14: SOJA score.

References

1. Janknegt R, Steenhoeck A (1997) The System of Objectified Judgement Analysis (SOJA). A tool in rational drug selection for formulary inclusion. Drugs 53: 550-562.
2. (2012) Scientific Discussion Enbrel. European Medicines Agency.
3. van Peet PG, Spuls P, Ek JW, Lantinga H, Lecluse LLA, et al. (2014) NHG standard Psoriasis. Huisarts Wet 57: 128-135.
4. Shaw JC. Overview of psoriasis.
5. Lebwohl M (2003) Psoriasis. Lancet 361: 1197-1204.
6. van de Kerkhof PC (2006) Consistent control of psoriasis by continuous long-term therapy: the promise of biological treatments. J Eur Acad Dermatol Venereol 20: 639-650.
7. Goldsmith DR, Wagstaff AJ (2005) Etanercept: a review of its use in the management of plaque psoriasis and psoriatic arthritis. Am J Clin Dermatol 6: 121-136.
8. Shear NH (2006) Fulfilling an unmet need in psoriasis: do biologicals hold the key to improved tolerability? Drug Saf 29: 49-66.
9. Strober BE, Clarke S (2004) Etanercept for the treatment of psoriasis: combination therapy with other modalities. J Drugs Dermatol 3: 270-272.
10. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, et al. (2005) British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. Br J Dermatol 153: 486-497.
11. Bos WE, Thio HB, Neumann HA, van der Fils L, Prens EP (2006) [New systemic treatments for psoriasis: etanercept, infliximab, adalimumab, efalizumab and alefacept]. Ned Tijdschr Geneeskd 150: 1065-1070.
12. Zhou H, Patel A, Parks V, Buckwalter M, Metzger D, et al. (2004) Absence of a pharmacokinetic interaction between etanercept and warfarin. J Clin Pharmacol 44: 543-550.
13. Zhou H, Mayer PR, Wajjula J, Fatenejad S (2004) Unaltered etanercept pharmacokinetics with concurrent methotrexate in patients with rheumatoid arthritis. J Clin Pharmacol 44: 1235-1243.
14. Zhou H, Parks V, Patel A, Le Coz F, Simcoe D, et al. (2004) Absence of a clinically relevant interaction between etanercept and digoxin. J Clin Pharmacol 44: 1244-1251.
15. Finlay AY, Khan GK (1994) Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. Clin Exp Dermatol 19: 210-216.
16. Shikir R, Bresnahan BW, Stone SP, Thompson C, Koo J, et al. (2003) Validity and reliability of patient reported outcomes used in psoriasis: results from two randomized clinical trials. Health Qual Life Outcomes 1: 53.
17. Chen MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ (1996) Skinex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. J Invest Dermatol 107: 707-713.
18. Prinz JC, Fitzgerald O, Boggs RJ, Foehl J, Robertson D, et al. (2011) Combination of skin, joint and quality of life outcomes with etanercept in psoriasis and psoriatic arthritis in the PRESTA trial. J Eur Acad Dermatol Venereol 25: 559-564.
19. Gordon KB, Langley RG, Leonard C, Toth D, Mentler MA, et al. (2006) Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 55: 598-606.
20. Menter A, Tyring SK, Gordon K, Kimball AB, Leonard CL, et al. (2008) Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol 58: 106-115.
21. Saurat JH, Stinl CG, Dubetler L, Papp K, Langley RG, et al. (2008) Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 158: 558-566.
22. Asahina A, Nakagawa H, Etob T, Ohtsuki M; Adalimumab M04-688 Study Group (2010) Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase III randomized controlled study. J Dermatol 37: 299-310.
23. Leonard CL, Powers JL, Matheson RT, Goffe BS, Zithik R, et al. (2003) Etanercept as monotherapy in patients with psoriasis. N Engl J Med 349: 2014-2022.

24. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, et al. (2003) A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 139: 1627-1632.

25. Papp KA, Tying S, Lahta M, Prinz J, Griffiths CE, et al. (2005) A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 152: 1304-1312.

26. Strohal R, Puig L, Chouela E, Tsai TF, Melin J, et al. (2013) The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). J Dermatolog Treat 24: 169-179.

27. van de Kerkhof PC, Segaert S, Lahta M, Luger TA, Karolyi Z, et al. (2008) Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol 159: 1177-1185.

28. Tyring S, Gottlieb A, Papp K, Gordon K, Leonard C, et al. (2006) Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 367: 29-35.

29. Palter AS, Siegfried EC, Langley RG, Gottlieb AB, Pariser D, et al. (2008) Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med 358: 241-251.

30. Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, et al. (2012) Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. J Am Acad Dermatol 67: 86-92.

31. Gottlieb AB, Leonard C, Kerdell F, Mehlis S, Olds M, et al. (2011) Efficacy and safety of biakunin vs. etanercept in patients with moderate to severe chronic plaque psoriasis. Br J Dermatol 165: 652-660.

32. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gott R, et al. (2010) Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 362: 118-128.

33. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, et al. (2004) Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomised, double-blind, placebo-controlled trial. J Am Acad Dermatol 51: 534-542.

34. Reich K, Nestle FQ, Papp K, Ortonne JP, Evans R, et al. (2005) Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 366: 1367-1374.

35. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, et al. (2007) A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 56: 31.

36. Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, et al. (2005) Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 367: 29-35.

37. Leonard CL, Kimball AB, Papp KA, Yelding N, Guzzo C, et al. (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial. J Am Acad Dermatol 59: 972-980.

38. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, et al. (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 371: 1655-1674.

39. Igarashi A, Kato T, Kato M, Song M, Nakagawa H (2012) Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol 39: 242-249.

40. Tsai TF, Ho JC, Song M, Szapary P, Guzzo C, et al. (2011) Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci 63: 154-163.

41. Krueger GG, Langley RG, Finlay AT, Griffiths CE, Woolley JM, et al. (2005) Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. Br J Dermatol 153: 1192-1199.
61. Puig L, López A, Villarrasa E, García I (2013) Efficacy of biologics in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials with different time points. J Eur Acad Dermatol Venereol.

62. Schmitt J, Rosumek S, Thomaschewski G, Sporbeck B, Haufe E, et al. (2014) Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol 170: 274-303.

63. Gnisci D, Kragballe K, Dam TN, Skov L (2011) Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Br J Dermatol 164: 1091-1096.

64. Armstrong AW, Harskamp CT, Armstrong EJ (2013) Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. JAMA 148: 84-91.

65. Armstrong EJ, Harskamp CT, Armstrong AW (2013) Psoriasis and major cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc 2: 00062.

66. Miller IM, Ellerick C, Yazdanyar S, Jemec GB (2013) Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. J Am Acad Dermatol 69: 1014-1024.

67. Hontu C, Pouplard C, Brenaut E, Bametche T, Misery L, et al. (2013) Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol 27 Suppl 3: 12-29.

68. Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, et al. (2011) Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. JAMA 306: 864-871.

69. Pouplard C, Brenaut E, Horreau C, Bametche T, Misery L, et al. (2013) Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies. J Eur Acad Dermatol Venereol 27 Suppl 3: 36-46.

70. Patel RV, Clark LN, Lebowitz M, Weinberg JM (2009) Treatments for psoriasis and the risk of malignancy. J Am Acad Dermatol 60: 1001-1017.

71. Kamangar F, Neuhaus IM, Koo JY (2012) An evidence-based review of skin cancer rates on biologic therapies. J Dermatolog Treat 23: 305-315.

72. van Lüning PP, Driessen RJ, Berends MA, Boezeman JB, van de Kerkhof PC, et al. (2012) Safety of treatment with biologics for psoriasis in daily practice: 5-year data. J Eur Acad Dermatol Venereol 26: 283-291.

73. Mariette X (2010) Lymphoma, rheumatoid arthritis, and TNFAlpha antagonists. Joint Bone Spine 77: 195-197.

74. García S, Demengeot J, Benito-García E (2013) The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 72: 1947-1955.

75. Maneiro JR, Salgado E, Gomez-Reino JJ (2013) Immuneogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis. JAMA Intern Med 173: 1416-1428.

76. Leonardi C, Papp K, Strober B, Reich K, Asahina A, et al. (2011) The long-term safety of adalimumab treatment in moderate to severe psoriasis: a comprehensive analysis of all adalimumab exposure in all clinical trials. Am J Clin Dermatol 12: 321-337.

77. Burmester GR, Panaccione R, Gordon KB, McIlraith M, Jacerad AP (2013) Adalimumab: long-term safety in 23 458 patients from global clinical trials. Clin Dermatol 12: 321-337.

78. Papp KA, Poulin Y, Bissonnette R, Bourcier M, Toth D, et al. (2012) Assessment of the long-term safety and effectiveness of etanercept for the treatment of psoriasis in an adult population. J Am Acad Dermatol 66: 33-45.

79. Pariser DM, Leonardi CL, Gordon K, Gottlieb AB, Tying S, et al. (2012) Integrated safety analysis: short- and long-term safety profiles of etanercept in patients with psoriasis. J Am Acad Dermatol 67: 245-256.

80. Kimball AB, Pariser D, Yamauchi PS, Menter A, Teller CF, et al. (2013) OBSERVE-S interim analysis: an observational postmarketing safety registry of etanercept for the treatment of psoriasis. J Am Acad Dermatol 68: 756-764.

81. Tsai TF, Ho V, Song M, Szapary P, Kato T, et al. (2012) The safety of ustekinumab treatment in patients with moderate-to-severe psoriasis and latent tuberculosis infection. Br J Dermatol 167: 1145-1152.

82. Papp KA, Griffiths CE, Gordon K, Lebwohl M, Szapary PO, et al. (2013) Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol 168: 844-854.

83. Tsellos T, Kyrigidis A, Zouboulis CC (2013) Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: a meta-analysis of randomized controlled trials. J Eur Acad Dermatol Venereol 27: 622-627.

84. Tsellos T, Kyrigidis A, Trigoni A, Zouboulis CC (2012) Association of ustekinumab and briakinumab with major adverse cardiovascular events: An appraisal of meta-analyses and industry sponsored pooled analyses to date. Dermatoendocrinol 4: 320-323.

85. (2013) Scientific Discussion Humira. European Medicines Agency.

86. Burst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, et al. (2003) Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 30: 2563-2571.

87. Keystone EC, Kavanagh AF, Sharp JT, Tannenbaum H, Hua Y, et al. (2004) Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 50: 1400-1411.

88. Gottlieb AB, Leonardi CL, Goffe BS, Ortonne JP, van der Kerkhof PC, et al. (2006) Etanercept monotherapy in patients with psoriasis: a summary of safety, based on an integrated multistudy database. J Am Acad Dermatol 54: 92-100.

89. Gisondi P, Cazzaniga S, Chimenti S, Giannetti A, Maccarone M, et al. (2013) Metabolic abnormalities associated with initiation of systemic treatment for psoriasis: evidence from the Italian Psicore Registry. J Eur Acad Dermatol Venereol 27: 30-41.

90. Lebwohl M, Leonardi C, Griffiths CE, Prinz JC, Szapary PO, et al. (2012) Long-term safety experience of ustekinumab in patients with moderate-to-severe psoriasis (Part I of II): results from analyses of general safety parameters from pooled Phase 2 and 3 clinical trials. J Am Acad Dermatol 66: 731-741.

91. Gordon KB, Papp KA, Langley RG, Ho V, Kimball AB, et al. (2012) Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (Part II of II): results from analyses of infections and malignancy from pooled phase II and III clinical trials. J Am Acad Dermatol 66: 742-751.

92. Tan JY, Li S, Yang K, Ma B, Chen W, et al. (2011) Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: a meta-analysis. J Dermatolog Treat 22: 323-336.