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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.

	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.

Psoriasis

Psoriasis is a frequently occurring inflammatory condition of the skin. Its prevalence in the Netherlands is estimated at 2-3%. This review focusses 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 ditranol [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 acitretine. 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].

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Indication	Ada	Eta	Inf	Ust
Plaque psoriasis	50%	50%	50%	50%
Psoriatric arthritis	20%	20%	20%	20%
Rheumatoid arthritis	10%	10%	10%	
Spondylitis ankylopoetica	10%	10%	10%	
Inflammatory bowel disease	10%		10%	
Total	100%	90%	100%	70%

Table 2: The percentage of the maximum score for approved indications.

Selection Criteria

Approved Indications

The number of licensed indications is a good measure of the applicability and documentation of the drugs. Although this analysis is limited to the treatment of plaque psoriasis, the fact that a drug is approved for (almost) all indications listed below is, from a formulary point of view, advantageous to another drug, which is approved for only one or two applications.

The percentage of the maximum score for approved indications was obtained as follows (Table 2):

Indication	Maximum Score (%)
Plaque psoriasis	50%
Psoriatric arthritis	20%
Rheumatoid arthritis	10%
Spondylitis ankylopoetica	10%
Inflammatory bowel disease	10%

Drug interactions

Interactions play a role only in patients who use other drugs which may interact with biologicals. However, it is a relevant criterion from a formulary point of view.

The score for each drug was dependent on the frequency and severity of observed drug interactions.

Clinical efficacy

Clinical efficacy is always a very important selection criterion for any group of drugs. The score for each drug was derived from the results of double-blind comparative studies.

Safety

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 clinical studies.

Dosage frequency

Subcutaneous administration is more patient-friendly than iv administration. Twenty percent is deducted for iv infusion compared to sc.

Documentation

The score for this criterion was divided over 4 sub criteria. The first two sub 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. 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.

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.

Number of patients in these 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.

Number of years marketed

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 year that the product is available on the market.

Number of patients treated worldwide

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 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 cyclosporine, 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 immunomodulatory, 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.

Psoriatric 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-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 therapy 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 ciclosporin, methotrexate (MTX) and PUVA (psoralen and ultraviolet A).

Psoriatic arthritis: Ustekinimab, 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.

It is recommended that therapeutic infectious agents 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 dermal 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 is 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 biologicals	25%	[19]
Adalimumab	40 mg/2 wk (+ load)				29%	
Placebo					28%	
Adalimumab	40 mg/2 wk (+load)	Dermal corticoster.	PASI-75	13%	26%	[20]
Placebo				12% (biologicals)	26%	
Adalimumab	40 mg/2 wk (+load)	Derma corticoster.	PASI-75	No biological or methotrexaate	34%	[21]
Methotrexaat	7,5 - 25 mg oral				32%	
Placebo					28%	
Adalimumab	40 mg/2 wk	Dermal corticoster.	PASI-75	No biological	43%	[22]
Adalimumab	40 mg/2 wk (+ load)				48%	
Adalimumab	80 mg/2 wk				46%	
Placebo					47%	
Etanercept	25 mg/wk	Dermal corticoster.	PASI-75	76% (systemic)	28%	[23]
Etanercept	25 mg 2x/wk				29%	
Etanercept	50 mg 2x/wk				30%	
Placebo					29%	
Etanercept	25 mg 2x/wk	Tar Dermal corticoster.	PASI-75	39%	30%	[24]
Placebo				36% (MTX)	34%	
Etanercept	25 mg 2x/wk	Emollients Tar Dermal corticoster.	PASI-75	35%	23%	[25]
Etanercept	50 mg 2x/wk			38%	25%	
Placebo				39% (MTX)	20%	
Etanercept	50 mg 1x/wk	Emollients Tar Dermal corticoster.	PASI-75		33%	[26]
Etanercept	50 mg 2x/wk				33%	
Etanercept	50 mg 1x/wk	Emollients Tar	PASI-75		27%	[27]
Placebo					30%	
Etanercept	50 mg 2x/wk	Dermal corticoster.	PASI-75		27%	[28]
Placebo					27%	
Etanercept	0,8 mg / kg / wk	Dermal corticoster.	PASI-75	55%	20%	[29]
Placebo (kinderen + adolescenten)				59%	21%	
Etanercept	50 mg 1 x pw	Dermal corticoster.	Percentage improved PASI score	6.7% anti TNF	16%	[30]
Placebo	1x/wk (week 13-24, first 12 wk etanercept 50 mg 2 x pw				15%	
Etanercept	50 mg 2 x pw	Dermal corticoster.	PASI-75	14% biol	24%	[31]
Briakinumab	200 mg, weeks 0 and 4, 100 mg at week 8			11% biol	24%	
Placebo				15% biol	24%	
Etanercept	50 mg 2x/wk	Dermal corticoster.	PASI-75	12% biol	23%	[32]
Ustekinumab	45 mg at week 0 + 4			12% biol	27%	
Ustekinumab	90 mg at week 0 + 4			10% biol	26%	
Infliximab	3 mg/kg	Emollients Tar Salicylic acid	PASI-75	87%	29%	[33]
Infliximab	5 mg/kg (weeks 0, 2 and 6)			89%	25%	
Placebo				82% (systemic)	26%	
Infliximab	5 mg/kg (weeks 0, 2 and 6)	Dermal corticoster.	PASI-75	42%	19%	[34]
Placebo				46% (MTX)	18%	
Infliximab	3 mg / kg	Dermal corticosteroid	PASI-75 PASI-90	33%	28%	[35]
Infliximab	5 mg / kg (weeks 0, 2 en 6)			35%	29%	
Placebo				34% (MTX)	28%	
Infliximab	5 mg / kg (weeks 0, 2 en 6)	Dermal corticosteroid	PASI-75 (10 wk)			[36]
Placebo						
Ustekinumab	45 mg	Dermal corticosteroid	PASI-75	51% biologicals	27%	[37]
Ustekinumab	90 mg				25%	
Placebo					28%	
Ustekinumab	45 mg	Dermale corticosteroid	PASI-75	38% biologicals	26%	[38]
Ustekinumab	90 mg				27%	
Placebo					26%	

Ustekinumab	45 mg	Dermal corticosteroid	PASI-75	0% biologicals	47%	[39]
Ustekinumab	90 mg				47%	
Placebo					50%	
Ustekinumab	45 mg	Dermal corticosteroid	PASI-75	18% biologicals	42%	[40]
Placebo					36%	

Table 3: Double blind studies, methodology - part I

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 de 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 etnercept 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 psoriatric 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 Adalimumab Placebo	45 (66% M)	19	16	[19]
Adalimumab Placebo	45 (66% M)	18	19	[20]
Adalimumab Methotrexaat Placebo	43 42 41	19	19	[21]
Adalimumab Adalimumab Adalimumab Placebo	45 (85% M)	14	28	[22]
Etanercept Etanercept Etanercept Placebo	45 (67% M)	19	18	[23]
Etanercept Placebo	47 (63% M)	22	19	[24]
Etanercept Etanercept Placebo	45 (66% M)	19	16	[25]
Etanercept Etanercept Placebo	44 (70% M)	17	21	[26]
Etanercept Placebo	45 (58% M)	198	21	[27]
Etanercept Placebo	46 (67%)	20	18	[28]
Etanercept Placebo	13 (51% M)	6	16	[29]
Etanercept Placebo	41 (55% M)	14	15	[30]
Etanercept	43 (70%)	17	19	[31]
Briakinumab	44 (69%)	16	18	
Placebo	44 (65%)	19	19	
Etanercept	46	19	29	[32]
Ustekinumab	45	19	21	
Ustekinumab	45	19	20	
Infliximab Infliximab Placebo	45 (70%)	17	19	[33]
Infliximab Placebo	43 (71%)	18	23	[34]
Infliximab	43 (66% M)	18	20	[35]
Infliximab	45 (65% M)	19	20	
Placebo	44 (69% M)	18	20	
Infliximab	39 (71% M)	16	24	[36]
Placebo	40 (78% M)	16	25	
Ustekinumab	45 (69% M)	20	21	[37]
Ustekinumab	46 (68% M)	20	20	
Placebo	45 (72% M)	20	20	
Ustekinumab	45 (69% M)	19	19	[38]
Ustekinumab	47 (67% M)	20	20	
Placebo	47 (69% M)	21	19	
Ustekinumab	45 (83% M)	16	30	[39]
Ustekinumab	44 (76% M)	17	29	
Placebo	49 (84% M)	16	30	
Ustekinumab	41 (82% M)	12	25	[40]
Placebo	40 (88% M)	14	23	

Table 4: Double blind studies, methodology - part II

Medicine	OLS Minimal or clean	PGA Excellent or clean	DLQI Improved	VAS Improved	PSA Improved	Ref.
Adalimumab		76%				[19]
Adalimumab		49%				
Placebo		NR				
Adalimumab		60%				[20]
Placebo		16%				
Adalimumab			-4,6			[22]
Adalimumab			-5,5			
Adalimumab			-7,0			
Placebo			+1,3			
Etanercept			47%			[23]
Etanercept			51%			
Etanercept			61%			
Placebo			11%			
Etanercept			64%			[24]
Placebo			7%			
Etanercept		37%	72%			[25,41]
Etanercept		54%	77%			
Placebo		3%	21%			
Etanercept		38%	54%			[27]
Placebo		4%	5%			
Etanercept			69%			[28]
Placebo			22%			
Etanercept		40%	21%			[31]
Briakinumab		71%	36%			
Placebo		3%	3% (score 0)			
Infliximab		72%	70%			[33,42]
Infliximab		90%	80%			
Placebo		10%	16%			
Infliximab		83%	75%			[34]
Placebo		4%	3%			
Infliximab		73%	67%			[35]
Infliximab		75%	70%			
Placebo		0% (wk 10)	0% (wk 10)			
Infliximab			57%			[36]
Infliximab			10%			
Placebo						
Ustekinumab		68%	76%			[37]
Ustekinumab		74%	79%			
Placebo		0%	4%			
Ustekinumab		60%	72%			[38]
Ustekinumab		62%	75%			
Placebo		4%	5%			
Ustekinumab		71%	70%			[40]
Placebo		8%	7%			

Table 5: Double-blind studies, results at 12 weeks - part I

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	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 (+ loadd)	814/783	76%	37%	68%		[20]
Placebo		398/355	15%	2%	5%		
Adalimumab	40 mg/2wk (+ load)	108/103	80%	52%	50%	88%	[21]
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%	
Adalimumab	40 mg/2 wk	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%	[24]
Placebo		55/40	1%	0%	2%	11%	
Etanercept	25 mg 2x/wk	196/191		11%	34%	64%	[25]
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%	[26]
Etanercept	50 mg 2x/wk	136/124		29%	62%	68%	
Etanercept	50 mg 1x/wk	96/90	55%	14%	38%	69%	[27]
Placebo		46/36	-9%	2%	2%	9%	
Etanercept	50 mg 2x/wk	311/305		21%	47%	74%	[28]
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 pw1x/wk	62/49	87%	25%	59%	85%	[30]
Placebo		62/49	20% (PSSI)	2%	5%	7%	
Etanercept	50 mg 2 x pw	141		20%	56%		[31]
Briakinumab	200 mg, weeks 0 and 4, 100 mg at week 8	138		60%	82%		
Placebo		68		2%	7%		
Etanercept	50 mg 2x/wk	347		23%	57%		[32]
Ustekinumab	45 mg at weeks 0 + 4	209		36%	68%		
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%	

Ustekinumab	45 mg	409	77%	42%	67%	84%	[38]
Ustekinumab	90 mg	411	82%	51%	76%	89%	
Placebo		410	5%	1%	4%	10%	
Ustekinumab	45 mg	64/64	73%	33%	59%	83%	[39]
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%	[40]
Placebo		60/55	3%	2%	5%	13%	

Table 6: Double-blind studies, results at 12 weeks-part II.

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 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 ustekunimab 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 Infliximab

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 en 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, 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 reached 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 (235). Infliximab improved disease-related quality of life as well [55].

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 PASI-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].

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 7: Etanercept 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	31/26/27	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

Table 8: Ustekinumab 45 and 90 mg vs placebo.

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 ustekunimab 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 ustekinunab 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. Etanerept 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 the drugs are combined with methotrexate or azathioprine. This combination is usual in the treatment of rheumatoid arthritis and inflammatory bowel disease, respectively, but much less so in the treatment of psoriasis.

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 1 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 for rheumatoid arthritis (4.6 per 100 patient years). Active tuberculosis was seen in 0.1 per 100 years. Mortal adverse events occurred in 0.2 per 100 patient years [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 pa-tient-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	78/63	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 adalumumab-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 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 etancercept [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 (and 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.

Study	Total incidence (%)	Withdrawal (%)	Dyspepsia (%)	Nausea (%)	Pain at injection site (%)
19	70/67	5/2	4/0	5/6	9/6
20	62/55	1.7/2.0			0.17/0.22 (cases per 100 years)

Table 10: Adalimumab vs placebo.

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

Table 11: De documentation concerning randomised clinical trials is summarised below.

	Dosage frequency	Score
Adalimumab	40 mg per two weeks, subcutaneously, after an 80 mg loading dose.	60%
Etanercept	25 mg twice per week subcutaneously or 50 mg twice per week subcutaneously during12 weeks, followed by 25 mg twice per week. Total duration of treatment 24 weeks.	20%
Infliximab	5 mg / kg as intravenous infusion during 2 hours, at baseline, 2 and 6 weeks and every 8 weeks thereafter.	80%
Ustekinumab	45 mg subcutaneously, repeated after 4 weeks, and then every 12 weeks. 90 mg is used in patients with body weight of 100 kg or above.	100%

Table 12: Dosage frequency.

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
Approved indications	40	40	36	40	32
Drug Interactions	60	54	54	54	54
Clinical efficacy	400	280	200	320	320
Safety	300	240	240	240	240
Dosage frequency	100	60	20	80	100
Documentation	100	79	88	80	68
Total	1000	723	638	814	814

Table 14: SOJA score.

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