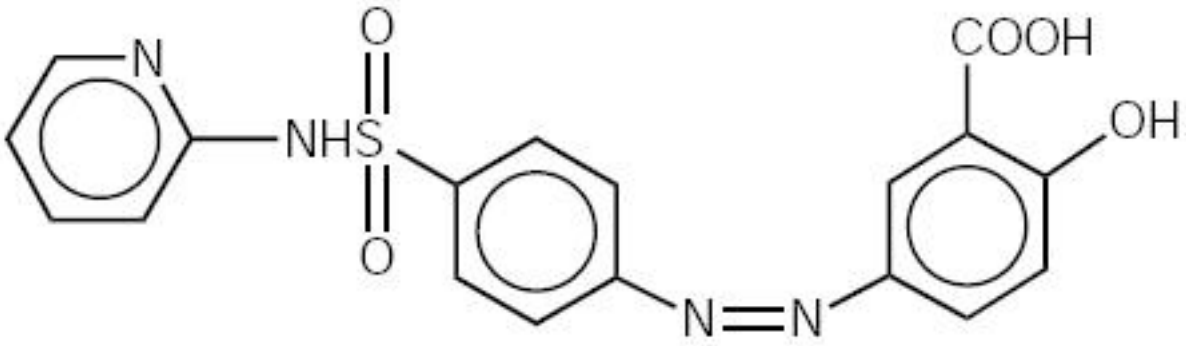
Guideline
Off-label drug use in dermatology
The GRADE approach



Guideline title: Off-label drug use in dermatology

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This guideline is formulated by a working group of the Dutch Society of Dermatology and Venereology, which was installed for this purpose. Subsequently, the guideline was approved by the general assembly of the Society. The guideline represents the current professional standard at the time of the guideline was drawn up.

The guideline contains recommendations of a general character. It is possible that these recommendations are not applicable in an individual case. The suitability and application of the guideline in practice is the responsibility of the treating physician. Facts or circumstances may occur in which it may be advisable to deviate from the guideline in the interest of the patient.

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List of conflicts of interest
None reported

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I. GENERAL INTRODUCTION

Objective
A guideline is a document with recommendations to support patient care in daily practice. The guideline is based on results of searching scientific literature and subsequent consensus of the working group, aimed at deciding on the appropriate medical intervention. A guideline and the documents derived from it (e.g. patient information), give recommendations for the treatment of patients, including psychosocial care.

Intended users
The guideline is intended for medical professionals, including: dermatologists, general practitioners and pharmacists. A text derived from the guideline is available for patients.

Composition of the working group
A working group was appointed for the development of the guideline. This group consisted of dermatologists, researchers, pharmacists and a general practitioner from Lareb (the Dutch pharmacovigilance centre). During the formation of the group, the geographical distribution of its members was taken into account as well as a balanced representation of academic and non-academic employment. The members of the working group have acted independently and no conflict of interest has been reported.

Methodology of the working group
During a period of 2 year 5 meetings the working group worked on a draft guideline. An expert group made a bottleneck analysis during the preparatory phase. The expert group compiled a list of drugs which are frequently subscribed for off-label use in dermatology. The listed drugs were prioritized according to frequency of use and occurrence of potential serious adverse events. The members of the working group had the opportunity to propose alterations in the list of selected drugs The members of the working group agreed on composing a guideline about the off-label use of the following six selected drugs:

azathioprine
cyclosporin
methotrexate
sulfasalazine
dapsone
hydroxychloroquine.

The working group agreed that the outcomes efficacy/effectiveness and safety are crucial for decision making. The working group started by making a draft guideline for azathioprine and decided that the applied methods would serve as a blueprint for the other five drugs. Useful literature was found by systematic searches and by checking of references (see "Methodology of literature search"). The members of the working group assessed the relevant literature with regard to content and quality. Subsequently, conclusions were drawn and recommendations were made for off-label use of the selected drugs by the members of the working group. The final version of the guideline was approved by all scientific societies involved on November 2012

Methodology of literature search
Research question
For each selected drug a research question according to PICO was made.
PICO stands for:

- Participants/population: population of patients with a dermatological disease who are treated with a drug that is not registered for the use in this particular disease.
- Intervention: the selected drug.
- Comparison: any other treatment (e.g. other systemic therapy, placebo, quality of life intervention), in case of lack of a control group; no other treatment.
- Outcome: safety and/or efficacy.

Search strategy
For each selected drug a standardized search was performed in the Medline (by PubMed) (1950-October 2009), EMBASE (1980- October 2009) and CENTRAL (until October 2009) databases. This search strategy was designed by a literature specialist of the department 'Professionele Kwaliteit van de Orde van Medisch Specialisten'. Also references of included articles were screened for eligibility.

Pre-exclusion with keywords
Since the goal of this guideline was to give an overview of off-label drug use, articles dealing with registered

indications were excluded. After the searches were uploaded in Reference Manager, articles labeled with possible keywords for exclusion were selected. A sample was taken of these selected articles to check if there were any relevant articles in that selection. The sample size was either 20 or 50 articles, depending on the number of articles labeled with a specific keyword. If the sample didn't contain any relevant articles, all the articles labeled with a specific keyword were excluded.

In the searches of cyclosporin, methotrexate, dapsone, hydroxychloroquine and sulfasalazine articles with the keywords 'case report' were excluded after a sample of 50 articles didn't reveal any relevant articles for inclusion.

In addition, articles with the following keywords were excluded after a sample of 20 articles didn't show any relevant articles:

Cyclosporine	**Dapsone**
- Transplantation	- Leprosy
- Transplantation immunology	- Mycobarterium leprae
- Transplantation immunology [Physiology]	- Pneumocystis carinii
- Acute graft rejection [Complication]	- Toxoplasmosis
- Acute graft rejection [Diagnosis]	- Spider
- Acute graft rejection [Drug therapie]	**Methotrexate***
- Acute graft versus host disease	- Psoriasis
- Bone Marrow Transplantation	- Reumathoid arthritis
- Breast cancer	- Leukemia
- Graft Survival	- Osteosarcoom
- Graft Recipient	- Lymphoma
- Kidney Graft	- Bladder
- Kidney Transplantation	- Breast Cancer
- Liver Transplantation	- Mycosis
- Proteinuria	- Multiple sclerosis
- Nephritis	- Colitis
- Irradiation	- Asthma
- Heart transplantation	- Cancer + skin + cutaneous
- Vitamin	**Sulfasalazine**
- Psoriasis	- Rheumatoid arthritis
Hydroxychloroquine:	- Arthritis
- Rheumatic disease	- Crohn
- Systemic lupus erythematosus	- Ulcerative colitis
- Discoid lupus erythematosus	
- Lupus erythematosus	
***** In the methotrexate search articles with the note 'review' were excluded after a sample of 20 articles didn't contain any relevant articles.	

An overall validation of this method was provided by the double search strategy on azathioprine. An initial/broad search (thus without using keywords) was compared with the search that used specific keywords for exclusion. Articles with the keywords 'case report', 'polymyositis' and 'idiopatic thrombocytopenic purpura' were excluded after a sample showed no relevant articles.
We found that all studies that were included in initial/broad search were present in the search using keywords for exclusion. This validates the method of excluding articles by using keywords.

Selection of articles

All articles with title and abstract referring to off-label treatment with the predefined drug in patients with dermatological diseases were selected. To determine eligibility, the full text of the selected articles was screened according to the predefined in-and exclusion criteria. Data on methodological quality, study characteristics, efficacy and safety were extracted by using a data extraction form. All stages of literature selection and data extraction were performed by two independent reviewers. Disagreements about study selection and data extraction were solved by discussion.

In- and exclusion criteria

Selection of the articles was performed by using the following pre-defined in- and exclusion criteria.
Inclusion criteria:

- The article concerns the selected drug and
- The selected drug is used in the treatment of a dermatological disease for which that particular drug is not registered in the Netherlands (up to date until 01-10-2009).

Exclusion criteria:

- Case reports with less than 5 subjects*
- Lack of data on safety and efficacy
- Articles concerning treatment other than systemic treatment with the selected drug
- Animal studies
- In vitro studies
- Double publications
- Articles concerning diseases that are primarily treated by other specialists
- Language other than English, French, German and Dutch

No restrictions were imposed regarding age, gender, skin type and number of subjects in a study and date of publication.
***** A random sample of the excluded articles was taken to check if any relevant adverse events were missed.

Data-extraction

Of all the included articles, data were extracted by two independent reviewers. This was done by using a standardized data extraction form. Discrepancies were discussed until agreement was reached.
Data- extraction was performed on:

- Methodological quality
- Demographics
- Efficacy
- Safety

Methodological quality

Randomized controlled trials (RCT's) were assessed following the criterion grading system described in the *Cochrane Handbook for systematic reviews of interventions 5.0.0* (updated February 2008). To assess the risk of bias within included RCT's, the following parameters for methodological quality were used; sequence generation, concealment of allocation, blinding (of participants, researchers and outcome assessment), reporting of incomplete data, presence of selective outcome reporting and other potential threats to validity.

The methodological quality of cohort studies was assessed by using the checklists for cohort studies described by the Dutch Cochrane Centre.

Demographics

Data of demographics were extracted concerning:

- Study design: randomized? controlled? prospective, retrospective?
- Treatment arms
- Disease of the subjects: severity, stage, subtype, duration
- Previous medications
- Diagnostics: what was the method of diagnosis? Clinical, histopathological, other diagnostic criteria?
- Subjects: number, male/female, age, subgroups (e.g. age, ethnic origin)
- Duration of treatment
- Duration of follow up
- Concomitant medication
- Dosing schedule of the selected drug

Efficacy/effectiveness

- Used outcome parameters: clinical assessment, global assessment, quality of life measurement,

laboratory markers, onset of effect, duration of remission, relapse rate, etc.

- Severity outcomes: the result of the used outcome parameters. Differences between baseline and end of the study and between treatment groups.

Safety
Safety is an important issue in off-label use of medication. The working group scored all adverse events, including a special focus on serious adverse effects. Within the included studies, every study that reported (serious) adverse events was taken into account. Adverse events reported in RCT's or cohorts will be compared with the adverse events that occurred in the control group. If possible a relative risk will be calculated.

Extracted safety data:

- Adverse events: which? how many? at what time during treatment or after treatment?
- Serious adverse events: which? how many? at what time during treatment or after treatment?
- Withdrawals due to adverse events?

An Adverse Event (AE) was defined as an unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless whether it is considered related to the medical treatment or procedure, that occurs during the course of the study.

A Serious Adverse Events (SAE) was defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is reported in the study as such.

Handling of the data
Extracted data will be presented in tables and with accompanying text per disease following standardized means.

Level of evidence
The description and assessment of the articles according to the data extraction (see above) are listed in separate sections under the headers "Safety data off -label sulfasalazine" or "Efficacy/effectiveness data off-label sulfasalazine" and in tables (see section Tables).
Not all data extracted from articles are equally valuable. Therefore every set of articles is summarised in a conclusion, in which the level of the evidence is indicated according to the GRADE system (see boxes below). Consequently the recommendations in this guideline are based on evidence generated by scientific research, with emphasis on the outcomes safety and effectiveness/efficacy. The search results that were used are up to date until at least 01-10-2009, unless stated otherwise.

GRADE system	
Type of evidence	Randomized trial = high Observational study = low Any other evidence = very low
Decrease* grade if	• Important inconsistency • Some or major uncertainty about directness • Imprecise or sparse data • High probability of reporting bias • Serious or very serious limitation to study quality
Increase grade if	• Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) • Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) • Evidence of a dose response gradient (+1) • All plausible confounders would have reduced the effect (+1)
*Each quality criterion can reduce the quality by one or, if very serious, by two levels.	

Conclusion

- High = further research is very unlikely to change our confidence in the estimate of effect
- Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low = any estimate of effect is very uncertain.

Development of the recommendations

For the development of a recommendation, other aspects than scientific evidence are also of importance, such as: patient preferences, availability of special techniques or expertise, organisational aspects, social consequences or costs. Known adverse events mentioned in the summary of product characteristics (SPC) are also taken into account, as far as they were not already distilled from scientific literature. These aspects are discussed after the conclusion(s). On the basis of literature, the conclusion is here placed in the context of daily practice, and the pros and cons of the various treatments are balanced against each other. The final formulated recommendation is the result of the available evidence in combination with these considerations and can be formulated as a weak or strong recommendation in favour of a certain therapy or as a weak or strong recommendation against a certain therapy (see box below). The aim of this procedure and the formulation of the guideline using this 'format' is to enhance the transparency of the guideline. It leaves room for an efficient discussion during the meetings of the working group and moreover, it improves clarity for the user of the guideline.

Recommendation

- Strong = if clinicians, based on the available evidence, are very certain that benefits do, or do not, outweigh risks or burdens, they will make a strong recommendation.
- Weak = if clinicians, based on the available evidence, believe that benefits and risks or burdens are finely balanced, or if considerable uncertainty exists about the magnitude of benefits and risks, they must make a weak recommendation.

Implementation and evaluation

During the various phases of developing the draft guideline, the implementation of the guideline and the actual workability of the recommendations are taken into account as much as possible. The guideline is distributed to all relevant professional groups and hospitals through the internet and in various medical journals attention will be given to the guideline.

Legal significance of guidelines

Guidelines are not legal regulations, but scientifically and broadly based insights and recommendations which medical professionals should meet in order to provide qualitatively good medical care. Since guidelines assume dealing with 'average patients', medical professionals can deviate in individual cases from the guidelines when necessary. Deviation from the guideline – if required by the situation of the patient – is sometimes even imperative. However, intentional deviation from the guideline should be explained and documented in the medical record and, when necessary, with consent of the patient. . Article 68 of the Dutch Medicines Act of juli 1st 2007 states the following about off-label drug prescription: 'Prescribtion of drugs outside of the registered indications of the Board is only licit when this is supported by guidelines and protocols developed by the profession. When the guidelines and protocols are still in the developmental stage, consultation between the attending physician and the pharmacist is required.' (Original text: *'Het buiten de door het College geregistreerde indicaties voorschrijven van geneesmiddelen is alleen geoorloofd wanneer daarover binnen de beroepsgroep protocollen of standaarden zijn ontwikkeld. Als de protocollen of standaarden nog in ontwikkeling zijn, is overleg tussen de behandelend arts en de apotheker noodzakelijk.'*)

Guideline validation

The guideline was authorised by:

- Dutch Society of Dermatology and Venereology (NVDV)
- Royal Dutch Association for the Advancement of Pharmacy (KNMP)
- Dutch Association of Hospital Pharmacists (NVZA)

Guideline maintenance

A guideline can only be leading, if it is maintained on a continuous base, with systematic monitoring of medical scientific literature as well as regular contributions from clinical practice .In case of important developments, it can be decided that the complete working group shall meet to propose amendments, which will be distributed among the various professional groups. A revision will be planned at least every five years.

II. SULFASALAZINE

Introduction
Sulfasalazine was developed in 1940 specifically to treat rheumatoid arthritis. Sulfasalazine is spilt in the colon into sulfpyridine en mesalazine under influence of bacterial enzymes. Mesalazine is responsible for the therapeutic effect in inflammatoiry bowel disease. The mechanism is unclear. It is probably founded on the direct local effect on the mucosa of the colon whereby the arachidonacid metabolism is influenced,which slows down the prostaglandinesynthesis. Sulfonamide sulfapyridine has barely any effect , it functions as a carrier, but contributes to most of the side effects. In rheumatoid arthritis sulfapyridine and/or sulfasalazine is probably responsible for the effect, mesalazine is definitely not responsible for the effect.

Sulfasalazine is used as an immunosuppressant either alone or, more commonly, in combination with other agents which influence the immune response. Therapeutic effect can include a steroid-sparing effect, thereby reducing the toxicity associated with high dosage and prolonged usage of corticosteroids. Sulfasalazine, either alone or more usually in combination with corticosteroids and/or other drugs and procedures, has been licensed in the Netherlands for treatment of the following diseases:

- severe rheumatoid arthritis
- ulcerative colitis and Crohn's disease

Research question
What is the safety and efficacy of off-label treatment with sulfasalazine in patients with dermatological diseases?

Methods literature search
Literature search
Between September 2009 and October 2009, a literature search in Medline (1950-2009), EMBASE (1980-2009) and CENTRAL was performed. As main search strategy 'sulfasalazine' and synonyms (not the active metabolites) were used in combination with all skin diseases; for example the search strategy in Medline:

1 derm*.jn.
2 Sulfasalazin/
3 (sulfasalazin* or salazopyrine* or azulfidine*, asulfidine*, azufadine*, pyralin*, ucine*, ulcol*, colo-pleon*, pleon*, salicylazosulfapyrindine* or sulphasalazine*).ab.
4 (sulfasalazin* or salazopyrine* or azulfidine*, asulfidine*, azufadine*, pyralin*, ucine*, ulcol*, colo-pleon*, pleon*, salicylazosulfapyrindine* or sulphasalazine*).ti.
5 (sulfasalazin* or salazopyrine* or azulfidine*, asulfidine*, azufadine*, pyralin*, ucine*, ulcol*, colo-pleon*, pleon*, salicylazosulfapyrindine* or sulphasalazine*).kw.
6 4 or 2 or 5 or 3
7 6 and 1
8 exp Skin Diseases/
9 6 and 8
10 7 or 9
11 limit 10 to (humans and (dutch or english or french or german))

There was no limit with respect to the date of the publication. Literature references of all relevant articles found were checked in order to find additional articles. In addition, data published in Micromedex concerning sulfasalazine were studied to retrieve further potential relevant references regarding safety in off-label use. None were found.

Study selection and data extraction
All articles with title and abstract referring to off-label treatment with sulfasalazine of patients with dermatological diseases were selected by two reviewers. Next, to determine eligibility, the full text of the selected articles was screened by two reviewers. Disagreements were solved by discussion. Predefined in- and exclusion criteria are described in detail in the introduction section. Data on methodological quality, demographics, efficacy and safety were extracted by two independent reviewers using a data extraction form. Disagreements about data extraction were solved by discussion.

Results of the literature search

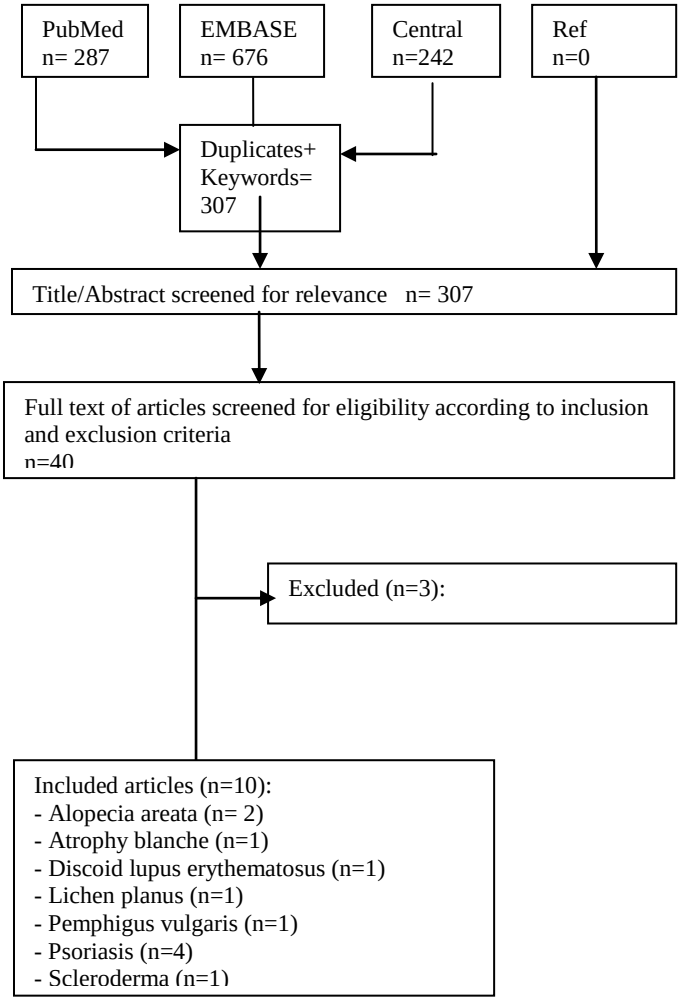
Search

Figure 1 summarizes the selection process. An initial search retrieved 1026 articles. Articles were selected using keywords. A random sample of 50 articles was taken from the publications that were selected. The random sample was screened on missed relevant data regarding effectiveness and adverse effects. If this was not the case, the selected articles were excluded. Articles with the following keywords were excluded; case report, rheumatoid arthritis, arthritis, crohn, ulcerative colitis.

After exclusion of these articles 307 articles were left.

After screening title and abstract for eligibility, 214 articles were selected. Then, after screening the full texts of the articles, 74 articles were considered relevant.

Figure 1. Flowchart summarizing the selection process for studies concerning off-label treatment with azathioprine in dermatological diseases.



General treatment considerations

Nota bene!

The text in this section is based on the summary of product characteristics (SPC) text of Salazopyrine 500 mg tablets and Sulfasalazine 500 mg tablets 25 mg ® (last update 28-11-2011). The text was modified by the working group to reflect the best practice in the Netherlands at the time the guideline was made. Modifications are depicted in a grey box. It is advisable to consider the recommendations when prescribing sulfasalazine, however the text is not intended as a substitute for the complete SPC text. The complete and up to date Dutch SPC text is available on www.cbg-meb.nl.

Dosage in other conditions then organ transplant patients - adults and children

- In general, starting dosage is from 0,5 g to 7 g/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks) and tolerance.
- When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs within 3 months, consideration should be given to withdrawing sulfasalazine .

Therapeutic response is evident after approximately 6-12 weeks

- The maintenance dosage required may range from less than 0,5 g/day to 7 g/day, depending on the clinical condition being treated and the individual patient response, including haematological tolerance.
- In patients with renal and/or hepatic insufficiency, dosages should be given at the lower end of the normal range (see Special Warnings and Precautions for Use for further details).

Use in the elderly (see also renal and/or hepatic insufficiency)
There is limited experience of sulfasalazine in elderly patients. Although the available data do not provide evidence that the incidence of side effects among elderly patients is higher than that among other patients treated with sulfasalazine, it is recommended that the dosages used should be at the lower end of the range.
Particular care should be taken to monitor haematological response and to reduce the maintenance dosage to the minimum required for clinical response.

Use in children (also see www.kinderformularium.nl)
Children that are younger than 8 years old should be dosed at 50 mg/kg/day.

Contraindications
Sulfasalazine is contra-indicated in patients known to be hypersensitive to sulfasalazine.

In addition (according to the Dutch 'Farmacotherapeutisch Kompas' (online available on www.fk.cvz.nl)

- Glucose-6-fosfaat-dehydrogenase-deficientie
- serious disrupted liver- or kidneyfunction.
- Hypersensitivity to sulfonamides and/or salicylates
- Patients with acute porfyrie; sulfonamiden can cause a acute attack
- Patients younger than 2 years of age

Special warnings and precautions for use

Monitoring
There are potential hazards in the use of sulfasalazine. It should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy. It is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly and more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly or at least at intervals of not longer than 3 months.

Complete blood counts should be repeated at least at intervals not longer than 3 months.

Patients receiving sulfasalazine should be instructed to immediately consult their doctor in case of evidence of fever, chills , unexpected bruising or bleeding or other manifestations of bone marrow depression (e.g. chest

pain, dizziness, fatigue, petechiae).
There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of sulfasalazine and prone to developing rapid bone marrow depression following the initiation of treatment with sulfasalazine. This problem can be exacerbated by co-administration TPMT prodrugs, such as azathioprine.

Bone marrow depression/myelotoxicity could also be exacerbated by co-administration of prodrugs such as azathioprine.

Sulfasalazine can cause kidneystones. Intake of sulfasalazine should be combined with the intake of sufficient fluids.

Renal and/or hepatic insufficiency
It has been suggested that the toxicity of sulfasalazine may be enhanced in the presence of renal insufficiency. Nevertheless, it is recommended that the dosages used should be at the lower end of the normal range and that haematological response should be carefully monitored. Dosage should be further reduced if haematological toxicity occurs. During the administration of sulfasalazine to patients with hepatic dysfunction, regular (two times a week in the first 8 weeks) complete blood counts and liver function tests should be undertaken. In such patients the metabolism of sulfasalazine may be impaired, and the dosage of sulfasalazine should therefore be reduced if hepatic or haematological toxicity occurs.

Interaction with other drugs and other forms of interaction

Antibiotics
Antibiotics, which influence the gastrointestinal tract, inhibit the transformation of sulfasalazine.

Salicytates, iron and colestyramine
Salicytates, iron and colestyramine can influence the absorbtion of the active particles of sulfasalazine.

Prodrugs of thiopurine-6-mercaptopurine
In vitro studies have shown that sulfasalazine inhibits thiopurine methyltransferase (TPMT). Eventhough the mechanism is unknown, bonemarrow depressions and leucopenia can occur when thiopurine6-mercaptopurine or its prodrug (azathioprine) are given simultaneously.

Coumarin derivatives
Sulfasalazine can intensify the anticoagulant effect of coumarins, when administered together.

Use in Pregnancy and Lactation
There is no evidence that the use of sulfasalazine is harmfull during pregnancy. But the risks and benefits should be considered very carefully. Sulfasalazine has been found in the colostrum and breast-milk of women receiving sulfasalazine treatment. There is no evidence that this is harmfull for the baby. Therefore sulfasalazine in a maximum of 2 g/day can be given during lactation.
The need for anti-conception in men during treatment is unclear and is currently subject of debate.

Efficacy and safety data

Alopecia Areata

Two case series by Aghaei *et al* and Rashidi *et al* were included.

Demography
Both Aghaei *et al* and Rashidi *et al* had one treatment arm with SSZ for patients with recalcitrant or severe Alopecia Areata.
Aghaei *et al* enrolled 26 patients (10 male and 16 female) with a mean age of 25 years and an age range from 16 to 35 years. Subjects did not receive any previous treatment. Treatment duration ranged from 6 to 24 months, depending on individual clinical improvement. Duration of follow-up is unknown.
Sulfasalazine started at 500 mg twice daily for 1 month, 1 gr twice daily for 1 month, and then 1.5 gr twice daily. The treatment was carried out for a further 3 months with the latter dose regimen. If no regrowth was observed after 6 months of treatment, the patient was considered to be a non-responder and was dropped from the study.
Rashidi *et al* enrolled 39 patients (26 male and 13 female) with a mean age of 25.5 years and an age range from 15 to 41 years. Treatment duration was 6 months and follow-up is unknown. Previous treatments were extensive and contained topical or intradermal corticosteroids and minoxidil for all the patients. 25 out of the 39 patients had the just mentioned medication in addition to PUVA (Psoralen plus UltraViolet A) as previous treatment. The dosage regimen was comparable to Aghaei *et al*; tablets were started at a dose of 1 gr daily, which was increased to 3 gr after 3 months of therapy, and continued for (up until) 6 months. The mean duration of previous treatment was 1.54 years for corticosteroids, 0.71 years for minoxidil and 0.5 years for PUVA.

Efficacy
Aghaei *et al* treated 22 patients with SSZ. Overall, 68.2% (15 of 22 patients) responded to therapy, thus had hair regrowth: 27.3% (6 of 22 patients) achieved complete hair regrowth (90%-100% terminal hair), and 40.9% (9 of 22 patients) had partial hair regrowth (10%-90% terminal hair). Of the 9 patients with partial response, 5 patients had 10%-20% regrowth, 2 patients had 30%-40%, 1 patient had 50%, and 1 patient had 60%-70% regrowth. Seven (31.8%) patients had no hair regrowth (<10% terminal hair regrowth; refractory). Results were statistically significant. Ten (45.5%) out of 22 patients suffered a complete or partial relapse either on maintenance treatment or following termination of therapy. Concomitant medication was never used.
Rashidi *et al* treated 39 patients with SSZ. Quantification of terminal hair regrowth was different compared to Aghaei *et al* making it difficult to give a relative comparison with Aghaei *et al*. Objective response to treatment was considered by more than 29% terminal hair regrowth. The range in the 'good to excellent response' was wider, 60% to 100% terminal hair regrowth. Good results were found in 10 patients (25.6%) and moderate hair regrowth in 12 patients (30.7%). There was no response to SSZ in 17 patients (43.5%). Of the 10 patients with good results, two showed recurrence a few months after hair regrowth, and there were three recurrences in patients with a moderate response.

Safety
Both Aghaei *et al* and Rashidi *et al* never described adverse events as serious.
In Aghaei *et al*, seven patients (31.8%) had adverse events. Adverse events were mostly side effects from SSZ treatment including gastrointestinal distress, rash, laboratory abnormalities and headache.
Rashidi *et al* described their adverse events more promptly. Dizziness and headache occurred in two patients (5.1%) and dyspepsia in eight (20.0%)

Conclusion on strength of evidence for efficacy of SSZ in alopecia areata

Low	Both available study were of low quality with sparse data and some uncertainty about directness.

Magnitude of effect

A very uncertain estimate of a moderate effect.

Clinical recommendation for alopecia areata

Weak	There is a weak recommendation for treating alopecia areata with SSZ if conventional treatment options are contra-indicated or have failed. It is very uncertain if the beneficial effects outweigh the safety aspects (very uncertain estimate for a very uncertain moderate effect).

Remarks on clinical recommendation for alopecia areata

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Only two studies have demonstrated some effect of SSZ in alopecia areata patients. Very uncertain estimate. -Uncertainty about the off-label safety of SSZ. -Costs may vary with the number of follow-up visits and dosage of SSZ.
Importance of the outcome that treatment prevents	-Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- Statistically significant hair regrowth - 10 patients good regrowth, 12 patients moderate hair regrowth an 17 patients no response.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Only descriptive outcomes. Very uncertain.
Risks associated with therapy	- side effects sulfasalazine
Burdens of Therapy	- see risks
Risk of target event	- Target event is alopecia areata; so risk is 100%.
Costs	- Costs of SSZ are between €4,75 and for 30 days 2 dd 500 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Great variation between patients in treatment result
Other	-There are other treatment options available.

Alopecia Areata

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of SSZ per day**
Alopecia Areata Case serie							
Aghaei *et al* 2008	SSZ	6-24	Unk	AA	22(8/14)	25(16-35)	3 g
Rashidi *et al* 2008	SSZ	6	Unk	AA	39(26/13)	25.5(15-41)	3 g

Table 3. Results

	Efficacy/ effectiveness	Time to response	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Alopecia Areata Case serie						
Aghaei *et al* 2008	- 27.3% (6 of 22 patients) achieved complete hair regrowth (90%-100% terminal hair) - 40.9% (9 of 22 patients) had partial hair regrowth (10%-90% terminal hair). - 31.8% (7 of 22) patients had no hair regrowth (<10% terminal hair regrowth). -45.5% (10 of 22) suffered a complete or partial relapse.	2	Unk	None	gastrointestinal distress, rash, laboratory abnormalities, and headache (7)	None
Rashidi *et al* 2008	Good results were found in 10 patients (25.6%) and moderate hair regrowth in 12 patients (30.7%). There was no response to sulfasalazine in 17 patients (43.5%). Of the 10 patients with good results, two showed recurrence a few months after hair regrowth, and there were three recurrences in patients with a moderate response.	Unk	Unk	None	dizziness and headache (2) dyspepsia (8) .	None

Table 4. Adverse events in RCT's en cohorts

	Aghaei et al	Rashidi et al
Adverse events	**SSZ**	**SSZ**
Infections		
Gastrointestinal symptoms	7	8
Musculoskeletal symptoms		
Neurological symptoms		2
Vascular symptoms		
Dermatological symptoms	7	
Malignancies		
Drug hypersensitivity		
Abnormalities in laboratory markers	7	
Serious adverse events		

Atrophy blanche

One case serie in 1990 was found in literature in which patients with Atrophie blanche (AB) were treated with Sulphasalazine (SSZ).

Demography
Bisalbutra *et al* with case series was included concerning 8 patients (1 male and 7 female). The mean age was 32.8 years with an age range from 21 to 54 years. The main outcome feature was not clear. Clinical remission of cutaneous lesions is the most plausible assumption.
Treatment duration was 2 months and follow-up after discontinuation of treatment was made for 6 to 10 months in all patients. No concomitant medication was used whereas previous treatment was extensive in almost all patients and consisted of colchicine, nicotinic acid, nifedipine, largactil, hydroxyzine, ASA, prednisone and cyclophosphamide.
The dosage regimen was as follows: patients started with an initial dose of 500 mg SSZ three times daily for the first 3 days, at which time the dosage was doubled. This regimen was discontinued after lesions healed in 2 to 8 weeks.

Efficacy
7 out of 8 patients in Bisalbutra *et al* had a complete remission. 1 patient was refractory. The mean duration of response was 3.6 weeks with a duration range from 2 to 8 weeks. One patient had a recurrence within 6 months after discontinuation of SSZ therapy.

Safety
Adverse events were never mentioned.

Conclusion on strength of evidence for efficacy of SSZ in atrophy blanche

Low	The only available study was of low quality with sparse data and some uncertainty about directness.

Magnitude of effect

A very uncertain estimate of a moderate effect.

Clinical recommendation for atrophy blanche

Weak	There is a weak recommendation for treating atrophy blanche with SSZ if conventional treatment options are contra-indicated or have failed. It is very uncertain if the beneficial effects outweigh the safety aspects (very uncertain estimate for a very uncertain good effect).

Remarks on clinical recommendation for atrophy blanche

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Only one study has demonstrated some effect of SSZ in atrophy blanche patients. Very uncertain estimate. -Uncertainty about the off-label safety of SSZ. -Costs may vary with the number of follow-up visits and dosage of SSZ.
Importance of the outcome that treatment prevents	- Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- 7 patients complete remission, 1 patient refractory.
Precision of estimate of treatment effect* * estimates are ranked by the working group as	- Only descriptive outcomes. Very uncertain.

very certain, certain, uncertain or very uncertain.	
Risks associated with therapy	- side effects sulfasalazine
Burdens of Therapy	- see risks
Risk of target event	- Target event is atrophy blanche; so risk is 100%.
Costs	- Costs of SSZ are between €4,75 and for 30 days 2 dd 500 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Moderate variation between patients in treatment result
Other	-There are other treatment options available.

Atrophie Blanche

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of SSZ per day**
Atrophie Blanche Case series							
Bisalbutra *et al* 1990	Case Series	2	6-10	AB	8(1/7)	32.75 (21-54)	1 g

Table 3. Results

	Efficacy/ effectiveness	**Time to response**	**Duration of remission (months)**	**Conco med (*n* of subjects)**	**AE's (*n* of events)**	**SAE's (*n* of events)**
Atrophie Blanche Case series						
Bisalbutra *et al* 1990	7 out of 8 patients had a complete remission. One was refractory	2	Unk	None	Unk	facial edema and paresthesia (1)

Discoid Lupus Erythematosus

One case serie in 1996 was found in the literature in which patients with Discoid Lupus Erythematosus (DLE) were treated with Sulphasalazine (SSZ).

Demography
Sabbagh *et al* with case series was included concerning 11 patients (6 male and 5 female). The mean age was 38 years with an age range from 27 to 62 years. Diagnoses was based on both clinical and histological features. Systemic Lupus Erythematosus was ruled out following the criteria of the American Rheumatism Association[1].
Response rates were quantified as responders complete or marked response) and/or non-responders.
Previous treatment is extensive concerning at least anti-malarials. Retinoids, dapsone, corticosteroids, gold salts and thalidomide were also used. Patients were refractory for the previous treatments or they presented contra-indications to these drugs, thus they were treated with SSZ. Concomitant medication were topical corticosteroids in three patients.
Treatment duration ranged from 3 to 54 months and follow up was unknown. The wide range for the duration of treatment was not deducible.
The dosage regimen was 0.5 g/day initially, increased (with weekly 0.5 g/day) up until 2.0 g/day.

Efficacy
Sabbagh *et al* showed very favourable results for SSZ treatment. Seven patients had a complete remission.. One of them had a marked response and the other three patients were unchanged after 3 to 6 months of SSZ therapy. The seven patients with a complete response had a total regression of cutaneous lesions within three months of therapy. The patient with a marked response was also classified as a responder, however temporary. This patient showed a relapse after 1 year of treatment. Thus, 8 out of 11 (72%) were responders and 3 out of 11 (28%) were non-responders.
Duration of remission was not described for the 'excellent responders' and time to response was not described for the 'marked responder.'

Safety
Sabbagh *et al* reported 4 adverse events by 4 different patients.
Elevated titre of anti-DNA antibodies and transient leukopenia occurred in 2 of the 7 excellent responders, that led to temporary withdrawal of SSZ treatment. Exacerbation of cutaneous lesions and skin rash occurred in two out of the three non-responders. Together with lack of treatment efficacy the two non-responders that got adverse events withdrew the treatment protocol. It is uncertain whether or not the just mentioned events shoutld be classified as serious adverse events.

Conclusion on strength of evidence for efficacy of SSZ in Discoid Lupus Erythematosus

Low	The only available study were of low quality with sparse data and some uncertainty about directness.

Magnitude of effect

A very uncertain estimate of a moderate effect.

Clinical recommendation for Discoid Lupus Erythematosus

Weak	There is a weak recommendation for treating discoid lupus erythematosus with SSZ if conventional treatment options are contra-indicated or have failed. It is very uncertain if the beneficial effects outweigh the safety aspects (very uncertain estimate for a very uncertain good effect).

Remarks on clinical recommendation for Discoid Lupus Erythematosus

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs*	-Only one studie has demonstrated some effect of SSZ in discoid lupus erythematosus patients. Very

* estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	uncertain estimate. -Uncertainty about the off-label safety of SSZ. -Costs may vary with the number of follow-up visits and dosage of SSZ.
Importance of the outcome that treatment prevents	- Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- 7 patients complete remission, 1 patient temporary response, 3 patient unresponsive.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Only descriptive outcomes. Very uncertain.
Risks associated with therapy	- side effects sulfasalazine
Burdens of Therapy	- see risks
Risk of target event	- Target event is alopecia areata; so risk is 100%.
Costs	- Costs of SSZ are between €4,75 and for 30 days 2 dd 500 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Great variation between patients in treatment result
Other	-There are other treatment options available.

Discoid Lupus Erythematosus

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of SSZ per day**
Discoid Lupus Erythematosus Case series							
Sabbagh *et al* 1996	Case series	3-54	Unk	DLE	11(6/5)	38(27-62)	2 g

Table 3. Results

	Efficacy/ effectiveness	**Time to response**	**Duration of remission (months)**	**Conco med (*n* of subjects)**	**AE's (*n* of events)**	**SAE's (*n* of events)**
Discoid Lupus Erythematosus Cohorts						
Sabbagh *et al* 1996	Seven patients had a complete response (complete remission). One of them had a marked response. Three patients had no response	1	Unk	Topical corticosteroids (3)	None	Exacerbation of lesions (1), skin rash (1), anti DNA antibodies (1), leukopenia(1)

Table 4. Adverse events in RCT's en cohorts

	Sabbagh et al		
Adverse events	**SSZ**	**pcb**	**RR**
Infections			
Gastrointestinal symptoms			
Musculoskeletal symptoms			
Neurological symptoms			
Vascular symptoms			
Dermatological symptoms			
Malignancies			
Drug hypersensitivity			
Abnormalities in laboratory markers			
Serious adverse events	4		

Lichen Planus

Methodological quality
One case series by Bauza *et al* was included in which patients with Lichen planus (LP) were treated with Sulphasalazine (SSZ). Patients with cutaneous as well as mucosal Lichen planus were enrolled in the study. Little is said about the methodological quality. The studie was prospective and uncontrolled and contained only a SSZ treatment arm.

Demography
Bauza *et al* enrolled 20 subjects (11 male and 9 female) with a mean age of 41 years and an age range from 5 to 65 years. One child (5 years) was included in the study who received a deviating dosage regimen.
The mean duration of treatment was 5.5 months and the duration range was 1 to 12 months. Dosage regimen could be either increasing or decreasing in dosage. Thus, dosage regimen differed in a very wide range and depended very highly on the individual clinical response. The initial dosage regimen was as follows: SSZ at initial doses of 1.5 g/day increasing 0.5 g per week until 3 g/day for a period of 4–16 weeks. As said before, the only child had a deviating dosage regimen: doses of 1 g/day SSZ maintained for 16 weeks followed by a further 12 weeks of 1.25 g/day.
Previous treatment existed of local or systemic corticosteroids or retinoids in 10 patients.
Concomitant therapy was not used and follow-up was unknown.

Efficacy
Bauza *et al* showed a favourable response for SSZ treatment, given the fact that all patients were responders to SSZ treatment. After the first 4 to 16 weeks, 11 patients achieved complete remission on SSZ treatment, in addition (that is on final assessment) 2 more patients received a complete response after at least 16 weeks of therapy. Partial response was observed in seven patients after at least 4 weeks of treatment. A partial response was considered when 50% or more of the cutaneous lesions cleared and pruritus ceased. Complete response was defined as the disappearance of pruritus and 100% disappearance of cutaneous lesions on clinical examination, leaving at most a residual hyperpigmentation. When treatment was discontinued (in most cases because of complete remission), 10 patients experienced a relapse with a latency of 2 weeks to 6 years. Five patients received further treatment with SSZ after the relapse, and except for one patient who abandoned the treatment because of adverse effects, a complete remission was obtained in all of them. The time to effect was short in most of the patients, first improvements were widely seen after only 5 to 7 days of treatment.
Final assessments were not done on mucosal LP, assessments that were made concerning mucosal LP showed no statistically significant improvement in any case.

Safety
Bauza *et al* showed that most of the patients tolerated the treatment well and only eight patients presented some minor side-effects, such as dyspepsia, skin rash, weakness or headache, which obligated five patients to abandon treatment. One of these patients only presented side-effects when treated with SSZ for a second time. The only child in the study tolerated the treatment well. No abnormalities were found in the laboratory tests other than a transient leukopenia in one patient who was not present in subsequent tests therefore negligible.

Conclusion on strength of evidence for efficacy of SSZ in Lichen planus

Low	The only available study were of low quality with sparse data and some uncertainty about directness.

Magnitude of effect

A very uncertain estimate of a low effect.

Clinical recommendation for Lichen planus

Weak	There is a weak recommendation for treating lichen planus with SSZ if conventional treatment options are contra-indicated or have failed. It is very uncertain if the beneficial effects outweigh the safety aspects (very uncertain estimate for a very uncertain good effect).

Remarks on clinical recommendation for lichen planus

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs*	-Only one studie has demonstrated some effect of SSZ in lichen planus patients. Very uncertain

* estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	estimate. -Uncertainty about the off-label safety of SSZ. -Costs may vary with the number of follow-up visits and dosage of SSZ.
Importance of the outcome that treatment prevents	- Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- After the first 4–16 weeks, 13 achieving a complete remission. Partial response was observed in seven patients after at least 4 weeks of treatment.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Only descriptive outcomes. Very uncertain.
Risks associated with therapy	- side effects sulfasalazine
Burdens of Therapy	- see risks
Risk of target event	- Target event is alopecia areata; so risk is 100%.
Costs	- Costs of SSZ are between €4,75 and for 30 days 2 dd 500 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Great variation between patients in treatment result
Other	-There are other treatment options available.

Lichen Planus

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of SSZ per day**
Lichen Planus Cohort							
Bauza *et al* 2005	SSZ	1-12	Unk	LP	20(11/9)	41(5-65)	3 g

Table 3. Results

	Efficacy/ effectiveness	**Time to response**	**Duration of remission (months)**	**Conco med (*n* of subjects)**	**AE's (*n* of events)**	**SAE's (*n* of events)**
Lichen Planus Cohorts						
Bauza *et al* 2005	After the first 4–16 weeks, 13 achieving a complete remission. Partial response was observed in seven patients after at least 4 weeks of treatment.	1	Unk	None	Dyspepsia (2), Leukopenia (1) and no appetite	Fever (1), Cutaneous rash(1), Poor glycemic control (1), Gastric pain and pruritis (1) All abondened treatment

Table 4. Adverse events in RCT's en cohorts

	Bauza et al		
Adverse events	**SSZ**	**pcb**	**RR**
Infections			
Gastrointestinal symptoms	3		
Musculoskeletal symptoms			
Neurological symptoms			
Vascular symptoms	1		
Dermatological symptoms			
Malignancies			
Drug hypersensitivity			
Abnormalities in laboratory markers			
Serious adverse events	4		

Pemphigus Vulgaris

Methodological quality
One RCT published in 2009 was included in which patients with pemphigus vulgaris were treated with SSZ. Randomisation, concealment of allocation and blinding were all done adequately in el-Darouti *et al*. All the patients were randomly assigned to either SSZ and Pentoxifylline (group 1) or placebo (group 2). SSZ and Pentoxifylline were considered and evaluated as adjuvant therapy, objective of el-Darouti *et al* therefore was to estimate the use of SSZ and Pentoxifylline as an adjuvant therapy for Pemphigus vulgaris.
Researchers, observers and outcome assessors had no knowledge which patients were treated with either SSZ and Pentoxifylline or placebo. The patients in group 2 received placebo tablets that were identical in size and shape to both the Pentoxifylline and SSZ. Two independent evaluators who were blinded to the drugs made the clinical assessment. A third group was included, that existed of five healthy volunteers and is used as an secondary control group. Unfortunately the group exists of a small number of patients and therefore a shortcoming in the efficacy analysis as an secondary control group. Henceforth, only the placebo group will be considered in the comparison.

Demography
el-Darouti *et al* compared SSZ and Pentoxifylline (group 1) with placebo (group2). Group 1 consisted of 42 patients (6 male and 36 female) with a mean age of 43 years and an age range from 22 to 65 years. The duration of treatment was 2 months, follow-up period is unknown.
In addition to the standard treatment (which consisted of pulsed steroid therapy and i.v. cyclophosphamide, given in both groups until full recovery), patients in group 1 received Pentoxifylline 400 mg sustained release tablet three times daily and SSZ 500 mg three times daily for two months.
The standard treatment has proven to sustain lifelong recovery from Pemphigus vulgaris.
Group 2 consisted of 22 patients (6 male and 16 female) with a mean age of 39 years and an age range from 24 to 50 years.
The diagnosis of Pemphigus vulgaris was based on a combination of clinical and histopathological examination and direct immunofluorescence findings.

Efficacy
el-Darouti *et al* showed favourable results for SSZ and Pentoxifylline compared to placebo in the adjuvant treatment of Pemphigus vulgaris.They compared the clinical improvement between group 1 and group 2. The degree of improvement was measured as follows: the absence of new lesions and complete healing of the lesions was considered an 'excellent response'; the presence of a few persistent lesions or the appearance of a few new lesions (fewer than 10 lesions in a week) was considered a 'moderate response'; and the persistence of old lesions as well as the appearance of numerous new lesions (more than10 lesions per week) was considered a 'poor response'.
The degree of improvement was poor in two patients (5%) of group 1 and in four patients of group 2 (18%), moderate in four patients of group 1 (10%) and in 14 patients of group 2 (64%), excellent in 36 patients of group 1 (86%) and in only four patients of group 2 (18%). The difference in clinical improvement between groups 1 and 2 was highly statistically significant ($P < 0.001$). Concomitant medication was Pentoxifylline (an antitumour necrosis factor drug) only. Time to response and duration of remission were never mentioned.

Safety
el-Darouti *et al* described their safety aspects briefly. Adverse events never led to withdrawal from the study protocol or (temporary) discontinuation from the study treatment.
The adverse events of PTX and SSZ were mainly gastrointestinal in the form of gastric pain (12 patients), nausea (4 patients) and headache (5 patients) in group 1. Three patients in group 2 experienced mild headache only. The side effects were treated by adding domperidone to the treatment regimen in patients complaining of gastric pain.
Serious adverse events did not occur.

Conclusion on strength of evidence for efficacy of SSZ in Pemphigus Vulgaris

Moderate	The only available study was of moderate quality with sparse data and some uncertainty about directness.

Magnitude of effect

A uncertain estimate of a moderate effect.

Clinical recommendation for Pemphigus Vulgaris

Weak	There is a weak recommendation for treating pemhigus vulgaris with SSZin combination with pentoxyfylline if conventional treatment options are contra-indicated or have failed. It is very uncertain if the beneficial effects outweigh the safety aspects (very uncertain estimate for a very uncertain good effect).

Remarks on clinical recommendation for Pemphigus Vulgaris

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Only one studie has demonstrated some effect of SSZ in combination with pentoxyfylline in pemphigus vulgaris patients. Uncertain estimate of effect. -Uncertainty about the off-label safety of SSZ. -Costs may vary with the number of follow-up visits and dosage of SSZ.
Importance of the outcome that treatment prevents	- Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	The degree of improvement was poor in two patients of group 1 (5%) and in four patients of group 2 (18%), moderate in four patients of group 1 (10%) and in 14 patients of group 2 (64%), excellent in 36 patients of group 1 (86%) and in only four patients of group 2 (18%). The difference in clinical improvement between groups 1 and 2 was statistically significant ($P < 0.001$).
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Only descriptive outcomes. Very uncertain.
Risks associated with therapy	- side effects sulfasalazine
Burdens of Therapy	- see risks
Risk of target event	- Target event is alopecia areata; so risk is 100%.
Costs	- Costs of SSZ are between €4,75 and for 30 days 2 dd 500 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Great variation between patients in treatment result
Other	-There are other treatment options available.

Pemphigus Vulgaris

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of SSZ per day**
Pemphigus Vulgaris RCT's							
el-Darouti 2009	SSZ + PTX	2	Unk	PV	42 (6/36)	43 (22-65)	Unk
	PB				22 (6/16)	39 (24-50)	

Table 3. Results

	Efficacy/ effectiveness	Time to response	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Pemphigus Vulgaris RCT's						
el-Darouti *et al* 2009	Group 1: Intervention, ie Pentoxifylline and Sulfasalazine, Group 2: Placebo and Group 3: five healthy individuals. The difference in clinical improvement between groups 1 and 2 was statistically significant (P < 0.001).	Unk	Unk	PTX	gastric pain (12), nausea (4) and headache (5 in group 1. Three patients in group 2 experienced mild headache only.	None

Table 4. Adverse events in RCT's en cohorts

	el-Darouti et al		
Adverse events	**SSZ +PTX**	**pcb**	**RR**
Infections	20	3	-
Gastrointestinal symptoms			
Musculoskeletal symptoms			
Neurological symptoms			
Vascular symptoms			
Dermatological symptoms			
Malignancies			
Drug hypersensitivity			
Abnormalities in laboratory markers			
Serious adverse events			

Table 5. Risk of bias of included RCT

	Adequate randomisation?	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
el-Darouti *et al* 2009	YES	YES	Participants YES Researchers YES Outcome assessment NO	NO	YES	YES

Psoriasis

A total of 4 published studies between 1989 and 1996 were found in the literature in which patients with psoriasis were treated with SSZ; 3 RCT's and 1 cohort

Efficacy/effectiveness
Efficacy/effectiveness was measured by the percentage of patients with a complete or partial remission or controlled disease, defined as: Erythema, amount of Scale and Thickness (EST) of plaques graded on an arbitrary scale (0 = absence; 4 = severe) and Total Body Surface Area (TBSA; using the rule of nines[1]) affected with cutaneous lesions.

RCT's
Methodological quality
Boyd *et al* and Gupta *et al* employed an adequate randomization and concealment of allocation. Randomization was unclear (not described) in Bharti *et al*. Bharti *et al* did not contain a placebo group. Blinding and concealment of allocation thereby, were inadequate.
It is likely that the outcome measurement was influenced in all three trials by the lack of blinding in the outcome assessment, since the main outcome measurement was EST on an arbitrary scale and thereby subject to the interpretation of the observer. However Boyd *et al* also described TBSA using the rule of nines which is far more objective, hence, not likely to be subject to the interpretation of the observer.
Adequate data reporting (free of selective and/or incomplete reporting) could hardly be assessed in any of the three trials since those methods were only briefly (i.e. insufficiently) described.

Demography
All three trials had two treatment arms. Boyd *et al* and Gupta *et al* had a SSZ and placebo arm whereas Bharti *et al* had a SSZ and methotrexate arm. There was no crossover between the treatment arms. SSZ was always given as mono-therapy.
Treatment duration ranged from 0.5 to 12 months in Boyd *et al* and Gupta *et al* and was unknown in Bharti *et al*. Treatment duration was little dependent on individual treatment response, it was mainly recorded prior to the trial.
Dosage regimens ranged from 500 mg to 4000 mg a day. Follow-up was only described in Bharti *et al* and had a duration of three months.
In total, 97 subjects (61 male and 36 female) were enrolled with a mean age of 40.3 years and a age range of 12-70 years. In all subjects the diagnosis of Psoriasis was established by more than 15% (Boyd *et al*) and 20% (Bharti *et al*) TBSA involvement. Gupta *et al* only described moderate-to-severe, stable, plaque-type psoriasis. There was no previous treatment in any of the trials.

Efficacy
Bharti *et al* compared methotrexate with SSZ. Efficacy was comparable for the 2 drugs: decrease in mean EST in patients on methotrexate and sulfasalazine therapy was 92.86% and 92.13% at 12 weeks therapy respectively.
In Boyd *et al* and Gupta *et al* SSZ was compared with placebo. Efficacy in Boyd *et al* was favourable for SSZ. The reduction in TBSA of psoriasis ranged from 0% to 24% with a mean of 7.44%, while in the placebo group the range was from 1% reduction to 13% increase (mean 2.75% increase) in TBSA involvement of psoriasis. The reduction in TBSA in the
SSZ-treated group was significant ($P < 0.005$), as was the reduction in amount of scale ($P < 0.02$). There was no significant reduction in erythema ($P = 0.0745$) or thickness of plaque ($P = 0.32$).
Efficacy in Gupta *et al* was analysed more specifically than in Boyd *et al*. At the end of the double blind phase of the study, in the 17 patients in the SSZ group there was a marked response (60% to 89% improvement compared with pretherapy status) in 7 patients, moderate response (30 to 59% improvement compared with pretherapy status) in 7 patients, and minimal or no response (0 to 29%) in three patients. No patient was graded as either being essentially clear (90 to 100% improvement) or as having worsened, compared with pretherapy. In the 27 patients who received placebo medication in the double-blind phase, there was a moderate response in 1 patient, minimal to no response in 22 patients, and worsening of psoriasis in 4 patients. Differences between SSZ and placebo treatment in Gupta *et al* were consequently highly significant.
Time to response and duration of remission was not reported
Adverse events were mostly seen in Gupta *et al*, compatible with the fact that Gupta *et al* had the most subjects included in the trial and the longest duration of treatment.

Safety
Adverse events that occurred during SSZ treatment compared to the other treatment protocols are shown in table

4. Bharti *et al* did not describe adverse events.
In the treatment arm receiving SSZ in Boyd *et al* 1 patient had gastro-intestinal symptoms and 1 patient had dermatological symptoms. Seven cases of gastrointestinal symptoms and 6 serious adverse events occurred in the SSZ treatment arm in Gupta *et al*.

Serious adverse events
Serious adverse events were only described in Gupta *et al*. Six patients in the SSZ group dropped out during the study and have not been included in the statistical analysis. Four of these6 patients dropped out because they developed a cutaneous eruption from SSZ therapy after having used the medication for an average of three weeks (range, one to six weeks). The remaining two patients dropped out within the first two weeks of therapy due to nausea.

Cohort
Methodological quality
One Cohort study by Gupta *et al* was included. Too little is described about the methods to assess the methodological quality.

Demography
Gupta *et al* contained only one group, in an observational and open study treatment with SSZ. 32 subjects (23 male and nine female) were enrolled, with a mean age of 46 years and an age range from 21 to 74 years. No previous medication was given. Treatment duration was 2 months and follow up was not reported.
The dosage regimen was dependent on the individual response. All subjects started with an initial dose of 500 mg three times daily. The dosage of those who had no adverse reactions up until three days was increased to 1g three times daily. A further increase of dosage until 1g four times daily was done by patients who had poor response after four weeks treatment.

Efficacy
Twenty-four of 32 patients completed the study. In these 24 patients, significant improvement was noted by the end of therapy in all the main outcome measures: TBSA affected (from 46% to 22%) and EST (Erythema, Scale and Thickness). EST was graded at a six point scale, 0 being absent and 6 being severe. The overall severity score was obtained by adding the single scores from erythema, scale and thickness therefore a maximum score of eighteen.
Evaluation of the response was made by the same physician beforehand, and every two weeks during the eight week trial. At the end of eight weeks the EST score was affected as follows:
scale from 4.7 to 1.3, erythema from 5.1 to 2.8 and thickness from 4.8 to 2.5.
In three patients with a poor response to therapy at week four, SSZ was increased from
1g three times daily to 1g four times a day, with only slight improvement.
Of the 24 patients who completed the trial, two patients were essentially clear at the end of therapy. There was a marked response (50% to 90% improvement compared with pre-therapy status) in 10 patients, modest response (25% to 50% improvement compared with pre-therapy status) in seven patients, and minimal response (0% to 25%; refractory) in five patients after eight weeks of SSZ therapy.
Of the 8 patients who dropped out of the study, two of them had a lack of compliance. The other six had adverse events.
Safety
Adverse events that occurred in Gupta *et al* in the twenty four patients that completed the therapy were generally mild and transient and included: nausea in 7 patients; fatigue in patients; indigestion in 2 patients; diarrhea in patient; elevated liver enzymes in 8 patients and a macular eruption with a photosensitive distribution in two patients which resolved in one week.
None of the adverse events in the six of eight patients that dropped out of the study were marked as serious or severe, so no correlation was deducible between dropping out and the concerned adverse events.

Conclusion on strength of evidence for efficacy of SSZ in Psoriasis

Moderate	The four available studies were of moderate quality with moderate data and some uncertainty about directness.

Magnitude of effect

An uncertain estimate of a moderate effect.

Clinical recommendation for Psoriasis

Moderate	There is a moderate recommendation for treating psoriasis with SSZ if conventional treatment options are contra-indicated or have failed. It is very uncertain if the beneficial effects outweigh the safety aspects (very uncertain estimate for a very uncertain good effect).

Remarks on clinical recommendation for Psoriasis

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Only one studie has demonstrated some effect of SSZ in psoriasis patients. Very uncertain estimate. -Uncertainty about the off-label safety of SSZ. -Costs may vary with the number of follow-up visits and dosage of SSZ.
Importance of the outcome that treatment prevents	- Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	- Moderate
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- EST, TBSA and descriptive outcomes. Uncertain.
Risks associated with therapy	- side effects sulfasalazine
Burdens of Therapy	- see risks
Risk of target event	- Target event is alopecia areata; so risk is 100%.
Costs	- Costs of SSZ are between €4,75 and for 30 days 2 dd 500 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Great variation between patients in treatment result
Other	-There are other treatment options available.

Psoriasis

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of SSZ per day**
Psoriasis RCT's							
Bharti *et al* 1996	MTX	Unk	3	PSS	15 (8/7)	46.4 (20-68)	-
	SSZ				15 (7/8)	35.6 (12-70)	1500 mg
Boyd *et al* 1991	SSZ	1/2	Unk	PSS	9 (7/2)	33.78 (32-66)	500 mg
	PB				8 (5/3)	33.13 (21-75)	
Gupta *et al* 1990	SSZ	8-12	Unk	PSS	23 (13/10)	44(41-47)	4 g
	PB				27 (21/6)	49(46-52)	
PsoriasisCohort							
Gupta *et al* 1989	SSZ	2	Unk	PSS	32(23/9)	46(21-74)	3-4 g

Table 3. Results

	Efficacy/ effectiveness	Time to response	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Psoriasis RCT's						
Bharti *et al*. 1996	In group A mean EST score decreased from 8.4 at the start of treatment to 1.13 (ie by 86.55%) at 4 weeks and to 0.6 (ie by 92.86%) at 12 weeks. Seven (46.7%) patients had complete clearance by 4 weeks, while a further 3 (20.0%) patients had complete clearance by 12 weeks.	Unk	Unk	All the patients were given local application of a combination of beclomethasone (0.025%) and salicylic acid (3%) not exceeding 50g/week; and/or tar shampoo on alternate days for scalp lesion	Unk	Unk
Boyd *et al* 1991	The reduction in TBSA of psoriasis ranged from 0% to 24% with a mean of 7.44%, while in the placebo group the range was from 1% reduction to 13% increase (mean 2.75% increase) in TBSA involvement with psoriasis. The reduction in TBSA in the sulphasalazine-treated group was significant (P <0.005), as was the reduction in amount of scale (P < 0.02). There was no significant reduction in erythema (P = 0.0745) or thickness of plaque (P = 0.32).	Unk	Unk	None	Headache, nausea, skin rashes	None
Gupta *et al* 1990	At the end of the double blind phase of the study, in the 17 patients in the sulphasalazine group there was a marked response (60% to 89% improvement compared with pretherapy status) in 7 patients, moderate response (30 to 59% improvement compared with pretherapy status) in 7 patients, and minimal or no response (0 to 29%) in three patients. No patient was graded as either being essentially clear (90 to 100% improvement) or as having	Unk	Unk	None	Intervention: Nausea (6), Heartburn (3), Headaches (2), diarrhea (1), salty taste in mouth (1) and fatigue (2) Placebo: diarrhea (1) and fatigue (1)	Intervention: Cutaneous eruption (4) and nausea (2)

	worsened, compared with pretherapy. In the 27 patients who received placebo medication in the double-blind phase, there was a moderate response in 1 patient, minimal to no response in 22 patients, and worsening of psoriasis in 4 patients.					
Psoriasis Cohorts						
Gupta *et al* 1989	24 of 32 patients completed the study. In these 24 patients, improvement was noted by the end of therapy in each of the following factors: TBSA affected (from 46% +/- 3% to 22% +/- 3%; p = 0.0001), scale (from 4.7 +/- 0.2 to 1.3 +/- 0.3; p = 0.0001), erythema (from 5.1 +/- 0.2 to 2.8 +/-0.3; p = 0.0001), and thickness (from 4.8 +/- 0.2 to 2.5 +/- 0.3 ;p= 0.0001)	4	Unk	None	nausea, seven patients; fatigue, four patients; indigestion, two patients; diarrhea, one patient; and a macular eruption with a photosensitive distributionin two patients, which resolved in 1 week.	None

Table 4. Adverse events in RCT's en cohorts

	Bharti et al.			**Boyd et al**			**Gupta et al**			**Gupta et al**		
Adverse events	**med**	**pcb**	**RR**	**SSZ**	**pcb**	**RR**	**SSZ**	**pcb**	**RR**	**SSZ**	**pcb**	**RR**
Infections	-	-	-		-	-						
Gastrointestinal symptoms				1			7	1		10		
Musculoskeletal symptoms							2	1		4		
Neurological symptoms							2					
Vascular symptoms							3					
Dermatological symptoms				1						2		
Malignancies												
Drug hypersensitivity												
Abnormalities in laboratory markers												
Serious adverse events							6					

Table 5. Risk of bias of included RCT

	Adequate randomisation?	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
Bharti *et al* 1996	UNCLEAR	NO	Participants NO Researchers NO Outcome assessment NO	UNCLEAR	UNCLEAR	UNCLEAR
Boyd *et al* 1991	YES	YES	Participants YES Researchers NO Outcome assessment NO	UNCLEAR	UNCLEAR	UNCLEAR
Gupta *et al* 1990	YES	YES	Participants YES Researchers YES Outcome assessment NO	UNCLEAR	YES	UNCLEAR

Scleroderma

Methodological quality
One cohort studie published in 1971 by Dover *et al* was included in which patients with Scleroderma were treated with Sulphasalazine (SSZ). Little is described about the methodological quality in Dover *et al*. Diagnoses was made on the base of histological appearance in skin biopsy, Raynaud's phenomena[1] and thickening of the skin. Laboratory investigations and findings were absent in Dover *et al*. The treatment arm consisted only of SSZ.

Demography
Dover *et al* included 19 patients (4 male and 15 female) with a mean age of 42.1 years and an age range from 13 to 65 years. The majority of patients (11 out of 19) had progressive systemic sclerosis. Duration of treatment and follow-up period ranged widely between all patients, probably depending on the individual treatment response but can not be said with any certainty. Duration of treatment ranged from 2 weeks to 35 months and follow up ranged from 2 weeks to 4 yours.
The initial and maintenance dosage regimen of SSZ treatment ranged from 1.0 to 7.0 g daily for two to three weeks and 0.25 to 7.0 g on maintenance.

Efficacy
Dover *et al* included 19 patients treated with SSZ, assessment of the efficacy was done separately for patients treated less than 4 months and for patients treated 4 to 35 months. The main outcome measures were subjective improvement (i.e. mood change from despair to optimism), disappearance of joint and muscle pain and ability to resume normal daily activities, softening of the skin of affected areas and decrease of pigmentation and renewed hair growth. Evaluation of the response was based on a 3 graded scale (mild, moderate and marked) for all the patients. Overall (all the main outcomes taken together) improvement was as follows: 7 patients treated for less than four months showed that improvement was mild in three, moderate in two and marked in two. In the remaining 12 patients treated from 4 to 35 months improvement was mild in two, moderate in three and marked in seven.
Dermatological outcomes (softening of the skin and decrease in pigment) taken separately, improvement was mild eight, moderate in eight and marked in two. The remaining patient had a normal pigmentation density and thickness of the skin prior to treatment.
Duration of remission was never mentioned, concomitant medication was never used and serious adverse events did not occur.

Safety
Dover *et al* reported a few adverse events that were all due to side effects of SSZ treatment. Fever and an erythematous rash occured in three patients, nausea in five, leukopenia in two, leukocytosis in three and thrombocytopenia in two. These were never severe.

Conclusion on strength of evidence for efficacy of SSZ in Scleroderma

Low	The only available study were of low quality with sparse data and some uncertainty about directness.

Magnitude of effect

A very uncertain estimate of a low effect.

Clinical recommendation for Scleroderma

Weak	There is a weak recommendation for treating scleroderma with SSZ if conventional treatment options are contra-indicated or have failed. It is very uncertain if the beneficial effects outweigh the safety aspects (very uncertain estimate for a very uncertain good effect).

Remarks on clinical recommendation for Scleroderma

Important subjects to consider	**Remarks**
Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs*	-Only one studie has demonstrated some effect of SSZ in scleroderma patients. Very uncertain estimate.

* estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Uncertainty about the off-label safety of SSZ. -Costs may vary with the number of follow-up visits and dosage of SSZ.
Importance of the outcome that treatment prevents	- Complete remission cutaneous lesions.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	11 of 19 patients had marked overall improvement. The beneficial effect in the 7 patients treated for less than 4 months indicates that improvement was mild in3, moderate in 2 and marked in 2. In 12 patients treated in 4 to 35 months improvement was mild in 2, moderate in three and marked in 7.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	- Only descriptive outcomes. Very uncertain.
Risks associated with therapy	- side effects sulfasalazine
Burdens of Therapy	- see risks
Risk of target event	- Target event is alopecia areata; so risk is 100%.
Costs	- Costs of SSZ are between €4,75 and for 30 days 2 dd 500 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	- Great variation between patients in treatment result
Other	-There are other treatment options available.

Scleroderma

	Study design/ groups	**Treatment (months)**	**FU (months)**	**Disease of subjects**	***N* subjects (male/ female)**	**Mean age of subjects in years (range)**	**Dose of SSZ per day**
Scleroderma Cohort							
Dover *et al* 1971	SSZ	0.5-35	0.5-48	SLD	19(4/15)	42.1(13-65)	1-7 g

Table 3. Results

	Efficacy/ effectiveness	**Time to response**	**Duration of remission (months)**	**Conco med (*n* of subjects)**	**AE's (*n* of events)**	**SAE's (*n* of events)**
Scleroderma Cohorts						
Dover *et al* 1971	11 of 19 patients had marked overall improvement. The beneficial effect in the 7 patients treated for less than 4 months indicates that improvement was mild in3, moderate in 2 and marked in 2. In 12 patients treated in 4 to 35 months improvement was mild in 2, moderate in three and marked in 7.	2-4	Unk	None	Fever (3), erythematous (3) rash (3), nausea (5), leukopenia (2), leukocytosis (3), trombocytopenia (2)	None

Table 4. Adverse events in RCT's en cohorts

		Dover et al	
Adverse events	**SSZ**	**pcb**	**RR**
Infections			
Gastrointestinal symptoms	5		
Musculoskeletal symptoms			
Neurological symptoms			
Vascular symptoms	7		
Dermatological symptoms	3		
Malignancies			
Drug hypersensitivity			
Abnormalities in laboratory markers			
Serious adverse events			

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