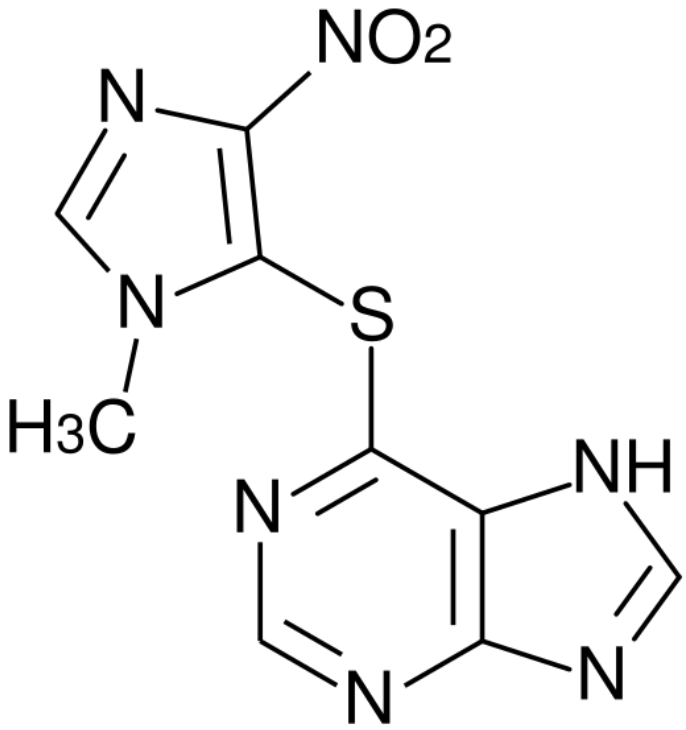
Guideline
Off-label drug use in dermatology
The GRADE approach



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 years 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.

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 azathioprine" or "Efficacy/effectiveness data off-label azathioprine" 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. AZATHIOPRINE

Introduction
Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP) and is available since 1963. It is rapidly broken down *in vivo* into 6-MP and a methylnitroimidazole moiety. The 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. The rate of conversion varies from one person to another. Nucleotides do not traverse cell membranes and therefore do not circulate in body fluids. Irrespective of whether it is given directly or is derived *in vivo* from azathioprine, 6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme that is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly. Determination of plasma concentrations of azathioprine or 6-MP have no prognostic values as regards effectiveness or toxicity of these compounds.
While the precise modes of action remain to be elucidated, some suggested mechanisms include:
1. the release of 6-MP which acts as a purine antimetabolite.
2. the possible blockade of -SH groups by alkylation.
3. the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response.
4. damage to deoxyribonucleic acid (DNA) through incorporation of purine thio-analogues.
Because of these mechanisms, the therapeutic effect of azathioprine may be evident only after several weeks or months of treatment.

Azathioprine is used as an immunosuppressant either alone or, more commonly, in combination with other agents (usually corticosteroids) 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. Azathioprine, in combination with corticosteroids and/or other immunosuppressive agents and procedures, is used to enhance the survival of organ transplants and to reduce the corticosteroid requirements of renal transplant recipients. Azathioprine, 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
- systemic lupus erythematosus
- dermatomyositis and polymyositis
- auto-immune chronic active hepatitis
- pemphigus vulgaris
- ulcerative colitis and Crohn's disease
- polyarteritis nodosa
- auto-immune haemolytic anaemia
- chronic refractory idiopathic thrombocytopenic purpura

Research question
What is the safety and efficacy of off-label treatment with azathioprine 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 'azathioprine' and synonyms (not the active metabolites) were used in combination with all skin diseases; for example the search strategy in Medline:

1 derm*.jn. (22039)
2 Azathioprine/ (11859)
3 (azathioprine* or imuran* or immuran* or imurel*).ab. (8887)
4 (azathioprine* or imuran* or immuran* or imurel*).ti. (2856)
5 (azathioprine* or imuran* or imurel* or immuran*).kw. (72)
6 4 or 2 or 5 or 3 (16781)
7 6 and 1 (72)
8 exp Skin Diseases/ (669358)
9 6 and 8 (1705)
10 7 or 9 (1711)
11 limit 10 to (humans and (dutch or english or french or german)) (1535)

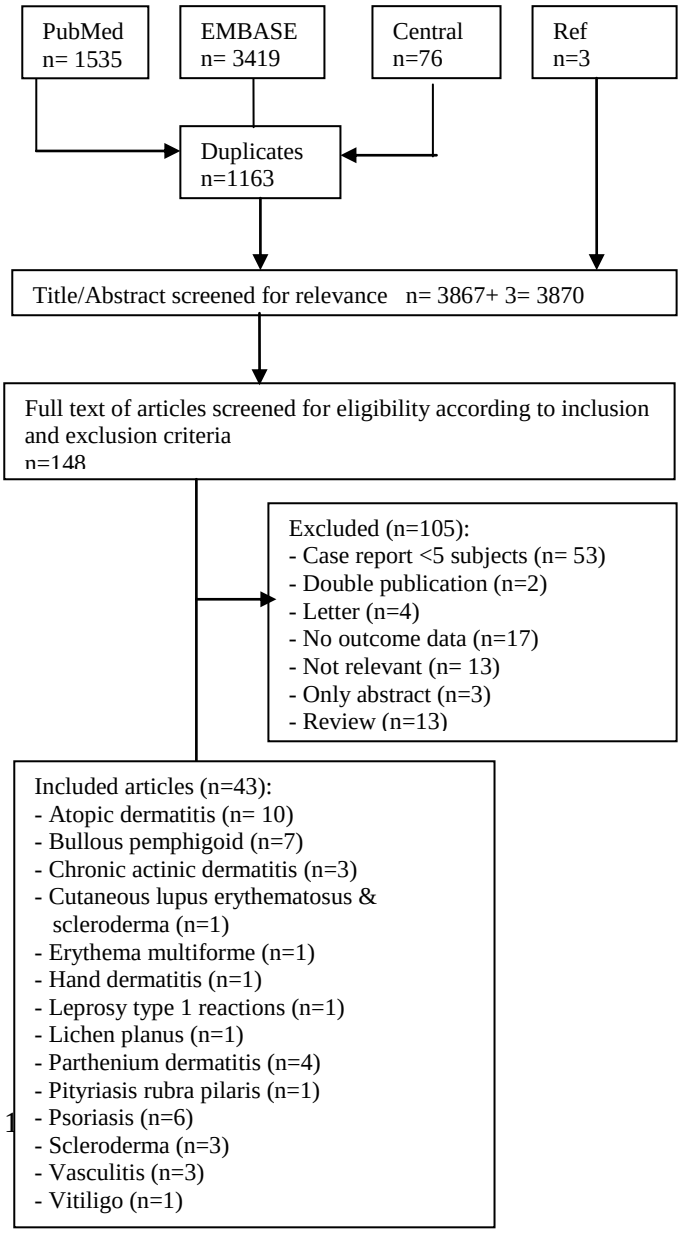
There was no limit with respect to the date of the publication. Literature references of all relevant articles found were checked in order to find additional articles. In addition, data published in Micromedex concerning azathioprine were

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 azathioprine 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 3867 articles. After screening title and abstract for eligibility, 148 articles were selected. Then, after screening the full texts of the articles, 43 articles were considered relevant. Reasons for exclusion were lack of relevance in 13 articles, review articles without additional new evidence in 13 articles and case report with less than 5 subjects in 53 articles. Outcome data on safety and efficacy were not available in 17 articles and for 3 articles only an abstract was available. Four other articles were comments and 2 were double publications. All those articles were therefore excluded. Included were 11 RCT's, 2 cohorts and 30 case series concerning 12 dermatological diseases.
A random sample of 20 articles was taken from the publications that were excluded because the case report had less then 5 subjects. The random sample was screened on missed relevant data regarding adverse effects. This was not the case.

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 Imuran tablets 25 mg ® (last update 27-5-2009). 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 azathioprine, 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 1 to 3 mg/kg body weight/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks or months) and haematological 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 azathioprine.

Therapeutic response is evident after approximately 6-12 weeks

- The maintenance dosage required may range from less than 1 mg/kg body weight/day to 3 mg/kg body weight/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 azathioprine 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 azathioprine, 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 elderly
All the studies concerning bullous pemphigoid were conducted with elderly patients only (see Table 5) (Beissert et al. 2007, Guillaume et al. 1993, Burton et al. 1978, Ahmed et al. 1977, Burton et al. 1974, Van Dijk et al. 1973, Greaves et al. 1971). The mean age range of the subjects in the studies ranged from 68.2 to 81.4. It is not possible to compare effectiveness and dosage of elderly for bullous pemphigoid with non-elderly because there are no studies available with non-elderly patients. Death was an important parameter with a total of 15 deaths among a total of 128 studied patients. However, the reported causes of death are comparable with the general population. As a result, the recommendations mentioned above (to be extra careful with the off-label use of in elderly patients) remain valid.

Use in children (also see www.kinderformularium.nl)
The only study concerning the off-label use of azathioprine in children is a case series in which 48 patients were treated for atopic dermatitis (Murphy et al. 2002). Mean age was 6.9 years (SD 6-16). The dosage was an individual determined dose of 2.5-3.5 mg/kg. Reported effectiveness was similar compared to other studies (Table 2). Reported adverse effects were transient mild lymphopenia (15), transient thrombocytopenia (1), transient abnormalities in liver enzymes (5), mild microcytosis (3), eczema herpeticum (1), nausea, vomiting, diarrhoea (1) and a hypersensitivity reaction (1). It is recommended that the dosages used should be at the lower end of the range and individually determined according to the weight of the patient.

Contraindications
Azathioprine is contra-indicated in patients known to be hypersensitive to azathioprine. Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to azathioprine. Azathioprine therapy should not be initiated in patients who may be pregnant, or who are likely to become pregnant without careful assessment of risk versus benefit (see Special Warnings and Precautions for Use and Pregnancy and Lactation).

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

- severe infections
- serious disrupted liver-, kidney- or bone marrow function.

- pancreatitis
- Lesh-Nyhan syndrome
- 'living' vaccin (especially BCG, smallpox, yellow fever)

Special warnings and precautions for use

Monitoring
There are potential hazards in the use of azathioprine. 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 azathioprine 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 azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with azathioprine. This problem can be exacerbated by co-administration with drugs that inhibit TPMT, such as sulfasalazine.

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

It has been reported that decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxic drugs (see section Undesirable effects).

The working group advises to determine the TPMT activity prior to the initiation of azathioprine. If this test is not available, starting azathioprine on a low dose (1.0 mg/kg) and frequent laboratory evaluations (see above) are an alternative.

Renal and/or hepatic insufficiency
It has been suggested that the toxicity of azathioprine may be enhanced in the presence of renal insufficiency, but it has not been supported by controlled studies. 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 azathioprine 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 azathioprine may be impaired, and the dosage of azathioprine should therefore be reduced if hepatic or haematological toxicity occurs.
Limited evidence suggests that azathioprine is not beneficial to patients with hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). Therefore, it is not recommended to give these patients azathioprine.

Carcinogenicity (see also section Undesirable Effects)
- Patients receiving immunosuppressive therapy are at an increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. It has been reported that reduction or discontinuation of immunosuppression may be associated with partial or complete regression of non-Hodgkin's lymphomas and Kaposi's sarcomas.
- Patients receiving multiple immunosuppressive agents may be at risk of over-immunosuppression, therefore such therapy should be maintained at the lowest effective level.
- Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity (see also section Undesirable Effects).
- Infection with varicella zoster virus (VZV; chickenpox and herpes zoster) may have a severe clinical outcome during the administration of immunosuppressants. Caution should be exercised especially with respect to the following: Before starting the administration of immunosuppressants, the prescriber should check if the patient has a history of VZV. Serologic testing may be useful in determining previous exposure. Patients who have no history of exposure should avoid contact with individuals with chickenpox or herpes zoster. If the patient is

exposed to VZV, special care must be taken to avoid patients developing chickenpox or herpes zoster and passive immunisation with varicella zoster immunoglobulin (VZIG) may be considered. If the patient becomes infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

Interaction with other drugs and other forms of interaction

- *Allopurinol*

Xanthine oxidase activity is inhibited by allopurinol which results in reduced conversion of biologically active 6 – thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol is given concomitantly with azathioprine, the dose of azathioprine should be reduced to one-quarter of the original dose.

- *Neuromuscular blocking agents*

Azathioprine can potentiate the neuromuscular blockade produced by depolarising agents such as suxamethonium and can reduce the blockade produced by non-depolarising agents such as tubocurarine. There is considerable variation in the potency of this interaction.

Coumarin derivatives
Inhibition of the anticoagulant effect of coumarins, when administered together with azathioprine, has been reported.

- *Cytostatic/myelosuppressive agents*

Where possible, concomitant administration of cytostatic drugs, or drugs which may have a myelosuppressive effect, such as penicillamine, should be avoided. There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine and co-trimoxazole. There has been a case report suggesting that haematological abnormalities may develop due to the concomitant administration of azathioprine and ACE inhibitors. It has been suggested that cimetidine and indometacin may have myelosuppressive effects, which may be enhanced by concomitant administration of azathioprine.

- *Other interactions*

As there is *in vitro* evidence that aminosalicylate derivatives (eg. sulfasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent azathioprine therapy (see Special Warnings and Special Precautions for Use). Furosemide has been shown to impair the metabolism of azathioprine by human hepatic tissue *in vitro*. The clinical significance is unknown.

- *Vaccines*

The immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines and the administration of live vaccines to patients receiving Azathioprine therapy is contra-indicated on theoretical grounds. A diminished response to killed vaccines is likely and such a response to hepatitis B vaccine has been observed among patients treated with a combination of azathioprine and corticosteroids.
A small clinical study has indicated that standard therapeutic doses of azathioprine do not deleteriously affect the response to polyvalent pneumococcal vaccine, as assessed by mean anti-capsular specific antibody concentration.

Use in Pregnancy and Lactation
Azathioprine should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit. There have been reports of premature birth and low birth weight following maternal exposure to azathioprine, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure. Azathioprine and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid after maternal administration of azathioprine. Leucopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine throughout their pregnancies. Extra care in haematological monitoring is advised during pregnancy. 6-Mercaptopurine has been found in the colostrum and breast-milk of women receiving azathioprine treatment. Treatment with azathioprine is therefore not recommended during lactation.
The need for anti-conception in men during treatment is unclear and is currently subject of debate.

Undesirable effects
There is no modern clinical documentation that can be used for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication. The following convention has been utilised for the classification of frequency: Very common, ≥ 1/10; common, ≥ 1/100 and < 1/10; uncommon, ≥ 1/1000 and < 1/100; rare, ≥ 1/10000 and < 1/1000; very rare, < 1/10000.

Azathioprine may be associated with a dose-related, generally reversible, depression of bone marrow function, most frequently as leucopenia, but also sometimes as anaemia and thrombocytopenia, and rarely as agranulocytosis,

pancytopenia and aplastic anaemia. These occur particularly in patients predisposed to myelotoxicity, such as those with TPMT deficiency and renal or hepatic insufficiency and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy.
Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with azathioprine therapy. Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia is rare.

A minority of patients experience nausea when first given azathioprine. This appears to be relieved by administering the tablets after meals. Pancreatitis has been reported in a small percentage of patients on azathioprine therapy, particularly in renal transplant patients and patients with inflammatory bowel disease. There are difficulties relating pancreatitis to the administration of one particular drug, although re-challenge has confirmed an association with azathioprine.

Cholestasis and deterioration of liver function have occasionally been reported in association with azathioprine therapy and are usually reversible on withdrawal. This may be associated with symptoms of a hypersensitivity reaction (see hypersensitivity reactions).
Rare, but life-threatening hepatic damage associated with chronic administration of azathioprine has been described primarily in transplant patients. In some cases withdrawal of azathioprine has resulted in either a temporary or permanent improvement in symptoms and histological changes.

Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of azathioprine. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis (see hepato-biliary disorders). In many cases, re-challenge has confirmed an association with azathioprine. Immediate withdrawal of azathioprine and institution of circulatory support where appropriate have led to recovery in the majority of cases. Other marked underlying pathology has contributed to the very rare deaths reported. Following a hypersensitivity reaction to azathioprine, the necessity for continued administration of azathioprine should be carefully considered on an individual basis.

Summary of registered adverse events	
Occurrence Events	**Undesirable effect**
Infections (indications other than transplant patients)	
Uncommon:	Viral, fungal and bacterial infections. Patients receiving azathioprine alone, or in combination with other immunosupressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection with varicella, herpes zoster and other infectious agents (see also section Special Warnings and Precautions for Use).
Neoplasms benign and malignant (including cysts and polyps)	
Rare:	Neoplasms including non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia (see also section Special Warnings and Special Precautions for Use)
Blood and lymphatic disorders	
Very common: Common: Uncommon: Rare:	leucopenia. Thrombocytopenia. Anaemia. Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia.
Respiratory, thoracic and mediastinal disorders	
Very rare:	Reversible pneumonitis.
Gastrointestinal disorders	

Common: Uncommon: Rare:	Nausea and vomiting Pancreatitis. Colitis, diverticulitis and bowel perforation reported in transplant patients, severe diarrhoea in inflammatory bowel disease.
Hepato-biliary disorders	
Uncommon: Rare:	Cholestasis and elevation of liver enzymes. Life-threatening hepatic damage (primarily in transplant patients).
Skin and subcutaneous tissue disorders	
Rare:	Alopecia, photosensitivity. Hair loss has been described in patients receiving azathioprine and other immunosuppressive agents. In many instances the condition resolved spontaneously despite continuing therapy. The relationship between alopecia and azathioprine treatment is uncertain.
Immune system disorders	
Uncommon: Very rare:	Hypersensitivity reactions Stevens-Johnson syndrome and toxic epidermal necrolysis.

Overdose

- *Symptoms and signs*

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with azathioprine and result from bone marrow depression which may be maximal after 9 to 14 days after overdosage. These signs are more likely following chronic overdosage, than after a single acute overdose.

- *Treatment*

There is no specific antidote. Gastric lavage has been used for acute overdose. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop. The value of dialysis in patients who have taken an overdose of azathioprine is not known, though azathioprine is partially dialysable.

Safety data off -label azathioprine

The safety data described here are derived from all the identified studies reporting about safety (see section 'Methodology' for more information. The total number of patients treated with azathioprine in studies that mentioned adverse events was 877. The individual studies and tables can be found in section IV: Tables.

Adverse events

Occurance event	**Adverse events without SAE (total number of patients = 877)**
Infections (indications other than transplant patients)	
Common:	Viral, fungal and bacterial infections. (36)
Neoplasms benign and malignant (including cysts and polyps)	
Uncommon:	Neoplasms including non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia (1)
Blood and lymphatic disorders	
Very common: Common: Uncommon:	Leucopenia. (127) Thrombocytopenia. (9) Anaemia (9) Pancytopenia (2), megaloblastic anaemia (1)
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Asthma (1)
Gastrointestinal disorders	
Very common:	Nausea, vomiting, diarrhea; gastro-intestinal complaints (120)
Hepato-biliary disorders	
Very common: Uncommon:	Cholestasis and elevation of liver enzymes . (131) Reverse mild portal fibrosis (8) Mild hepatitis (2)
Skin and subcutaneous tissue disorders	
Immune system disorders	
Common: Uncommon:	Hypersensitivity reactions (12) Fever (3)
Other	
Common: Uncommon:	Joint and muscle pain (15) Paresthesia of hands (1) Weight loss 2-3 kg (2) Abnormalities of taste (2) Otitis media (1) Fatigue (8) Migraine (2) Depression (1) Hay fever (1) Headache (6) Sore tongue (1) Yawning (1)
The following classification has been utilised for the classification of frequency: Very common, ≥ 1/10; common, ≥ 1/100 and < 1/10; uncommon, ≥ 1/1000 and < 1/100; rare, ≥ 1/10000 and < 1/1000; very rare, < 1/10000.	

Serious adverse events

- *Atopic dermatitis*

Four serious adverse events (SAE) were described, 2 of which occurred during treatment with azathioprine, leading to discontinuation of azathioprine.[1-3] One subject experienced a severe pancytopenia, which required blood transfusion. The time between initiating azathioprine and the occurrence of the severe pancytopenia was not reported. It is noteworthy that in this study the TPMT activity was not measured prior to initiation of azathioprine. Another subject developed pancreatitis after 15 days of treatment, which resolved after discontinuation. Two SAE occurred in the follow up period. A non Hodgkin Lymphoma developed 8 months after treatment with azathioprine (duration of treatment 12

months). A fatal event due to a ruptured cerebral aneurysm occurred 7 years after azathioprine treatment.

- *Bullous pemphigoid*

Due to the high mean age of the subjects, relatively long follow up period and the severity of the disease, serious adverse events were not uncommon. Beissert *et al.* reported 2 deaths, 2 cases of severely raised liver enzymes and 1 severe infection.[4] Guillaume *et al.* reported 15 serious adverse events, 6 of which deaths, 4 cases of severe cytopenia and 3 hepatitis.[5] The remaining 2 adverse events were not further specified. The causes of death were unspecified. Burton *et al.* described 3 deaths, 2 due to cerebrovascular accidents (CVA) and one due to heart failure.[6]Another study by Burton *et al.* reported 4 serious adverse events , all occurring during treatment with azathioprine and leading to death .[7] The causes of death were adenocarcinoma, a pre-exisisting mammacarcinoma, myocardal infarction and CVA.

- *Psoriasis*

Three serious adverse events were described which occurred during treatment with azathioprine, leading to discontinuation of the treatment.[8,9] One patient died due to respiratory insufficiency 6 years after azathioprine treatment was stopped. In that same study (Le Quintrec *et al.*) another subject died due to a pulmonary embolus. The time between initiating azathioprine and the pulmonary embolus was not reported. In the publication of Hewitt *et al.*, one subject experienced a severe anemia, which required blood transfusions. The time between initiating azathioprine and the occurrence of the severe anemia was not reported. Another subject had a myocard infarction in the third week of the third treatment course of azathioprine.

- *Chronic actinic dermatitis*

Three subjects died: CVA (1), airway disease (1) and heart disease (1) after 15, 15 and 12 months of azathioprine treatment respectively.[10]

- *Cutaneous vasculitis*

Two serious adverse events occurred, both of infectious origin; a septic arthritis and an epidural abcess.[11] One subject with severe and rapid onset of vasculitis died during treatment with azathioprine due to renal failure, which could be attributed to the natural course of the underlying disease.

- *Cutaneous lupus erythematosus*

One serious adverse event occurred; pancreatitis.[12]

Serious adverse events	
Occurrence Event?	**Serious adverse events (total number of patients = 877)**
Infection (indications other than transplant patients)	
Uncommon:	Severe infection (3)
Neoplasms benign and malignant (including cysts and polyps)	
Uncommon:	Death due to neoplasm (adenocarcinoma, pre-existing mammacarcinoma) (2) Non-Hodgkin's lymphoma (1)
Blood and lymphatic system disorders	
Uncommon:	Severe anaemia (1) Pancytopenia (5)
Respiratory, thorasic and mediastinal disorders	
Uncommon:	Myocardial infarction (1) Death due to heath failure (1) Death due to heath disease (2) Death due to airway disease (2) Death due to pulmonary embolus (1)
Gastrointestinal disorders	
Uncommon:	Pancreatitis (2)
Hepato-biliary disorders	
Uncommon:	Severely increased liver enzymes (2) Hepatitis (3)
Other	
Uncommon:	Death due to CVA (4) Death unspecified (8) Ruptured cerebral aneurysm (1) Unspecified serious adverse event (2)

Evidence on safety derived from included RCT's
There is a limited number of eligible RCT's comparing one treatment with another. However, the relative risk of specific adverse events from a particular RCT could be of value in formulating a recommendation for a therapy.
In the study of Beissert *et al.* the subjects randomized to the azathioprine group had significant higher elevated liver enzymes than the mycofenolaat group; the number of subjects having elevated liver enzymes was comparable (Table 7). Adverse events that occurred during azathioprine treatment compared to betamethasone treatment are shown in Table 30. There were statistically significant (Fisher exact $\leq$ 0.05) more AE's related to corticosteroid use (acne, striae, Cushingoid features, weight gain, rise in blood pressure) in the group B. However, there was no difference in the other AE's. Adverse events that occurred during azathioprine treatment compared to CYC are shown in Table 38.

Conclusion on the strength of evidence concerning overall safety

Low	There is important inconsistency in the way that safety issues are addressed and (serious) adverse events are reported. There is also a considerable amount of indirectness and probability of reporting bias. The remaining body of evidence, consisting of other fundamental study designs (case series and cohort studies) do not deliver the strong evidence needed to increase the grade.

Considerations working group
When comparing the tables about off-label use with the known undesirable effects distilled from the summary of product characteristic and the Dutch "Farmacotherapeutisch kompas" and "SPC", it becomes clear that although the profile of undesirable effects versus adverse events is the same, the number of adverse events reported in the off -label studies is generally larger. An explanation could be the limited number of patients in the off-label studies, which widens the confidence interval and standard deviation. The same can be said about the occurrence of serious adverse effects. Remarkable is the number of deaths due to neoplasms, CVA, pulmonary and heart disease. However, these causes of death are also the most common in general society. Therefore it is questionable whether those deaths are related to the treatment with AZA, especially when taking into account the time window between the occurrence and the treatment.
Considering that the strength of evidence regarding safety is low (see above 'Conclusion') there remains uncertainty about the exact safety risk when using azathioprine as an off-label prescribed drug. The working group took this uncertainty into consideration when formulating recommendations for the separate dermatological diseases.

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Efficacy/effectiveness data off-label azathioprine

Atopic dermatitis

Introduction

In total, 10 studies published between 1996 and 2008 were found in which AD patients were treated with azathioprine; 2 RCT's and 8 case series, 3 of which prospective.

The severity outcome assessments employed were the six area six sign atopic dermatitis score (SASSAD), scoring atopic dermatitis (SCORAD), quality of life (QoL) measurement (Dermatology Life Quality Index, etc). Also symptom based outcome measurements on visual analogue scale (VAS), such as pruritus, sleep disturbance and disruption of work and daytime activity were used. Laboratory markers like serum IgE levels, serum CD30 levels and eosinophil blood counts were also used to monitor disease severity. As these laboratory markers do not clearly reflect disease severity, the clinical importance of those measurements can be questioned. The amounts of topical steroids, oral anti-histamines and antibiotics used during a study and the frequency of *S. aureus* carriage of the skin are also being used to reflect the therapeutical effect of azathioprine. However, in most cases disease severity was only documented by descriptive means.

Besides the severity outcome measurements also onset of action, loss of initial response and duration of remission were reported.

RCT's

Methodological quality

Both RCT's were double-blind placebo controlled trials. The methodological quality of the studies was assessed by using the risk of bias table used by the Cochrane library. Results are shown in Table 4. Overall, there was a low risk of bias. Especially, the study by Meggitt *et al.* was very specific about the procedures before, during and after the clinical study. Berth-Jones *et al.* failed to report if any incomplete data were present and how they dealt with that. (Table 4.)

Demography

The study by Berth-Jones et al. used a cross-over design in which there were two groups of subjects (ratio 1:1). The first group started with azathioprine treatment and crossed over to placebo after 3 months. The second group started on placebo and crossed over to azathioprine treatment after 3 months. In total, 37 subjects (25 male, 12 female) were enrolled, with a mean age of 38 years. Dose of azathioprine was 2.5 mg/kg/day.

Meggitt et al. randomized the 61 subjects (35 male, 26 female) with a mean age of 30 years to either azathioprine or placebo treatment in a 2:1 ratio. The dosage of azathioprine depended on both weight and TMPT activity of the subjects and ranged from 0.5-2.5 mg/kg/day. All patients were allowed to use concomitant topical steroids.

No follow-up was reported in both RCT's. Previous treatments were not reported. (Table 1.)

Efficacy

Both RCT's performed intention to treat (ITT) analysis to compare azathioprine treatment with placebo. Berth-Jones *et al.* found a mean SASSAD improvement of 10.1 points (26%) on ITT analysis on azathioprine treatment and a mean SASSAD improvement of 1.0 points (3%) on placebo ($p < 0.01$). Analysis of changes in symptom scores (pruritus, sleep disturbance and disruption of work and daytime activity) on VAS scales all showed an improvement in the AZA group over the placebo group. Only the improvement on the disruption of work and daytime activity was significant. It is noteworthy that 12 of the 37 subjects withdrew during azathioprine treatment compared to 4 of the 37 subjects during placebo treatment. Reasons for withdrawal when treated with azathioprine were multiple: non compliance (n=6), adverse events (n=4), clearing of eczema (n=1) and lack of response (n=1). Withdrawals during placebo treatment were all due to non-compliance.

Meggitt *et al.* found a mean SASSAD improvement of 37% in the azathioprine group versus 20.6% in the placebo group on ITT analysis. This difference was significant. There was also a significant reduction in body area involvement, patient reported itch, investigator and patient global assessment and Dermatology Life Quality Index. Improvement of sleep loss, reduction of soluble serum CD30 and reduction in the use of topical steroids were non-significant between the two groups. There was no difference in efficacy of azathioprine between the patients on low dosage and high dosage according to their TMPT activity. In total, 7 patients withdrew from the study; 6 patients in the azathioprine group withdrew from the study, (2 due to hypersensitivity, 4 due to severe nausea) and one in the placebo group due to headache and malaise. Time to effect was not reported in both RCT's (Table 2.).

Meta-analysis could not be performed due to insufficient data to calculate the required standard deviations.

Case series

Demography
Eight studies with case series concerning 221 AD patients, 3 of which were prospective were included. The 4 studies with the largest patient populations were all retrospective. Patients included in the trials had moderate to severe atopic dermatitis and were often refractory to conventional therapy. A clear definition of eczema was almost never given. Previous treatments were emollients, topical and oral steroids, cyclosporin, UVB, PUVA and in-hospital treatment. Not all patients received systemic treatment before starting AZA. One study was performed solely with children, in 3 studies the population consisted of both children and adults and in 4 adults only.
The dose employed ranged from 0.5 mg/kg/day to 3.5 mg/kg/day. Two studies adjusted their dose regimen to TMPT activity. Duration of treatment varied from 1 week to 94 months and the follow-up period ranged from 0 to 216 months. (Table 1)

Effectiveness
Two of the 3 prospective studies used clinical parameters to define disease severity. In the study of Hon *et al*., a mean SCORAD improvement of 36.6 units in females and 21.4 units in males was seen over a 6 months period. Meggitt *et al.* found a mean SASSAD improvement of 12.3 units which was statistically significant ($p < 0.05$). In all the other studies descriptive means were used to report changes in disease severity. In those studies, at least 60% of the patients had a 'good' response to azathioprine, although there was no clear definition given of what a 'good response' actually means. There was no clear difference in outcomes of retrospective and prospective studies.
Besides the clinical severity measures also other parameters were explored. Two studies found a significant decrease of serum IgE levels. Hon *et al.* also found significant decrease in S. aureus carriage of the skin and use of anti-histamines, but not in a decreased use of topical corticosteroids. Murphey *et al.* found that the eosinophil counts decreased significantly over time.
Complete remissions were reported in 40.5% to 58.3%. The duration of the remission ranged from 1- 35 months and often lasted until the follow-up period was ended. Lear *et al.* found that in the year after treatment with AZA fewer antibiotic treatments were used and fewer hospital admissions, outpatient attendances and changes to potent topical steroids occurred compared with the year before azathioprine treatment.
In some cases loss of initial response is reported. For example, in the study of Buckley *et al.* 30% of the patients became refractory to azathioprine treatment. Time to treatment response ranged from 1 week to 7 months (Table 2).

Conclusion on strength of evidence for efficacy in atopic dermatitis

High	The two available RCT's are of high quality without any serious limitations or flaws (also see table 4). The effect of azathioprine in atopic dermatitis is a SASSAD score improvement ranging from 26 to 37% after 3 months of treatment with dosages ranging from 0.5 to 2.5 mg/kg/day. The other evidence, consisting mostly of case series, shows no inconsistency with the RCT's.

Clinical recommendation for atopic dermatitis

Strong	There is a strong recommendation for treatment with azathioprine in atopic dermatitis (very certain estimate for a very certain moderate effect). Azathioprine can therefore be used for the treatment of atopic dermatitis if registered treatment options fail or are contra-indicated. Attention should be given to safety aspects when prescribing azathioprine (uncertain safety in off-label use).

Remarks on clinical recommendation for atopic dermatitis

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.	-Two randomized trials (high quality of evidence) and case series have demonstrated the benefit of azathioprine in AD patients (high quality of evidence). Very certain estimate. -Frequent side-effects: gastro-intestinal complaints, abnormal laboratory results. Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine, but are generally low.
Importance of the outcome that treatment prevents	-Diminishing the symptoms of atopic dermatitis (itch, erythema, exudation, excoriation, dryness, cracking and lichenification). -Preventing a negative effect on the health related quality of life. -Less infections

	-Reducing length of stay in hospital -Reducing the long term side-effect of treatments
Magnitude of treatment effect * * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening.	-SASSAD score improvement ranges from 26 to 37% after 3 months of treatment with 0,5 to 2,5 mg/kg/day azathioprine. Moderate effect. - SASSAD score improvement in cyclosporin treatment ranged from 39% to 57% (ref J Schmitt (2007))
Precision of estimate of treatment effect * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Significant effect azathioprine compared with placebo ($p < 0,01$). Very certain precision. -Patient reported itch was significantly decreased in 1 RCT and non-significantly in the other RCT.
Risks associated with therapy	-See section "general treatment considerations" and "safety".
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section "general treatment considerations". There seems to be no difference compared with other systemic treatment options.
Risk of target event	-
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-

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Bullous pemphigoid

Introduction

In total, 7 studies published between 1971 and 2007 were found in which patients with bullous pemphigoid (BP) were treated with azathioprine: 3 RCT's, 1 cohort and 3 case series.

Efficacy/effectiveness was measured by the percentage of patients with a complete remission or controlled disease (defined as: no new blisters in the last week, mild pruritus and resolution of erythema), number of cumulative doses of concomitant oral corticosteroids, dose of oral corticosteroids at which the patient relapsed and duration of hospitalization.

Also the time to remission, duration of remission, time to relapse and number of deaths were used to assess efficacy.

Laboratory markers like anti-basement membrane zone (BMZ) antibodies were also used to monitor disease severity. Anti-BMZ antibodies are believed to correlate to disease severity. (Jordon *et al.* 1967, p751)

RCT's

Methodological quality

All three RCT's employed an adequate randomization. Concealment of allocation was adequate in 2 and unclear (not described) in the study of Beissert *et al.* None of the trials were double blinded. Beissert *et al.* judge that the outcome measurement is not likely to be influenced by lack of blinding, since complete clearance of the lesions was their primary outcome and this could not be subject to interpretation of the observer. However, the cumulative dose of oral corticosteroids used during the study was also used as a primary outcome and this outcome is prone to bias. The same is true for the study of Burton *et al.* Guillaume *et al.* They defined their primary outcome as 'controlled disease' which could clearly be subject to interpretation of the observer.

The study by Guillaume *et al.* was interrupted after the interim analysis and (hence) no significantly results were found. Moreover, safety aspects were insufficiently described. In the publication of Burton *et al.* the methods were only briefly delineated and the methodological quality could hardly be assessed. Overall, Beissert *et al.* performed the most methodological sound study. An overview of the methodological quality can be seen in the risk of bias table (Table 8).

Demography

Two treatment arms were compared in the studies of Beissert *et al.* and Burton *et al.* and 3 treatment arms in Guillaume *et al.* AZA was never applied as monotherapy, but always in combination with oral steroids. There was no crossover between the treatment arms. Duration of treatment ranged from 6 to 36 months and depended highly on individual treatment response. The dosage employed ranged from 100-150 mg and 2.0-2.5 mg/kg/day. Follow-up was carried out in one study for the duration of 10 months.

In total, 196 subjects (86 male, 110 female) were enrolled, with a mean age of 76 years. In all subjects the diagnosis of BP was established by histological analysis of skin biopsies demonstrating subepidermal blistering and linear deposition of immune reactants (IgG and/or C3) along the BMZ junction. Usually, there were no previous treatments as only patients with acute onset of BP were treated. TMPT activity was never measured prior to initiation of azathioprine (Table 5)

Efficacy

Beissert *et al.* compared methylprednisolone plus azathioprine with methylprednisolone plus mycofenolate mofetil. Results show that in both groups a 100% remission was achieved. Time to remission was more prompt in the azathioprinegroup, although this was not statistically different. Cumulative dose of oral steroids and duration until relapse after tapering the medications were not significantly different between the two groups. In the study of Guillaume *et al.* prednisolone monotherapy was compared with prednisolone plus azathioprine and prednisolone plus plasma exchange. The study was interrupted after the interim analysis showed that there was neither an appreciable benefit resulting from addition of azathioprine or plasma exchange to prednisolone nor that this could be expected on completion of the study.

Burton *et al.* found a significant reduction (45%) of the cumulative prednisone dose over a 3 years period when comparing prednisolone monotherapy with prednisolone plus azathioprine. Although the percentage of remissions and numbers of deaths favored the oral corticosteroids plus azathioprine group, there was no significant difference between the groups.

After withdrawal of concomitant oral corticosteroids, duration of remission of the lesions was approximately 5.5 months on AZA monotherapy. Onset of action was never mentioned (Table 6.).

Cohort

Methodological quality

One cohort study by Ahmed *et al.* was included. Concerning the methodological quality a few remarks can be made. Firstly, demographic information about the individual treatment groups is missing. Therefore, a selection bias could not be excluded. Secondly, the two treatment groups were not comparable in terms of disease severity. Thirdly, some outcome data (length of hospitalization) mentioned in the methods section were not addressed in the results section. Fourthly, the method of outcome assessment was not validated and not blinded for the treatment arm.

Demography
Two groups were compared; prednisone and prednisone plus azathioprine. Twenty-nine subjects participated, 43-92 years of age. Subjects were not previously treated with other medication. The dosage of azathioprine employed was 1.5 mg/kg/day. Prednisone was given in reduction schedule after clinical remission occurred. The individual or mean duration of treatment was not reported. Follow up ranged from 8 to 45 months (Table 5).

Efficacy
A 50% reduction in maintenance dose of prednisolone dose was found in the azathioprine group and a 30% reduction in the length of systemic therapy. Whether these outcomes were statistically significant, is uncertain (Table 6).

Case series
Demography
Three studies with case series were included concerning 17 BP patients. Diagnosis of BP was histologically proven in all studies. The age of the subjects ranged from 47 to 91 years. Previous treatments were oral steroids. Van Dijk *et al.* was the only study in which azathioprine was used without concomitant prednisolone.
Burton *et al.* conducted a 4 years follow-up study monitoring the same subjects that were initiated on treatment during the Greaves *et al.* study. Two subjects were lost to follow up. The dose employed was 2.5 mg/kg/day in two studies and ranged from 75 to 250 mg/day in the third. Duration of treatment varied from 2 to 48 months and the follow-up period could be as long as 48 months (Table 5).

Effectiveness
Greaves *et al.* found that the dose of prednisolone at which the subjects relapsed (e.g. the relapse dose) was lower when subjects were using concomitant azathioprine. They found that by giving azathioprine it was possible to withdraw prednisolone maintenance treatment without relapses in 9 out of 11 subjects. .
In the follow-up study by Burton *et al.* 4 of the above mentioned subjects remained in remission during 4 years, 1 became refractory, 1 experienced a moderate response and 4 subjects died.
Van Dijk *et al.* showed a very good response (no new blisters) in 2 subjects, a good response (occasional new blisters) in 2 subjects and one patient withdrew after 2 weeks because of a deterioration of the renal function by pre-existent renal disease. Time to response was 4-6 weeks (Table 6).

Monotherapy

Conclusion on strength of evidence for efficacy of monotherapy in bullous pemphigoid

Very low	The only available case series considering monotherapy with azathioprine is of very low methodological strength with sparse data and some uncertainty about directness. The reported effect shows 40% well controlled disease/remission, 10% moderate response, 10% stopped due to AE and 40% died.

Clinical recommendation for monotherapy with azathioprine in bullous pemphigoid

Weak	There is a weak recommendation for treating bullous pemphigoid with azathioprine alone if treatment with oral corticostroids is contraindicated or has failed (very uncertain estimate for an effect of very uncertain magnitude).

Combination therapy

Conclusion on strength of evidence for effectiveness of combination therapy in bullous pemphigoid

Moderate	The three available RCT's are of moderate quality due to serious limitations in study quality (also see Table 8). Although there seems to be a steroid sparing effect, there is no significant effect of azathioprine in addition to oral corticosteroids. The other evidence consisting of one cohort study and three case series shows some inconsistency with the RCT's regarding the effectiveness. A reduction of maintenance dose of oral corticosteroids, a reduction in length of therapy and a lower dose of oral corticosteroids at which subjects will relapse was seen. The inconsistency does not decrease the level of evidence (heterogenous outcome parameters).

Clinical recommendation for combination therapy with azathioprine in bullous pemphigoid

Weak	There is a weak recommendation for treating bullous pemphigoid with a combination of azathioprine and oral corticosteroids (no significant benefit of azathioprine). When there is a need for a corticosteroid sparing effect and a reduction of the cumulative steroid dose combination therapy may be considered (uncertain estimate for a moderate steroid sparing effect). Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks on clinical recommendation for bullous pemphigoid

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.	-Three randomized trials (moderate quality of evidence) have demonstrated no significant benefit of azathioprine in bullous pemphigoid patients already treated with oral corticosteroids. Certain estimate. -One randomized trial and one case series found a significant oral corticosteroid sparing effect. One cohort showed no significant corticosteroid sparing effect. Uncertain estimate. -One case series reported 40% well controlled disease/remission, 10% moderate response, 10% stopped due to AE and 40% died. Very uncertain effect. -Frequent side-effects: gastro-intestinal complaints, abnormal laboratory markers. Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Complete clearance of blisters -Controlled disease -Cumulative steroid dose -Death
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-No significant effect regarding to complete clearance of blisters and controlled disease compared with oral corticosteroids. No effect. -45%-50% sparing in cumulative oral corticosteroids dose. Moderate effect. -One case series 40% well controlled disease/remission, 10% moderate response, 10% stopped due to AE and 40% died. Very uncertain magnitude (worsening to good).
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Large confidence intervals; for example complete remission was achieved after 23.8 days treatment with azathioprine but with a standard deviation of 18.9 days. Uncertain precision. Monotherapy: very uncertain precision (see Magnitude of treatment effect).
Risks associated with therapy	-See section “general treatment considerations” and “safety”.
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, afterwards every one to three months. See also section “general treatment considerations”.
Risk of target event	- 100%.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-

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Chronic actinic dermatitis

Introduction
In total, 3 studies published between 1984 and 2003 were found in the literature in which patients with chronic actinic dermatitis (CAD) were treated with azathioprine: 1 RCT and 2 case series. Outcome measurements to assess efficacy were the affected body surface area (BSA), severity of the rash and itch score on a visual analogue scale (VAS). Effectiveness was assessed by descriptive means. Also the duration of remission, time to relapse and mortality rate were used to assess aspects of efficacy and effectiveness.

RCT's
Methodological quality
Although details on randomization, allocation concealment of allocation and blinding were not provided, Murphy *et al.* stated in the title of the article to have performed a double-blinded randomized controlled trial. It was described that the code was broken after it was considered ethically inappropriate to continue the trial and therefore the trial was early terminated. Furthermore, it was not clear how the affected body surface area was measured. At baseline the two treatment groups are not comparable concerning severity of the disease and during the study the active treatment group had a greater UV exposure. It is unclear if this led to bias in this study. An overview of the methodological quality can be seen in the risk of bias table (Table 11).

Demography
Two treatment groups are described. One group received azathioprine and the other placebo treatment. Patients from both groups were required to wear polysulphone film lapel-badges to ensure equivalent ultraviolet exposure during treatment and to permit a valid comparison of the groups. Duration of treatment was 1.5 to 12 months. Dosage of azathioprine employed was 50 mg/day. In total, 18 subjects (16 male, 2 female) were enrolled, 8 patients in the azathioprine group and 10 patients in the placebo group. In the azathioprine group the mean age was 64 years and in the placebo group 66 years. In all subjects the diagnosis of CAD was confirmed by irradiation monochromator testing on the skin of the back.
TMPT activity was not measured prior to initiation of azathioprine (Table 9).

Efficacy
Mean reduction in itch VAS was 4.6 (95% CI 0.3-5.8) in the azathioprine group versus 3.5 (95% CI not given) in the PCB group at 6 months. The mean reduction in rash VAS was 4.9 (95% CI 1.3-7.0) in the azathioprine group versus 1.1 (95% CI not given) in the PCB group at 6 months. The mean reduction in BSA of rash was 34.4% (95% CI 11.8-112.5%) in the azathioprine group versus 27.8 (95% CI not given) in the PCB group at 6 months. The differences between the groups were statistically significant. The mean reduction in itch score, rash score and extent of rash was also significantly higher at 1 and 3 months. One patient withdrew due to gastrointestinal adverse events in the azathioprine group (Table 10).

Case series
Methodological quality
While Yap et al treated CAD patients with azathioprine, prednisone and cyclosporine, we did not consider it a cohort study by our predefined criteria, as the groups could not be compared due to lack of data.

Demography
In total, 14 patients with CAD were included. The diagnosis of CAD was based on clinical, and if necessary, histological features, and the results of photodiagnostic tests. The age of the subjects ranged from 26-85 years. Previous treatments consisted of topical steroid therapy and restriction of light exposure. The dose of azathioprine employed in Yap *et al.* was 1.0-2.5 mg/kg/day; the dose in Leigh *et al.* 100 to 200 mg/day. In Yap *et al.* the duration of treatment and follow-up period depended highly on individual requirement and was not described. In Leigh *et al.* the duration of treatment ranged from 1.5-33 months (Table 9).

Effectiveness
All outcome measurements were by descriptive means. In the study of Yap *et al.* 11 subjects (92%) had a partial to good clinical response; 1 subject (1%) withdrew from the study due to unknown reasons. In the study of Leigh *et al.* 9 (57%) of the subjects cleared or improved markedly, 2 (14%) of the subjects cleared and relapsed while on treatment, 2 (14%) had no response to the treatment and 2 (14%) subjects withdrew from the study for unknown reasons (Table 10).

Conclusion on strength of evidence for efficacy in chronic actinic dermatitis

Low	The only available RCT is of low quality with serious limitations in study quality and sparse data (also see Table 11). The other evidence (case series) shows no inconsistency with the RCT.

Clinical recommendation for chronic actinic dermatitis

Weak	There is a weak recommendation for treating chronic actinic dermatitis with azathioprine if other effective options have failed or are contra-indicated (uncertain estimate for an uncertain moderate effect). Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks on clinical recommendation for chronic actinic dermatitis

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.	-One randomized trial (low quality of evidence) and case-series have demonstrated the benefit of azathioprine in patients with chronic actinic dermatitis. Uncertain estimate. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Diminishing the symptoms of chronic actinic dermatitis (itch, rash) and the affected body surface area.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-VAS score reduction for itch 4.6 and for rash 4.9 after 1.5 to 12 months treatment with azathioprine 50 mg/day. -Mean body surface area reduction (rash) of 34.4%. -Working group: moderate effect.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-95% confidence interval reduction itch VAS was 0.3-5.8. -95% confidence interval reduction rash VAS was 1.3-7.0. -95% confidence interval reduction BSA was 11.8-112.5%. -Working group: uncertain precision.
Risks associated with therapy	-See section "general treatment considerations" and "safety".
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section "general treatment considerations".
Risk of target event	- Risk is 100% regarding to chronic actinic dermatitis itself. Risk regarding malignancy or death unclear.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-There are numerous other effective treatment options.

References

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Cutaneous vasculitis

Introduction
In total, 3 studies published between 1987 and 1991 were found in the literature in which patients with cutaneous vasculitis (CV) or cutaneous involvement of systemic vasculitis were treated with azathioprine; 1 RCT and 2 case series.
All outcome measurements were by descriptive means; no outcome measurement tools were used.
The number of patients with a complete remission (defined as complete resolution of the lesions) was used to define effectiveness. Also, the number of subjects with effective treatment defined as resolution of lesions, returning to normal of abnormal laboratory markers and/or ability to lower dosage of oral corticosteroids, were employed. Duration of remission, time to relapse and mortality rate were also reported to assess aspects of efficacy.

RCT
Methodological quality
Heurkens *et al.* performed a non-blinded randomized controlled trial. Details on randomization and allocation of concealment were not given. Furthermore it was not clear how the severity of vasculitis was measured and by whom.
An overview of the methodological quality can be seen in the risk of bias table (Table 15).

Demography
Three treatment groups are described, but only two groups are comparable with each other according to disease severity and were actively compared in this study, namely groups A and B. Group C consisted of patients with severe systemic involvement of vasculitis and was therefore excluded from our analysis. Group A received prednisolone with azathioprine and group B received conventional antirheumatic treatment including non steroid anti-inflammatory drugs, hydroxychloroquine, penicillamine, sulfasalazine and aurothioglucose. Duration of treatment was 3 months and follow-up 29 months. Dosage employed was 2.0 mg/kg/day with 10-60 mg concomitant prednisolone.
In total, 19 subjects (12 male, 7 female) were enrolled, with a mean age of approximately 66 years (range 37-86) in groups A & B. In all subjects the diagnosis of CV was established by presence of clinical features of CV (palpable purpura, ulcers, nail fold infarcts, peripheral gangrene) and by histological analysis of skin biopsies demonstrating infiltration of small vessels. TMPT activity was not measured prior to initiation of azathioprine (Table 13).

Efficacy
There was a significant reduction of skin vasculitis after 18 months in group A; 7 subjects (88%) achieved complete remission. In group B, 6 subjects (55%) achieved remission, but this outcome was not significant. The difference between the treatment groups was also not statistically significant. One patient in the azathioprine group withdrew due to gastrointestinal side effects (Table 14).

Case series
Demography
Two studies of one author were included of which the most recent one was prospective. In total, 19 patients with various forms of cutaneous vasculitis were described, including subjects with recalcitrant and severe disease appearing as palpable purpura, livedo reticularis, bullous lesions, ulcerations, urticaria like lesions and nodules. In all cases, there was only mild systemic involvement. Clinical diagnosis was confirmed by histological investigation. The age of the subjects ranged from 20-50 years. Previous treatments included oral corticosteroids, dapsone, methotrexate, hydroxychloroquine sulfate, colchicine and indomethacin. The dose of AZA employed ranged from 150 to 250 mg/day. Duration of treatment and follow-up period depended highly on individual requirement and was not described in the two studies of Callen *et al.* (Table 13).
Effectiveness
All outcome measurements were done by descriptive means. In the study of Callen et al (1991) 2 (33%) of the subject had a complete response defined as disappearance of existing lesions, no new lesions and being able to stop other treatment. Three subjects (50%) had partial response, defined as clearing of the lesions, but inability to lower the dose without relapse and 1 subject experienced no response. In the other study of Callen et al (1987) all patients responded well on treatment with azathioprine, defined as resolution of lesions, returning to normal of abnormal laboratory markers or ability to lower dosage of prednisolone (Table 14).

Conclusion on strength of evidence for efficacy of combination therapy in cutaneous vasculitis

Low	The only available RCT is of very low quality with serious limitations in study quality, sparse data and some uncertainty about directness (also see Table 15). The other evidence consisting of case series shows no inconsistency with the RCT.

Clinical recommendation for combination therapy in cutaneous vasculitis

Weak	There is a weak recommendation for treating cutaneous vasculitis with azathioprine in combination with oral corticosteroids if conventional treatment options are contra-indicated or have failed. It is very uncertain if the efficacy outweighs the safety aspects (very uncertain estimate for a very uncertain moderate effect). Patients with cutaneous vasculitis caused by an identifiable agent that can be eliminated should not be initiated on this treatment. Elimination of the identifiable agent should be the first treatment step. Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks on clinical recommendation for cutaneous vasculitis

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.	-One randomized trial (very low quality of evidence) and case-series have demonstrated the benefit of azathioprine with concomitant oral corticosteroids in cutaneous vasculitis patients. Very uncertain estimate. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Complete remission cutaneous vasculitis.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-Complete remission ranges from 33 to 88% after various treatment duration and dosage. Moderate effect.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Descriptive outcomes; wide range. Very uncertain precision.
Risks associated with therapy	-See section “general treatment considerations” and “safety”
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section “general treatment considerations”.
Risk of target event	-Target event is cutaneous vasculitis; so risk is 100%.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-Patients with CV caused by an identifiable agent that can be eliminated should not be initiated on this treatment. Elimination of identifiable agent should suffice.

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Cutaneous lupus erythematosus

Introduction
One study was found, which was published in 1991. It concerned a case series, in which patients with subacute and chronic cutaneous lupus erythematosus were treated with azathioprine. Only descriptive means were used to describe efficacy.

Case series
Demography
In the study of Callen *et al.*, 6 subjects were included with a mean age of 42.5 years. The dose of azathioprine employed was 100-150 mg/day and in all subjects concomitant oral steroids were used. The duration of treatment and follow-up were not reported, though some subjects were treated for over a year. Previous treatments included oral steroids, dapsone, hydroxychloroquine sulfate, methotrexate, isotretinoin and quinacrine (Table 17).

Effectiveness
One subject (17%) achieved a complete remission after 6 weeks of azathioprine treatment and could taper the daily dose of steroids. Three subjects (50%) achieved a partial response and 2 subjects (33%) no response (Table 18).

Conclusion strength of evidence effectiveness cutaneous lupus erythematosus in combination therapy

Very low	The only available study is of very low quality (observational study) with sparse data and some uncertainty about directness.

Clinical recommendation on combination therapy in cutaneous lupus erythematosus

Weak	There is a weak recommendation for treating cutaneous lupus erythematosus with azathioprine in combination with oral corticosteroids 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 low effect).

Remarks on clinical recommendation for cutaneous lupus erythematosus

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 azathioprine with concomitant oral steroids in cutaneous lupus erythematosus patients. Very uncertain estimate. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
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	-17% achieved complete remission. Low effect.
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	-See section “general treatment considerations” and “safety”
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section “general treatment considerations”.
Risk of target event	- Target event is cutaneous lupus erythematosus; so risk is 100%.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic.

	(*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-There are other treatments available.

References

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Erythema multiforme

Introduction
One study, a case series, was found, published in 1995, in which patients with cutaneous recurrent erythema multiforme were treated with azathioprine. Only descriptive means were used to describe efficacy.

Case series
Demography
In the study of Farthing *et al*. 6 subjects were included with a mean age of 29.6 years (range(16-39). The dose of azathioprine employed was 50-150 mg/day. The duration of treatment ranged from 15 to 60 months and follow-up was performed in 2 patients for a duration of 8 and 12 months. Previous treatments included oral steroids, dapsone, gammaglobulin and acyclovir (Table 19).

Effectiveness
Three subjects (60%) achieved a complete remission. Two subjects (40%) were well controlled with azathioprine (Table 20).

Conclusion on strength of evidence effectiveness in erythema multiforme

Very low	The only available study is of very low quality (observation study) with sparse data and some uncertainty about directness.

Clinical recommendation for erythema multiforme

Weak	There is a weak recommendation for treating recurrent erythema multiforme with azathioprine if conventional treatment options are contra-indicated or have failed (very uncertain estimate for a very uncertain good effect). Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks on clinical recommendation for erythema multifiorme

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.	-Very uncertain benefit. Only one study available. -Uncertain risk profile. -Cost may vary, but are generally low.
Importance of the outcome that treatment prevents	-Symptoms of erythema multiforme.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-60 % complete remission; 40% well controlled. Good effect.
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	-See section “general treatment considerations” and “safety”
Burdens of Therapy	- See also section “general treatment considerations”.
Risk of target event	- 100%.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-

References

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Hand dermatitis

Introduction
In total, 1 eligible study published in 2009 was found, in which patients with hand dermatitis and concomitant lymphoedema were treated with azathioprine; it was a case series. Severity outcome assessments employed were percentage of improvement in swelling and dermatitis judged by the subjects themselves.

Case series
Demography
The included case series concerned 6 subjects with hand dermatitis (dyshidrotic, allergic and irritant contact dermatitis) and concomitant lymphoedema of the hand and forearm, which is a rare complication of hand dermatitis. They were often refractory to conventional therapy. A clear definition of hand dermatitis and lymphoedema was not given. Previous treatments were topical and oral steroids and penicillin. All patients received systemic treatment (unknown which) before initiating azathioprine. During treatment with azathioprine, oral antibiotics and potent topical steroids were also given. All subjects were adults. The dosage of azathioprine used and duration of treatment was unclear. The follow-up period ranged from 3 to 48 months. The TPMT activity was not measured prior to initiation of azathioprine (Table 21).

Effectiveness
Over 75% improvement of swelling was achieved in 2 (33%) of the subjects and 50-75% improvement in 1 subject. Three patients withdrew from treatment (Table 22).

Conclusion on strength of evidence for effectiveness in hand dermatitis

Very low	The only available study is of very low quality (observation study) with sparse data and some uncertainty about directness.

Clinical recommendation for hand dermatitis

Weak	There is a weak recommendation for the use of azathioprine to reduce swelling in patients with chronic hand dermatitis if conventional treatment options are contra-indicated or have failed (very uncertain estimate for a very uncertain moderate effect). Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks on clinical recommendation for hand dermatitis

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.	-One study has demonstrated some effect of azathioprine in patients with hand dermatitis. Very uncertain benefit. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Improvement swelling and dermatitis.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-33% achieved over 75% improvement of swelling. Moderate effect.
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	-See section “general treatment considerations” and “safety”
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section “general treatment considerations”.
Risk of target event	-Target event is hand dermatitis; so risk is 100%.

Costs	-- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-

References

27. Pearce VJ, Mortimer PS, Pearce VJ *et al*. Hand dermatitis and lymphoedema. *Br J Dermatol* 2009; **161**: 177-80

Leprosy type 1 reaction

Introduction
In total, 1 RCT published in 2004 was found in which patients with leprosy type 1 reaction were treated with azathioprine. To measure the efficacy in this trial, a special instrument was made, which was not previously validated. This outcome tool assessed three categories of symptoms. Category A includes skin symptoms and nerve pain, category B sensory testing and category C voluntary muscle testing. Furthermore the need for rescue medication was assessed as an aspect of efficacy.

RCT
Methodological quality
Marlowe *et al.* performed a non blinded randomized controlled trial. However, methods of randomization and concealment of allocation were not described. Nonetheless, the two treatment groups were described in great detail and were comparable at randomization. All predefined outcomes were addressed in the article, so selective outcome reporting was considered unlikely. An overview of the methodological quality can be seen in the risk of bias table (Table 25).

Demography
There are two treatment groups; group I received azathioprine (3.0 mg/kg/day) and prednisolone (from 5 mg/day to 40mg/day) during the first 8 weeks in a reduction schedule and group II received prednisolone for 12 weeks in a reduction schedule (from 5 mg/day to 40 mg/day). The 3 months period of active treatment was followed by a 3 months follow-up period. In total, 40 subjects were enrolled and completed the study. The diagnosis of severe leprosy type 1 reaction was established by the presence of erythematous and raised skin lesions with or without evidence of neuritis in patients with borderline tuberculoid, borderline lepromatous or lepromatous leprosy. TMPT activity was not measured prior to initiation of azathioprine (Table 23).

Efficacy
The skin symptoms improved in 11/21 patients (52%) compared to baseline in the prednisolone plus azathioprine group versus improvement in 12/19 patients 65% in the prednisolone group at week 12; the improvement was significant in both groups. This effect was sustained in the follow up period. Need for rescue medication in the first 12 weeks was found in 48% of the subjects in the azathioprine group versus 37% in the prednisolone group. At 12 weeks and 24 weeks, the nerve function (sensory and voluntary muscle testing) showed no improvement in both groups. Nerve pain and tenderness did improve in both groups. There was no statistically significant difference between the groups concerning all the above mentioned outcomes (Table 24).

Conclusion on strength of evidence for efficacy of combination therapy in leprosy type 1 reactions

Low	The available RCT is of low quality because it has very serious limitations in study quality (Table 23).

Clinical recommendation for combination therapy in leprosy type 1 reactions

Weak	There is a weak recommendation for the use of azathioprine with concomitant oral steroids for the treatment of a severe leprosy type 1 reaction. Although there was no significant beneficial effect of azathioprine compared with conventional (steroid) treatment, a possible steroid sparing effect was suggested. Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks on clinical recommendation for leprosy

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.	-One randomized trial (low quality of evidence) has demonstrated no significant difference in therapeutic effect of azathioprine and prednisolone treatment compared with prednisolone treatment alone. There was a significant beneficial effect compared with baseline symptoms. Uncertain estimate. -There is an uncertain steroid sparing effect. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Diminishing the skin symptoms of leprosy.

Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-Skin symptom improvement was seen in 52% of the patients after 3 months treatment. Moderate effect.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Descriptive outcome. Uncertain.
Risks associated with therapy	-See section "general treatment considerations" and "safety"
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section "general treatment considerations".
Risk of target event	-Skin symptoms are the target event, so the risk is 100%.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	Duration of treatment was considered to short by the working group to evaluate treatment effect.

References

28. Marlowe SNS. Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. Transactions of the Royal Society of Tropical Medicine and Hygiene 2004; 98: 602-9.

Lichen planus

Introduction
One study was found, which was published in 2001. It concerned a case series in which patients with severe erosive oral and generalized lichen planus were treated with azathioprine. Only descriptive means were used to describe efficacy. Duration of remission was also reported.

Case series
Demography
In the study of Verma *et al.*, 9 subjects were included in whom the clinical diagnosis was confirmed by skin or mucosal biopsies. The mean age of the subjects was 32.2 years and the dose of azathioprine employed was 100mg/day. The duration of treatment ranged from 3 to 7 months with a mean duration of 5 months. The follow-up period ranged from 6 to 9 months. Previous treatments were not reported (Table 27).

Effectiveness
Seven subjects (77.8%) had an excellent response to treatment which implies a 75-100% improvement of the lesions and itching/irritation. One subject had a good response implying 50-75% improvement of the lesions. Another subject experienced only a 40% improvement which was considered a poor response. All subjects with an excellent response remained in remission during the whole follow-up period (Table 28).

Conclusion on strength of evidence for effectiveness in lichen planus

Very Low	The only available case series is of very low quality (observation study) because of sparse data.

Clinical recommendation for lichen planus

Weak	There is a weak recommendation for treating lichen planus with azathioprine, if conventional treatment options are contra-indicated or have failed (very uncertain estimate for a uncertain good effect). Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

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* * estimates for benefit (efficacy/effectiveness) and safety are ranked by the working group as very certain, certain, uncertain or very uncertain.	-One case series (very low quality of evidence) demonstrated a benefit of azathioprine in severe lichen planus patients. Very uncertain treatment effect. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Improving the lesions and symptoms of lichen planus
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-77.8% has a 75-100% improvement of the lesions and itching/irritation. Good effect.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Descriptive outcomes. Uncertain.
Risks associated with therapy	-See section “general treatment considerations” and “safety”
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section “general treatment considerations”.
Risk of target event	-Target event is lichen planus, therefore the risk is 100%.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic.

	(*www.medicijnkosten.nl).
Varying Values between patients	-
Other	- There are numerous other effective treatment options.

References

29. Verma KK, Mittal R, Manchanda Y *et al*. Azathioprine for the treatment of severe erosive oral and generalized lichen planus. *Acta Derm Venereol* 2001; **81**: 378-9.

Parthenium dermatitis

Introduction
In total, 4 studies all performed in India, published between 1998 and 2009 were found in the literature in which patients with parthenium dermatitis (PD) were treated with azathioprine; 1 RCT, 1 cohort and 2 case series. Clinical outcome measurements used were a modified version of the Psoriasis Activity and Severity Index (PASI) and the clinical severity score (CSS). The CSS is an outcome tool especially developed for determining the severity of parthenium dermatitis. In CSS the degree of itching, type of lesions (e.g. papules, plaques, degree of lichenification), presence of erythema and areas of involvement are assessed and given a certain value. Furthermore, the efficacy and effectiveness were assessed by the number of patients with a complete remission, use of concomitant corticosteroid, duration of remission, time to relapse and number of relapses.

RCT
Methodological quality
Verma *et al.* performed a blinded randomized controlled trial. Randomization and allocation, concealment of allocation were described in sufficient detail. It was not clear by whom the severity of PD was measured and if this was done blinded for the treatment. During the study a substantial number of subjects were lost to follow up in both groups, 14 in total. The reasons for this were not specified for the treatment groups and also not available for the whole study population. Furthermore, the amount of topical corticosteroids used during the study was not compared between the groups. An overview of the methodological quality can be seen in the risk of bias table (Table 31).

Demography
There were two treatment groups: group A received azathioprine (100 mg/day) and group B received oral betamethasone (2 mg/day). Duration of treatment and follow-up period were both 6 months. In total, 55 subjects (41 male, 14 female) were enrolled, with a mean age of approximately 46 years. In all subjects the diagnosis of PD was established by presence of clinical features and positive patch testing for Parthenium hysterophorus. Previous treatments were not reported. TMPT activity was not measured prior to initiation of azathioprine (Table 29).

Efficacy
In group A (azathioprine) 19 patients (73%) had an excellent response to treatment, 1 patient (4%) had a poor response to treatment and 6 patients (23%) were lost to follow-up. The CSS decreased from 64.5 $\pm$ SD 16.4 to 4.3 $\pm$ SD 5.6 ($p < 0.01$).
In group B (betamethasone) 21 patients (72%) had an excellent responds to treatment and 8 patients (28%) were lost to follow-up. The pre-treatment CSS decreased from 67.1 $\pm$ SD17.4 to 0.6 $\pm$ SD 2.2 ($p < 0.01$). It was not reported whether the differences between the groups were significant. In group A, 45% of the patients had a relapse compared to 67% of the patients in group B ($p > 0.05$) (Table 30).

Cohort
Methodological quality
Subjects who were using azathioprine for at least 6 months were included for analysis, thereby excluding patients who stopped treatment for unknown reasons. Selection of the subjects and assignment to a treatment group was not described. A selection bias is likely. Furthermore, the groups were not clearly described; gender and severity of the disease were not given. The outcome measurement was not defined, validated and blinded.

Demography
One cohort study was included. In total, 43 patients with parthenium dermatitis were included. Clinical diagnosis was confirmed by patch-testing. Previous treatments were not reported. The age of the subjects ranged from 31 to 75 years and previous treatments were not given. The subjects were assigned into 3 groups, each with a different dose regimen. The dose of azathioprine employed in group I is 100 mg/day, in group II 50 mg/day and 300 mg every 28 days and in group III 100 mg/day and 300 mg every 28 days. Duration of treatment was at least 6 months with 36 months of follow-up (Table 29).

Effectiveness
All outcome measurements were done by descriptive means. Complete remission was achieved by 11 subjects (50%) of group I, 2 (18%) in group II and 3 (30%) in group III. Subjects who required additional corticosteroids to achieve complete remission were 9 (40%) in group I, 7 (64%) in group II and 6 (60%) in group III. Incomplete remissions were seen once in all groups. In groups I and II one subject withdrew. Level of significance was not provided pre- versus posttreatment. Between the groups there was no statistically significant difference (Table 30).

Case series
Demography
In total, 32 patients with parthenium dermatitis were included. Clinical diagnosis was confirmed by patch-testing. The

age of the subjects ranged from 39 to72 years. Previous treatments were only described in Verma *et al.* (2006) and consisted of systemic prednisone.
The dose of azathioprine employed ranged from 100 to 150mg/day in the study of Verma *et al.* In the study of Sharma *et al.* the dose of azathioprine was 300 mg/week. Duration of treatment in both studies was 6 months. In the study of Sharma *et al.* the follow-up ranged from 9 to 12 months (Table 29).

Effectiveness
In the study of Verma *et al.* 37 subjects (58%) had 80-100% clearance and 5 subjects (42%) had 60% clearance. Post-treatment CSS decreased from mean SD 40.4±7.95 to 10.9±8.43 (P<0.01).
In the study of Sharma *et al.*, 10 subjects (66%) had a 90% reduction in the modified PASI score, 3 (20%) achieved a reduction of 50%, 1 (2%) achieved less than 50% reduction in the PASI score and 1 (2%) had no improvement (Table 30).

Conclusion on strength of evidence for efficacy in parthenium dermatitis

Moderate	The available RCT is of moderate quality because it has serious limitations in study quality (Table 29). The other body of evidence, consisting of case series and a cohort study, shows no inconsistency with the RCT.

Clinical recommendation for parthenium dermatitis

Strong	There is a strong recommendation for treating parthenium dermatitis with azathioprine (certain estimate for a certain good effect). Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks on clinical recommendation for parthenium dermatitis

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.	-One randomized trial (moderate quality of evidence), a cohort study and case-series have demonstrated a benefit of azathioprine in parthenium dermatitis patients. Certain estimate. - In two studies oral steroids were given concomitantly, but the dosage was tapered during treatment with azathioprine. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine. -Three articles were from the same author.
Importance of the outcome that treatment prevents	-Remission in symptoms/signs: itching, type of lesions (e.g. papules, plaques, degree of lichenification), presence of erythema and areas of involvement.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-50 to 73% has an excellent response (> 80% clearance). -Clinical severity score reduced from 67.1 to 0.6. -Working group: good effect.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Outcomes definitions vary. -Standard deviation clinical severity score post treatment was 2.2; difference statistically significant. Certain estimate.
Risks associated with therapy	-See section “general treatment considerations” and “safety”
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section “general treatment considerations”.
Risk of target event	-
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery,

	laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-There are other treatment options available.

References

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31. Verma KK, Manchanda Y, Pasricha JS *et al*. Azathioprine as a corticosteroid sparing agent for the treatment of dermatitis caused by the weed Parthenium. *Acta Derm Venereol* 2000; 80: 31-2.
32. Verma KK, Mahesh R, Srivastava P *et al*. Azathioprine versus betamethasone for the treatment of parthenium dermatitis: a randomized controlled study. *Indian J Dermatol Venereol Leprol* 2008; 74: 453-7.
33. Verma KKB. Parthenium dermatitis treated with azathioprine weekly pulse doses. *Indian J Dermatol, Venereol Leprol* 2006; 72: 01.

Pityriasis rubra pilaris

Introduction
One study was found, published in 1972, in which patients with pityriaisis rubra pilaris were treated. It concerned a case series. Only descriptive means were used to describe effectiveness. Duration of remission was also reported.

Case series
Demography
Hunter *et al*. described subjects suffering from pityriasis rubra pilaris, who were previously treated with oral and topical steroids, methotrexate and oral vitamin A. In total, 5 patients were included in whom the clinical diagnosis was confirmed histologically. The mean age of the subjects was 55.2 years. The dose of azathioprine employed ranged from 50 to 200 mg. The duration of treatment ranged from 2 to 48 months and follow-up from 18 to 36 months. In 2 cases there was no follow up (Table 33).

Effectiveness
Four subjects (80%) cleared completely during treatment with azathioprine and those subjects could discontinue the use of azathioprine for periods from 3 months to approximately 3 years before a relapse occurred. One subject withdrew due to severe stomach ache after an initially good response (Table 34).

Conclusion on strength of evidence for effectiveness in pityriasis rubra pilaris

Very low	There is very low quality of evidence (one case series) because of sparse data.

Clinical recommendation for pityriasis rubra pilaris

Weak	There is a weak recommendation for treating pityriasis rubra pilaris with azathioprine if conventional treatment options are contra-indicated or have failed (very uncertain estimate for a uncertain good effect). Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks on clinical recommendation for pityriasis rubra pilaris

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.	-One case series (very low quality of evidence) demonstrated a benefit of azathioprine in patients with pityriasis rubra pilaris. Very uncertain effect. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Improving the lesions and symptoms of pityriasis rubra pilaris.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-80% cleared completely during treatment. Good effect.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Descriptive outcomes. Uncertain.
Risks associated with therapy	-See section “general treatment considerations” and “safety”
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section “general treatment considerations”.
Risk of target event	-Target event is pityriasis rubra pilaris, therefore the risk is 100%.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery,

	laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	-There are other treatment options available.

References

34. Hunter GA, Forbes IJ, Hunter GA *et al*. Treatment of pityriasis rubra pilaris with azathioprine. *Br J Dermatol* 1972; 87: 42-5.

Psoriasis

Introduction
In total, 6 eligible studies published between 1969 and 1990 were found in the literature in which patients with different forms of psoriasis were treated with azathioprine. All studies were case series. Severity outcome assessments employed were body surface area (BSA) of affected skin and improvement of symptoms (e.g. erythroderma, pustules and degree of exfoliation). In most cases however, disease severity was only documented by descriptive means.
Besides the severity outcome measurements also time to effect, loss of initial response and duration of remission were reported as aspects of effectiveness.

Case series
Demography
Six case series were included concerning 147 psoriasis patients. Patients included in these studies were having moderate to severe psoriasis, erythrodermic psoriasis and/or arthritis psoriatica and were often refractory to conventional therapy. A clear definition of psoriasis was never given, nor was the method of diagnosis provided. Previous treatments included topical and oral steroids, methotrexate and oral arsenic. Not all patients received systematic treatment before initiating azathioprine. The population in all 6 studies consisted of adults. The TPMT activity was not measured prior to initiation of azathioprine. The dosage employed ranged from 50 mg/day to 450 mg/day or was 2.5 mg/kg/day. In 4 studies dosage of azathioprine was lowered after the initiation. Duration of treatment varied from 20 days to 34 months and overall there was sparse information about the follow-up period (Table 35).

Effectiveness
In the study of Hewitt *et al.* complete remission was reported in 20% of the subjects, almost complete remission in 30%, good response but incomplete remission in 45% and no response in 5%. Greaves *et al.* used reduction in area of involvement as outcome assessment. In 50% of the subjects there was 0-25% reduction, in 20% there was 25-50% reduction, in 10% there was 50-75% reduction and in 20% there was 75-100% reduction. Percentage of improvement was used as an outcome assessment by Du Vivier *et al*., this was not further specified. In 24% of the patients there was no improvement, 10.3% of the patients had an improvement of 50-75% and 55% of the patients had an improvement of 75-100%. Reduction of psoriasis efflorescences was the outcome assessment by Weitgasser *et al.* Forty subjects (60%) had complete remission, 20 (30%) had partial reduction and 6 (10%) had no significant reduction. In the series of Le Quintrec *et al.* complete remission was found in 80% of the subjects, incomplete remission in 10% and in 10% of the subjects there was a relapse of the psoriasis. Complete remission was attained in 91% of the subjects in the study of Baum *et al.* and 9% had marked improvement. There was no loss of initial response reported. Time to treatment response ranged from 1 week to 10 weeks and duration of remission varied from 0 to 93 months (Table 36).

Conclusion on strength of evidence for effectiveness in psoriasis

Low	The only available studies are of low quality (case series) without important inconsistency between the case series.

Clinical recommendation for psoriasis

Weak	There is a weak recommendation for treating moderate to severe psoriasis, erythrodermic psoriasis and/or arthritis psoriatica with azathioprine when registered/conventional treatment fails or is contra-indicated (uncertain estimate for a very uncertain moderate effect). Extra attention should be given to safety aspects when prescribing azathioprine (uncertain off-label safety).

Remarks clinical recommendation 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.	-Six case series (low quality of evidence) have demonstrated a benefit of azathioprine in psoriasis patients. Uncertain estimate. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Improving the symptoms and affected area of psoriasis.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-Complete remission 20-91% -Improvement in affected area of 75-100% in 20-55%. -Working group: moderate effect

Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Wide ranges between studies and outcome measures vary. Mostly descriptive. Very uncertain precision. - Not possible to compare this efficacy data to conventional treatments.
Risks associated with therapy	-See section "general treatment considerations" and "safety"
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section "general treatment considerations".
Risk of target event	-100 %
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	There are numerous other (registered) treatment options available with a stronger clinical recommendation.

References

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37. Greaves MW, Dawber R, Greaves MW *et al*. Azathioprine in psoriasis. *Br Med J* 1970; 2: 237-8.
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Scleroderma

Introduction
In total, 4 studies published between 1968 and 2007 were found in the literature in which patients with scleroderma or cutaneous involvement of systemic sclerosis were treated with azathioprine: 1 RCT and 3 case series.
Jansen *et al.* compared their results against an undefined control group. Since no demographics or information of the selection was given concerning this group, it was excluded from analysis and therefore the study was considered a case series. Two studies used the modified Rodnan skin score (mRss) to assess efficacy and the other two studies only used descriptive methods. The mRss score is a validated tool to assess systemic sclerosis and scleroderma. Also the mortality rates were used to assess efficacy.

RCT
Methodological quality
Radashkevich *et al*. performed a non-blinded randomized controlled trial. The subjects were randomized according to their birthdates. Even numbers received cyclophosphamide (CYC), odd numbers were given azathioprine. When the group sizes tended to outbalance, subjects were assigned to the smallest group. This was done in blocks of 3.
An overview of the methodological quality can be seen in the risk of bias table (Table 39).

Demography
Subjects with cutaneous involvement of systemic sclerosis were randomized to two treatment groups; azathioprine and cyclophosphamide treatment. In total, 60 subjects (7 male, 53 female) were enrolled, who were evenly distributed between the treatment arms. The method of diagnosis was not described. In the azathioprine group the mean age was 36 years and in the cyclophosphamide group the mean age is 38 years. Duration of treatment was 30 months. Dosage of azathioprine employed was 2.5 mg/kg/day in the first 12 months and 2.0 mg/kg/day during the last months. The dosage of cyclophosphamide was 2mg/kg/day day in the first 12 months and then maintained at 1.0 mg/kg/day. All patients received concomitant prednisolone 15 mg/day which was tapered off to zero by the end of the 6th month. TMPT activity was not measured prior to initiation of AZA (Table 37).

Efficacy
In the azathioprine group the mean baseline mRss was 14.3 (SD $\pm$ 1.0). At 18 months, the mean mRss was 14.5 (SD $\pm$ 1.2), which was not significant. In the cyclophosphamide group however, the mean mRss was 14.7 (SD $\pm$ 1.1) at baseline and 5.2 (SD $\pm$ 0.5) after 18 months. This was a significant difference. Also the difference between the groups had a *p*-value <0.01.
Thereby the proportion of subjects experiencing a 30% improvement of the mRss was substantially lower in the azathioprine group: 46% of the subjects versus 100% of the subjects. Level of significance was not provided (Table 38).

Case series
Demography
In the study of Paone *et al.* 13 subjects suffered from early diffuse systemic sclerosus with cutaneous involvement. New patients were initially treated with cyclophosphamide for 12 months and subsequently with azathioprine for the following 12 months. In Dethlefs *et al.* all 5 subjects suffered from scleroderma. In the study of Jansen *et al.* 19 subjects suffered from acrosclerotic scleroderma, 1 from generalized scleroderma and one from systemic sclerosis with cutaneous involvement. In total, 39 patients with scleroderma or systemic sclerosis with cutaneous involvement were included. The method of diagnosis was not provided in the studies. The age of the subjects ranged from 12 to 71 years. Previous treatments consisted of oral corticosteroids and cyclophosphamide.
The dose of azathioprine employed ranged from 50 to 250 mg. The duration of treatment ranged from 0.5 to 23 months and there was no follow up.

Effectiveness
Paone *et al.* found a statistically significant difference in the mRss score between start of treatment with azathioprine (mRss 8.23 $\pm$ SD 2.9) and 12 months later (mRss 6.38 $\pm$ SD 3.4). Dethlefs *et al.* showed a good improvement in 2 subjects, a moderate in 2 and no response in one. A lesser result was seen in the study of Jansen *et al*.: 40% of the patients improved, 35% experienced no change and 5 % worsened. Three patients (15%) withdrew.

Conclusion on strength of evidence for efficacy in scleroderma

Low	The only available RCT is of moderate quality with serious limitations in study design (also see Table 37). However, there is important inconsistency between the results published in the RCT and the results from the case series. Therefore, the overall evidence is low.

Clinical recommendation for scleroderma

Weak	There is a weak recommendation against the use of azathioprine in the treatment of scleroderma or

	cutaneous involvement of systemic sclerosis, because there seems to be no significant benificial effect of azathioprine (uncertain estimate for a very uncertain low effect or worsening).

Remarks on clinical recommendation for scleroderma

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.	-One RCT has demonstrated no benefit of azathioprine in scleroderma patients and identified azathioprine as a less effective treatment compared with cyclophosphamide. Uncertain estimate. -Uncertainty about the off-label safety of azathioprine. -Costs may vary with the number of follow-up visits and dosage of azathioprine.
Importance of the outcome that treatment prevents	-Diminishing scleroderma symptoms
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-Worsening of mRss with 0.2 in RCT - Improvement of 1.85 on mRss scale in case series. Worsening to low effect.
Precision of estimate of treatment effect* * estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	-Wide confidence interval; ranges from worsening to slight improvement. Very uncertain estimate of effect.
Risks associated with therapy	-See section "general treatment considerations" and "safety"
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section "general treatment considerations".
Risk of target event	-Target event is scleroderma, therefore risk is 100%.
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-
Other	There are other treatment options available.

References

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43. Nadashkevich O, Davis P, Fritzler M et al.. A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. *Clin Rheumatol* 2006; 25: 205- 12
44. Paone C, Chiarolanza I, Cuomo G et al.. Twelve-month azathioprine as maintenance therapy in early diffuse systemic sclerosis patients treated for 1-year with low dose cyclophosphamide pulse therapy. *Clin Exp Rheumatol* 2007; 25: 613-6 .

Vitiligo

Introduction
In total, 1 RCT published in 2006 was found in the literature in which patients with vitiligo were treated with azathioprine.
Clinical outcome parameter used was the body surface area (BSA) measurement of the affected area and of repigmentation during treatment. Furthermore, the efficacy was assessed by time to response.

RCT
Methodological quality
Radmanesh *et al.* performed a non-blinded randomized controlled trial in which randomization and concealment of allocation were sufficient. However, very little information was given on the demographics of the treatment groups. Furthermore, 32 subjects were lost to follow up during the study. Although it was stated that these subjects discontinued due to nonmedical problems, the reasons were not specified per group. An overview of the methodological quality can be seen in the risk of bias table (table 43).

Demography
There are two treatment groups: group I received PUVA (2 times a week) and azathioprine (0.6-0.75 mg/day) and group II received only PUVA (2 times a week). Duration of treatment was 4 months. In total, 92 subjects were enrolled, 60 subjects completed the study. The diagnosis of vitiligo was established by presence of clinical features. Age, gender distribution and previous treatments if any, were not provided. TMPT activity was not measured prior to initiation of azathioprine (table 41).

Efficacy
After 4 months, the mean total repigmentation rate in percentage of BSA was 58.4% in the PUVA plus azathioprine group versus 24.8% in the PUVA group. A statistical significance level of $p<0.001$ was given. Unfortunately, it was not clear whether the authors measured a significant difference of treatment effect from baseline or a significant difference between the 2 treatment groups. Initial treatment effect (early perifollicular repigmentation) was seen after 5.4 (95% CI .4.4-6.4) sessions of oral PUVA in group I and after 8.4 (95% CI 7.1-9.7) sessions in group II. Level of significance not provided (table 42).

Conclusion on strength of evidence for efficacy of combination therapy in vitiligo

Low	The only available RCT is of low quality with serious limitations in study design and sparse data (also see table 41).

Clinical recommendation for combination therapy in vitiligo

Weak	There is a weak recommendation against treating vitiligo with a combination of azathioprine and PUVA. Although there is low evidence for a very uncertain moderate repigmentation, there are additional risks associated with the combination of oral immunosuppressive therapy and photo therapy (non-melanoma skin cancer) that outweigh the potential benefits.

Remarks on clinical recommendation for vitiligo

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.	-One randomized trial (low quality of evidence) has demonstrated an effect after treatment with PUVA and azathioprine. Uncertain estimate. -Uncertainty about the off-label safety of azathioprine in combination with phototherapy.
Importance of the outcome that treatment prevents	-Diminishing the body surface area with depigmentation.
Magnitude of treatment effect* * the magnitude of treatment effect is ranked by the working group as good, moderate, low, no effect or worsening	-Mean repigmentation in affected body surface area of 58.4 %. Moderate effect.
Precision of estimate of treatment effect*	-Unclear level of significance. No confidence interval

* estimates are ranked by the working group as very certain, certain, uncertain or very uncertain.	reported. Very uncertain.
Risks associated with therapy	-See section “general treatment considerations” and “safety” -A combination of azathioprine and phototherapy might induce non-melanoma skin cancer.
Burdens of Therapy	-During the first weeks of therapy laboratory monitoring at weekly intervals is necessary, after wards every one to three months. See also section “general treatment considerations”.
Risk of target event	-Target event is depigmentation. Risk = 100%
Costs	- Costs of azathioprine are between € 10,14 and 10,17 for 15 days 3dd 50 mg, not included are the costs for delivery, laboratory monitoring and visits to the clinic. (*www.medicijnkosten.nl).
Varying Values between patients	-Young patients tent to value appearance more then elderly patients
Other	A combination of oral immunosuppressives and phototherapy is no longer used in daily practice. PUVA therapy is no longer considered to be the phototherapy of choice in the management of vitiligo

References

45. Radmanesh MS. The efficacy of combined PUVA and low-dose azathioprine for early and enhanced repigmentation in vitiligo patients. *J Dermatol Treat* 2006; 17: 01.

III. TABLES

Atopic dermatitis

Table 1. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Atopic Dermatitis RCT's							
Berth Jones *et al.* 2006	AZA/PCB	3	3	AD	37 (25/12)	38 (17-73)	2.5mg /kg
	PCB/AZA		-				2.5mg /kg
Meggitt *et al.* 2006	AZA	3	6.5	AD	41 (19/22)	30 ± SD 11	0.5-2.5 mg/kg
	PCB				20 (16/4)	36 ± SD 12	-
Atopic Dermatitis Case series							
Hon *et al* .2008	Prospective Case series	6	-	AD	17 (9/8)	16.1 (9-22)	1.2-3.5 mg/kg
Meggitt *et al.* 2001	Prospective Case series	1-4 (mean 2)	6	AD	12	18-53	0.5-2.5 mg/kg
Buckley *et al.* 1998	Prospective Case series	12-84	8	AD	10 (5/5)	39.7 (28-56)	0.7-2.5mg /kg
Hudges *et al.* 2008	Case series	4-35	0-216	AD	37 (17/20)	43 (19-83)	0.7-2.5 mg/kg
Malthieu *et al.* 2005	Case series	0.3-108 (mean 24)	120	AD	24	29 (13-48)	1.5-3.0 mg/kg
Murphy *et al.* 2002	Case series	Mean 20.5	-	AD	48 (28/20)	6.9 (6-16)	2.5-3.5 mg/kg
Kuanprasert *et al.* 2002	Case series	24	unk	AD	38 (21/17)	42.4 (23-87)	25-200 mg
Lear *et al.* 1996	Case series	1-21	12	AD	35 (24/11)	31 (5-70)	100 mg

AD; atopic dermatitis, AZA; azathioprine, PCB; placebo, SD; standard deviation, unk; unknown.
- = not applicable

Table 2. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Atopic Dermatitis RCT's						
Berth Jones *et al.*2006	AZA: Mean SASSAD decreased from 39.7 to 29.6. PCB: Mean SASSAD decreased from 33.6 to 32.6. Between groups: $p<0.01$.	unk	-	Topical corticosteroids (all)	Transient elevation of liver enzymes (8) Upper respiratory tract infection (5) Fatigue (3) Yellow urine (3) Migraine (2) Malaise (2) Folliculitis (2) Arthalgia (1) Asthma(1), Bruising (1) Depression (1) Hay fever (1) Headache (1) Impetigo (1) Lymphopenia (1) Mild neutropenia and lymphopenia (1)	None

					Painful foot (1) Shaking (1) Sore tongue (1) Yawning (1)	
Meggitt *et al.* 2006	AZA: Mean SASSAD improvement of 37% PCB: Mean SASSAD improvement of 20.6% Between groups: $p<0.05$.	unk	3	Topical steroids (all)	>1 episode of lymphopenia (28) Nausea (17) ALAT increase (6) Severe nausea (4) Headaches (5) Abdominal pain (4) Lightheadedness (3) Folliculitis (3) Drug hypersensitivity (2) Lower respiratory tract infection (2) Upper respiratory tract infection (2) >1 episode of neutropenia (2) Malaise (1)	None
Atopic Dermatitis Case series						
Hon *et al.* 2008	Mean SCORAD improvement females 36.6, males 21.4 (total 27%) after 6 months	unk	-	Topical steroids (all)	Serum bilirubine increasment (2) Transient gamma-glutamyl transferase increasement (1)	None
Meggitt *et al.* 2001	Mean ASSAD improvement 12.3 units (1.0-23.7 95% CI) 7 (58.3%) initial response 4 (33.3%) lack of response 2 (16.6%) stopped due to SE 1 (8.3%) poor attendance	4	3-6	unk	Transient hepatotoxicity (2)	None
Buckley *et al.* 1998	5 (50%) complete remission 3 (30%) became refractory after initial response 1 (10%) good reaction, but persistent sites 1 (10%) poor reaction	unk	80% remain in remission after median of 3 y FU	unk	Transient lymphopenia (3) Transient gamma-glutamyl transferase increasement(1) Lethargia (1) Recurrent herpes simplex labialis (1)	Non Hodgekin Lymfoma (1)*
Hudges *et al.* 2008	15 (40.5%) complete remission 9 (24%) good response, no remission 7 (19%) under treatment, no remission 5 (13.5%) stopped due to SE 1 (3%) no response	8	1-35	Topical steroids (all)	Transient and mild lymphopenia (19) Transient neutropenia (5) Nausea (4) Persistant lymphopenia (2) Flu-like reaction (1) Pancytopenia (1) Abdominal cramps (1) Myalgia (1) Severe nausea and vomiting (1)	None
Malthieu *et*	20 (83.3%) patients	2-28	Mean 9	unk	Pancytopenie (1)	Pancreatitis

al. 2005	94% improvement of involved body surface 2 (8.3%) lack of response 2 (8.3%) stopped due to SE	(mean 8)			Abdominal distress (1) Acute bronchitis (1) Severe herpes labialis (1) Transient abnormalities in liver function tests (1)	(1) ruptured aneurysm (1)†*
Murphy *et al.* 2002	28 (58.3%) excellent improvement after 3 months 13 (27.1%) good improvement 7 (18.4%) inadequate improvement	2-6 (mean 4)	-	Oral prednisolone during first weeks (23)	Transient mild lymphopenia (15) Transient thrombocytopenia (1) Transient abnormalities in liver function tests (5) Mild microcytosis (3) Eczema herpeticum (1) Nausea, vomiting, diarroea (1) Hypersensitivity reaction (1)	None
Kuanprasert *et al.*2002	30 (79%) good response 4 (10.5%) stopped due to SE 4 (10.5%) lack of response	1-8 (mean 3.7)	-	Topical steroids (all)	Nausea (5) Fatigue (5) Leukopenia (3) Myalgia (2) Drug eruption (2) Megaloblastic anemia (1)	Severe pancytopenia (1)
Lear *et al.* 1996	18 (69.2%) responded good 3 (8.6%) little effect 3 (8.6%) stopped due to SE	4- 24	12 (61.5%)	Topical steroids (all)	Severe nausea and epigastric pain (3) Mild nausea (3)	None

CI; confidence interval, FU; follow up, SD; standard deviation, unk; unknown, y; years.
- = not applicable
* post-treatment
†subject deceased.

Table 3. Adverse events in RCT's

	Berth-Jones et al.			**Meggitt et al.**		
Adverse events	**AZA**	**PCB**	**RR**	**AZA**	**PCB**	**RR**
Infections	8	6		7	3	
Gastrointestinal symptoms	14	2	7.00	25	7	
Musculoskeletal symptoms	3	2		8	4	
Neurological symptoms	4	0		0	0	
Malignancies	0	0		0	0	
Drug hypersensitivity	0	0		2	0	
General symptoms	4	1		1	2	
Abnormalities in laboratory markers	10	2		36	13	
Serious adverse events	0	0		0	0	

AZA; azathioprine, PCB; placebo, RR; relative risk.

Table 4. Risk of bias of included RCT

	Adequate randomization?	**Adequate concealment of allocation?**	**Adequate blinding?**	**Incomplete data reported?**	**Free of selected reporting?**	**Free of other bias?**
Berth-Jones et al. (2002)	YES	YES	Participants YES Researchers YES Outcome assessment YES	UNCLEAR	YES	YES
Meggitt *et al.* (2006)	YES	YES	Participants YES Researchers YES	YES	YES	YES

	Outcome assessment YES

Bullous pemphigoid

Table 5. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Bullous pemphigoid RCT's							
Beissert *et al.* 2007	Pred plus AZA	24[1]	10	BP	38 (12/26)	75.3 ± SD 12.8	2.0 mg/kg
	Pred plus MM				35 (15/20)	74.8 ± SD 13.4	-
Guillaume *et al.* 1993	Pred plus AZA	6	-	BP	36 (19/17)	77.2 ± SD 8.3	100-150mg
	Pred plus PE				31 (14/17)	74.8 ± SD 10	-
	Pred				31 (17/14)	75.4 ± SD 11	-
Burton *et al.* 1978	Pred plus AZA	36	-	BP	12 (6/6)	75.6 (unk)	2.5 mg/kg
	Pred				13 (3/10)	74.1 (unk)	-
Bullous pemphigoid Cohort							
Ahmed *et al.* 1977	Pred plus AZA	unk[1]	8-45	BP	15	unk (43-92)	1.5 mg/kg
	Pred				14		
Bullous pemphigoid Case series							
Burton *et al.* 1974[2]	Case series		48	BP	10 (3/7)	68.2 (53-87)	2.5 mg/kg
Van Dijk *et al.* 1973	Case series	2-30	-	BP	5 (3/2)	81.4 (70-91)	75-250 mg
Greaves *et al.* 1971	Case series	unk[1]	7	BP	12	Unk (47-79)	2.5 mg/kg

AZA; azathioprine, BP; bullous pemphigoid, MM; mycofenolaat mofetyl, PE; plasma exchange SD; standard deviation, unk; unknown.
[1] Depended highly on individual clinical response
[2] Follow up study. Same patients as Greaves *et al.*
- = not applicable

Table 6. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Bullous Pemphigoid RCT's						
Beissert *et al.* 2007	100% complete remission after a median ± SD duration of 23.8 ± 18.9 days in the Pred & AZA group vs 100% complete remission after a median ± SD duration of 42.0 ± 55.3 days in Pred & MM group. (p=0.09)	unk	5.8 ± SD 4.8	0.5 mg/kg Prednisolone, reduction schedule after clearing of BP (all)	Liver fuction abnormalities (106) Dizziness (2) Hyperglycemia (1) Myalgia (1) *	Death(2) Infection (1) Abnormal liver function (2)
Guillaume *et al.* 1993	80.5% (95% CI 68-93%) of the subjects are controlled at week 4, 39.0% (95% CI 23-55%) at 6 months in	unk	-	Prednisolone 1mg/kg, reduction schedule after 4 weeks (all)	Leukopenia (4) *	Death (6) Hepatitis (3) Severe cytopenia (4)

	AZA group No statistically significant difference between 3 groups at 4 weeks and 6 months.					
Burton *et al.* 1978	7 (58%) remission in Pred plus AZA group versus 3 (23%) in Pred group. Not significant. Significant reduction in prednisone dose (45%) in Pred plus AZA group.	unk	-	Prednisone 30-80mg/day (all)	Transient leucopenia (2)	Death (3) due to heart failure (1) and CVA (2)
Bullous Pemphigoid Cohorts						
Ahmed *et al.* 1977	50% reduction in maintainance dose of prednisolone in AZA group 30% reduction in length of medicinal therapy in AZA group	unk	unk	Prednisolone 40-240 mg/day, maintainance dose 10-60mg/day (all)	None	None
Bullous pemphigoid Case series						
Burton *et al.* 1974	4 (40%) well controlled/remission 1 (10%) moderate response 1 (10%) Intolerant 4 (40%) Deceased	unk	4-36	prednisolone	Herpes zoster (1) Mild urticaria (1) Diarrhoea & vomiting (1)	adenocarcinoma (1)†, pre-existent mammacarcinoma (1)†, MI. (1)†, CVA(1)†
Van Dijk *et al.* 1973	2 (40%) very good, no new blisters 2 (40%) good, occasional new blister 1 (20%) withdrew after 2 weeks	4-6	-	None	None	None
Greaves *et al.* 1971	9 (82%) withdrawal of oral pred without relapse 2 (18%) considerable reduction of pred dose	unk	0.3- 7	prednisolone	Transient leucopenia (4) Nausea, vomiting, diarrhea (2)	None

CI; confidence interval, CVA; cerebrovascular accident, FU; follow up, MI.; myocardinal infarction, SD; standard deviation, y; years.
* Incomplete reporting of adverse events, - = not applicable
†subject deceased.

Table 7. Adverse events in RCT's en cohorts

	Beissert et al.*			**Guillaime et al.***				**Burton et al.**			**Ahmed et al.**		
Adverse events	**Pred AZA**	**Pred MM**	**RR**	**Pred**	**Pred & AZA**	**Pred & PE**	**RR**	**Pred**	**Pred & AZA**	**RR**	**Pred**	**Pred & AZA**	**RR**
Infections	0	4	*p*=0.67	-	-	-		-	-		-	-	
Gastrointestinal symptoms	-	-	*p*=0.60	-	-	-		-	-		-	-	
Musculoskeletal symptoms	1	2		-	-	-		-	-		-	-	
Neurological symptoms	2	0		-	-	-		-	-		4	0	
Abnormalities in laboratory markers	108	103		-	4	-		-	2		-	-	
Serious adverse events	5	2		10	15	6		3	4		3	0	

AZA; azathioprine, BP; bullous pemphigoid, MM; mycofenolaat mofetyl, PE; plasma exchange, Pred;

prednisone/prednisolone/methylprednisolone, RR; relative risk.

* only severe, serious adverse events and liver function abnormalities were reported

Table 8. Risk of bias of included RCT

	Adequate randomization?	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
Beissert *et al.* 2007	YES	UNCLEAR	Participants NO Researchers NO Outcome assessment NO	YES	YES	YES
Guillaume *et al.* 1993	YES	YES	Participants NO Researchers NO Outcome assessment NO	UNCLEAR	UNCLEAR	NO
Burton *et al.*1978	YES	YES	Participants NO Researchers NO Outcome assessment NO	UNCLEAR	UNCLEAR	UNCLEAR

Chronic actinic dermatitis

Table 9. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Chronic actinic dermatitis RCT							
Murphy *et al.* 1989	AZA	1.5-12 (Mean 8.4)	Unk	CAD	8 (6/2)	64 (48-75)	50 mg
	PCB				10 (10/0)	66 (48-84)	-
Chronic actinic dermatitis Case series							
Yap *et al.* 2003	Case series	Unk[1]	Unk	CAD	12 (unk)	62.7 (26-85)[‡]	1.0-2.5 mg/kg
Leigh *et al* 1984	Case series	1.5-33 (Mean 11.5)	Unk	CAD	14 (11/3)	69.1 (55-80)	100-200 mg

AZA; azathioprine, CAD; chronic actinic dermatitis, PCB; placebo, Unk; unknown.
- = not applicable
[1]; Depended highly on individual response
[‡]; age of total group

Table 10. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Chronic actinic dermatitis RCT						
Murphy *et al.* 1989	*Mean reduction in itch VAS*: AZA; 4.6, PCB; -3.5 at 6 months *Mean reduction in rash VAS*: AZA; 4.9, PCB; -1.1 at 6 months *Mean reduction in BSA of rash:* AZA; 34.4%, PCB; -27.8% at 6 months Diff. between groups $p<0.05$	< 4	Unk	Unk	Gastro-intestinal intolerance (1)	None
Chronic actinic dermatitis Case series						
Yap *et al.* 2003	11 (92%) Partial to good response	4-6	Unk	Unk	Hepatotoxicity (1)	None

	1 (8%) Withdrawal					
Leigh *et al.* 1984	9 (57%) Cleared/improved 2 (14%) Cleared, but refractory 2 (14%) No response 2 (14%)Withdrawals	6-20	10	None	Vomiting (2) Diarrhoea (2) Abdominal discomfort (2)	CVA (1)† Airway disease(1)† heart disease(1)†

AE; adverse event, AZA; azathioprine, CVA; cerebro vascular accident, Diff; difference, PCB; placebo, SAE; serious adverse event, Unk; unknown
†subject deceased.

Table 11. Risk of bias of included RCT

	Adequate randomization?	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
Murphy *et al.* 1989	UNCLEAR	UNCLEAR	Participants UNCLEAR Researchers UNCLEAR Outcome assessment UNCLEAR	NO	UNCLEAR	UNCLEAR

Tabel 12. Adverse events in RCT

	Murphy et al.		
Adverse events	**AZA**	**PCB**	**RR**
Gastrointestinal symptoms	1	0	
Serious adverse events	0	0	

AZA; azathioprine, PCB; placebo, RR; relative risk.

Cutaneous vasculitis

Table 13. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Cutaneous vasculitis RCT							
Heurkens *et al.* 1991	Pred plus AZA	3	29	RA/CV	8 (5/3)	66 (51-86)	2 mg/kg
	Conventional				9 (2/7)	65 (37-81)	-
Cutaneous vasculitis Case series							
Callen *et al.* 1991	Prospective Case series	Unk[1]	Unk	CLV[3]	6 (2/4)	32.2 (20-50)	150-250 mg
Callen *et al.* 1987	Case series	Unk	Unk	CLV	8	Unk	150 mg

AZA; Azathioprine, CV; Cutaneous vasculitis, CLV; Cutaneous leukocytoclastic vasculitis, FU; follow up, LV; leukocytoclastic vasculitis, Pred; prednisolone, RA; rheumatoid artritis, UV; urticarial vasculitis
[1] Depended highly on individual reponse
[3] Severe and recalcitrant disease with mild systemic involvement

Table 14. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Cutaneous vasculitis RCT						
Heurkens *et al.* 1991	7 (88%) complete remission in AZA group (p<0.05). 6 (55%) complete	unk	18	Pred 10-60 mg (all)	Gastrointestinal complaints (1)	Septic arthritis (1) Epidural abcess (1)

	remission in conventional group. (p>0.05). Not sign. between groups.					
Cutaneous vasculitis Case series						
Callen *et al.* 1991	2 (33%) complete response 3 (50%) Partial response 1 (17%) No response	4-6	unk	Pred (3), colchicine (1)	Verrucae (3) Elevated liver enzymes (1) Herpes zoster (1)	None
Callen *et al.* 1987	8 (100%) responsive to treatment	4-8	unk	Pred (all)	Mild hepatitis (1)	None

AE; adverse event, AZA; azathioprine, Pred; prednisolone, SAE; serious adverse event, Unk; unknown
- = not applicable,

Table 15. Risk of bias of included RCT

	Adequate randomization?	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
Heurkens *et al.* 1991	UNCLEAR	UNCLEAR	Participants NO Researchers NO Outcome assessment NO	NO	UNCLEAR	UNCLEAR

Table 16. Adverse events in RCT

	Heurkens *et al.*		
Adverse events	**AZA plus pred**	**CT**	**RR**
Infections	3	2	
Gastrointestinal symptoms	1	0	
Serious adverse events	3	2	

AZA; azathioprine, pred; prednisone; CT; conventional treatment, RR; relative risk.

Cutaneaous lupus erythematosus

Table 17. Characteristics of included articles.

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Lupus erythematosus Case series							
Callen *et al.* 1991	Prospective Case series	Unk[1]	Unk	SCLE, CCLE	6 (2/4)	42.5 (31-62)	100-150mg

AZA; Azathioprine, CCLE; chronic cutaneous lupus erythematosus, SCLE; subacute cutaneous lupus erythematosis
[1] Depended highly on individual reponse, mostly > 12 months
[2] Severe and recalcitrant disease

Table 18. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Lupus erythematosus Case series						
Callen *et al.* 1991	1 (17%) complete response 3 (50%) partial response	<6	unk	Pred 20-30mg (all)	Drug induced fever (2) Nausea (1)	Pancreatitis (1)

	2 (33%) no response					Leucopenia (1)	

AE; adverse event, SAE; serious adverse event, AZA; Azathioprine, Pred; prednisolone, unk; unknown
-= not applicable

Erythema multiforme

Table 19. Characteristics of included articles.

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA (per day)
Erythema multiforme Case series							
Farthing *et al.* 1995	Case series	15-60[1]	0-12	EM	5 (2/3)	29.6 (16-39)	100-150mg

AZA; Azathioprine, EM ; erythema multiforme.
[1] Depended highly on individual reponse

Table 20. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Erythema multiforme Case series						
Farthing *et al.* 1995	3 (60%) complete remission 2 (40%) well controlled disease	unk	8	Pred (1), dapsone (1)	unk	unk

AE; adverse event, SAE; serious adverse event, AZA; Azathioprine, Pred; prednisolone, unk; unknown

Hand dermatitis

Table 21. Characteristics and level of evidence of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Hand dermatitis Case series							
Pearce *et al.* 2009	Case series	unk	3-48	HD and LO	6 (5/1)	49.0(34-60)	unk

HD; hand dermatitis, FU; follow up, LO; lymfoedema, Unk; unknown.

Table 22. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Hand dermatitis Case series						
Pearce *et al.* 2009	2 (33%) >75% improvement 1 (17%) >50 % improvement 3 (50%) withdrew	unk	unk	Oral Antibiotics, topical steroids (all)	unk	unk

Leprosy

Table 23. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Leprosy type I reactions RCT							
Marlowe *et al.* 2004	Pred plus AZA	3	3	Lep T1R	21 (18/3)	46 (22-65)	3 mg/kg
	Pred				19 (17/2)	41 (20-65)	-

AZA; azathioprine, Lep T1R; severe leprosy type 1 reactions, Pred; prednisolone.
- = not applicable

Table 24. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Leprosy type I reactions RCT						
Marlowe *et al.* 2004	*Skin symptoms:* AZA: 52% improvement from baseline (p<0.01) Pred: 65% improvement from baseline (p<0.01) *Rescue medication*: 48% subjects in AZA versus 37% in pred group. *Nerve function*: no effect in both groups. No sign. Difference between groups	1	>3	Pred 5-40mg (all)*	Mild nausea (2) Herpes zoster (1) Transient leucopenia (1)	None

AE; adverse event, AZA; azathioprine, Pred; prednisolone, SAE; serious adverse event, sign; significant.
*; during the first 8 weeks, tapered

Table 25. Risk of bias of included RCT

	Adequate randomization	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
Marlowe *et al.* 2004	NO	NO	Participants NO Researchers NO Outcome assessment NO	UNCLEAR	YES	NO

Tabel 26. Adverse events in RCT

	Marlowe *et al.*		
Adverse events	**Pred/ AZA**	**Pred**	**RR**
Infections,	1	0	
Gastrointestinal symptoms	2	1	
Vascular symptoms	0	1	
Abnormalities in laboratory markers	1	0	
Serious adverse events	0	0	

AZA; azathioprine, Pred; prednosone, RR; relative risk.

Lichen planus

Table 27. Characteristics of included article

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Lichen planus Case series							
Verma *et al.* 2001	Case series	3-7 (mean 5)	6-9	LP	9(4/5)	32.2 (5-54)	100 mg

AZA; Azathioprine, LP, lichen planus, MTX; methotrexate, Unk; Unknown.

Table 28. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Lichen planus Case series						
Verma *et al.* 2001	7 (77.8%) excellent response 1 (11.1%) good response 1 (11.1%) poor response	4-6	>6-9	unk	Gingivitis (1) *	None

Unk; unknown
*; during follow up.

Parthenium dermatitis

Table 29. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Parthenium dermatitis RCT							
Verma *et al.* 2008	AZA	6	6	PD	20 (13/7)	48.5 (25-60)	100 mg
	Betamethason				21 (16/6)	50.7 (26-73)	
Parthenium dermatitis Cohort							
Verma *et al.* 2000	AZA: 100mg/day	6-36	36	PD	22 (2/20)	31-75	50-100mg/day 0-300mg/28 days
	AZA: 50 mg/day + 300 mg/28 days				11 (5/6)		
	AZA: 100 mg/day + 300 mg/28 days.				10 (10/0)		
Parthenium dermatitis Case series							
Verma *et al.* 2006	Case series	6	-	PD	12 (10/2)	53.5 (39-65)	300 mg/ week
Sharma *et al* 1998	Case series	6	9-12	PD	20 (19/1)	54 (40-72)	100-150 mg

AZA; azathioprine, PD; parthenium dermatitis, Unk; unknown

Table 30. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Parthenium dermatitis RCT						

Verma *et al.* 2008	AZA: CSS decreased from 64.5 ± 16.4 to 4.3 ± 5.6 (p <0.01) Betamethason: CSS decreased from 67.1 ± 17.4 to 0.6 ± 2.2 (p <0.01)	4	1-6	Antihistamines, Topical steroids (all)	Infections (15) Loss of appetite (7) Dyspepsia (5) Fever (5) Nausea/vomiting (3) Weight gain (3) Backache (3) Hirsutism (1)	None
Parthenium dermatitis Cohort						
Verma *et al.* 2000	38 (88%) complete remission. 3 (7%) incomplete remission. 2 (5%) withdrawal No statistically significant differences between the groups.	unk	unk	Oral betamethason (n=22)	Infection (8) Increase serum transaminase (2) Fever (1) Hepatitis (1) Malaise (1) Nausea (1) Palpitations (1) Vomiting (1)	None
Parthenium dermatitis Case series						
Verma *et al.* 2006	CSS decreased from mean SD 40.4±7.95 to 10.9±8.43 (P<0.01) 37 (58%): 80-100% clearance 5 (42%): 60% clearance	4-6	-	Antihistamines Topical steroids (all)	Vomiting (2) Weight loss 2-3 kg (2) Paresthesia of hands (1)	None
Sharma *et al.* 1998	10(66%): 90% reduction in score* 3 (20%): 50% reduction in score* 1(2%): <50% reduction in score* 1 (2%): No improvement*	8-28	unk	Antihistamines, oral steroids(all)[#]	None	None

AE; adverse event, AZA; azathioprine, CSS; Clinical Severity Score, SAE; serious adverse event, SD; Standard deviation, Unk; unknown.
- = not applicable
* = PASI score
[#] = was tapered during the first 1-3 months

Table 31. Risk of bias of included RCT

	Adequate randomization	**Adequate concealment of allocation?**	**Adequate blinding?**	**Incomplete data reported?**	**Free of selected reporting?**	**Free of other bias?**
Verma *et al* 2008	YES	YES	Participants YES Researchers YES Outcome assessment UNCLEAR	NO	UNCLEAR	UNCLEAR

Tabel 32. Adverse events in RCT

	Verma et al.		
Adverse events	**AZA**	**Bet**	**RR**
Infections,	15	17	
Gastrointestinal symptoms	15	15	
Musculoskeletal symptoms	3	4	
Neurological symptoms	-	-	
Vascular symptoms	-	5	
Dermatological symptoms	1	18	
Malignancies	-	-	
Drug hypersensitivity	-	-	
General symptoms	8	13	
Abnormalities in laboratory markers	-	-	
Serious adverse events	-	-	

AZA; Azathioprine, Bet; betamethasone, RR; relative risk.

Pityriasis rubra pilaris

Table 33. Characteristics of included article

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Pityriasis rubra pilaris Case series							
Hunter *et al.* 1972	Case series	2-48	18-36	PRP	5(4/1)	55.2 (47-67)	50-200 mg

AZA; Azathioprine, PRP; pityriasis rubra pilaris.

Table 34. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Pityriasis rubra pilaris Case series						
Hunter *et al.* 1972	4 (80%) cleared completely 1 (20%) withdrew	1	3-appr.36	Oral steroids(1)	Stomach ache (2) Gastric hiatus hernia (1) Nausea (1) Solar keratosis (1) Skin cancers (1)	None

AE; adverse event, Appr.; approximately, AZA; Azathioprine, SAE; serious adverse event

Psoriasis

Table 35. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Psoriasis Case series							
Le Quintrec *et al*. 1990	Case series	32.5±34*	0-93	PsA	11(6/5)	46.3 ± SD11.2	Mean 2.14mg/kg
Du Vivier *et al*.1974	Case series	2-31* (Mean 21)	unk	Ps	29	51 (23-79)	100-300 mg
Baum *et al*. 1973	Case series	unk	unk	PsA	11 (9/2)	47.2 (27-68)	25-150 mg
Weitgasser *et al*. 1972	Case series	2.5- 7.5	24	Ps	66 (42/24)	20-60	50-100 mg ‡
Greaves *et al.* 1970	Case series	1,5	-	Ps	10 (2/8)	54.3 (31-73)	2.5 mg/kg
Hewitt *et al.* 1969	Case series	2/3 – 23 (Mean 2)	unk	Ps & PsA	20 (11/9)	50.6 (23-87)	50-450 mg

AZA; Azathioprine, FU; follow up, Ps; psoriasis, PsA; psoriatic arthritis, Unk; unknown
*; Treatment until remission was achieved
‡; with reduction to 50 mg/week

Table 36. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission (months)	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Psoriasis Case series						
Le Quintrec *et al.* 1990	8 (80%) complete remission 1 (10%) incomplete remission 1 (10%) relapse	6.1 ± SD 6.7	0-93 (Mean 18)	Oral steroids(5) salazopyrine (2)	Herpes zoster infection (1) Transient leucopenia(1) Transient leucothrombopenia (1)	Pulmonary embolus(1)† Respiratory insuf (1)†
Du Vivier *et al.* 1974	3 (10.3%) 50-75% improvement 16 (55%) 75-100% 7 (24%) no improvement 3 (10.3%) stopped due to SE	unk	6-9	None	Nausea, diarrhoea, abdominal pain (12) Leucopenia (10) Reversable mild portal fibrosis (8) Abnormalities of taste (2) Cholestasis (2) Thrombocytopenia (1)	None
Baum *et al.*1973	10 (91%) complete remission 1 (9%) marked remission	0.5-4.5	1-10	unk	Nausea, vomiting, diarrhea (5) Leukopenia (2) Anemia (1) Elevation of liver enzyme (1)	None
Weitgasser *et al.* 1972	40 (60%) complete remission 20 (30%) partial reduction 6 (10%) no significant reduction	<10	0-12	unk	Fever (Unk) Nausea (Unk)	None
Greaves *et al.* 1970	2 (20%) 75-100% BSA reduction 1 (10%) 50-75% BSA reduction 2 (20%) 25-50% BSA reduction 5 (50%) 0-25% BSA reduction	2-6	-	None	Transient leucopenia (2) Transient aneamia (1) Transient raised bilirubin (1)	None
Hewitt *et al.*1969	4 (20%) complete remission 6 (30%)almost complete remission 9 (45%) incomplete remission 1(5%) no response	1-8	1-8	unk	Transient leucopenia (14) Transient aneamia, (5) Transient thrombocytose (3) Gastro-intestinal complaints (3) Transient thrombocytopenia (1)	Aneamia (1) Myocard infarct (1)

AE; adverse event, AZA; azathioprine, BSA ; body surface area, SAE; serious adverse event, SD ; standard deviation, Unk; unknown
- = not applicable, †subject deceased.

Scleroderma

Table 37. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day

Scleroderma RCT							
Nadashkevich *et al.* 2006	AZA	30	-	SSc	30 (4/26)	36 (19-63)	2.0-2.5 mg/kg
	CYC				30 (3/27)	38 (20-65)	2.0 mg/kg
Scleroderma Case series							
Paone *et al.* 2007	Case series	12	-	SSc	13 (1/12)	38 (23-53)	50-100 mg
Dethlefs *et al.* 1973	Case series	0.5- 1.7	-	ScD/SSc	5 (2/3)	34.2 (9-71)	50-150 mg
Jansen *et al.* 1968	Case series	5-23	-	ScD	20 (14/6)	43.5 (12-65)	50-250 mg

AZA; azathioprine, CYC; cyclophosphamide, FU; follow up, ScD; sceloderma, SD; standard deviation, SSc; systemic sclerosis with cutaneous involvement.

Table 38. Results

	Efficacy/ effectiveness	**Onset of action (weeks)**	**Duration of remission**	**Conco med (*n* of subjects)**	**AE's (*n* of events)**	**SAE's (*n* of events)**
Scleroderma RCT						
Nadashkevich *et al.* 2006	AZA: mRss 14.3 (SD ± 1.0) to 14.5 (SD ± 1.2) after 18 months. $p>0.05$ CYC: mRss 14.7 (SD ± 1.1) to 5.2 (SD ± 0.5) after 18 months. $p<0.01$ Difference between groups $p<0.01$	unk	-	Pred 15 mg/day (all)	Nausea (3) Dyspepsia (2) Leukocytopenia (2) Otitis media (1)	None
Scleroderma Case series						
Paone *et al.* 2007	mRss 8.23 (SD ± 2.9) to 6.38 (SD ± 3.4) $p<0.01$	unk	-	Oral steroids 10 mg (all)	unk	unk
Dethlefs *et al.* 1973	2 (40%) sign. improvement 2 (40%) moderate improvement 1 (20%) no response	unk	-	Oral steroids (4), penicillin (4)	unk	unk
Jansen *et al.* 1968	8 (40%) improved 7 (35%) no change 1 (5%) worsening 1 (5%) loss to FU, 3 (15%) withdrawal	unk	-	-	Granulocytopenie (4) Anemie (3) Gastro-intestinal complaints (3) Serum sickness (3) Thrombocytopenie (2) Joint and muscle pain (1)	None

AE; adverse event, AZA; Azathioprine, CYC; cyclophosphamide, FU; follow up, Pred; prednisolone, SAE; serious adverse event, SD; standard deviation, Unk; unknown.
-; not applicable

Table 39. Risk of bias of included RCT

	Adequate randomization?	**Adequate concealment of allocation?**	**Adequate blinding?**	**Incomplete data reported?**	**Free of selected reporting?**	**Free of other bias?**
Nadashkevich *et al.* 2006	NO	NO	Participants NO Researchers NO Outcome assessment NO	NO	YES	UNCLEAR

Tabel 40. Adverse events in RCT

	Nadashkevich *et al.*		
Adverse events	**AZA**	**CYC**	**RR**
Infections	1	0	
Gastrointestinal symptoms	5	7	
Dermatological symptoms	0	3	
Abnormalities in laboratory markers	2	4	
Serious adverse events	0	0	

AZA; azathioprine, CYC; cyclophosphamide, RR; relative risk.

Vitiligo

Table 41. Characteristics of included articles

	Study design/ groups	Treatment (months)	FU (months)	Disease of subjects	*N* subjects (male/ female)	Mean age of subjects in years (range)	Dose of AZA per day
Vitiligo RCT							
Radmanesh *et al.* 2006	PUVA plus AZA	4	-	Vi	30(unk)	unk	0.6-0.75 mg
	PUVA				30(unk)		-

AZA; azathioprine, Vi; vitiligo, Unk; unknown

Table 42. Results

	Efficacy/ effectiveness	Onset of action (weeks)	Duration of remission	Conco med (*n* of subjects)	AE's (*n* of events)	SAE's (*n* of events)
Vitiligo RCT						
Radmanesh *et al.* 2006	Mean BSA repigmentation after 4 months: 58.4% in PUVA plus AZA versus 24.8% in PUVA group. ($p<0.01$)	3-5	-	-	Gastric complaints (2)	None

AE; adverse event, AZA; azathioprine, BSA; body surface area, SAE; serious adverse event, Unk; unknown.
-= not applicable

Table 43. Risk of bias of included RCT

	Adequate randomization?	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
Radmanesh *et al.* 2006	YES	YES	Participants NO Researchers NO Outcome assessment NO	NO	NO	NO

Tabel 44. Adverse events in RCT

	Radmanesh et al.		
Adverse events	**PUVA AZA**	**PUVA**	**RR**
Gastrointestinal symptoms	2	0	
Serious adverse events	0	0	

AZA; azathioprine, RR; relative risk.