Cost – effectiveness of alitretinoin (Toctino®) for severe chronic hand eczema in adults

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Foreword

The thesis was submitted as a part of the Master of Philosophy Degree in Health Economics, Policy and Management at the University of Oslo.
Before choosing the topic of the master thesis I got interested in economic evaluation and paid a visit to the Norwegian Medicines Agency. The NOMA suggested looking at Toctino®, a new treatment of chronic hand eczema that had not been approved for public funding, and evaluating its cost-effectiveness.
No external funding of this study was received.

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And finally I would like to thank my fellow students who helped me during this work.

Abstract

Background: Chronic hand eczema (CHE) is a chronic dermatological condition that entails skin dryness, blistering and pruritus, and reduces the quality of life. 0.5 to 0.7% of the general population suffer from a severe form of this disease which leads to seriously impaired quality of life, manual dexterity, work absenteeism, and prevents employment. (1, 2) There are several treatment options for CHE, pharmaceutical and others, but they are unlicensed for treatment of eczema. There is a new drug, alitretinoin (Toctino®), that is a licensed medication for severe CHE. It is expensive, however, the evidence of effectiveness has been disputed. The Norwegian Medicines Agency denied alitretinoin reimbursement due to lack of clinical data on effectiveness.

Aim: To estimate the additional costs and additional health benefits of replacing azathioprine by alitretinoin in the treatment of severe CHE.

Methods: A systematic literature review was conducted to estimate the clinical effectiveness of competing treatments for severe CHE, among which alitretinoin and azathioprine were the only relevant treatments. A decision tree was developed to compare the cost-effectiveness of two different doses of alitretinoin versus azathioprine. The estimated time horizon of the model was 1 year. The incremental cost per QALY was calculated and two types of sensitivity analyses were performed.

Results: The model indicated that a one-year expected QALY was 0.681 with azathioprine, 0.701 for alitretinoin 30 mg and 0.695 for alitretinoin 10 mg, while the expected costs were NOK6061 for azathioprine, NOK37,297 for alitretinoin 30 mg, and NOK40,339 for alitretinoin 10 mg, respectively. While alitretinoin 10 mg is dominated (higher costs and lower effectiveness), the incremental cost of replacing azathioprine with alitretinoin 30 mg was NOK1.562 million per QALY. One-way sensitivity analyses indicate that the quality-of-life (QoL) parameters were the most important in terms of uncertainty. The probabilistic sensitivity analysis showed that the probability that alitretinoin 30 mg would be cost-effective is less than 24%.

Conclusion: Replacing azathioprine by alitretinoin is not cost-effective by conventional cost-effectiveness threshold.

Abbreviations

AE/AD	Atopic Eczema/Atopic Dermatitis
CE	Cost-Effectiveness
CEA	Cost-Effectiveness Analysis
CHE	Chronic Hand Eczema
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
HECSI	Hand Eczema Severity Index
HRQoL	Health-Related Quality of Life
PGA	Physicians' Global Assessment
POEM	Patient-Oriented Eczema Measure
PSA	Probabilistic Sensitivity Analysis
RCT	Randomized Controlled Trial
SASSAD	Six Area, Six Sign Atopic Dermatitis Severity Score
SCORAD	Severity Scoring of Atopic Dermatitis Index
SF-36	Short Form-36
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
WTP	Willingness-to-Pay

Contents

Introduction

1. Hand eczema

Hand eczema is a common non-contagious dermatological condition, also called dermatitis, and manifests itself in inflammation of the upper layers of the skin. Clinical signs of eczema are erythema, scaling, edema, vesicles, papules, often oozing, fissures, hyperkeratosis, pruritus and pain. (1, 3, 4) Eczema is a general term for a skin condition that can be classified into several subtypes.

Aetiology (type of hand eczema)

Exogeneous

- Irritant HE (ICD10 L24: Toxic contact dermatitis)
- Allergic HE (ICD10 L23: Allergic contact dermatitis)

Endogeneous

- Atopic HE (ICD10 L20: Atopic dermatitis)
- Other endogeneous HE (ICD10 L30: Other dermatitis)

Localization

- Dorsum of the hands
- Palmar
- Sides of the fingers
- Finger tips
- Finger webs
- Wrist

Morphology

- Vesicular (pompholyx type)
- Erythematoaquamous, scaling, fissures
- Hyperkeratotic – rhagadiform/tylotic

  Discoid (nummular patches) (1)

Etiologic classification includes irritant contact dermatitis, allergic contact dermatitis, atopic hand dermatitis, hybrid hand eczema (the combination of the three types mentioned above), and protein contact dermatitis. (3) Irritant contact dermatitis is associated with repeated use of irritants (mild toxic agents) that lead to an inflammation of the skin. Exposure to water and soaps and other detergents (the so called “wet work”) may provoke the development of hand eczema. This is the most

frequent external cause of hand eczema. Allergic contact dermatitis is provoked by exposure to contact allergens, such as nickel (in tools or jewellery), chromate (in leather or cement), rubber additives (in gloves) and preservatives (in creams and cosmetics). (3) Atopic hand dermatitis often happens in individuals with a history of asthma, hay fever or "childhood eczema". Atopy is an endogeneous factor of eczema development. Protein contact dermatitis frequently occurs in patients who are occupied in food industry. (3) Unfortunately, hand eczema does not always fall under a certain subtype description and is not caused by a specific factor. In many cases this condition is multifactorial, especially in patients with chronic hand eczema.

No currently existing classification of eczema excludes hybrids and combinations of the various morphological categories. It especially refers to a chronic form of the disease, when the aetiological factor is not easily identified. It often has a remitting and relapsing character, but unfortunately this condition is incurable (it mostly refers to atopic and other endogeneous types of eczema or exogeneous types, when the causative factor cannot be avoided or eliminated).

Occupation-related hand eczema takes the first rank of all occupational diseases in many countries. (1) According to Scandinavian studies, the incidence of hand eczema ranges from 5.53 to 8.8 per 1000 person-years. (5) A 2006 survey in Denmark reported a prevalence of 14%. (5) Population- and occupation-based studies conducted in Sweden found that the 1-year prevalence of chronic hand eczema was in the range of 7% to 12%, with a higher prevalence among female patients and those aged 20 to 39 years.(6) Atopic dermatitis, only one form of hand eczema, is one of the most common dermatological conditions affecting 15 mln people in the United States. (4)

As reported, the point prevalence of hand eczema is 4% [95% CI] among adults in the general population, and a 1-year prevalence of up to 10% [95% CI], depending on whether the disease definition includes mild cases, and lifetime prevalence of 15%. [95%] (3, 7) The results are summarized from population-based studies performed during 1964 - 2007 time period; 30 out of 36 studies were from Sweden, Denmark, Norway and Finland. (7) The incidence of work-related cases (which are usually more severe than cases in the general population) that are reported to occupational health authorities is between 0.7 and 1.5 cases per 1000 workers per year. (3) There are certain occupations that suffer from hand eczema more frequently than others. These

are healthcare professionals, including nurses and cleaners, veterinarians, metalworkers, cement workers, hairdressers, gardeners and farmers. (1)

When it comes to differential diagnosis, it is important to differentiate hand eczema from other dermatological conditions it may be confused with. There are several skin diseases that mimic its symptoms and signs. Most frequently hand eczema is confused with psoriasis, mycosis (fungal infection), pustulosis palmoplantaris, herpes simplex, latex allergy and self-induced lesions. (3)

Correct diagnosis of eczema leads to better management of the disease. Diagnosis of hand eczema usually consists of collecting medical history of previous episodes of hand eczema and atopy; examining the localization (palmar, dorsal, wrist, involvement of the feet etc.) and morphology of the lesions (dry scaly skin, hyperkeratosis, fissures, vesicles etc.); duration of remissons and relapses of the diseases, and possible exposure to any irritants and allergens. (1)

In order to exclude contact allergy to external agents patch tests should be conducted on patients. In case of protein contact dermatitis, determining the level of IgE in blood serum may be of value. But as was mentioned above, hand eczema is often triggered by several factors and distinguishing the cause of the disease on examination may be impossible.

Apart from immediate pharmacotherapy, treatment of hand eczema includes preventive measures. It is routinely recommended to all patients with hand eczema to use emollients and ointments as an adequate skin protection measure. Specifically, since many patients with eczema are prone to allergies and responsive to irritants, ointments should be hypoallergenic and should not contain any preservatives. Protective measures are especially important to those suffering from occupational eczema since they are exposed to potential risk factors. It is argued that the role of protective gloves is controversial, because gloves in themselves can lead to allergic contact dermatitis, but they offer protection to those patients doing the “wet work”. An experimental study showed that cotton lining or inner glove is recommended to individuals wearing protective gloves. (3)

There is a general recommendation to eczema patients to reconsider their lifestyle; education is required. (1)

When it comes to therapy, there are two escalating steps of treatment: topical treatments and systemic treatments. (1) Most common topical treatments include

topical corticosteroids, topical immunomodulators, irradiation with ultraviolet rays (UVA/UVB) or X-rays. Systemic treatments include oral pharmaceuticals: azathioprine, cyclosporine (and other immunosuppressants), retinoids and corticosteroids. (1)

Topical corticosteroids are the first-line therapy for hand eczema. (3) They are efficient in the short-term, but their efficiency and safety in the long run are unknown. (5) Topical tacrolimus and pimecrolimus are calcineurin inhibitors (an immunosuppressant) are prescribed if topical glucocorticosteroids either failed or were not well tolerated or were inappropriate, but they are slightly more or equally efficient in treating hand eczema. (3, 5) The next alternative is phototherapy. It is frequently used as second-line treatment for the patients who were refractory to topical therapy. (3) It includes irradiation with ultraviolet light: UVA alone, photochemotherapy with psoralen (oral or topical) and UVA, and UVB.

Once hand eczema becomes chronic and irresponsive to topical treatments, systemic therapy may be identified. Oral retinoids are preferred to oral immunisuppressant agents first, due to their better safety. (3) But retinoids (including alitretinoin) also have a list of side effects associated with them, and they are used in case of severe chronic hand eczema only. Immunosuppressive therapy (cyclosporine, azathioprine, methotrexate, etc.) are also used in severe chronic hand eczema refractory to topical treatments, but has a potential risk of adverse events, hence the burden of disease should be weighted against these risks. (3)

It is important to note that the above-mentioned guidelines for management of hand eczema refer to all forms of the disease, including mild cases. However, in the following part of the thesis I will concentrate only on the treatment of chronic hand eczema. Patients with severe chronic hand eczema make up 0.5 - 0.7% of the general population. (2) They experience psychological distress because of its visibility, apart from immediate skin discomfort, which adds to the burden of the disease. Some manifestations of hand eczema, like painful fissures, vesicles, susceptibility to secondary infections, limit manual dexterity and lead to unemployment. (2) It was shown in several studies that chronic hand eczema has been a major cause for work absenteeism and even job loss. (2, 6)

There are several types of therapies used for treatment of hand eczema. The first-line therapy is topical steroids with potency that matches the disease severity. In case of chronic eczema refractory to steroidal treatment, topical immunomodulators

(tacrolimus/pimetacrolimus) may be used. When topical treatments have no impact on the disease, oral pharmaceutical therapy is used. Oral drug therapy includes retinoids (alitretinoin, acitretin) and immunosuppressants (cyclosporin, azathioprine, methotrexate). These treatment options are not used in mild cases of eczema. Another type of therapy is Grenz rays irradiation and photo(chemo)therapy (i.e. irradiation with UVA/UVB rays or a combination of psoralen with UVA irradiation – PUVA).

Although the patient population suffering from severe CHE is small, the disease has a high impact on disability, and leads to an economic loss to both individuals and society. Therefore the main subject of this study is to evaluate the effectiveness and cost-effectiveness of alitretinoin (Toctino®) comparing to another treatment for severe chronic hand eczema. In practice there are many treatment options available, including cyclosporin, azathioprine, methotrexate, Grenz rays, UVA/UVB/PUVA irradiation, topical immunosuppressants (tacrolimus/pimecrolimus), acitretin, Chinese herbal therapy etc. The clinical data on these treatments are very limited, and for the purposes of this study I chose azathioprine as a comparator since it had the best documentation.

Health-related quality of life (HRQoL) measurement is an important point in estimating the effectiveness of a treatment in hand eczema. In hand eczema it can be done with the help of generic utility instruments and dermatology-specific and disease-specific instruments. The most commonly used generic utility instrument is SF-36. The dermatology-specific instruments for measuring QoL are DLQI and Skindex-29/17. These instruments allow measuring utilities, while eczema-specific instruments (EASI, SASSAD, SCORAD, HECSI, POEM, PGA, PBI, Photographic guide etc.) only measure the disease activity and disease severity, and cannot evaluate the HRQoL in eczema patients, but are widely used in assessing the effectiveness of different eczema treatments. More on the instruments description will come in the section about the HRQoL measurement.

2. **Measures of effectiveness in dermatology**

Health-related quality of life (HRQoL) is an important measure of the severity of the disease based on the patients' perception of its effects and the impact on the patients' life. (8) HRQoL combines physical, psychological and social dimensions, which are particularly significant in dermatology. "In dermatology, QoL and its measurement hold a special meaning as many skin diseases are chronic and their burden is associated more in living with the disease than in dying from it. Moreover, the visible nature of many skin diseases is associated with significant psychosocial impact, something not directly measurable with traditional clinical outcome measures and which makes evaluation of QoL even more crucial in dermatology. It was for this reason that various dermatology-specific and disease-specific measures have been developed to quantify the impact of skin diseases on patients' QoL."(9) "In dermatology, HRQOL can be assessed with generic instruments (i.e., applicable in a broad range of conditions allowing for comparisons between diseases), dermatology-specific instruments (i.e., applicable in all skin diseases and allowing for comparisons between skin diseases) and disease-specific instruments (i.e., use is restricted to a specific skin disease and only comparisons between patient groups with the same skin condition are possible)." (10) The most commonly used generic instrument is SF-36; dermatology-specific – DLQI and Skindex-29/17. There are also several disease-specific scores developed, that are used for evaluation of disease severity and disease activity. These eczema-specific scores are EASI, HECSI, SASSAD, SCORAD, POEM, PGA, PBI, and photographic guide. A more detailed description of all the instruments is given below.

EASI (Eczema Area and Severity Index)

EASI is a scoring system used in the assessment of disease severity in atopic dermatitis. EASI was developed as an instrument of "accurate assessment of the extent and severity of atopic dermatitis". (11) PASI (psoriasis area and severity index) was used as a prototype for the eczema-specific scoring system as a standardized instrument. It consists of two components: body region involvement and disease severity, which can be used separately or in combination to yield a more complete assessment. (11)

"It focuses on the key acute and chronic signs of inflammation (i.e. erythema, induration/papulation, excoriation, and lichenification). EASI excludes non-key signs such as xerosis and scaling, oozing and crusting, and subjective parameters such as

pruritus and sleep loss in order to focus the index on key disease signs and to avoid mixing objective parameters with subjective symptoms." (11) EASI can be used in both pediatric and adult dermatology since it is adaptable for children.

In the scope of this work, EASI cannot be considered as a universal disease-specific score, because it concentrates only on atopic dermatitis as a form of eczema, and it is not limited to hands.

HECSI (Hand Eczema Severity Index)

HECSI is also a scoring system for assessing the extent and severity of the disease. The body area that it assesses is constrained by the hands and the scoring system does not specify which type of eczema it implies. "Each hand is divided into five areas [fingertips, fingers (except the tips), palms, back of hands and wrists]. For each of these areas the intensity of the six following clinical signs: erythema, induration/papulation, vesicles, fissuring, scaling and oedema was graded on the following scale: 0, no skin changes; 1, mild disease; 2, moderate and 3, severe. For each location (total of both hands) the affected area was given a score from 0 to 4 (0, 0%; 1, 1–25%; 2, 26–50%; 3, 51–75% and 4, 76–100%) for the extent of clinical symptoms. Finally, the score given for the extent at each location was multiplied by the total sum of the intensity of each clinical feature, and the total sum called the HECSI score was calculated, varying from 0 to a maximum severity score of 360 points." (12)

HECSI is an assessment instrument based on objective clinical signs, and it does not include subjective symptoms, such as pruritus, into their assessment, as well functional impairment and quality of life.(12) The assessment process is run by physicians, but patient-oriented questionnaires, where they can evaluate subjective parameters, should be used in combination with HECSI. These parameters are highly important for estimating the level of impairment, and therefore it is suggested to use with a HRQoL measure, such as DLQI. (12)

SASSAD (Six Area, Six Sign Atopic Dermatitis Severity Score)

SASSAD is another disease-specific scoring system for assessing the disease activity in atopic eczema by six objective signs of the eczema affecting six zones of the body. "The score comprises assessment of six signs: erythema, exudation, excoriation, dryness, cracking and lichenification; at six sites: arms, hands, legs, feet, head and neck, trunk;

each on a scale of 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). The total range is therefore 0-108." (13, 14)

The SASSAD is quite often used in assessing the severity and extent of the disease, but it is only used in atopic dermatitis. Since hands as an eczema-affected area are specificated into a separate body area, the score can as well be used in assessing hand eczema.

SCORAD (Scoring Atopic Dermatitis index)

"SCORAD index consists of the interpretation of the extent of the disorder (A: according to the rule of nines; 20% of the score), the intensity composed of six items (B: erythema, oedema/papules, effect of scratching, oozing/crust formation, lichenification and dryness; 60% of the score; each item has four grades: 0, 1, 2, 3) and subjective symptoms (C: itch, sleeplessness; 20% of the score). (15) The rule of nines implies that the whole body surface area is divided into areas, which are given 9% each: head and neck, each arm, the front and back of each leg and the four trunk quadrants, and 1% for the genital area. (16, 17)

SCORAD is also a widely used scoring system in eczema severity assessment in RCTs. It can be used in pediatric dermatology, since it is adaptable to children. Its advantage is that, as opposed to SASSAD, it takes subjective symptoms into account, apart from the extent and severity of the disease. But due to its extention it is not often used in clinical practice.

Photographic guide

Photographic guide is an instrument of visual assessment of the morphological severity of CHE. (18) It includes five severity levels: clear, almost clear, moderate, severe, very severe; provided with four photographs each, demonstarting various degrees of severity of CHE on each stage. There are photos of both palmar and dorsal views presented to complete the picture. Visual assessment is made by physicians. This instrument can be used in clinical trials. Though the main limitation of this method is that it provides purely visual examination, and does not take into consideration such subjective aspects as pruritus or pain and the overall functional impact of disease on the patient's professional and everyday activity. (18) And therefore, solely photographic guide cannot do a comprehensive evaluation of disease severity.

PGA (Physicians' Global Assessment)

PGA severity scale is an instrument used for evaluation of severity of CHE. It consists of five degrees of severity: clear, almost clear, mild, moderate, severe; and includes such signs and symptoms as erythema, scaling, hyperkeratosis/lichenification, vesiculation, oedema, fissures, pruritus/pain. The intensity of each parameter (the description of severity is made on a scale from 0 to 3) and the hand area involved are considered when defining the degree of severity.(19) The assessment is done by healthcare professionals. In the RCT of alitretinoin done by the NICE, PGA was used for assessment of CHE. "Severe" PGA score was an eligibility criterion for patients; "almost clear" and "clear" were treatment-stopping criterions. (19)

POEM (Patient-Oriented Eczema Measure)

The POEM is an instrument of assessing atopic eczema in adults and children. This is a questionnaire that is filled out by patients themselves basing on their subjective perception of their disease. It consists of 7 questions evaluating the disease activity during the past week. (20) It includes both symptoms, such as pruritus and sleep disturbance, and signs: skin dryness, bleeding, flaking, oozing, cracking. The score is given on a scale from 0 to 4, and the maximum score is 28. (20) The advantage of this tool is that it provides the evaluation of the disease by the patients according to their experience, not by healthcare professionals. It has a form of a short questionnaire, and therefore can be used in routine clinical practice.

PBI (Patient Benefit Index)

PBI is an innovative instrument for evaluation of the treatment benefit. (21) PBI-HE is used specifically in the assessment of chronic hand eczema threatment effectiveness. The index consists of two questionnaires: the Patient Need Questionnaire and the Patient Benefit Questionnaire. " (1) The 'Patient Needs Questionnaire' (PNQ) is filled in by the patients before therapy. It contains 27 standardized items on the patient's needs (treatment objectives) such as 'to no longer experience itching' and 'to be able to lead a normal everyday life'. Patients rate the importance of each need on a 5-step Likert scale ranging from 0 1/4 'not at all important' to 4 1/4 'very important'. (2) The 'Patient Benefit Questionnaire' (PBQ) is filled in by the patients during or after therapy. It

consists of the same items as the PNQ, but the instruction differs: patients rate the extent to which the treatment needs have been fulfilled by therapy on a Likert scale ranging from 0 1/4 'treatment didn't help at all' to 4 1/4 'treatment helped a lot'." (21)

An advantage of this instument is that it makes allowance for patients' views on the needs and benefits of a therapy, as they may differ from those of physicians'. (21) Though, since the PBI combines two domains – needs and benefits – the computation of a final PBI score is rather complicated: "each importance rating of a treatment need is divided by the sum of all importance ratings of a patient to obtain relative importance weights. To calculate the PBI, each benefit rating is multiplied by the respective relative importance rating and the products are summed. The PBI ranges from 0 (no benefit) to 4 (maximal benefit)." (21)

This method has not yet been widely used, but it was validated in the study of efficacy and safety of alitretinoin in CHE (22). (21)

DLQI (Dermatology Life Quality Index)

The DLQI is the most frequently and internationally used instrument in randomised controlled trials in dermatology. A.Y. Finlay and G.K. Khan developed it in 1994. (23) The motivation for creating a conceptually new dermatology-specific measure was "a need for a simple, compact uniform measure, applicable to patients with any skin disease, for use as an assessment tool in routine daily clinical practice." (23) Now it has been used in 33 different dermatoses in 202 studies. (9)

"The DLQI is a self-administered, easy and user-friendly questionnaire with an average completion time of 126 s. It consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their QoL over the last week."(9) It has been validated for dermatology patients from the age of 16 and above. The items of the DLQI encompass aspects such as symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each item is scored on a four-point Likert scale: 0, not at all/not relevant; 1, a little; 2, a lot; and 3, very much. Scores of individual items are added to yield a total score (0–30). (9, 23) The higher the scores - the greater the impairment of the patient's QoL.

But despite great popularity of the DLQI, there have been some concerns that it does not give a full assessment of HRQoL in all skin conditions that it is used in. For

instance, it underrepresents some emotional aspects of life of dermatological patients. "This might be one of the reasons for unexpectedly low DLQI scores in some patients with more emotionally disabling diseases such as vitiligo." (9) Or, when it comes to chronic hand eczema, there also have been some inconsistencies in QoL measurement. "Despite the widespread use of the DLQI, it is important to realize that a 'generic' dermatology-specific QoL measure such as the DLQI may not be sufficient to capture the unique constellation of specific skin conditions such as CHE. For example, the number of work impairment-related items in the DLQI is underrepresented. Moreover, some items may become redundant in CHE, e.g. choice of clothes. This fact is well demonstrated in studies of CHE where a score of DLQI even for severe hand disease has been < 10." (24) Therefore, it is recommended to combine the DLQI with a generic instrument, such as SF-36, in order to overcome its shortcomings. (9)

Skindex-29/Skindex-17

The Skindex-29 is a 29-question, three-dimensional, dermatology-specific HRQoL instrument, which may well be applied to hand eczema, because it contains questions specific to the hands. It consists of 3 main domains: symptoms, emotions, and functioning over the past 4 weeks. The domain scores and an overall score are expressed on a 100-point scale. A higher score indicates a lower quality of life. (6, 25) Obviously the time that it takes to fill out the Skindex-29 questionnaire may be significantly longer, than, for instance, DLQI. For that reason there was a shorter version of the same questionnaire created – Skindex-17. It consists of 17 items instead of 29, and answers are given on a three-point scale instead of a five-point scale. (26) There was a study conducted, that investigated whether there were large discrepancies in responses to Skindex-29 and Skindex-17. (26) The results of the study showed that "the overall correlation was 0.957 for the symptoms scale and 0.940 for the psychosocial scale." (26) Due to a shorter form, and, however, a similar level of precision, specifically saving some important phychometric aspects that were mentioned in Skindex-29, Skindex-17 may be more frequently used in routine clinical practice. (26)

SF-36 (Short Form – 36)

"Short Form-36 (SF-36) has been used internationally to assess functional health and well being, that is, HRQL, in several long-standing diseases and illnesses. In

dermatology, the SF-36 has been used in acne, atopic dermatitis, and psoriasis. Selected questions from the SF-36 have also been used in occupational contact dermatitis". (27) The SF-36 is a multi-purpose, short-form health survey with 36 questions, most of which cover the health state during the past 4 weeks. It yields an 8-scale profile of functional health and well-being scores as well as physical and mental health summary measures and a preference-based health utility index. (www.sf-36.org) The 8 domains that the questionnaire covers are physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, mental health. (27)

Since it is a generic measure, it can be used in assessing HRQoL in different health conditions enabling comparisons among them. It is possible to use it in the scope of dermatology as it includes the aspects of interest for it: limitations of physical functioning, social and emotional problems. In dermatology it is used more often than another generic instrument – EQ-5D, and it is typically combined with the dermatology-specific HRQoL measures, like DLQI.

3. **Effectiveness of the therapies**

Here we will concentrate on the treatment of severe chronic hand eczema. Once hand eczema has evolved into chronic (hand eczema of > 6 months' duration should be considered chronic (5)), its prognosis for the patients becomes poor. It is a recurring condition with a long-lasting and chronically relapsing course. (2) Individuals suffering from CHE refractory to topical corticosteroids have a limited number of treatment options with indeterminate effectiveness. For the purposes of this thesis I studied several treatment options, including alitretinoin, azathioprine, cyclosporin, methotrexate, Grenz (Bucky) rays and UVA/UVB/PUVA irradiation. The information on the treatment alternatives is quite limited; it lacks head-to-head trials of the therapies and is presented by small-scale RCTs, in most cases, with fewer than 50 patients (see Table 1). Therefore I chose azathioprine as the one comparator with the best documentation.

The effectiveness of the treatments presented below is measured by means of disease-specific instruments: PGA, SASSAD, SCORAD, and EDI. One study also uses a non-formalized scale from 0 to 10. The primary endpoints are "clear"/"almost clear" PGA state for alitretinoin, and reduction of disease activity/severity during active treatment measured by one of the scales (SASSAD, SCORAD, EDI) for azathioprine.

Alitretinoin

Alitretinoin is an oral retinoid (9-cis retinoic acid) used in patients with severe CHE refractory to topical corticosteroids. This medication has not yet been approved for reimbursement in Norway since there is no certainty with respect to its effectiveness. There have been no comparative studies of Toctino® *versus* other systemic treatment published.

The pivotal study of alitretinoin was the largest RCT conducted in the history of eczema trials. There were several steps of trials: a 12-week phase II trial (n=319) comparing three doses of alitretinoin (10 mg, 20 mg and 40 mg) with placebo; a 24-week phase III trial (n=1032) comparing daily 10 mg and 30 mg doses with placebo; and a trial of extended treatment for those patients who did not respond to alitretinoin within the 24-week trial period (n=243). (28, 29) The phase III trial is of most interest to this thesis as it included only patients with "severe" chronic hand eczema, whereas

the phase II trial included people with both “moderate” and “severe” CHE as defined by the PGA score. (29)

The BACH study (29) was a large (n=1032), randomized, double-blind, placebo-controlled, multicentre study of up to 24-week duration. The sample was 418, 409 and 205 adult patients randomized to alitretinoin 10 mg/day, 30 mg/day, and placebo, respectively. (2, 22) Refractory status was verified by the following criteria:

- The patients had received topical corticosteroids for at least 8 weeks (including 4 weeks of very potent corticosteroids) 6 months before the trial, and had no or partial response;
- They received standard skin therapy (emollients, barrier protection etc.) and avoided irritants and allergens without visible improvement;
- Other conditions mimicing CHE were excluded. (22)

The exclusion criteria from the trial were:

- Other dermatological conditions that would interfere with the conduct or evaluation of the study;
- ALT/AST values >250% of the upper limit of normal, tryglycerides > 200% of the upper limit, cholesterol >200% of the upper limit and haemoglobin below the limit of normal;
- History of major psychiatric disorders;
- Other investigational drugs used within the previous 2 months; UVB, PUVA, X-ray irradiation, systemic corticosteroids, retinoids or immunosupressants within the previous 4 weeks; any drugs with potential drug-drug interaction within the previous 2 weeks. (22)

Alitretinoin has a range of adverse events specific to it. It is highly teratogenic, so women of child-bearing age participating in the study were required to use at least two forms of contraception 1 month prior to, during and 1 month after the trial, and take monthly pregnancy tests. (22) The most common side effect was headache, mycocutaneous events (dry skin, dry lips, cheilitis), reduced level of thyroid-stimulating hormone and increase in total cholesterol and tryglycerids. All adverse events were dose-dependent. (22)

Patients in both alitretinoin groups (10 mg and 30 mg) had a significantly better effect than those in the placebo group and responded with “clear”/”almost clear” hands as assessed by the PGA. (22)

A total of 47.7% (195 of 409 patients; $p < 0.001$ *versus* placebo) of alitretinoin 30 mg/day recipients responded to treatment (22.0% had a 'clear' and 25.7% had an 'almost clear' disease area) compared with 16.6% (34 of 205) of placebo recipients (2.9% 'clear' and 13.7% 'almost clear'). Alitretinoin 10 mg/day was also significantly (p = 0.004) more effective than placebo, with 27.5% (115 of 418) of recipients responding (9.3% 'clear' and 18.2% 'almost clear'). (22, 29, 30)

"Treatment-related adverse events occurred in 34.5%, 37.1% and 49.5% of patients on placebo, alitretinoin 10 mg and 30 mg groups, respectively. 1%, 4% and 1% of patients withdrew from the alitretinoin 10 mg, 30 mg and placebo groups, respectively, due to adverse events." (30)

A study of extended therapy with alitretinoin recruited participants of the initial alitretinoin trial who did not respond to it. Of the 243 patients enrolled, 53 (21.8%) had 'severe' disease, 136 (56%) had 'moderate' disease and 53 (21.8%) had 'mild' disease. All patients received 30 mg of oral alitretinoin once daily, irrespective of their previous treatment regime. (28) Of the patients who had previously received alitretinoin 30 mg, alitretinoin 10 mg and placebo, 39.1%, 50.4% and 50.9%, respectively, were rated "clear" or "almost clear" by PGA score by the end of this follow-on study. (28) The median duration of exposure to alitretinoin 30 mg treatment in the follow-on study was 168 days. The study showed that alitretinoin 30 mg/day was well tolerated in extended treatment as well as during the initial trial. (28)

The results of the initial study confirm that alitretinoin has a considerable therapeutic effect on severe chronic hand eczema refractory to topical corticosteroids. (22)

Azathioprine

Azathioprine is an immunosuppressive medication. There are several RCTs that compared its effectiveness with placebo in severe and moderate-to-severe AD.

The first trial (31) enrolled 37 participants with severe atopic dermatitis (AD), divided into azathioprine group (n=18) and placebo group (n=17). Total duration of the trial was 12 weeks with assessments held at week 0, 2,4, 8, and 12. There were 16 withdrawals from the study (12 *versus* 4, in azathioprine and placebo group, respectively). The primary endpoint was an objective assessment of the disease activity from baseline to week 12 by means of SASSAD. The mean SASSAD score at baseline was

41 units. At week 12 the mean improvement in the azathioprine group was 10.2 (27%) against 0.8 (2%) units in the placebo group (P<0.01). (31)

The second trial (32) enrolled 63 patients with moderate-to severe AD, divided into azathioprine group (n=42) and placebo group (n=21). The TPMT activity was measured in each patient, because the dosage of azathioprine depends on it. Patients with low or absent TPMT activity were excluded from the trial due to high risk of myelotoxicity. There were 9 withdrawals from the trial (7 *versus* 2, in azathioprine and placebo groups, respectively). The trial duration was 12 weeks with a 12-week follow-up. The primary endpoint was the mean change in disease activity with SASSAD from baseline to week 12. The secondary endpoint combined measurements of itch score, body surface affected, QoL (measured with DLQI), global response to the treatment assessed by both investigators and participants. At week 12 the mean improvement in the azathioprine group was 12.0 (37%) compared to 6.6 (20%) in the placebo group. (32) In the secondary endpoint azathioprine also showed significant improvement compared to placebo. (32)

The third trial (33) studied 35 patients with severe long-standing AD, resistant to conventional therapy. The QoL was measured with EDI; improvement of the patients' eczema after treatment was measured on a scale from 0 (no effect) to 10 (100% improvement). The median length of treatment was 7 months (from 1 to 21 months). "In the year after azathioprine therapy was stopped, patients received fewer antibiotic courses (median, 2; range, -1 to 7), had fewer hospital admissions (median, 1; range, -1 to 3), fewer outpatient attendances (median, 4; range, -1 to 10), and required fewer changes to topical steroids of similar or higher potency (median, 2.5; range, -1 to 7). Three patients (8.6%) had little effect from the azathioprine. Eighteen of the 26 patients (69.2%) interviewed responded to the azathioprine within 1 month." (33) Within the year after therapy the median difference before and after treatment in EDI score was 22 (from 6.5 to 32); the mean effect of azathioprine on disease severity on the scale was 6.9. (33)

All three trials demonstrate significant improvement in disease severity with azathioprine compared to no treatment.

Azathioprine vs. methotrexate

Both azathioprine and methotrexate are immunosuppressants. There is a trial that compared the effectiveness of azathioprine and methotrexate in adults with severe AD. (34) It is a single-blind parallel-group RCT (n=42 1:1 ratio). The trial lasted for 12 weeks with a 12 weeks follow-up. Twenty patients were randomized to methotrexate, the other 22 – to azathioprine. The primary endpoint was the mean reduction in eczema severity score. At baseline the methotrexate group had a mean SCORAD score of 57.2, the azathioprine group – 58. (34) Only antihystamines and topical ointments were allowed during treatment as concomitants. Patients, who had undergone phototherapy, had been taking any systemic medication or potent topical medication 2 weeks prior to the trial, as well as pregnant/nursing women or those planning pregnancy etc. were excluded from the study.

At week 12 of the trial the methotrexate group showed a mean relative reduction of SCORAD of 42% (from 57.2 to 34.4), while the azathioprine group - 39% (from 58 to 36.3). (34) At week 24, the difference between the medications in all outcome measurements was reported to be not statistically significant (p=0.58). (34)

Both azathioprine and methotrexate are effective in treating severe AD, but there was no evidence about their efficiency in severe hand eczema of other types.

METHODS

1. Literature search

Using the Pubmed database, I conducted two systematic literature reviews, one on effectiveness of therapies (RCTs) and one on cost-effectiveness. A systematic review of the RCTs was conducted through the PubMed database. The main keywords for the RCT search were *randomized controlled trial AND eczema.* They were in turn combined with additional keywords such as *hand eczema, severe eczema, placebo, alitretinoin, azathioprine, cyclosporine, methotrexate, Grenz rays, UVA UVB, PUVA*. Each Pubmed hit was scrutinized with respect to title relevance. In case it was relevant, the abstract was read. If this was also relevant, the full article was acquired. Additionally I scrutinized the reference lists of the identified articles and obtained PDF files for the relevant papers. All the articles used in this thesis are mentioned in the reference list.

For the search for the previous CEAs of hand eczema therapy the main keywords were *cost-effectiveness AND hand eczema.* They were combined with additional terms such as *CEA, dermatitis, alitretinoin, cyclosporin, azathioprine, methotrexate, Grenz rays, UVA, UVB, and PUVA*. There were in total nine hits for all keyword combinations, and they were studied with respect to relevance of the titles. Among the nine titles, four seemed relevant, but two of them were excluded on the basis of abstract. The remaining two papers were read in full and were relevant. The two papers are briefly presented below.

Blank and co-workers (35) assessed the cost-effectiveness of alitretinoin in patients with chronic hand eczema from a third party payer perspective in Switzerland. A Markov model with two arms, alitretinoin and standard emollient therapy, and a time-horizon of 22.4 years was used for the simulation. The costs were measured in Euros (€) and the effectiveness in QALYs. At the end of the simulation the long-term costs of alitretinoin and emollient therapy were €42,208 and €38,795, respectively, while the net QALY gain of alitretinoin was 0.230 QALYs. (35) The estimated ICER was consequently €14,814 per QALY, which was deemed cost-effective from the Swiss perspective. (35)

A NICE Single Technology appraisal of alitretinoin in CHE (2) encompassed economic evaluation of alitretinoin compared to placebo. The study presented estimates of the costs and QALYs from the NHS perspective. The authors conclude that "in the manufacturer's original submission to NICE, the base-case ICERs reported for alitretinoin were **£**8,614 per QALY *versus* ciclosporin, -£469 per QALY *versus* PUVA (with alitretinoin dominant) and **£**10,612 per QALY *versus* azathioprine. In the revised model, which compared alitretinoin only with placebo, the ICER was estimated at **£**12,931 per QALY." (2) However, the Evidence Review Group considered the results presented by the manufacturer unreliable, because they did not include a probabilistic sensitivity analysis. According to the review group, there was considerable uncertainty associated with the results of the study, therefore cost-effectiveness of alitretinoin cannot be claimed.

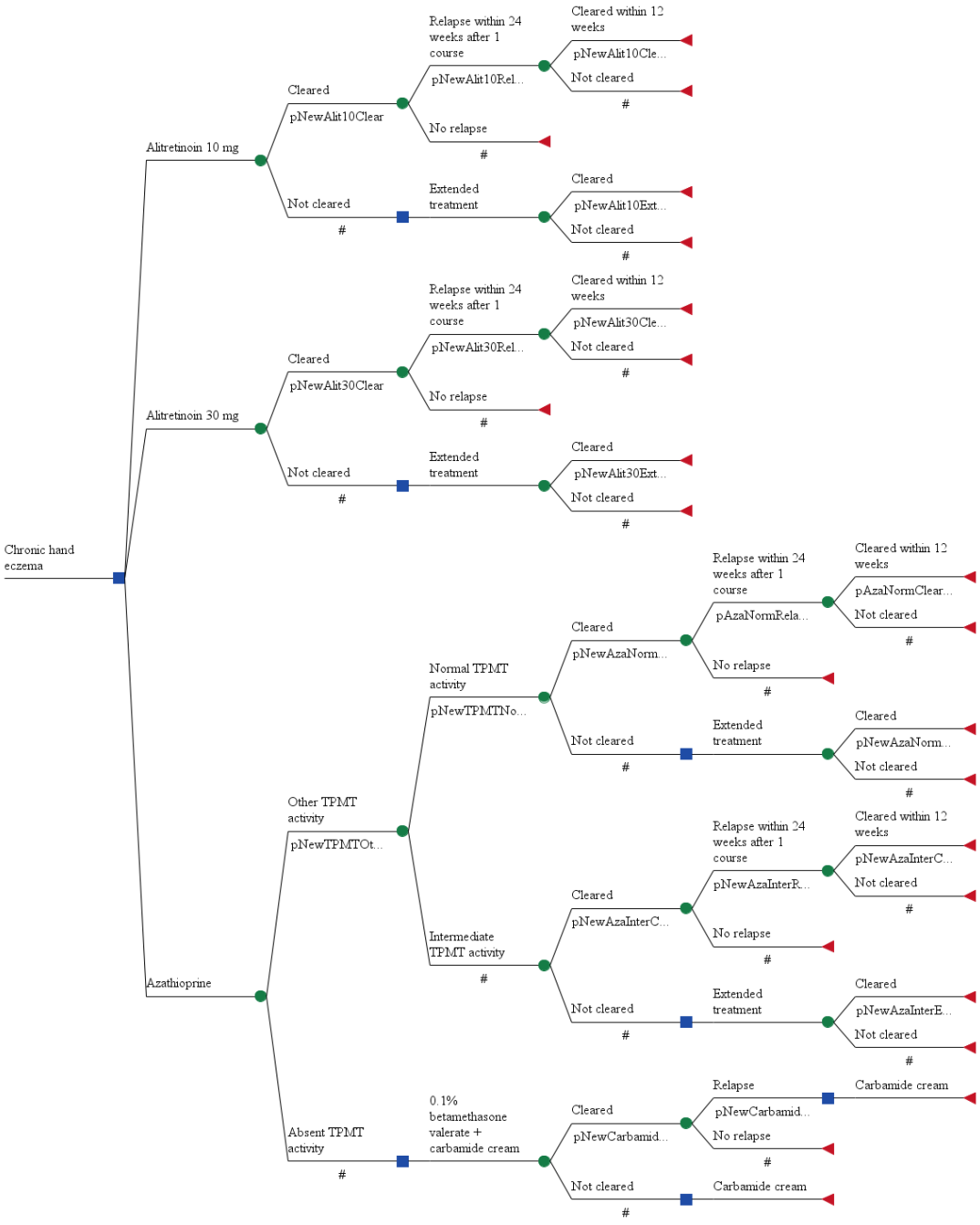
As long as there is a lack of valid data on the comparative effectiveness of the therapy alternatives for hand eczema, it makes it difficult to estimate the cost-effectiveness of alitretinoin compared to other treatments.

2. Model

To estimate the expected costs and outcomes of alitretinoin and azathioprine for the treatment of hand eczema I developed a decision tree model using TreeAge Pro® 2014. Though it is not often used for chronic or relapsing diseases, such as chronic hand eczema, the short-term time horizon of this model (12 months) makes decision trees suitable. (Drummond M. et al., 2005)

A decision tree has the following structure (Drummond M. et al., 2005): *decision nodes* that represent the decision(s) being addressed in the model; *chance nodes* that indicate uncertain outcomes; *branches* that represent possible strategies or events that a patient can experience; and *pathways* that are made of branches and that patients pass along though the model. The pathways are mutually exclusive (i.e. a patient can only follow one) and collectively exhaustive (i.e. they cover all pathways a patient could possibly follow). Each event in the decision tree is assigned a certain *probability*. Pathway probabilities must sum to 1, since they are mutually exclusive. The costs and outcomes associated with the presented pathways are weighted by the respective probabilities in order to calculate the *expected values* of the treatments.

Figure 1. Decision tree model



The model has three strategies: alitretinoin 10 mg, alitretinoin 30 mg and azathioprine. The two different alitretinoin doses imply different probabilities of cure associated with them, different costs and different quality of life.

The alitretinoin strategies entail the following events: cleared or not within 24 weeks; relapse or not within 24 weeks after becoming cleared; cleared or not within 12 weeks after relapse; cleared or not during extended treatment of 48 weeks.

The azathioprine strategy first entails a TPMT test (a test for thiopurine methyltransferase activity) as long as there is a correlation between the TPMT activity and potentially severe adverse events in a patient. (36) People with very low or absent TPMT activity taking azathioprine have a high risk of myelotoxicity (32), and should not receive this medication. If the test indicates no TPMT activity, a patient receives topical corticosteroid 0.1% betamethasone valerate and carbamide cream instead. This pathway has the following events: cleared or not during the 24 weeks, and relapse or not within 24 weeks after becoming clear. In case of a relapse or not becoming clear after 24 weeks patients are assumed to receive only carbamide cream. If the test indicates "normal TPMT activity" or "intermediate TPMT activity", patients receive azathioprine treatment and the course of the treatment is modelled as for alitretinoin: cleared or not within 24 weeks; relapse or not within 24 weeks after becoming cleared; cleared or not within 12 weeks after relapse; cleared or not during extended treatment of 48 weeks. Patients with "absent TPMT activity" are assigned to a topical steroid 0.1% betamethasone valerate cream and carbamide cream.

The chosen time perspective of the model is 48 weeks (≈1 year). The initial course duration is 24 weeks. After successful treatment patients are followed-up for 24 weeks with respect to a possible relapse. In case treatment has failed during the first 24-weeks course, patients receive another 24-weeks course.

The costs of the treatments are counted from the third-party payer perspective.

Two types of sensitivity analyses were conducted in this study. I conducted a one-way sensitivity analysis by means of a Tornado diagram to describe the uncertainty deterministically, as well as a probabilistic sensitivity analysis be means of a Monte Carlo simulation with 10,000 samples. Distributions were assigned depending on the type of the parameter. *Probabilities* take values from 0 to 1, and therefore beta distribution was assigned to these parameters. Beta distribution is conjugate to binomial distribution and is restricted to the interval from 0 to 1. *Costs* can take values from 0 to +∞. Since it cannot take negative values and is not restricted to 1 on the upper bound, I assigned gamma distribution to the parameters of costs. *Utility* parameters, in principle, can take any values; negative values can be used in case of a "worse than death" state. Since hand eczema is not a state "worse than death", it takes only positive values. Since utility parameters in this case are restricted to an interval between 0 and 1, beta distribution is used. (Briggs A., Sculpher M., Claxton K. *Decision Modeling for*

Health Economic Evaluation, 2006) The mean values for the distributions were taken from the deterministic values. The standard deviation from the mean was assumed to be 20%.

Dosage

The treatment dosage was based on the trials (2, 22, 29, 31, 32, 37) and guidelines (36, 38, 39). The BACH study explored two alitretinoin doses: 10 mg or 30 mg. Indication for the choice of the doses was not specified.

Indication for the choice of azathioprine dose is specified in the RCTs (31, 32) and guidelines (36, 38, 39) studying the use of azathioprine in dermatology. The dose in the range of 1-3 mg/kg/day is suggested for prescription if a patient has intermediate or normal TPMT activity. People with intermediate TPMT activity require a daily dose of 1.0-1.5 mg/kg, while those with normal TPMT activity require 2.0-3.0 mg/kg/day, respectively. (36) For the purposes of this thesis I took the dose regimen from the study by Meggitt et al. (32), where patients with intermediate TPMT activity receive 1.0 mg/kg/day, and patients with normal TPMT activity – 2.5 mg/kg/day. The mean weight of an adult in Norway is assumed to be 75 kg.

Costs

All costs associated with both strategies are listed in Table 1. The drug costs mentioned in the model were obtained from the Norwegian "physician desk book" Felleskatalogen (www.felleskatalogen.no). The mean cost of oral contraception was calculated from the prices of the medications listed under the register code G03A A at Felleskatalogen.

Costs of most laboratory tests were obtained from the regulations on compensation of expenses for medical care (*Forskrift om godtgjørelse av utgifter til helsehjelp som utføres poliklinisk ved statlige helseinstitusjoner og ved helseinstitusjoner som mottar driftstilskudd fra regionale helseforetak, 2014*). The mean cost of urine test is assumed to be NOK 5 based on an expert opinion. The cost of a TPMT test was taken from the British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011 (36), and was converted from English pounds (£) to Norwegian kroner (NOK).

All the pregnancy-related costs (cost of oral contraception and pregnancy tests) were calculated assuming that the proportions of men and women in the sample equaled 50%.

The costs of visit to a GP visit (NOK335) and to a private practicing dermatologist (NOK514) were based on the Fee Schedule for the Norwegian Medical Association (40) and included patients copayments for consultations, fees paid by the health insurance system (NAV), annual capitation fees and block grants (driftstilskudd) paid by the regional health authority. The cost of a visit to a dermatologist in a hospital (NOK774) was based on the Norwegian DRG price list. (41) It was assumed that 50% of the physician visits were made to a dermatologist in private practice and 50% to an outpatient-clinic. The mean of the two costs was taken as a cost of a dermatologist visit.

VAT is excluded from the costs of drugs that are used in the model.

Table 1. Unit costs and period costs in 2014 Norwegian Kroner (NOK)*

Cost Item	Unit cost	Cost per week	Cost per 24 weeks
Drugs			
Alitretinoin 10mg/30mg (30 tab) (*Toctino*®, Stiefel, GSK)	3510.00	819.00	19656.00
Azathioprine 50mg (100 tab) (*Imurel*®, Aspen Europe GmbH)	106.425	(2.5mg/kg) – 27.93 (1.0mg/kg) – 11.18	(2.5mg/kg) – 670.32 (1.0mg/kg) – 268.38
0.1% betamethasone valerate cream (*Betnovat*® GSK, 100ml)	64.00	21.00	64.00
Carbamide cream *Canoderm*® *5%* (ACO hud, 500 g)	359.25	15.00	359.25
Oral contraception (assuming the proportion of women is 50%)	70.875	17.70	424.80
Procedures			
TPMT test (AZA)	300.00	-	300.00
Pregnancy test (assuming the proportion of women is 50%)	15.50	-	108.50
CBC	70.00	-	140.00
Blood chemistry (Alit)	100.00	-	200.00
Liver function test (AZA)	60.00	-	120.00
Iron metabolism (Alit)	50.00	-	100.00
Thyroid function (Alit)	30.00	-	60.00
Urine analysis (Alit)	5.00		10.00
Other			
GP visit	334.75	-	334.75
Dermatologist visit (private practice)	513.93	-	1541.79
Dermatologist visit (out-patient clinic)	774.67	-	2324.01

* Drug costs excluding VAT

Probabilities

The probabilities of response are based on the data from alitretinoin (22, 28, 37) and azathioprine (32) trials. These probabilities are the probabilities of response within 24 weeks, the probabilities of a relapse within 24 weeks after achieving the "clear/almost clear" state, the probabilities of moving back to the "clear/almost clear" state within 24 weeks after the relapse, and the probabilities of response during extended treatment of 48 weeks.

The probabilities in alitretinoin strategies, as reported in the trials, are dose-dependent. The azathioprine strategies are assumed to have equal probabilities of response in 1.0 mg/kg and 2.5 mg/kg dose regimens, because the dose-dependence was not reported in the trial.

The probabilities of interest for the carbamide branch were also obtained from the trials (42-44).

Table 2. Probabilities of treatment response

Variable	Base-case value	Range
Alit10Clear24	0.28	0.224-0.336
Alit10ClearAfterRelapse	0.48	0.384-0.576
Alit10ExtTreatClear	0.5	0.4-0.6
Alit10Relapse24	0.25	0.2-0.3
Alit30Clear24	0.48	0.384-0.576
Alit30ClearAfterRelapse	0.8	0.64-0.96
Alit30ExtTreatClear	0.39	0.312-0.468
Alit30Relapse24	0.38	0.304-0.456
AzaClear	0.2	0.16-0.24
AzaClearAfterRelapse	0.5	0.4-0.6
AzaExtClear	0.5	0.4-0.6
AzaRelapse	0.5	0.4-0.6
CarbamideImp	0.5	0.4-0.6
CarbamideRelapse	0.32	0.256-0.384

The probabilities of patients having different TPMT activities are obtained from the respective studies (45, 46).

Table 3. Probabilities of different TPMT activity

Variable	Base-case value	Range	Reference
Normal TPMT activity	0.887	0.7096-1	(45, 46)
Intermediate TPMT activity	0.110	0.088-0.132	(45, 46)
Absent TPMT activity	0.003	0.0024-0.0036	(45, 46)

Health-Related Quality of life

All the trials used the DLQI instrument to estimate the health-related quality of life (HRQoL). Since no direct utility data were collected in the trials, the HRQoL values needed to be translated into EQ-5D utility scores. For these purposes I used the following formula mentioned in the study by Blank et al:

EQ-5 D utility score = 0.956 - [0.0248 × (DLQI total score)] (35, 47)

The formula was extracted from the Health Technology Assessment of psoriasis treatment by Woolacott et al (47), p.48. The analysis conducted by Woolacott et al estimated "each one-point increase in the DLQI to be associated with a fall of 0.0248 in

patient utility."(47) Blank and coworkers argue that patients with severe psoriasis with a DLQI score greater than 10 can be compared with severe chronic hand eczema patients with a DLQI score greater than 10 with regard to their impaired quality of life, and hence a "mapping" exercise can be conducted in order to estimate the utility weights (measured with EQ-5D) from the associated quality of life scores (measured by DLQI). (35)

The utilities were calculated this way for all the health states in the model.

Table 4. Utility weights

Health state	EQ-5D weight	DLQI score	Reference
Severe	0.625	15.08	(36)
Moderate	0.761	7.86	(35)
Clear	0.913	1.74	(35)
Carbamide (clear)	0.836	4.84	(42)
Carbamide (relapse)	0.779	7.1	(42)

Cost-effectiveness threshold

The Directorate of Health issued a guide for the economic evaluation of healthcare (*Økonomisk evaluering av helsetiltak – en veileder, 2012*) in which the statutory cost-effectiveness threshold was considered to be NOK588,000 (2012-kroner) per life-year gained. (48) It estimates the maximum cost the society should be willing to pay for a life-year gained with an intervention. This value is used as the WTP in the current model.

RESULTS

The base-case results show that a one-year expected QALY was 0.681 for the azathioprine strategy, 0.701 for alitretinoin 30 mg and 0.695 for alitretinoin 10 mg, while the expected costs were NOK6061 for azathioprine, NOK37,297 for alitretinoin 30 mg, and NOK40,339 for alitretinoin 10 mg, respectively. The incremental cost-effectiveness ratio of alitretinoin 30 mg shows that this strategy is not cost-effective, since it is way above the proposed cost-effectiveness threshold. The alitretinoin 10 mg strategy is dominated since its ICER has taken a negative value.

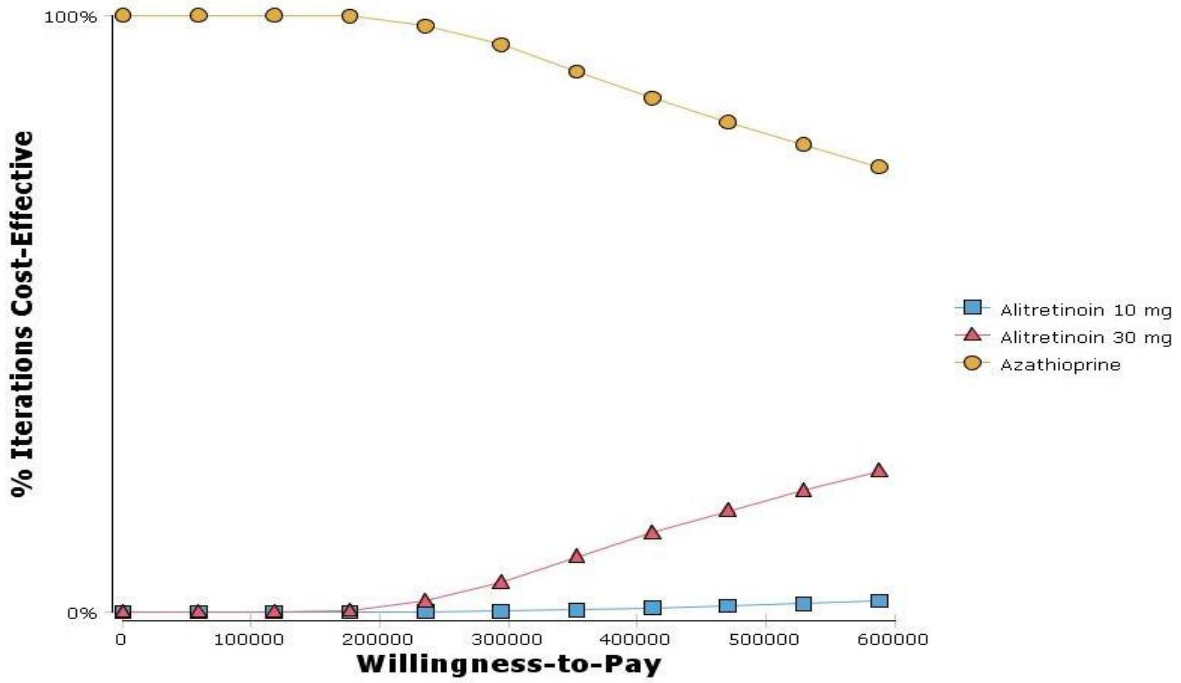
Table 5. Costs (2014 Norwegian Kroner (NOK)), effectiveness and incremental cost-effectiveness (ICER) of three treatments for severe hand eczema

	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Azathioprine	6061		0.681		
Alitretinoin 30 mg	37297	31236	0.701	0.02	1,561,800
Alitretinoin 10 mg	40339	3042	0.695	-0.006	dominated

Sensitivity analyses

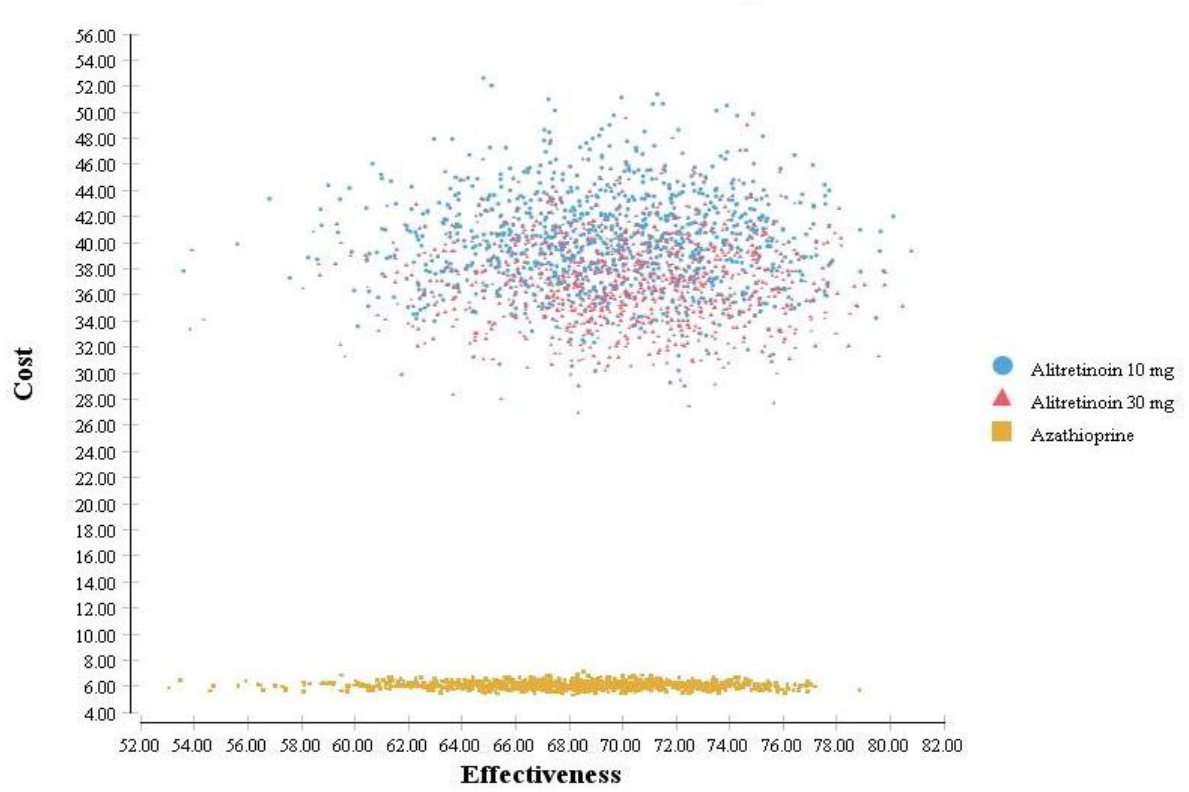
The main results are presented in the cost-effectiveness acceptability curve, scatter plot and Tornado diagram below.

Figure 2. Cost-effectiveness acceptability curve of the strategies



In the CEAC we can see that azathioprine is a cost-effective strategy with the probability of more than 74% regardless of the WTP for a QALY. It indicates that the ICER falls below the cost-effectiveness threshold in 100% of the time when the WTP is NOK0, and reaches 74.6% while the WTP reaches NOK588,000. Alitretinoin 30 mg is cost-effective 23.6% of the time with the WTP value of NOK588,000, while alitretinoin 10 mg is cost-effective 1.8% of the time at the maximum WTP.

Figure 3. Joint distribution of cost and outcome from Monte Carlo Simulation in 10,000 iterations



From the scatterplot we can see that azathioprine demontrates higher effectiveness at a much lower cost than both alitretinoin strategies. With 10,000 iterations the effectiveness values of azathioprine fall between 0.53 and 0.79 QALYs with the approximate cost of NOK6000. Distributions of alitretinoin 10 mg and 30 mg are represented by two overlapping clouds, but it is still possible to define that both strategies demonstrate approximately equal effectiveness, with alitretinoin 10 mg requiring higher costs, up to NOK53000.

The deterministic sensitivity analysis was conducted in order to get more insight into the importance of uncertainty in the individual parameters. I constructed a Tornado diagram to check which parameters had the greatest impact on the results. Lacking empirical data on uncertainty of the parameter values, I assumed a range of +/- 20% of the base case value for each parameter. The diagram shows that the QoL at "severe" state in the azathioprine strategy, QoL at "moderate" state in azathioprine, QoL of "clear" state, QoL in "moderate" state in alitretinoin, and QoL in "severe" state in alitretinoin strategy are the parameters that have the greatest impact on the result. Even taking this uncertainty into consideration, however, azathioprine is more cost-effective than the other strategies. For instance, with the QoL value of the "severe" state in the azathioprine strategy at the lowest bound of 0.5752, the ICER would be 388,784 NOK/QALY, while at the upper bound of 0.8628 the ICER would be 445,878 NOK/QALY.

Figure 4. Tornado diagram (deterministic sensitivity analysis)

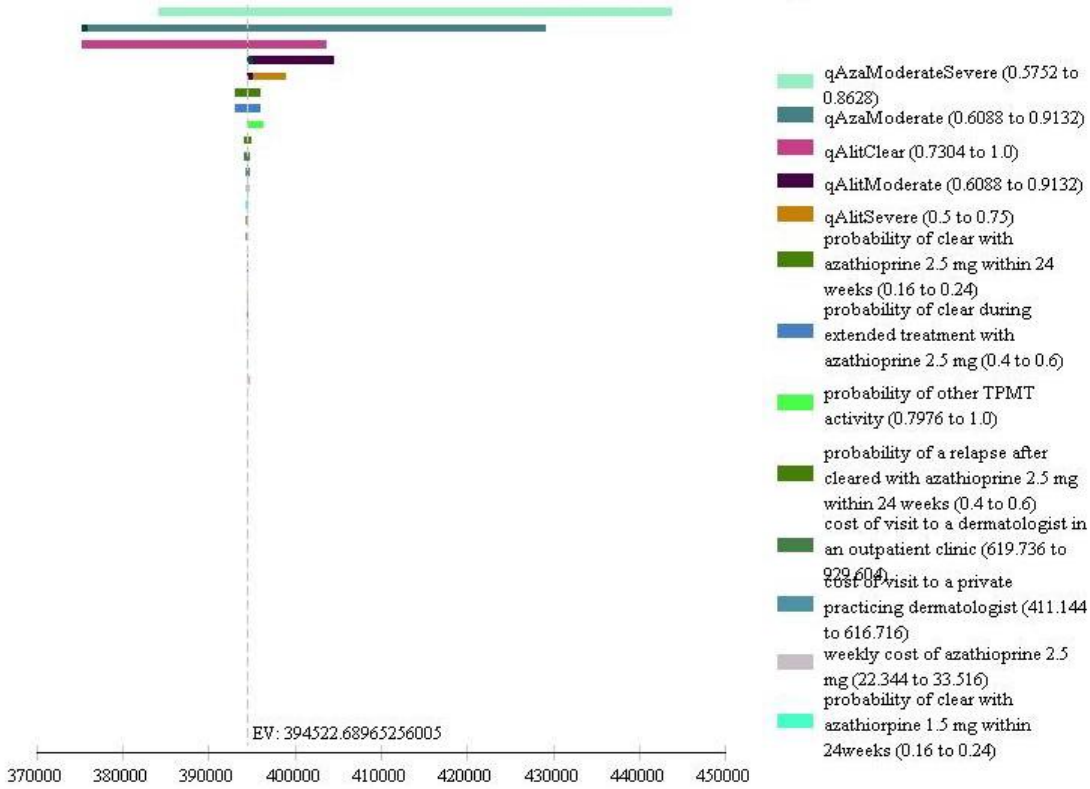


Table 6. One-way sensitivity analysis of the parameters that were the most important according to the Tornado analysis

		ICER (lower-upper)	ICER (lower-upper)	ICER (lower-upper)
Parameter	**Base case (range)**	**Alitretinoin 10 mg**	**Alitretinoin 30 mg**	**Azathioprine**
qAzaModerateSevere	0.625 (0.5752-0.8628)	(dominated/ dominated)	(1,030,151/ dominated)	NA
qAzaModerate	0.761 (0.6088-0.9132)	(dominated /dominated)	(448,028/ dominated)	NA
qAlitClear	0.913 (0.7304-1.0)	(944,228/dominated)	(ext.dominated/ 1,648,835)	NA
qAlitModerate	0.761 (0.6088-0.9132)	(dominated/ 1,027,516)	(dominated/ 493,545)	NA
qAlitSevere	0.625 (0.5-0.75)	(dominated/dominated)	(dominated/514,405)	NA

Discussion

The results of this study indicate that the azathioprine strategy dominates alitretinoin 10mg and is more cost-effective than alitretinoin 30mg strategy, since azathioprine entails lower costs and similar health outcomes. The results, however, should be considered against the methodological limitations of the study.

Strengths of the study

In this thesis I conducted a literature search and a systematic review of the RCTs and cost-effectiveness analyses. As far as I had decided upon the two comparators for my analysis (alitretinoin and azathioprine), I excluded all the articles studying other treatment alternatives from the thesis (cyclosporin, methotrexate, Bucky rays, UV-irradiation), however, the overview of the treatments' effectiveness is presented in the Appendix. This study adds to the current literature in that it compares alitretinoin to active treatments while published economic evaluation of alitretinoin have used placebo as the comparator.

Limitations of the study

There were several assumptions made in the thesis either due to the lack of data or in order to simplify the model.

Chronic hand eczema is a recurrent condition, and under ideal conditions the time horizon of the model should be a life time or at least several years. However, the lack of data on the long-term effectiveness of the drugs may justify a shorter time perspective.

One of the drugs, azathioprine, is used only in treatment of atopic eczema, while alitretinoin may, in principle, be used for treating any type of chronic eczema.

The trial data for effectiveness stems from the UK and other European countries. However, the effectiveness of the two drugs is likely to be the same across countries.

The model was developed according to the reporting of the RCTs, but the model was not validated by a dermatologist. Some of the parameters, such as number of dermatologist visits, amount of carbamide cream used, amount of steroids used, number of lab tests conducted etc., may need to be adapted to reflect real life practice.

For simplicity purposes it was assumed that a relapse after being "cleared" happens at week 36 in all the strategies, and eczema gets "cleared" or "not cleared" until the end of the time horizon of 48 weeks, i.e. within 12 weeks.

Dosage

Azathioprine is assumed to be given to patients in full dose (1.0 mg and 2.5 mg) from the onset of the treatment. Meggitt and coworkers (32) reported that the doses were reduced from 1.0 mg and 2.5 mg to 0.5 mg and 1.0 mg, respectively, for the first 4 weeks of the treatment in order to avoid adverse events. This could be a precaution measure for the purposes of the trial, and I did not follow this dose regimen in this thesis.

The different doses of azathioprine for patients with intermediate and normal TPMT activity, 1.0 mg and 2.5 mg, respectively, are assumed to be equally effective. Since the TPMT activity is lower, the lower dose of azathioprine is considered to be as effective as of the normal dose.

Probabilities

Assumptions referring to the probabilities had to be made in the azathioprine strategy due to the lack of trial data or a qualified expert panel. The probabilities of a relapse, becoming clear after the relapse, becoming clear after extended treatment, and becoming clear with corticosteroids and carbamide treatment were not available from the trials, and therefore were assumed to be 50%. I assumed they should be equal in order to avoid making any inferences about the possible outcome.

Lacking an expert panel on the TPMT test specificity and sensitivity, it is assumed to be perfect.

Health Related Quality of Life

Primarily different instruments for measurement of effectiveness are used in the alitretinoin and azathioprine studies. PGA is used in the alitretinoin study, while SASSAD is used in the azathioprine study. These instruments might not be fully consistent with each other.

The utilities in the model are measured only basing on the HRQoL of the health states and their duration. Adverse events from the treatments are assumed not to have any influence on the QoL.

I assumed that for the purposes of consistency the QoL in which the patients enter the model and which they end up after becoming clear should be the same in all

the strategies. In the azathioprine trial that had been used, patients are in a moderate-to-severe state at the onset of the treatment, and, hence, have higher utilities and higher clearance rate. The probabilities of becoming clear with azathioprine of either dosage were reduced from 0.39 claimed in the trial, to 0.20. The respective utilities were reduced to those in the alitretinoin branches.

The effectiveness of carbamide treatment is adjusted to the PGA "severe" state. The patients entered the trials in the mild-to-moderate state, and hence the QoL scores before and after treatment, that were claimed in the trials (42, 44), are high. These utility weights were unsuitable for the patients in "severe" state. Therefore, I assumed the QoL at the onset of treatment to be 0.625 ("severe" state, since all patients are assumed to start with this QoL), the QoL of the moderate state – 0.761, the QoL after some improvement of eczema – 0.771 (patients at relapse after treatment with carbamide cream (42)), and the QoL of the "cleared" state - 0.836 (patients at inclusion of the carbamide treatment (42)). It is assumed that the patients from the carbamide branch never reach the "clear" state with the utility of 0.913.

Costs

For purposes of simplicity I assumed that the proportions of men and women in the samples are equal and make 50%. Hence, all the costs associated with pregnancy prevention were halved. The proportions of patients visiting a privately practicing dermatologist and a dermatologist at an outpatient clinic are also assumed to be 50%, and a mean cost of a dermatologist visit was calculated accordingly.

The cost of a TPMT test was taken from the British guidelines for prescribing azathioprine in dermatology (36) since the Norwegian cost was not available. The costs are assumed to correlate with each other.

Comparison with other studies

To the best of my knowledge, no other cost-effectiveness studies of alitretinoin against active comparators have been published. The two CEAs mentioned in the Methods section explored its cost-effectiveness compared to placebo.

Rodgers et al (2) evaluated a cost-effectiveness analysis of alitretinoin against placebo conducted by the manufacturer (Basilea Pharmaceuticals Ltd, Basel, Switzerland) for NICE. Rodgers concluded that the cost-effectiveness claimed by the manufacturer, is highly uncertain. "The base case ICERs of alitretinoin reported for

alitretinoin were £8614 per QALY versus ciclosporin, -£469 per QALY versus PUVA (with alitretinoin dominant) and £10,612 per QALY versus azathioprine (year 2007–8 values)."(2) The revised analysis with placebo as a comparator indicated an ICER of £12,931 per QALY.

There were several points of uncertainty of the result. Firstly, no probabilistic sensitivity analysis was conducted. Secondly, adverse events associated with the treatments were omitted from the analysis. The CEA performed by the NICE was based on HRQoL reductions that accounted for side effects. This revision doubled the ICER, that reached £30 000 per QALY. (2) Due to a high degree of uncertainty about the ICER, NICE concluded that alitretinoin is not considered cost-effective for use in the NHS.

Blank et al (36) conducted a CEA of alitretinoin comparing it to standard emollient treatment from the Swiss third party payer perspective. Carbamide cream was probably used in the comparator arm, but since it is not specified in the trial, standard emollient therapy can be considered a placebo. They developed a Markov model with a cycle length of 1 year and a time perspective of 22.4 years. The base case total costs of treatment with alitretinoin and emollients were estimated at €42,208 and €38,795, respectively. The mean QALY in the alitretinoin group was 11.21 QALYs, while in the comparator group it was 10.98 QALYs, implying an ICER of €14,816 per QALY. Alitretinoin was considered cost-effective from the Swiss perspective.

There are several uncertainties associated with this study. Firstly, they did not use an active treatment as a comparator, which may have influenced the final result. Secondly, they did not run a probabilistic sensitivity analysis, only several one-way sensitivity analyses, so the overall decision uncertainty was not evaluated.

The results of my study are consistent with the CEA run by NICE, which indicated that alitretinoin is not cost-effective. The study by Blank and coworkers had different results due to the difference in the study design and input data.

Implications

The results of this study indicate that alitretinoin is either dominated (10mg) or has an ICER beyond what is usually accepted for the Norwegian health care system (30mg). The Norwegian Directorate of Health has suggested a threshold of NOK588,000 per QALY, and the ICER for alitretinoin 30 mg is beyond that amount (48). Based on these results, alitretinoin should not be publicly funded at the current price. If the price of

alitretinoin were reduced to NOK1847 (excluding VAT), it would be considered cost-effective with the ICER of NOK588,000 per QALY.

Conclusion

The study indicates that under current conditions alitretinoin is not a cost-effective treatment of chronic hand eczema. There is, however, considerable uncertainty associated with the results of this study. Due to the lack of trial data or an expert panel, assumptions had to be made which may influence the conclusive result of the cost-effectiveness analysis. We need additional information on the clinical effectiveness of alitretinoin compared to other active treatments in order to make decisions about its cost-effectiveness.

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Appendix

1. DLQI questionnaire

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick 🗐 one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	 Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒

Please check you have answered EVERY question. Thank you.

2. PGA severity score

Physician's Global Assessment (PGA) severity score[1]

The severity of each PGA sign or symptom was described in the modified Total Lesion Symptom Score (mTLSS). Together the PGA and mTLSS were developed as a verbal description to corresponding to CHE severity grades.

Parameter	Description of severity[a]
Erythema	0 = Absent
	1 = Faint erythema
	2 = Prominent redness
	3 = Deep intense red colour
Scaling	0 = Absent
	1 = Slight flaking over limited areas, mostly fine scales
	2 = Flaking over widespread area(s), coarser scales
	3 = Desquamation covering over 30% of the hand, with coarse thick scales
Lichenification/hyperkeratosis	0 = Absent
	1 = Mild thickening with exaggerated skin lines over limited areas
	2 = Palpable thickening over widespread area(s)
	3 = Prominent thickening over widespread area(s) with exaggeration of normal skin markings
Vesiculation	0 = Absent
	1 = Scattered vesicles affecting up to 10% of hand, without erosion
	2 = Scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation
	3 = High density of vesicles extending over large area(s), or with erosion or excoriation
Oedema	0 = Absent
	1 = Dermal swelling over less than 10% of hands
	2 = Definite dermal swelling over more than 10% of hand
	3 = Dermal swelling with skin induration over widespread area(s)
Fissures	0 = Absent
	1 = Cracked skin affecting a small area of the hand
	2 = Cracked skin affecting multiple areas of the hand and causing pain
	3 = One or more deep fissures and causing bleeding or severe pain
Pruritus/pain	0 = Absent
	1 = Occasional, slight discomfort a few times per day
	2 = Intermittent, causing discomfort frequently during the day
	3 = Persistent or interfering with sleep

[a]1 = mild; 2 = moderate; 3 = severe.

PGA severity	Features	Intensity	Area involved
Severe	Erythema, scaling, hyperkeratosis, lichenification. Vesiculation oedema, fissures, pruritus/pain	At least one moderate or severe At least one severe	> 30% of affected hand surface
Moderate	Erythema, scaling, hyperkeratosis, lichenification. Vesiculation oedema, fissures, pruritus/pain	At least one mild or moderate At least one moderate	10 – 30% of affected hand surface
Mild	Erythema, scaling, hyperkeratosis, lichenification. Vesiculation oedema, fissures, pruritus/pain	At least one mild At least one mild	< 10% of affected hand surface
Almost clear	Erythema, scaling, hyperkeratosis, lichenification. Vesiculation oedema, fissures, pruritus/pain	At least one mild Absent	< 10% of affected hand surface
Clear	Erythema, scaling, hyperkeratosis, lichenification. Vesiculation oedema, fissures, pruritus/pain	Absent Absent	Not detectable

3. POEM questionnaire

Patient-Oriented Eczema Measure

Please circle one response for each of the seven questions below. Young children should complete the questionnaire with the help of their parents. Please leave blank any questions you feel unable to answer.

1. **Over the last week, on how many days has your/your child's skin been itchy because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
2. **Over the last week, on how many nights has your/your child's sleep been disturbed because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
3. **Over the last week, on how many days has your/your child's skin been bleeding because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
4. **Over the last week, on how many days has your/your child's skin been weeping or oozing clear fluid because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
5. **Over the last week, on how many days has your/your child's skin been cracked because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
6. **Over the last week, on how many days has your/your child's skin been flaking off because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day
7. **Over the last week, on how many days has your/your child's skin felt dry or rough because of the eczema?**
   No Days 1-2 Days 3-4 Days 5-6 Days Every Day

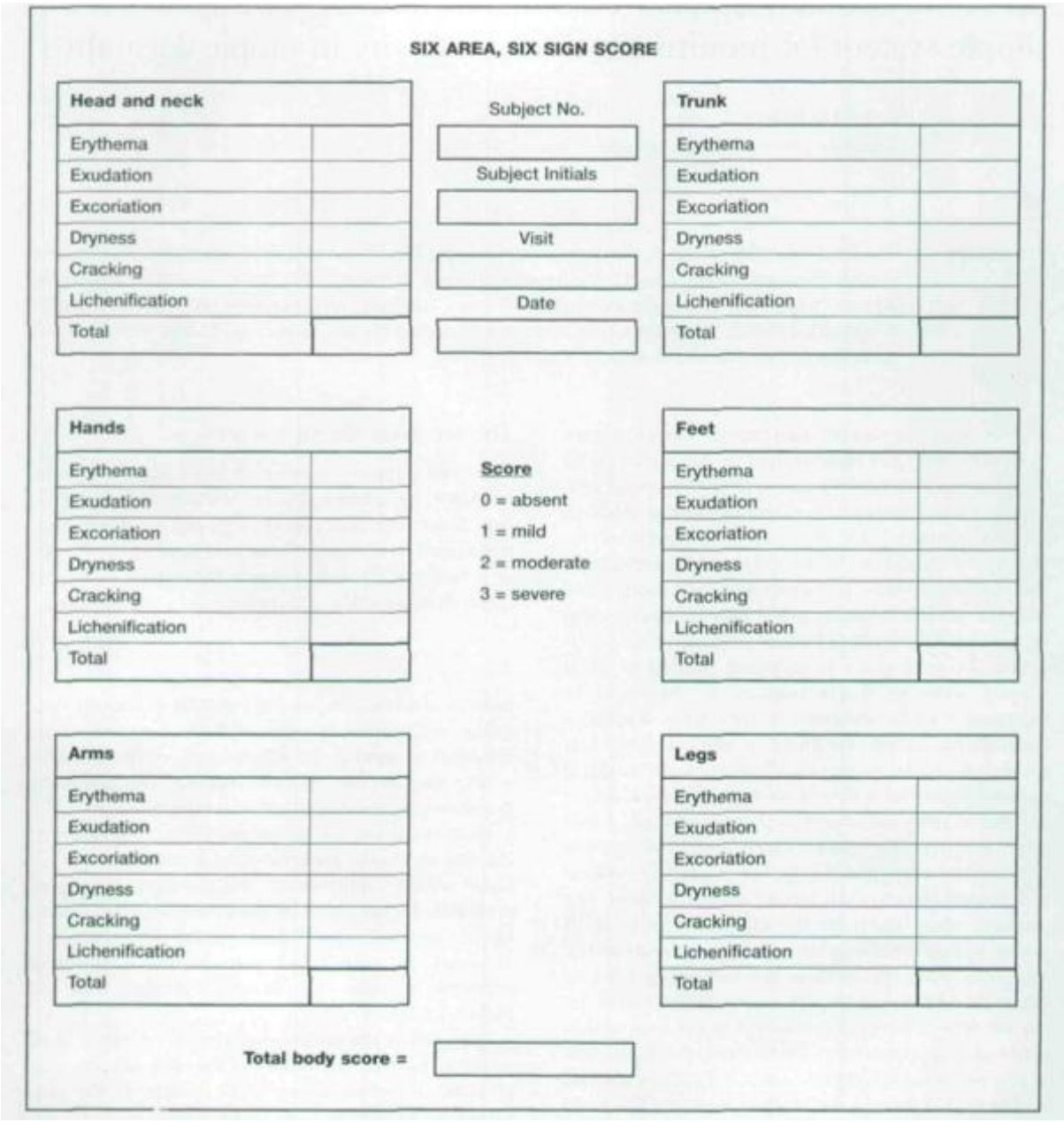
Total Score (maximum 28) _____

4. HECSI

Clinical signs	Fingertips	Fingers (except tips)	Palm of hands	Back of hands	Wrists
Erythema (E)					
Infiltration/papulation (I)					
Vesicles (V)					
Fissures (F)					
Scaling (S)					
Oedema (O)					
SUM (E + I + V + F + S + O)					
Extent (Ex)					
Total HECSI score =	Sum × Ex +	Sum × Ex +	Sum × Ex +	Sum × Ex +	Sum × Ex +

Total HECSI score (min 0; max 360). For each location (total of both hands) the affected area was given a score from 0 to 4 (0, 0%; 1, 1–25%; 2, 26–50%; 3, 51–75% and 4, 76–100%) for the extent of clinical symptoms. Finally, the score given for the extent for each location was multiplied by the total sum of the intensity of each clinical feature (each contributing equally to the final score), and the total sum called the HECSI score was calculated, varying from 0 to a maximum severity score of 360 points.

5. SASSAD



SIX AREA, SIX SIGN SCORE

Head and neck	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Subject No.

Subject Initials

Visit

Date

Trunk	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Hands	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Score

0 = absent

1 = mild

2 = moderate

3 = severe

Feet	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Arms	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Legs	
Erythema	
Exudation	
Excoriation	
Dryness	
Cracking	
Lichenification	
Total	

Total body score =

Table 1. Effectiveness of the treatements overview

Name of study	Com-parator	Dose	Type of patients	Number of patients in study group	Number of patients in comparator group	Endpoint	Result study group	Result comparator	Test of significance	Treatment duration
Alitretinoin										
BACH study	Placebo	10 mg, 30 mg of alitretinoin	Severe refractory hand eczema	418+409	205	"clear"/"almost clear" PGA score	47.7% - 30mg, 27.5% - 10mg (p=0.04)	16.6%	p<0.001	12-24 weeks
Cyclosporin										
Sowden et al.	Placebo (self-control)	5 mg/kg	Severe refractory atopic eczema	17 (cyclosporin+ placebo)	16 (placebo+cyclosporin)	Efficacy measured on a five-point scale (from none to very good)	No evidence of sequence effect; 31 of 33 patients graded cyclosporin efficacy as "good"/"very good"	-	p<0.001	8 weeks
Schmitt et al.	Placebo+	cyclosporin -	Severe	17	21	>50% SCORAD score	6/17 (35%)	1/21 (5%)	p=0.031	6 weeks
Azathioprine										
Berth-Jones et al.	Placebo (selfcontrol)	2.5 mg/kg per day	Severe atopic eczema	19 (azathioprine +placebo)	18 (placebo+azathioprine)	SASSAD	26% (from 39.7 to 29.6)	3% (from 33.6 to 32.6)	p<0.01	12 weeks
Meggitt et al.	Placebo	1.0 mg/kg, 2.5	Moderate-	42	21	SASSAD	37% (12.0 units)	20% (6.6 units)	95%CI 4.3-	12 weeks
Lear et al.	-	50 mg twice daily	Severe refractory atopic eczema	35	-	Effect measured on a scale 0-10	mean grade 6.9	-	p<0.001	median=7 months (1-21)
Schram et al.	Methotrexate	methotrexate - 10-22.5 mg/wk, azathioprine - 1.5-2.5 mg/kg/d	Severe atopic eczema	22	20	SCORAD improvement	RR=39% (58 to 36.3)	RR=42% (57.2 to 34.4)	p<0.001	12 weeks
Methotrexate										
Weatherhead et al.	-	Dose ranging: increased from 10 mg/wk by 2.5 mg/wk until response was achieved	Moderate-to-severe atopic eczema	12	-	SASSAD improvement	52%	-	95%CI 45-60%	24 weeks
Grenz rays										
Lindelof et al.	Placebo (selfcontrol)	6 doses of 3Gy at 1-week intervals	Chronic refractory hand eczema	24	24	Symptoms assessed on a scale 0-4	20 patients gave higher scores to Grenz rays	1 patient gave higher scores to placebo	p<0.001	11 weeks
Cartwright et al.	Placebo (selfcontrol)	3 doses of 3Gy at 21-day intervals	Chronic refractory hand eczema	30	30	Observers' assessment on a scale 0-4; patients' personal assessment on a scale 0-10	No significant difference between the treatment sequences (Grenz rays->placebo or placebo->Grenz rays) identified	-	Not reported	18 weeks
UVA										
Polderman et al.	Placebo	11 min. 5 times/wk	(Chronic) dishidrotic hand eczema	15	13	DASI	Decrease of the DASI 8.7 points	Decrease of the DASI 0.4 points	p<0.005	3 weeks
Reynolds et al.	UVB, placebo	24 exposures, 2 times/wk	Moderate-to-severe atopic eczema	23	UVB-24, placebo-22	SASSAD	5 points	UVB=10 points, placebo=0.6 points	95% CI	12 weeks
Gambichler et al.	UVB (selfcontrol)	3 times/wk	Atopic eczema	UVA followed by UVB: 22	UVB followed by UVA: 25	SASSAD	RR=43.7 ± 31.4%	RR=39.4 ± 24.1%	p=0.5	6 weeks
PUVA										
Sezer et al.	UVB (selfcontrol)	3 times/wk	Chronic refractory hand eczema	12	12	Symptoms assessed on a scale 0-3	75.48% (reduction in total clinical scores)	75.43% (reduction in total clinical scores)	p=0.823	9 weeks