EVALUATION SUMMARY

Omalizumab
for treatment of severe idiopathic urticaria

South Australian Medicines Evaluation Panel

July 2014

Government of South Australia
SA Health

Summary of SAMEP review

Receipt of High Cost Medicine (HCM) formulary application:	9th April 2014
Date of SAMEP meeting:	2nd July 2014
Date of appeal against SAMEP recommendation:	10th Oct 2014
Date of consideration of appeal by SAMAC:	19th Nov 2014

Name of medicine	Omalizumab (Tradename: Xolair®)
Dosage form	Injection (powder for reconstitution)
Requested Statewide HCM Formulary Listing	For treatment of severe chronic idiopathic urticaria
Cost	$425.00 per vial. The proposed dose in the application is 300mg every four weeks. The annual cost at this dose is $11,050 per patient. The application proposes that patients will require three years treatment.

SAMEP recommendations

Following the review of the current available evidence (appendix 1) and consideration of formal feedback from immunology and dermatology department heads, or their delegates/ clinicians with an interest in this area, SAMEP recommend rejecting the application to list omalizumab on the Statewide High Cost Medicines formulary for the treatment of chronic idiopathic urticaria (CIU) for the following reasons:

- High level of uncertainty with regards to safety; it is not known whether the observed increase in reported cases of anaphylaxis and other hypersensitivity reactions is related to the expanding use in a new patient population (CIU as opposed to asthma).
- Omalizumab is currently off-label and under evaluation by the TGA for CIU. Members felt that it would be appropriate to await the outcome of that evaluation, especially with regards to highlighted concerns regarding safety.
- While SAMEP acknowledge that CIU may significantly impact quality of life, including sleep deprivation and psychological comorbidities such as depression

and anxiety, there is a high level of uncertainty regarding the comparative clinical benefit attained by omalizumab (Quality of life improvements, reduction in pruritis & wheals) compared to cyclosporin. Members noted that concerns regarding side effects of cyclosporin (that were highlighted as a reason for listing omalizumab), are less of a problem at low dose.

- All currently published RCTs are industry-designed and/or industry-funded and are only of short duration. None of the published trials directly reflect the proposed patient population (refractory to high dose antihistamines), therefore it is unclear if the quality of life improvements seen in the trials would be reflected in the proposed population given the severity of the disease. In addition, the proposed duration of treatment in the submission is three years, yet there are currently no published long-term follow-up studies of efficacy or safety in the CIU population beyond 28 weeks.
- There is no consensus in the state between immunologists and dermatologists. CIU is treated by immunologists, by dermatologists, and sometimes by a combination of both. Feedback from dermatologists suggests that they would prefer to use cyclosporin, as there is some evidence that in addition to symptomatic relief it may provide some disease-modifying effects as well. In addition, limiting omalizumab for use by immunologists/allergists would produce an inequity of access across the state depending upon which specialist clinician the patient attends.
- It is not clear whether current resources would be able to support the provision of monthly injections for up to 240 patients per annum, which was highlighted in the feedback from immunologists.

Additional issues noted by SAMEP:

- The 150mg dose does not appear to be inferior to 300mg in terms of efficacy, and was also associated with fewer adverse events [1]. The proposal to use high-dose (300mg) up front, and back titrate with a life-threatening drug, for the treatment of a non-life-threatening condition is not supported by evidence, given that there appears to be similar efficacy at the lower 150mg dose.
- Recent safety concerns with regards to anaphylactic risk were highlighted by adverse events reported to the FDA. The timing of anaphylaxis following administration of the drug appears variable; in over half the reported cases to the FDA, the reaction occurred more than an hour after administration of the drug. Data from the FDA in 2007 reported that 39% of anaphylactic reactions occur after the first dose, 19% after the second, but may occur even after a year of treatment. Feedback from one immunologist recommended that all patients currently on the drug need an Anaphylaxis Action Plan and be provided with an adrenaline auto-injector (Epipen®). Therefore, in addition to the recommendation to reject the formulary listing, SAMEP recommends that no further IPUs are

approved for this condition, pending the evaluation by the TGA, and that all patients currently receiving omalizumab are advised of the risk of anaphylaxis, provided with written information on the risk, and have an appropriate action plan to follow in the event of a hypersensitivity reaction.

Appendix 1 Review of the evidence

Evaluation by other jurisdictions:

Pharmaceutical Benefits Advisory Committee (PBAC)	Omalizumab has not been evaluated by the PBAC for chronic urticaria
Canadian Agency for Drugs and Technologies in Health (CADTH)	Omalizumab has not been evaluated by the CADTH for chronic urticaria
Scottish Medicines Consortium (SMC)	Omalizumab has not been evaluated by the SMC for chronic urticaria
National Institute for Health and Clinical Excellence (NICE)	Omalizumab is currently under review by the NICE for urticarial (chronic, spontaneous, previously treated). The appraisal is expected to be published in April 2015 (http://guidance.nice.org.uk/TAG/463)
National Institute for Health Research (NIHR) – Horizon Scanning Centre	A horizon scanning briefing was published in September 2012 “Omalizumab for chronic spontaneous urticaria – second line” [2]
All Wales Medicines Strategy Group (AWMSG)	Omalizumab has not been evaluated by the AWMSG for chronic urticaria

In March 2014, omalizumab gained licensing approved in the European Union and by the FDA in the USA for treatment of chronic spontaneous urticaria in patients unresponsive to antihistamines.

In Australia, treatment of chronic urticaria is currently (as of June 2014) off-label, however Novartis have confirmed they have applied to the TGA for licensing approval and are expecting the result later this year (personal communication with Novartis).

Search strategy

Population	Patients with chronic idiopathic urticaria Refractory to antihistamine treatment &/or immmunosuppresive medicines
Intervention	Omalizumab (Tradename: Xolair®)
Comparator	Cyclosporin
Outcome(s)	Quality of life Pruritis symptoms Number of wheals Urticaria Activity Score over 7 days (UAS7) Adverse events

Databases searched (refer to appendix for search terms)

- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- Medline

Search terms

Cochrane Database of Systematic Reviews

Search strategy:

1. omalizumab.mp. [mp=title, short title, abstract, full text, keywords, caption text]

Search conducted: 11 June 2014

Medline

Search strategy:

1. clinical trial.mp.
2. clinical trial.pt.
3. random$.mp.
4. tu.xs.
5. 1 or 2 or 3 or 4
6. randomised clinical trial.mp.
7. randomized.ab.
8. placebo.ab.
9. 5 or 6 or 7 or 8
10. omalizumab.mp.
11. xolair.mp.
12. 10 or 11
13. 9 and 12
14. exp Urticaria/ or urticaria.mp.
15. 13 and 14
16. limit 15 to english language

Search conducted: 11 June 2014

Clinical Trials Registries searched

· Australian and New Zealand Clinical Trials Registry	www.anzctr.org.au
· US National Institutes of Health Trial Registry	www.clinicaltrials.gov
· European Clinical Trials Register	www.clinicaltrialsregister.eu
· World Health Organisation International Clinical Trials Registry Platform	http://apps.who.int/trialsearch

OVERVIEW OF CHRONIC IDIOPATHIC URTICARIA

Chronic idiopathic urticaria (CIU) / chronic spontaneous urticaria is defined by the presence of urticarial (hives) on most days of the week, for a duration of longer than six weeks [3]. In approximately 40% of cases, there will be associated angioedema. Urticaria is characterised by a red, raised, itchy rash resulting from vasodilatation, increased blood flow and increased vascular permeability due to mast cell activation and the release of histamine [4]. CIU impacts on quality of life, including sleep deprivation and psychological comorbidities such as depression and anxiety[5]. Treatment is aimed at symptomatic relief [6].

Epidemiology

CIU affects an estimated 0.5-1% of individuals (life time prevalence)[4]. CIU can occur at any age, however a recent review of CIU publications reported the peak incidence between 20 and 40 years of age [7]. The duration of CIU is generally 1-5 years, however in patients with disease severe enough to warrant hospital referral, up to 20% may still be symptomatic at 10 years [4].

Pathophysiology

The mechanisim for mast-cell triggering in CIU is unknown [4]. Functional autoantibodies against the high-affinity IgE receptor (FcεRI) have been demonstrated in one third of CIU patients [4].

Diagnosis

Diagnosis is based primarily on the clinical history and the identification of possible triggers [4]. Laboratory investigations may assist in excluding other causes [4].

Treatment

The goal of therapy is to achieve a level of symptom control and improvement in quality of life that is acceptable to the patient, while minimising therapy-related side effects [3]. First-line treatment is with oral antihistamines [6]. If monotherapy is unsuccessful, a combination of two antihistamines is recommended, however a significant number of patients with chronic urticaria are unresponsive to antihistamines[6]. If a combination of antihistamines is not effective, an H2-receptor antagonist may be trialed. In refractory cases other medications which may be of benefit include leukotriene inhibitors (eg montelukast), hydroxychloroquine, dapsone and colchicine. Cyclosporin can be very effective for chronic autoimmune urticaria, but needs to be weighed against the potential adverse effects [6]. Corticosteroids should be avoided long-term if possible [8]

Omalizumab

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody produced in the Chinese hamster ovary cells. Omalizumab selectively binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate [9]. The mechanism by which these effects of omalizumab result in an improvement of CIU symptoms is unclear but may be multi-factorial [9].

Measurement of outcomes

The applicant has suggested using the UAS7 (Urticaria Activity Score over 7 days) to provide a quantitative measure of omalizumab efficacy. The daily intensity of pruritis (range: 0=none to 3=severe) and number of hives (range: 0=none to 3=more than 12 hives) are summed to create a daily UAS score (range: 0-6 points per day). The daily scores are summed to create the UAS7 score for the week (range: 0-42) [10].

URTICARIA ACTIVITY SCORE

How many wheals have appeared during the last 24 hours?

Wheals	**Score**
None	0
Less than 20 wheals (mild)	1
Between 20 and 50 wheals (moderate)	2
More than 50 wheals or large confluent wheals (severe)	3

How severe was the itch during the past 24 hours?

Itch	**Score**
None	0
Mild (present but not annoying or troublesome)	1
Moderate (troublesome but not interfering with activity or sleep)	2
Severe (interfering with daily activity or sleep)	3

Score wheals and itch for each day of the week (maximum score 6 per day)

Add up at the end of the week (maximum score 42)

Currently at the Royal Adelaide Hospital (RAH), the immunology unit have developed a scoring system for patient-reported outcomes that incorporates both the UAS and daily medications used.

Patient-reported outcome tools for measuring health-related quality of life in CIU

The Dermatology Quality of Life Index (DLQI) is tool used frequently to measure health-related quality of life in patients with dermatological conditions. Although CIU was not one of the skin diseases on which the index was developed, the tool includes the dimensions most frequently reported as affecting the quality of life in patients with CIU, including patient assessment of the severity of pruritis, sleep disturnbance, self-consciousness & affect on work and leisure activities [11]. The patient's quality of life is rated on a scale of 0 to 30 based on 10 questions asked, with each question contributing up to 3 points of the score (appendix 2). The higher the score, the greater the impairment on quality of life [11].

In addition, the interpretation of any change in the measured quality of life is clinically important. The DLQI was analysed for use in patients with CIU, to assess how much change on the scale of 0 to 30 would be clinically meaningful [12]. Following the assessment of data from 826 patients with CIU enrolled in two clinical trials, it has been determined that a change in the DLQI of approximately 2.2 to 3.1 is the minimum change that could be considered clinically significant [12].

SUMMARY OF EVIDENCE FOR THE USE OF OMALIZUMAB IN CHRONIC IDIOPATHIC URTICARIA

Systematic reviews

No systematic reviews were identified. A protocol for a Cochrane systematic review of all interventions for CIU excluding antihistamines was published in 2014 [13].

Randomised controlled trials

No head-to-head randomised trials comparing omalizumab with cyclosporin were identified. The following three placebo-controlled randomised controlled trials were provided by the applicant:

Citation	Maurer M, Rosen K, et al (2013). *Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria*. New England Journal of Medicine. 368(10): 924-35. (ASTERIA II)[1]
Funding of study	Funded by Genentech and Novartis Pharma Employees of Genentech & Novartis were involved in the study design, data collection, the interpretation and statistical analysis, and the preparation of the manuscript.
Design	Phase III, multicentre, randomised, double-blind study
ClinicalTrials.gov number	NCT01292473
Study duration	28 weeks
Patient population	Inclusion criteria: · Adults and adolescents (≥ 12 years) · History of ≥ 6 months of chronic idiopathic urticaria · Presence of hives associated with itching for at least 8 consecutive weeks of treatment with approved doses of H_1-antihistamines, including at least 3 days with a long-acting second generation H_1-antihistamine immediately preceeding the screening: · UAS7 of 16 or more (including weekly itch-severity score of ≥8 on scale of 0-21, during the 7 days before randomisation) Exclusion criteria: · 'A clearly defined underlying cause for urticaria', e.g. physical urticaria · Use of H1-antihistamines at greater than licenced doses within 3 days preceeding the screening visit · Routine use (i.e daily, or every other day for ≥ 5 consecutive days), within 30 days of screening visit, of: o Systemic glucocorticosteroids o Hydroxychloroquine, methotrexate, cyclosporin, cyclophosphamide, IVIg · Use of H2-antihistamines of leukotriene-receptor antagonists within 7 days preceding the screening visit · History of cancer · Weight of less than 20kg · Known hypersensitivity to omalizumab · Pregnancy · Treatment with omalizumab within the previous year
Intervention	75mg subcutaneous omalizumab x 3 doses (at 4-weekly intervals) ***or*** 150mg subcutaneous omalizumab x 3 doses (at 4-weekly intervals) ***or*** 300mg subcutaneous omalizumab x 3 doses (at 4-weekly intervals)

	Patients continued with their pre-randomisation H_1-antihistamine during the omalizumab treatment period. During the 16-week follow-up patients could use one of the following additional long-acting H_1-antihistamines: o Cetirizine 5 or 10mg once daily o Levocetirizine 2.5 or 5mg once daily o Fexofenadine 60mg twice daily or 180mg daily o Loratadine 10mg daily o Desloratadine 5mg daily In addition, patients could take diphenhydramine 25mg up to three times daily as rescue medication for itch relief.
No. of patients on intervention	75mg dose: 82 patients 150mg dose: 83 patients 300mg dose: 79 patients
Comparator	Placebo Patients continued with their pre-randomisation H_1-antihistamine during the treatment period. During the 16-week follow-up patients could use one of the following additional long-acting H_1-antihistamines: o Cetirizine 5 or 10mg once daily o Levocetirizine 2.5 or 5mg once daily o Fexofenadine 60mg twice daily or 180mg daily o Loratadine 10mg daily o Desloratadine 5mg daily In addition, patients could take diphenhydramine 25mg up to three times daily as rescue medication for itch relief.
No. of patients on comparator	79
Primary efficacy outcome(s)	Change from baseline to week 12 in weekly itch-severity scores (the week 12 score was calculated as the sum of the averaged daily itch-severity score for the previous 7 days; the baseline score was the sum of the daily itch-severity score during the 7 days before randomisation). [Patient-reported itch severity 0=none, 1=mild, 2=moderate, 3=severe]
Secondary outcome(s)	· Change from baseline to week 12 in UAS7 · Change from baseline to week 12 in weekly number of hives · The time to reduction from baseline of at least 5 points in the weekly itch severity score · The proportion of patients with UAS7 of 6 or less · Number of patients with a weekly 'minimally important difference' (MID) in the itch severity score. · Change from baseline to week 12 in the score for the size of the largest hive · Change from baseline to week 12 in the overall score on the Dermatology Life Quality Index (range 0-30, with higher scores indicating worse QoL) · Proportion of angioedema-free days from week 4 to week 12
Blinding of patients	Yes
Blinding of outcome assessors	Yes
Allocation concealment	Unclear
Withdrawals from intervention arm of study	75mg dose: 7/82 (9%) 150mg dose: 9/83 (11%) 300mg dose: 12/79 (15%)
Withdrawals from placebo arm of study	5/79 (6%)

Primary Outcome:	**Placebo**	**75mg**	**150mg**	**300mg**
Average change from baseline to week 12 in itch severity score	-5.1 ± 5.6	-5.9 ± 6.5	-8.1 ± 6.4	-9.8 ± 6.0

Secondary outcomes:	Placebo	75mg	150mg	300mg
Average change from baseline to week 12 in weekly no of hives	-5.2 ± 6.6	-7.2 ± 7.0	-9.8 ± 7.3	-12.0 ± 7.6
Number of patients with UAS7 ≤ 6 at week 12	15 (19%)	22 (27%)	35 (43%)	52 (66%)
Average change from baseline to week 12 in Dermatology Life Quality Index	-6.1 ± 7.5	-7.5 ± 7.2	-8.3 ± 6.3	-10.2 ± 6.8
% of angioedema-free days from week 4 to week 12	89.2 ± 19.0	93.5 ± 14.9	91.6 ± 17.4	95.5 ± 14.5
Adverse Events:	**Placebo**	**75mg**	**150mg**	**300mg**
Deaths (all causes)	0	0	0	0
Adverse event leading to discontinuation of study drug	0	3 (4%)	2 (2%)	0
Severe adverse events	7 (9%)	4 (5%)	5 (6%)	6 (8%)
At least 1 adverse event	48 (61%)	45 (59%)	59 (67%)	51 (65%)

The above industry-funded study shows some evidence that the average change from baseline to week 12 in the itch severity score in the 150mg and 300mg omalizumab groups appears larger than the change in the placebo and 75mg omalizumab group, however the difference between the 150mg and 300mg groups is not significant. The trial duration is stated as 28 weeks however all primary and secondary outcomes were reported at 12 weeks only. Withdrawals from all the omalizumab groups were higher than the placebo group, with 15% withdrawing from the 300mg dose group compared to 6% withdrawal from the placebo group. The percentage of patients who withdrew due to disease progression was 1% in the 75-mg group, 4% in the 150-mg group, and 8% in the 300-mg group.

The authors have not provided details on the relative number of antihistamine tablets used by patients in each group of the study at week 12. The use of antihistamine tablets is a potential confounder, and without the details of the tablets taken in each group over the 12 week period, it is difficult to determine whether the outcomes could have been affected by antihistamine use.

The supplementary index to the study provided the medications (other than H_1-antihistamines) used by patients in each group prior to enrolling in the study (supplementary appendix to [1]), shown below. The patients in the 300mg omalizumab group used notably less corticosteroids and other immunosuppresants compared to the placebo group, prior to enrolment in the study.

	Placebo (n=79)	75mg (n=82)	150mg (n=82)	300mg (n=79)
Corticosteroids	41 (52%)	46 (56%)	38 (46%)	36 (46%)
Immunosuppressants (overall)	9 (11%)	3 (4%)	9 (11%)	5 (6%)
Cyclosporin	8 (10%)	3 (4%)	8 (10%)	5 (6%)

The original protocol included the secondary endpoint of the proportion of patients who maintained their response (UAS7 ≤6) to week 24, however this was excluded when the protocol was amended in January 2011 (Supplementary appendix to [1])

Patients were included in the trial if they had hives and persistant itching despite 8 weeks of standard approved doses of H_1-antihistamines. Guidelines for the management of chronic urticaria recommend up-titrating the antihistamine dose (up to 4 times) if symptoms persist after two weeks, or consider adding a second antihistamine [14]. It therefore unclear what proportion of the patients in the above trial would have responded to higher doses of antihistamines.

Citation	Maurer M, Altrichter S, et al. (2011) *Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase*. J Allergy Clin Immunol. 128(1):202-9.e5.
Funding of study	Funded by Novartis Pharma GmbH, Germany 3 authors were employees of Novartis, 4 received research grants from Novartis, and a further 4 authors received honoraria from Novartis for lectures or research support.
Design	Phase III, multicentre, randomised, double-blind placebo-controlled study
ClinicalTrials.gov number	-
Study duration	24 weeks
Patient population	Inclusion criteria: · Adults (18-70 years) with CIU · Symptomatic for ≥ 6 weeks despite maximal H1-antihistamine therapy · Body weight between 20 and 150kg · Total serum IgE level between 30IU/mL and 700IU/mL · A specific serum IgE-anti TPO antibody level of 5.0IU/mL or more within 3 months of randomisation · Weekly UAS7 of greater than 10 during screening Exclusion criteria: · Acute urticaria · Chronic diarrheoa · Severe renal dysfunction · Increased serum IgE levels for reasons other than allergy or urticaria · History of epilepsy, allergy to antibiotics, malignancy within 5 years, cerebrovascular attacks or ischemia · Taken systemic corticosteroids, methotrexate, cyclosporin or other immunosuppressants within 4 weeks of screening
Intervention	Omalizumab 75-375mg subcutaneously every 2 or 4 weeks for 24 weeks (Dose individualised based on body weight and total serum IgE levels at screening) Patients could continue with H1-antihistamine (10mg loratadine) 'on demand' and 1mg clemastine as rescue medication.
No. of patients on intervention	27
Comparator	Placebo Patients could continue with H1-antihistamine (10mg loratadine) 'on demand' and 1mg clemastine as rescue medication.
No. of patients on comparator	22
Primary efficacy outcome(s)	Change in UAS7 score from baseline to 24 weeks
Secondary outcome(s)	· Area under the curve (AUC) of UAS's over 24 weeks · Daily scores for wheals, pruritis, erythema, angioedema · Use of concommittant medication · Patient and investigator's global assessment of symptoms · Patient's health-related quality of life · Adverse events
Blinding of patients	Yes
Blinding of outcome assessors	Yes
Allocation concealment	Yes

Withdrawals from intervention arm of study	2/27 (7%)	
Withdrawals from placebo arm of study	5/22 (23%)	
Primary Outcome:	**Placebo**	**Omalizumab**
Mean change in UAS7 from baseline to 24 weeks	-7.9 (Mean UAS7 score at 24 weeks was 15.5 ± 11.0)	-17.8 (Mean UAS7 score at 24 weeks was 6.8 ± 10.0
Secondary outcomes:	**Placebo**	**Omalizumab**
Mean reduction in score for wheals at week 24	-3.3	-9.2
% of patients with no pruritis at 24 weeks	2 (9.1%)	16 (59.3%)
Mean concommittant medication use	Before: 3.5 loratadine tablets / 7 days + 6.1 clemastine tabs / 7 days 24 weeks: 3.3 loratadine tablets/ 7 days + 1.4 clemastine tabs/ 7 days	Before: 2.9 loratadine tablets/7 days + 6 clemastine tabs / 7 days After: 0.3 loratadine tablets/7 days + 0.7 clemastine tabs / 7 days

The authors reported that the difference between the two arms in the primary outcome (reduction in weekly UAS7 scores) was statistically significant, however the numbers enrolled were extremely small, the 95% confidence intervals for the mean UAS7 scores at 24 weeks was large, and major protocol deviations were reported in 36% of subjects.

The authors hypothesised that IgE-anti TPO is critical for the development of urticarial symptoms, however further studies are required with a control group and larger patient numbers to assess if omalizumab is more effective in patients with high total serum IgE levels.

Concomittant medication use was reported in this study, and patients in the omalizumab group reported taking less tablets at 24 weeks, however it is noted that even at baseline, the mean use of antihistamines was low.

Three QoL questionnaires were used to assess any change in health-related quality of life from baseline to 24 weeks. Very little detail is provided by the authors with regards to the results of the questionnaires other than to give a mean percentage improvement in total scores between the groups. The CU-Q2oL is a disease-specific tool for measuring patient-reported outcome. The authors reported an improvement in the omalizumab group of 55% compared to 6% with placebo [15].

Citation	Saini S, Rosen KE, et al. (2011) *A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria*. J Allergy Clin Immunol. 128(3):567-73.e1.
Funding of study	Funded by Genentech and Novartis Pharma All authors declared they were either employees of Genentech, had consulted for Genentech or Novartis, or had received research support from either company
Design	Phase II, prospective, double-blind, randomised dose-ranging study
ClinicalTrials.gov number	NCT00130234
Study duration	16 weeks
Patient population	Inclusion criteria: · CIU patients aged 12-75 years, with no clearly defined cause for CIU, and moderate to severe disease (defined as pruritis and hives >3 days in 7 day

	period for > 6 weeks despite treatment with an approved dose of one of the following H1-antihistamines: o 10mg cetirizine daily o 5mg levocertirizine dihydrochloride daily o 60mg fexofenadine twice daily (or 180mg once daily) o 10mg loratadine daily o 5mg desloratadine daily · Daily UAS of ≥4 in clinic, and diary based UAS7 of ≥12 in run-in phase prior to randomisation despite treatment with H1-antihistamines Exclusion criteria: · Weight less than 40kg · Pregnancy or lactation · Other skin disease associated with pruritis · Treatment with omalizumab in 12 months prior to study · Contraindications to diphenhydramine · Treatment with any investigational drug within 30 days of screening · Treatment with the following in the 3 months prior to screening: o Hydroxychloroquine o Sulfasalazine o Dapsone o Methotrexate o Cyclophosphamide o IV Ig o Plasmapheresis o Other monoclonal antibody therapies · Treatment with doxepin in the 6 weeks prior to screening · Treatment with cyclosporin in the month prior to screening · Treatment with H2-antihistamines and leukotriene receptor antagonists in the week prior to screening. Use of systemic corticosteroids was not allowed in the screening, run-in or treatment (4 weeks after study dose) periods.
Intervention	Single dose of 75mg subcutaneous omalizumab ***or*** Single dose of 300mg subcutaneous omalizumab ***or*** Single dose of 600mg subcutaneous omalizumab In addition, patients could take diphenhydramine 25mg up to three times daily (in the US) or twice daily (in Germany) as rescue medication for itch relief.
No. of patients on intervention	75mg dose: 23 patients 300mg dose: 25 patients 600mg dose: 21 patients
Comparator	Placebo In addition, patients could take diphenhydramine 25mg up to three times daily (in the US) or twice daily (in Germany) as rescue medication for itch relief.
No. of patients on comparator	21
Primary efficacy outcome(s)	Change from baseline to week 4 in UAS7
Secondary outcome(s)	· Change from baseline to week 4 in weekly itch-severity scores · Change from baseline to week 4 in weekly number of hives · Frequency & severity of adverse events · Pharmacokinetic laboratory measures (total serum concentration, max serum conc and time to max conc)
Blinding of patients	Yes
Blinding of outcome assessors	Yes
Allocation concealment	Yes
Withdrawals from intervention arm of	75mg dose: 6/23 (26%)

study	300mg dose: 2/25 (8%) 600mg dose: 5/21 (29%)			
Withdrawals from placebo arm of study	6/21 (24%)			
Primary Outcome:	**Placebo**	**75mg**	**300mg**	**600mg**
Average change in UAS7 from baseline to week 4 (± 95% CI)	-6.9 ± 9.4	-9.8 ± 11.75	-19.9 ± 12.38	-14.6 ± 10.17
Secondary outcomes:	**Placebo**	**75mg**	**300mg**	**600mg**
Average change from baseline to week 4 in weekly hive score	-3.5 ± 5.2	-5.3 ± 6.9	-10.7 ± 6.8	-8.1 ± 6.0
Average change from baseline to week 4 in weekly itch score	-3.5 ± 5.2	-4.5 ± 5.8	-9.2 ± 6.0	-6.5 ± 5.6
Adverse Events:	**Placebo**	**75mg**	**300mg**	**600mg**
Adverse event leading to discontinuation of study drug	0	3 (13%)	0	1 (5%)
At least 1 adverse event	10/21 (48%)	8/23 (35%)	12/25 (48%)	10/21 (48%)

This trial, sponsored and designed by the manufacturer of omalizumab, suggests there may be some clinical improvement in symptoms of CIU with a single dose of 300 or 600mg omalizumab, however patient numbers in the trial were small and change in the primary outcome from baseline to week 4 had wide confidence intervals in all groups. This trial did not investigate the 150mg dose that was included in the subsequent trial by Maurer et al published in 2013. Although the study was followed to 16 weeks following the single dose of omalizumab, all outcomes were reported to 4 weeks only therefore the duration of efficacy is unclear.

Level III or IV evidence

One RCT investigating the efficacy of omalizumab in patients refractory to high dose antihistamines and/or immunosuppressants, was identified. No NCT registration number is referenced in the publication and it appears that the trial was designed to investigate safety [16] (see under clinical trials below).

There are a number of retrospective uncontrolled studies, published case reports and case series reporting the use of omalizumab to treat CIU [17-21].

Altman, Naimi et al treated 30 patients with omalizumab for chronic idiopathic urticaria, chronic autoimmune urticaria, or other (physical) urticaria. All patients had moderate-to-severe symptoms at least four times per week despite the use of immunosuppressive medications. After treatment with omalizumab, 10 patients had complete resolution of their symptoms, 8 had a significant response, 4 had a partial response, and 8 had no response [22]. The case reports provide some evidence of the effect of omalizumab in patients refractory to high dose antihistamines and/or immunosuppressive medicines, however the cases also suggest that high proportion of patients refractory to other immunosuppressants may also be refractory to omalizumab. The publication of clinical trials currently in progress, that are investigating omalizumab in the refractory population will provide more evidence in this patient group.

Clinical Trials in progress / Unpublished trials

A number of completed clinical trials registered have not been published, including ASTERIA I (ASTERIA II is the NEJM publication). The following clinical trial in refractory patients has been completed but not published. The results provided below have been extracted from the ClinicalTrials.org website:

Title	A Safety Study of Xolair (omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Treatment With H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists	
NCT Number	NCT01264939	
Intervention	Omalizumab 300mg every 4 weeks for 24 weeks (+ H1-antihistamines (up to 4x approved dose), H2-antihistamines, leukotriene-receptor antagonist)	
Comparator	Placebo (+ H1-antihistamines (up to 4x approved dose), H2-antihistamines, leukotriene-receptor antagonist)	
Design	Phase III, Randomised open-label	
Completion date	November 2012	
No. of patients on intervention	252	
No. of patients on comparator	84	
Withdrawals from intervention arm	28 (11%)	
Withdrawals from placebo arm	18 (21%)	
Results:	Omalizumab	Placebo
Percentage of Participants With Adverse Events	83.7%	78.3%
Serious adverse events	18/252 (7.14%)	5/83 (6.02%)
Change From Baseline to Week 12 in the Weekly Itch Severity Score	-8.55 ± 6.01	-4.01 ± 5.87
Change From Baseline to Week 12 in the Urticaria Activity Score Over 7 Days (UAS7)	-19.01 ± 13.15	-8.50 ± 11.71
Change From Baseline to Week 12 in the Weekly Number of Hives Score	-10.46 ± 7.74	-4.49 ± 6.33
Percentage of Participants With a UAS7 Score ≤ 6 at Week 12	52.4%	12%
Change From Baseline in the Overall Dermatology Life Quality Index (DLQI) Score at Week 12	-9.69 ± 6.85	-5.11 ± 7.53
Percentage of Angioedema-free Days From Week 4 to Week 12	91.0 ± 21.0	88.1 ± 18.9

The comparative details regarding additional medications (including amount and frequency) taken in each group is not provided.

It appears that the above trial has been published, however the publication does not quote the the NCT reference number above in their publication [16]. The trial was originally registered as a safety study, but published as a safety and efficacy study.

On-going clinical trials

The following registered clinical trials are active, either recruiting or not recruiting:

Title	OPTIMA: Efficacy of Optimized Re-treatment and Step-up Therapy With Omalizumab in Chronic Spontaneous Urticaria (CSU) Patients
NCT Number	NCT02161562
Intervention	Omalizumab (increased dose)
Comparator	Omalizumab
Design	Phase III, Randomised open-label
Estimated end date	August 2016

Title	Efficacy and Safety Study of Omalizumab (Xolair®) to Treat Chronic Urticaria
NCT Number	NCT01713725
Intervention	Omalizumab
Comparator	Placebo
Design	Phase II, Randomised cross-over
Estimated end date	November 2014

Title	Effect of Omalizumab (Xolair) on Basophils in Patients With Chronic Idiopathic Urticaria
NCT Number	NCT01701583
Intervention	Omalizumab
Design	Open-label, pharmacodynamic study
Purpose	To measure change in basophil proteome in responders to omalizumab compared to non-responders
Estimated end date	December 2014

Title	Efficacy Study of Omalizumab in Cholinergic Urticaria
NCT Number	NCT02012387
Intervention	Omalizumab
Comparator	Placebo
Design	Phase II, Randomised double-blind
Outcome measures	Effect on exercise challenge test, quality of life, treatment drop-off (compliance with diaries)
Estimated end date	June 2017

Title	Impact of Omalizumab on Quality of Life Measures and Angioedema Occurrence in Patients With CSU Refractory to Therapy (X-ACT)
NCT Number	NCT01723072
Intervention	Omalizumab
Comparator	Placebo
Design	Phase III, Randomised double-blind
Outcome measures	Quality of life (CU-Q20L), angioedema QoL score (AE-Q20L), Weekly UAS7, Use of rescure medication
Estimated end date	May 2014

Title	A Randomized, Double-Blind, Placebo-Controlled Study of Omalizumab for Idiopathic Anaphylaxis
NCT Number	NCT00890162
Status	Recruiting
Intervention	Adrenoline/Omalizumab
Design	Phase II
Aim	If treatment with omalizumab over 6 months reduces number and timing of anaphylactic events in patients with a history of frequent idiopathic anaphylaxis
Estimated end date	Jan 2015

Overview of Evidence

Study Design and Quality

There are currently no systematic reviews of RCTs of omalizumab in CIU. The highest level of evidence is a number of industry-funded RCTs comparing omalizumab to placebo [1, 15, 16, 23] . There are no head to head clinical trials with cyclosporin or any other immunosuppressive agent.

Effectiveness

The impact of omalizumab on health-related quality of life appears to be the primary measure of effectiveness in CIU, with reduction in pruritis and wheals translating to an improvement in quality of life.

A large proportion of patients with CIU will respond to high dose H1-antihistamines [24]. Long-term systemic corticosteroid use is not recommended due to side effects, and therefore patients who are refractory to antihistamines are treated with cyclosporin. An estimated 75% of patients refractory to antihistamines will respond to cyclosporin, however treatment with cyclosporin requires renal function monitoring and monitoring of blood pressure [24]. Cyclosporin is considered standard level of care in patients refractory to antihistamines [24-26], and treatment with low dose cyclosporin (3mg/kg/day) is associated with less side effects than the higher daily doses [24].

There are no head-to-head trials comparing omalizumab to cyclosporin. The strongest evidence of effectiveness is a placebo-controlled double-blind study published in 2013 [1]. Although there are limitations to the study design, it appears that both the 150mg and 300mg doses of omalizumab are superior to placebo in reducing pruritis, the number of wheals and improving quality of life. There is however no significant difference in the primary outcome between the two doses.

In the RCT by Maurer et al, during the follow-up period the itch scores returned to baseline in all groups, suggesting that while omalizumab provides temporary symptomatic relief, it does not appear to have disease-modifying effects [1].

Safety

Hypersensitivity reactions to therapeutic drugs reported to the FDA have highlighted concern regarding omalizumab-induced anaphylaxis. A recent report, published in May 2014, of hypersensitivity reactions reported to the FDA in the year March 2012 - March 2013, warned that reactions to omalizumab were so frequently reported and severe that the risk should be carefully considered in deciding whether clinical use is appropriate [27]. Omalizumab accounted for more reported cases of anaphylaxis than any other drug despite a small patient population, with 64 cases of severe hypersensitivity including 59 cases of anaphylactic shock [27]. Of the 59 cases, 2 resulted in patient death, 3 resulted in permanent disability, and 9 were hospitalised.

In 2007, the FDA required a black box warning regarding anaphylaxis, following 124 reported cases in the 3 years from 2003-6. In these reported cases, 39% occurred after the first dose and 19% after the second, but reactions could occur at any time, with more than half the reported cases occurring more than an hour after administration [27]. Therefore even if administered in the outpatient setting where emergency care is available, anaphylaxis may occur once the patient leaves the hospital following administration of the drug.

The high number of recently reported cases raises concerns with regards to the changing patient demographic being administered the drug. The use in CIU is an emerging patient population, and it is unclear if the incidence differs in the CIU patient population compared to the asthma population for which is has predominantly been used.

COMPARATIVE COSTS & PHARMACOECONOMICS

Cost of omalizumab per treatment course

$425.00 per 150mg vial

The proposed dose in the application is 300mg every four weeks.

The annual procurement costs for omalizumab at this dose is $11,050 per patient.

Comparative Costs with oral cyclosporin

Comparative drug acquisition costs per patient per annum are provided below:

Omalizumab 300mg every 4 weeks	Omalizumab 150mg every 4 weeks	Cyclosporin 100mg twice daily
$11,050	$5,525	$3,964

Additional costs for omalizumab include monthly outpatient visits for the injection:

- Dermatology outpatient visit = $193.78 (as per communication with Finance department, SA Health)
- 13 dermatology outpatient visits (for 4-weekly injections) = $2,519 per annum

Cost offsets

There are no expected cost-offsets to the public hospital system. The benefits of omalizumab treatment are predominantly societal, with possible changes in productive output, less missed work or school days. From the perspective of SA Health, there are no expected cost off-sets by listing omalizumab on the statewide High Cost Medicines formulary. Treatment with omalizumab is an add-on treatment, currently only available on an Individual Patient Use (IPU) basis through hospital outpatient departments.

Cost-effectiveness

Given the available evidence (limited information about the change in QALYs and good information about incremental costs) it is very unlikely that the incremental cost-effectiveness ratio (ICER) is less than $150K per QALY – whether taken at a 150 or 300mg dose, whether compared to cyclosporin or placebo . This makes omalizumab cost ineffective.

The following evidence of comparative effectiveness of placebo and omalizimab is reported by Maurer et al using the Dermatology Life Quality Index (DLQI) from baseline to week 12. The % change for each group is calculated below:

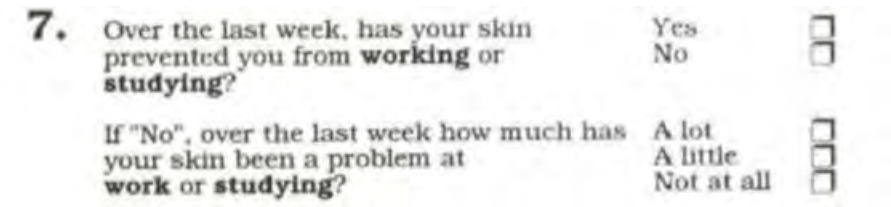
	placebo	75mg omalizumab	150mg omalizumab	300mg omalizumab
Mean DLQI at baseline	12.6	12.6	13.0	12.7
Mean change in DLQI	-6.1	-7.5	-8.3	-10.2
% change in DLQI	48%	60%	64%	80%

Why is the incremental effect likely to be small?

Translation to QALY: There is no equation that can translate the score to a QALY. The evidence indicates that there is no clear relationship between this score and a QALY, such as an EQ5D [28]. Hence it is necessary to unpack what it means to have a change, on average, of say 2 points on the score. Does a 2 point change mean the same thing for a variety of initial values of the tool? How long is the benefit sustained for? What size change is clinically meaningful?

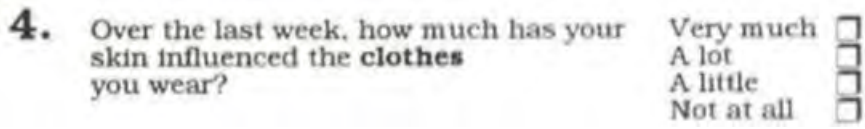
The DLQI tool was examined (Appendix 2):

While the DLQI tool can tell whether there was an improvement in a given domain, it is not a tool which is consistently additive. For example, note that a one point change is not consistent in terms of its clinical or patient significance within a domain. So a change in response to the following question of "a lot" to "a little" is one point. So is a change from "a little" to "not at all". A more useful indicator for quality of life relating to working or studying would be a count of days that the patient took off work or studying, or shopping etc.



7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes ☐ No ☐
	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 ☐

Furthermore the domains are not weighted by their value when the score is added. Hence a change from "a lot" to "a little" about influencing the clothes that you wear (question 4) is the same as a change from "a lot" to "a little" in preventing studying or working.



4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐

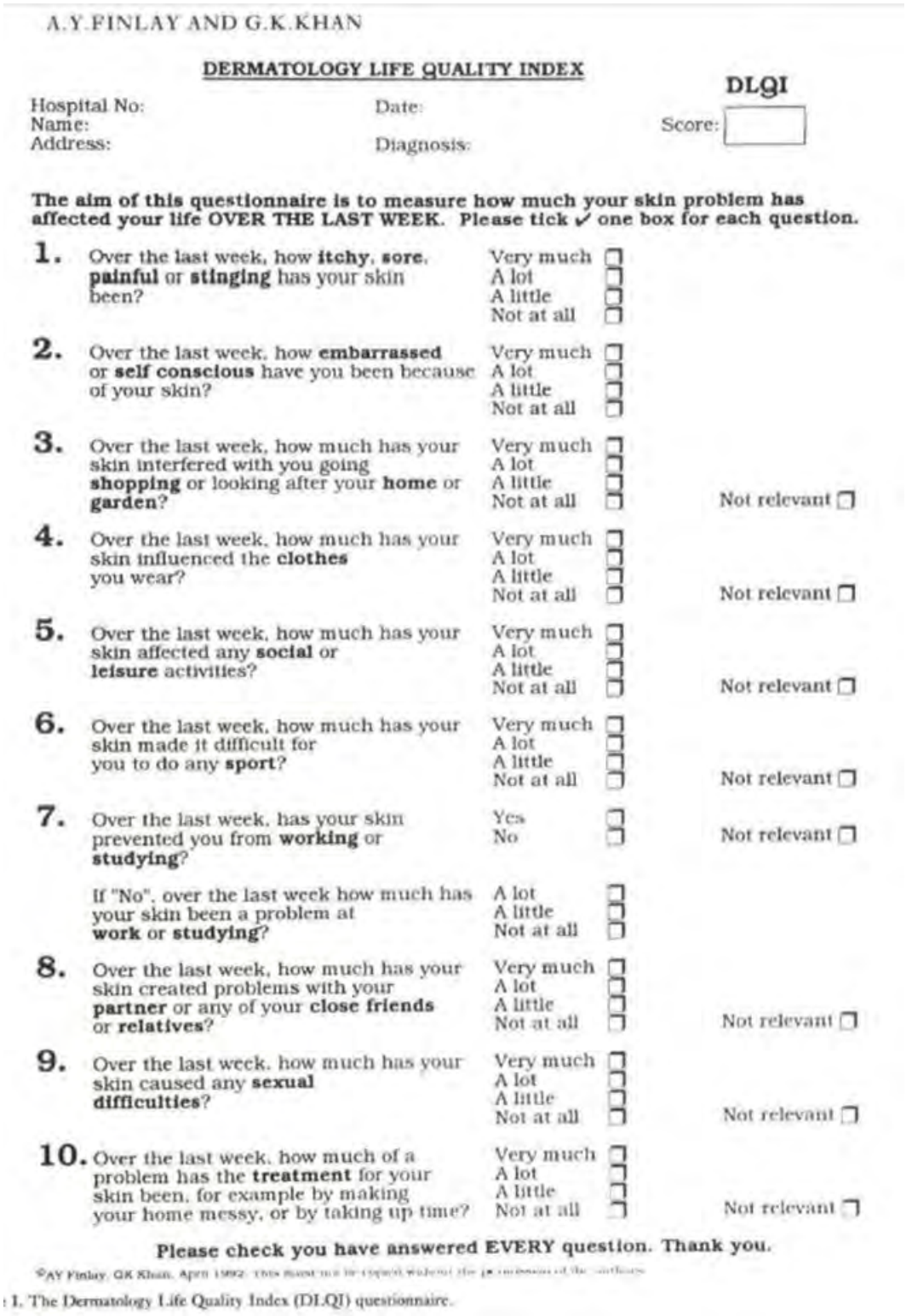
Researchers found that a clinical meaningful change in this score is between 2.24 to 3.10, for urticaria patients [12]. The difference in the change between placebo and 300mg is 4.1, which is in the clinically significant range. But this gain on the DLQI is still small. The baseline score in the trial is around 12. The highest possible value on this scale is 30. If a person had "a little" on most questions and "a lot" on one or two – they would have this score. A 4 point change from a baseline of 24 is likely to be more meaningful than a change from this baseline of 12. By definition, the smallest meaningful change in a QALY is very small – say 0.01. Hence it is unlikely that the average incremental change in the DLQI of 4, from a baseline of 12 has a value of more than 5 times the smallest meaningful change, that is 0.05.

The gain compared to cyclosporine is likely to be small.

There is no head to head clinical trials against cyclosporin. It is reasonable to assume that if it were compared to cyclosporin, the incremental effect would be larger and the incremental cost would be higher.

Appendix 2 DLQI tool

Reference: Finlay, A. and G. K. Khan (1994). "Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use." Clinical & Experimental Dermatology **19**(3): 210-216.



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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.

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1. The Dermatology Life Quality Index (DLQI) questionnaire.

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