Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

REVIEW ARTICLE

Alpine climate treatment of atopic dermatitis: a systematic review

K. B. Fieten[1,2], A. C. G. Weststrate[1], E. J. van Zuuren[3], C. A. Bruijnzeel-Koomen[1] & S. G. M. A. Pasmans[1,4]

[1]Department of (Pediatric) Dermatology and Allergology, University Medical Center Utrecht, Utrecht, the Netherlands; [2]High Altitude Clinic Merem Dutch Asthma Center Davos, Davos, Switzerland; [3]Department of Dermatology, Leiden University Medical Center, Leiden; [4]Department of Pediatric Dermatology, Sophia Children's Hospital, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands

To cite this article: Fieten KB, Weststrate ACG, van Zuuren EJ, Bruijnzeel-Koomen CA, Pasmans SGMA. Alpine climate treatment of atopic dermatitis: a systematic review. *Allergy* 2015; **70**: 12–25.

Keywords
alpine; atopic dermatitis; climate; high altitude; systematic review.

Correspondence
Suzanne G. M. A. Pasmans, MD, PhD, Department of Pediatric Dermatology, Sophia Children's Hospital, Erasmus MC University Medical Center Rotterdam, Wytemaweg 80, 3015 CN Rotterdam, the Netherlands.
Tel: +31 10 7034580
Fax: +31 10 7033822
E-mail: s.pasmans@erasmusmc.nl

Accepted for publication 12 August 2014

DOI:10.1111/all.12514

Edited by: Thomas Bieber

Abstract

Climate therapy has been used for decades in the treatment of atopic dermatitis (AD), but evidence of its effectiveness has not yet been assessed systematically. A systematic literature search in Medline, Embase, and the Cochrane library was performed to identify all original studies concerning alpine climate treatment. The risk of bias of individual studies was assessed following the Cochrane Handbook, and level of evidence was rated using GRADE guidelines. Fifteen observational studies were included concerning 40 148 patients. Four studies concerning 2670 patients presented follow-up data over a period of 1 year. Disease activity decreased in the majority of patients during treatment (96% of n = 39 006) and 12-month follow-up (64% of n = 2670). Topical corticosteroid use could often be reduced or stopped during treatment (82% of n = 1178) and during 12-month follow-up (72% of n = 3008). Quality assessment showed serious study limitations, therefore resulting in a very low level of evidence for the described outcomes. Randomized controlled trials designed with a follow-up period including well-defined patient populations, detailed description and measurement of applied interventions during climate therapy and using validated outcomes including cost-effectiveness parameters, are required to improve the evidence for alpine climate therapy as an effective treatment for patients with AD.

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by subsequent exacerbations and remissions (1). Its prevalence is increasing worldwide, and AD is currently among the most common skin diseases in children (2). Itching, disturbed sleep, and time-consuming medical treatment regimens lead to a reduced experienced quality of life in patients with AD (3, 4).

AD is a complex disease with several genetic and environmental factors involved (5). A genetic predisposition leads to an atopic constitution and a disturbed immune response which results in chronic inflammation and an impaired skin barrier (6, 7). In several eczema birth cohorts, the association between AD and the subsequent development of asthma and allergic sensitization has been established (8, 9). Prevalence of allergic sensitization in children with AD varies between countries, ranging from 52% in Belgium to 83% in Australia (8). Around 30% of children diagnosed with AD will develop asthma later in life (10). Among adults with AD, there is also great variation in prevalence of allergic sensitization and asthma diagnosis (11).

Exposure to irritants and allergens, changes in physical environment (pollution, humidity), infections, and psychosocial or emotional factors are possible triggers for exacerbations (12). AD treatment is based on control of inflammation/infection, skin hydration, and trigger avoidance (13, 14). Treatment approaches include anti-inflammatory therapy with topical immunosuppressives (dermatocorticosteroids, calcineurin inhibitors) and antimicrobial treatment, according to current guidelines (13, 14). In more severe cases, phototherapy or systemic immunosuppressive treatment is needed. Patients are often reluctant and concerned about the use of corticosteroids and systemic immunosuppressive treatment. Because of the chronic nature of AD, alternative therapies are often considered, such as acupuncture, homeopathy,

dietary supplements/restrictions, and Chinese herbal medicine (15, 16). However, the efficacy of these therapies over regular therapy could not be demonstrated (17–19).

Climate therapy has been used since the 20th century for the treatment of various chronic inflammatory dermatoses and pulmonary diseases (20, 21). It combines anti-inflammatory treatment in a trigger-free environment with being hospitalized in a specialized clinic for a period of 4 weeks to 3 months. Climate therapy at seaside or mountain resorts has shown improvement in disease activity and reduced corticosteroid use in patients with AD (22–26). In asthma, treatment in high-altitude clinics has resulted in improved asthma control, asthma-related quality of life, and a reduced corticosteroid requirement (27–30). Clinics were built specifically for the rehabilitation of patients with AD or asthma in mountain areas of Switzerland ('Dutch Asthma Center Davos', Davos 1560 m, 'Alexanderhausklinik' Davos, 1560 m, 'Hochgebirgsklinik' Davos, 1560 m), Italy ('Istituto Pio XII' Misurina 1756 m), and south Germany ('Santa Maria', Oberjoch 1200 m, 'Prinzregent Luitpolt', Scheidegg 1000 m). However, it is unclear which mechanisms lead to the observed effect. Limited healthcare resources and further advances in evidence-based medicine have put the existence of specialized high-altitude clinics under pressure. It is important to quantify the direct and long-term effects of climate treatment, as significant improvement in AD severity is also observed after clinical treatment in unspecified climate zones (31).

Objective

The current systematic review summarizes the existing evidence for the clinical effect of alpine climate treatment for patients with AD.

Methods

Search process

A systematic literature search was performed including original studies published until July 3rd 2013. A sensitive search strategy was designed to retrieve all relevant articles from Medline, Embase, and the Cochrane library. We searched for ['atopic dermatitis' OR 'eczema' OR 'neurodermatitis' OR 'neurodermitis'] AND ['climate' OR ''climatology'' OR 'climatotherapy' OR 'climatic therapy' OR 'altitude' OR 'mountains' OR 'alpine'] as medical subject headings or as main key words in the title or abstract. Two researchers (KF and GW) selected potentially eligible reports independently. Any disagreement on inclusion of studies was resolved by discussion with the other author (SP) until consensus was reached. Reference lists of retrieved articles and previously published reviews were hand-searched to identify further relevant studies.

Inclusion and exclusion criteria

Studies were included when alpine climate treatment was mentioned in title or abstract, and part of the study population was diagnosed with AD. No limitation was set on study design, age of the patients, duration of treatment, or outcome measure. Studies written in English or German were included. Studies concerning climate treatment in other climate regions, such as maritime climate, or in artificial conditions, such as climate chambers, were excluded.

Outcomes

The main outcome was disease severity after climate therapy, measured with any scoring system. Secondary outcomes were topical or systemic corticosteroid use, disease severity during follow-up, corticosteroid use during follow-up, and other reported outcomes.

Risk of bias assessment

We assessed the risk of bias of the included studies according to the domain-based evaluation described in Chapter 8 and 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (32). We evaluated selection bias, performance bias, attrition bias, detection bias, reporting bias, and publication bias.

Data extraction

The following study characteristics were collected: author and year of publication, target population of the study (including age and sample size), altitude, name and location of the clinic, treatment duration, and reported outcome variables. Outcome variables direct after treatment and during follow-up were separately extracted. Not all studies reported the same outcome measures; therefore, different studies contribute to the different outcomes. Data from studies with similar outcome measures were transformed and pooled. Regarding disease severity, several scoring systems were used. All PGAs (physician graded assessments) with a 4- or 5-point scale were reduced to a 3-point scale (better, same, and worse) for comparability. One study used number of exacerbations during follow-up as an outcome, and this was transformed to a course of disease outcome where no or less exacerbations were counted as better, more exacerbations as worse, and the same number of exacerbations as same (33). Studies reporting SCORAD scores are reported separately. Self-assessments by patients with a 4 or 5-point scale were also transformed to a 3-point scale (better, same, and worse) and pooled.

Data on corticosteroid use were differentiated for topical and systemic treatment, reduced to a yes/no variable for current use, and pooled.

Authors were contacted to clarify results when needed. When data extraction was not possible or when no absolute patient numbers were provided and authors did not respond to the request for additional information, studies were not included in the outcome tables. The overall quality of evidence was rated using GRADE guidelines (34). The review was reported according to the PRISMA statement (35).

Data analysis

For each outcome, data from the different studies were transformed and pooled, and total and relative patient numbers were calculated. It was not possible to further analyze the extracted data or to do a meta-analysis.

Results

Studies included in the review

Results of our search strategy are shown in Fig. 1. The search yielded 143 hits in Medline and 112 hits in Embase of which 61 were duplicate hits. Of a total of 200 articles, 65 were eligible for full text screening. Three were excluded because of language (two Russian and one Bulgarian) (36–38). Two were excluded because they showed duplicate data from an already included study (33, 39). Six were excluded because they were part of two growing cohorts (33, 39–45), and the most recent publications with the largest cohorts were included (22, 46). Three were excluded because they described only individual case reports (47, 48). Fifteen studies were finally included concerning 40 148 patients. Study characteristics are shown in Table 1. No randomized trials were identified. All studies were observational, and control groups were not incorporated in the study design. The majority of studies was written in German and published in German journals, restricting their accessibility to international readers.

Risk of bias

A risk of bias assessment was carried out and summarized in Table 2.

Selection bias

Some studies used specific inclusion criteria, but most studies included patients with AD who were admitted to an alpine clinic. These patients may be different from the wider population of patients with AD. Patient characteristics of relevant atopic comorbidities, such as asthma and rhinitis, were provided, but the results of climate therapy were not differentiated accordingly. There may be further selection bias due to the language restriction on the systematic search (language bias) and because most studies were published by German research groups.

Performance bias

None of the studies mentioned an intervention protocol or any details concerning climate therapy, and it was not possible to assess whether the intervention was carried out according to protocol. Duration of climate therapy varied between patients and between different clinics. Furthermore, little or no information was provided on received pharmacological interventions other than corticosteroids during climate therapy.

Detection bias

In none of the studies, outcomes were assessed blinded. Outcome measures such as course of disease or exacerba-

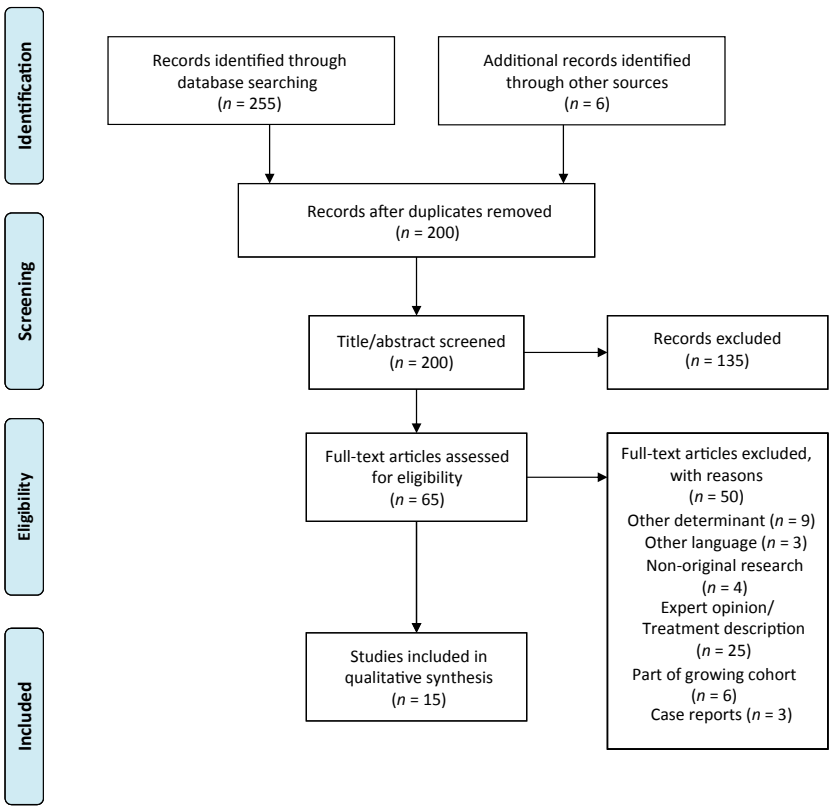

Figure 1 PRISMA flow diagram.

Table 1 Characteristics of included studies

Author/Year	Period of data collection	Population (*n*)	Treatment center	Altitude (m)	Duration of treatment	Duration of follow-up	Outcome	Outcome during follow-up
à Porta 2000	1990–1994	adults (*n* = 97)	Davos: Zürcher Höhenklinik	1600 m	32 days	1 year	PGA Corticosteroid use	Period until first relapse. Course of disease during followup. Start of corticosteroid use
Borelli 1967	1966–1967	Adolescents/adults (*n* = 230)	Davos: Alexanderhausklinik	1560 m	Not mentioned	n/a	Change in eosinophils SPT	n/a
Borelli 1995	1961–1995	Adults/children (*n* = 31 438)	Davos: Sanatorium Valbella (Alexanderhausklinik)	1560 m	6 weeks	n/a	PGA Corticosteroid use	n/a
Drosner 1988	1986	Adults (*n* = 56)	Davos: Alexanderhausklinik	1560 m	4–5 weeks	n/a	SPT	n/a
Drzimalla 1999	1995–1997	Adults (*n* = 4660)	Davos: Alexanderhausklinik	1560 m	4–6 weeks	1 year	PGA	Number of flares. Skin assessment. Corticosteroid use
Duve 1991	Not mentioned	Adults/children (*n* = 624)	Davos: Alexanderhausklinik	1560 m	4–8 weeks	1 year	PGA	Course of disease. Corticosteroid use
Eberlein 2009	2003–2004	Adults/children (*n* = 139/*n* = 165) diagnosed with asthma, AD and/or COPD	Germany: Santa Maria, Fachklinik Allgau, Asthmazentrum Buchenhöhe	1200 m 1000 m 870 m	3–4 weeks	n/a	SCORAD TARC IL16 eosinophils ECP	n/a
Fuchs 1959	1958	Adults (*n* = 393)	Germany: Sachsenbaude	1130 m	8 weeks	n/a	PGA	n/a
Heine 1995	1987–1988	Children/adolescents (*n* = 375)	Davos: Alexanderhausklinik	1560 m	Around 6 weeks	1 year	PGA Corticosteroid use	Course of disease Corticosteroid use
Kneist 1987	1986	Adults/children (*n* = 1465)	Davos: Alexanderhausklinik	1560 m	6 weeks	1 year	PGA Corticosteroid use	Course of disease. Corticosteroid use
Petermann 2000	Not mentioned	Children/adolescents (*n* = 102), SCORAD >25, use of systemic CS excluded	Germany: Santa Maria Prinzregent Luitpold	1200 m 1000 m	4 weeks	2 years	SCORAD	Number of flares. Missed school days, doctor visits, and hospitalizations
Petermann 2004	1996–1998	Children/adolescents (*n* = 55), SCORAD >25	Germany: Santa Maria	1200 m	4 weeks	n/a	SCORAD ECP EPX	n/a
Simon 1999	Not mentioned	Adults (*n* = 33), use of systemic CS excluded	Davos: Alexanderhausklinik	1560 m	4–6 weeks	n/a	SCORAD ECP	n/a
Triebskorn 1991	Not mentioned	Adults (*n* = 20)	Davos: Alexanderhausklinik	1560 m	4 weeks	n/a	TEWL	n/a
Walker 1993	Not mentioned	Adults (*n* = 12)	Davos: Zürcher Höhenklinik	1600 m	3–6 weeks	n/a	Skin intensity score eosinophils ECP	n/a

CS, corticosteroids; PGA, physician graded assessment; SPT, skin prick test; SCORAD, scoring of atopic dermatitis; TARC, thymus and activation regulated chemokine; IL-16, interleukin 16; ECP, eosinophil cationic protein; EPX, eosinophil urinary protein X; TEWL, transepidermal water loss; n/a, not applicable.

Table 2 Risk of bias assessment of studies

Risk of bias	Selection bias			Performance bias	Detection bias		Reporting bias		Attrition bias
Study	Was AD diagnosis according to criteria?	Were clear inclusion/ exclusion criteria used?	Were detailed patient characteristics on other atopic diseases provided?	Were concurrent interventions or unintended exposures described?	Validated outcome measures	Blinded assessment of outcome	Complete study protocol stated	All measurements from protocol reported	Loss-to-follow-up or dropout
à Porta 2000	Y	N	Y	N	N	N	Y	Y	8%
Borelli 1995	N	N	Y	N	N	N	Y	Y	U
Borelli 1967	N	N	Y	N	Y	N	Y	N	U
Drosner 1988	N	Y	N	N	Y	N	Y	Y	U
Drzimalla 1999	N	N	Y	N	N	N	Y	Y	49%
Duve 1991	N	N	N	N	N	N	Y	N	Y†
Eberlein 2009	Y	N	Y	N	Y	N	Y	N	U
Fuchs 1959	N	N	N	N	N	N	Y	Y	U
Heine 1995	N	N	Y	N	N	N	Y	N	50%
Kneist 1987	N	N	N	Y	N	N	Y	N	Y*
Petermann 2000	Y	Y	Y	N	Y	N	Y	N	Y*
Petermann 2004	Y	Y	N	N	Y	N	Y	Y	U
Simon 1999	N	N	Y	N	Y	N	Y	Y	U
Triebskorn 1991	N	Y	N	N	Y	N	Y	Y	U
Walker 1993	Y	N	Y	N	Y	N	Y	Y	U

Y, yes; N, no; U, unclear.

*Follow-up numbers were not mentioned.

†Only patients with complete data at all time points were included.

tions were not clearly defined, and in most studies, unvalidated outcome measures, such as PGA, were used. When patients and dermatologists both assessed disease severity after treatment, the treating dermatologists reported greater improvement compared to the self-assessment of the patient.

Reporting bias

Six of fifteen included studies did not report all outcome variables that were stated in the study protocol or reported outcome variables only for a part of the cohort, without providing an explanation for the missing data. One study was designed with a follow-up period of 2 years, but did not report any data at this point (49). One study did not report absolute patient numbers but only percentages during the follow-up period, whereas another study did not present numbers but vaguely described disease activity after 6 months follow-up as 'disease stabilized for more than 6 months in more than 50% of patients' (50, 51).

Attrition bias

In none of the studies, handling of missing data or dropout during intervention was reported. During follow-up, either no absolute patient numbers were provided, making it impossible to assess the rate of loss-to-follow-up or only patients with complete data were included. When absolute patient

Table 3 GRADE evidence table with summary of findings

Summary of findings table of alpine climate treatment for atopic dermatitis (65)

Patient or population: patients with atopic dermatitis
Settings: clinics at 1000–1600 m altitude
Intervention: alpine climate treatment

Outcomes	Effect estimate		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Control	Alpine climate treatment			
Improvement of disease severity Physician's global assessment (better, same, and worse). Scale from: 0% to 100%.	No control	88.8% to 99% of the participants improved according to the dermatologist	39 006 (7 studies)	⊕⊖⊖⊖ very low*·†	Combined data showed PGA was better in 96.5%, same in 3%, and worse in 0.5% of the participants
Improvement of disease severity SCORAD. Scale from: 0 to 103.	No control	Relative decrease in SCORAD ranged from −4.3 to −25.4	201 (3 studies)	⊕⊖⊖⊖ very low*	At one location in a study by Eberlein (2009), baseline SCORAD was lower and the reduction was smaller. For the other locations and studies reduction ranged from −12.7 to −25.4 (see Table 4)
Improvement of disease severity during follow-up Self-assessment (better, same and, worse). Scale from: 0% to 100% Follow-up: up to 12 months	No control	56% to 64.8% of the participants considered their disease severity to be improved during follow-up	2670 (6 studies‡)	⊕⊖⊖⊖ very low†·§	Combined data showed that according to the participants, disease severity was better in 64%, same in 25%, and worse in 11% of the participants
Free of topical steroid use after alpine climate treatment Scale from: 0% to 100%	No control	70% to 84% of participants was free of corticosteroids at the end of the intervention	1178 (3 studies)	⊕⊖⊖⊖ very low*·†	Combined data across the 3 studies showed that 964 of 1178 (82%) were free of corticosteroid use
No or less topical corticosteroid use at follow-up Scale from: 0% to 100% Follow-up: up to 12 months	No control	26% to 87% of participants used no or less topical corticosteroids during follow-up	3008 (4 studies¶)	⊕⊖⊖⊖ very low†·§	Combined data across the 4 studies showed that 2171 of 3008 (72%) used no or less topical corticosteroids

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

*No control population; not controlled for confounding; unblinded and unvalidated assessment of outcome; reporting bias, attrition bias.
†The limitations of the study design did not allow to upgrade for large effect.
‡One study, Petermann 2000, did not provide data on this prespecified outcome, and the number of participants is therefore not included, nor is this study included for treatment effect. Number of participants at follow-up of Kneist 1987 is unknown, and only percentages are provided.
§Follow-up numbers were either not mentioned or up to 50%. No control population; not controlled for confounding; unblinded and unvalidated assessment of outcome; reporting bias.
¶Number participants at follow-up of Kneist 1987 is unknown, and only percentages are provided and therefore not included.

numbers were provided, loss-to-follow-up increased up to 50%, making attrition bias very likely.

Publication bias

For this review, only published studies were considered. None of the studies was sponsored by industry; however, most studies were carried out by alpine clinics assessing the effectiveness of their own therapy. There were no reports identified with negative results, but as there were no control groups, it was not possible to create funnel plots to find evidence of publication bias.

Outcomes

The quality of the evidence for the pooled outcome measures as summarized in Table 3 was rated very low. Data extrac-

Table 4 Disease severity measured with Physician Graded Assessment or SCORAD by dermatologist or self-assessment by the patient

Author/Year	Study population (*n*)	Outcome (*n* reported for outcome)	Proportion (%) and (*n*)	Outcome (*n* reported for outcome)	Proportion (%) and (*n*)	Mean (SD) decrease from baseline	Follow-up	Outcome during follow-up (*n* reported for outcome)	Proportion (%) and (*n*)
à Porta 2000	Adults ($n = 97$)	PGA (better, same and, worse) ($n = 97$)	99%, 1%, 0% $n = 96$ $n = 1$ $n = 0$	Self-assess-ment at discharge ($n = 89$)	93%, 7%, 0% $n = 83$, $n = 6$, $n = 0$		1 year	Course of disease 6–12 months after treatment (better, same and, worse) ($n = 89$)	56%, 35%, 9% $n = 50$, $n = 31$, $n = 8$
Borelli 1995	Adults/ children ($n = 31\ 438$)	PGA (better, same and, worse) ($n = 31\ 438$)	97.2%, 2.4%, 0.4% $n = 30\ 558$, $n = 754$, $n = 126$				n/a	n/a	
Drzimalla 1999	Adults ($n = 4660$)	PGA (better, same and, worse) ($n = 4660$)	93.6%, 5.4%, 1% $n = 4362$, $n = 251$, $n = 47$				1 year	Course of disease 8–12 months after treatment (better, same and, worse) ($n = 2392$)	*64.8%, 24.4%, 10.8% $n = 1550$, $n = 584$, $n = 258$
Duve 1991	Adults/ children ($n = 624$)	PGA (better, same and, worse) ($n = 624$)	97.6%, 2.2%, 0.2% $n = 609$, $n = 14$, $n = 1$				1 year	Course of disease ($n = 624$)	Not clear reported, disease stabilized more than 6 months in more than 50% of patients
Fuchs 1959	Adults ($n = 393$)	PGA (better, same and, worse) ($n = 393$)	88.8%, 9.4%, 1.8% $n = 349$, $n = 37$, $n = 7$				n/a	n/a	
Heine 1995	Children/ adolescents ($n = 375$)	PGA (better, same and, worse) ($n = 329$)	98.5%, 0.6%, 0.9% $n = 324$, $n = 2$, $n = 3$	Self-assess-ment (better, same and, worse) ($n = 368$)	91%, 6%, 3% $n = 335$, $n = 22$, $n = 11$		1 year	Course of disease 7–12 months after treatment (better, same and, worse) $n = 189$	63%, 23%, 14% $n = 120$, $n = 43$, $n = 26$
Kneist 1987	Adults/ children ($n = 1465$)	PGA (better, same and, worse) ($n = 1065$)	96%, 3%, 1% $n = 1012$ $n = 30$ $n = 14$	Self-assessment (better, same and, worse)	‡95.5%, 0%, 1.5% $n = 1399$ $n = 22$		1 year	Course of disease 6-12 months after treatment (better, same and, worse)	†63.4%, 31.7%, 4.9%
Total	$n = 39\ 052$	PGA (better, same and, worse) ($n = 39\ 006$)	96.5%, 3%, 0.5% $n = 37\ 719$, $n = 1088$, $n = 199$	Self-assess-ment (better, same and, worse) ($n = 1922$)	‡95%, 1.5%, 1.7% $n = 1817$, $n = 28$, $n = 33$			Course of disease up to 12 months after treatment (better, same and, worse) ($n^{\S} = 2670$)	64%, 25%, 11% $n = 1720$, $n = 658$, $n = 292$

Table 4 (continued)

Author/Year	Study population (*n*)	Outcome (*n* reported for outcome)	Proportion (%) and (*n*)	Outcome (*n* reported for outcome)	Proportion (%) and (*n*)	Mean (SD) decrease from baseline	Follow-up	Outcome during follow-up (*n* reported for outcome)	Proportion (%) and (*n*)
Eberlein 2009	Children (*n* = 43) Treatment center Oberjoch	SCORAD				−15.70 (12.57)	n/a	n/a	
	Children (*n* < 24, exact number unknown) Treatment center Berchtesgaden					−4.30 (8.04)	n/a	n/a	
	Adults (*n* = 23) Treatment center Pfronten					−25.4 (11.81)	n/a	n/a	
	Adults (*n* < 24, exact number unknown) Treatment center Berchtesgaden					−7.50 (11.04)	n/a	n/a	
Petermann 2000	Children/ adolescents (*n* = 102), SCORAD >25	SCORAD				−22.70 (8.68)	2 years	Self-assess-ment of skin	Not mentioned
Simon 1999	Adults (*n* = 33)	SCORAD				−12.7	n/a	n/a	
Walker 1993	Adults (*n* = 12)	Skin intensity score				51%	n/a	n/a	

n/a, not applicable.

*Percentages are deduced from graph, not mentioned in text.

†Percentages were mentioned, but no exact patient numbers.

‡Percentages do not add up to 100%.

§Excluding Kneist and Duve.

Table 5 Corticosteroid use

Author/ Year	Population (*n*)	Outcome (*n* reported for outcome)	Proportion (%) and (*n*)	Outcome (*n* reported for outcome)	Proportion (%) and (*n*)	Follow-up	Outcome during follow-up	Proportion (%) and (*n*)	Outcome during follow-up	Proportion (%) and (*n*)
à Porta 2000	Adults (*n* = 97)	Free of topical corticosteroids (*n* = 71)	70% (50 of 71)	Free of systemic corticosteroids (*n* = 13)	92% (12 of 13)	1 year	Topical corticosteroid use (none, less, same, more)	26% (13 of 50)		
Drzimalla 1999	Adults (*n* = 4660)					1 year	Topical corticosteroid use (none, less, same, more)	†*n* = 2156 none or less 77%, same 15%, more 9%	Systemic corticosteroid use after 12 months follow-up	†*n* = 2156 95% none or less 3% same 2% more
Duve 1991	Children and adults (*n* = 624)	Free of topical corticosteroids (*n* = 624)	†,**57%	Free of systemic corticosteroids (*n* = 624)	†,**86%	1 year	Topical corticosteroid use (none, less, same, more)	†,¶*n* = 624 none 36% less 19% same 38% more 9%	Systemic corticosteroid use after 12 months follow-up	†,¶*n* = 624 90% none, 4% less, 2% same, 2% more
Heine 1995	Children and adolescents (*n* = 375)	Free of topical corticosteroids (*n* = 188)	75% (140 of 188)	Free of systemic corticosteroids (*n* = 7)	57% (4 of 7)	1 year	Topical corticosteroid use (none, less, same, more)	†*n* = 178 none 62% less 25% same 9% more 4%	Systemic corticosteroid use	†*n* = 133 none 94% less 3% same 1.5% more 1.5%
Kneist 1987	Children and adults (*n* = 1465)	Free of topical corticosteroids (*n* = 919)	84% (774 of 919)	Free of systemic corticosteroids (*n* = 82)	77% (63 of 82)	1 year	Topical corticosteroid use (none, less, same, more)	Not mentioned in text	Topical corticosteroid use (none, less, same, more) after 6 months follow-up	*none 40.2% less 38.5% same 17.4% more 3.8%
Total	*n* = 7221	*n*§ = 1178 using topical cortico-steroids	82% (*n* = 964 of 1178)	*n* = 102 using systemic cortico-steroids	77% (*n* = 79 of 102)		*n*‡ = 3008	72%‡ (*n* = 2171 of 3008)		

*Follow-up numbers were not mentioned in the text.
†Data presented for entire patient cohorts and not subset of patients treated with corticosteroids.
‡Excluding Kneist.
§Excluding Duve.
¶Percentages are deduced from graph, not mentioned in text.
**Percentages do not add up to 100%.

Table 6 Eosinophil markers

Author/Year	Population (*n*)	Outcome	ECP mean (SD)	Number of eosinophils mean (SD)	EPX	Remarks
Borelli 1967	Adolescents/adults ($n = 140$)	Change in number of eosinophils		$n = 80$ less, $n = 15$ unchanged, $n = 25$ more		No correlation calculated with clinical outcome. Magnitude of change not calculated. Data not reported for all patients. Statistical significance not reported
Eberlein 2009	Adults/children ($n = 139/n = 165$)	Change in number of eosinophils ECP	Berchtesgaden 24.0 (15.1) to 21.7 (11.7) $P < 0.05$. Oberjoch 20.0 (20.2) to 16.9 (12.0) p not reported Pfronten 16.9 (21.3) to 15.2 (15.4) p not reported	Berchtesgaden 5.8 (3.4) to 4.8 (2.4) $P < 0.05$. Oberjoch 280.0 (231.2) to 247.3 (172.4). Pfronten 4.6 (3) to 4.3 (3.5)		Results are divided by treatment center and not by diagnosis (AD, asthma and COPD reported together)
Petermann 2004	Children/adolescents ($n = 55$), SCORAD >25	ECP EPX	No change in ECP after treatment $P = 0.7$		Decrease in EPX after treatment $P = 0.000$	Significant correlation between SCORAD and EPX, not ECP
Simon 1999	Adults ($n = 33$)	ECP	Median ECP 33 mcg to 17.5 mcg $P = 0.001$			Parallel improvement in SCORAD, significant correlation with ECP calculated, p not mentioned
Walker 1993	Adults ($n = 12$)	Number of eosinophils ECP	21% decrease $P < 0.05$	43% decrease $P < 0.003$		

tion was complicated because of incomplete reporting; therefore, not all studies with relevant outcomes could be included.

Disease activity

Direct after climate treatment, disease activity was decreased in the majority of 39 503 patients (included in 11 studies) as scored by a dermatologist. Validated scoring systems, such as SCORAD, were used in four studies including 451 patients (49, 52–54). PGA was used in seven studies including 39 052 patients (22, 46, 50, 51, 55–57). In three studies including 1922 patients, patients were asked to judge their clinical improvement and reached similar conclusions as the dermatologist, but differed on the degree of improvement (51, 55, 57). Six studies were designed with a follow-up period, but one did not report outcomes of the 2-year follow-up period, the other mentioned percentages, and no exact patient numbers during follow-up (49, 51). Dropout during follow-up was not addressed in any of the studies, and one study simply excluded patients with incomplete data. In the remaining four studies, 2670 patients were asked to return questionnaires after 3, 6, and 12 months to judge AD activity with a scoring system, a global assessment or period until first relapse (50, 55–57) (Table 4). The majority (64%) of these patients reported a decreased disease activity up to 12 months after treatment and an overall improved course of disease compared to the year before treatment.

Corticosteroid use

Corticosteroid use was mentioned in six studies, but one study did not differentiate between patients with AD, psoriasis, contact dermatitis, and other diagnoses, and its data could therefore not be included in Table 5 (46). In one study, percentages were mentioned, but these did not add up to 100% [50]. In the three studies in which exact patient numbers on topical corticosteroid use are mentioned, 1178 of 1937 patients (61%) used topical corticosteroids at start of climate therapy (51, 55, 57). Corticosteroid use during follow-up is reported in most studies for the whole patient cohort, including patients who were not using corticosteroids during climate treatment. Only one study provided data on topical corticosteroid use during follow-up in the subgroup of patients who were able to stop corticosteroids during climate therapy (55).

Other outcomes

Several studies were identified reporting biomarkers or other translational parameters (Table 6). Five studies including 634 patients measured number of eosinophils, eosinophil cationic protein (ECP), and eosinophil protein X (EPX) in urine direct after climate treatment (52–54, 58, 59). ECP decreased in three of four studies, EPX decreased in one study, and number of eosinophils decreased in three studies paralleling the observed improvement in SCORAD. A significant correlation between SCORAD and EPX was reported in one study (59).

Skin prick tests with intracutaneously applied histamine, serotonin, acetylcholine, and bradykinin showed a decrease in skin reactivity after alpine climate therapy; statistical significance was not calculated (58). Skin prick tests with recall antigens showed a significant increase in skin reactivity after climate therapy (60). Transepidermal water loss decreased significantly after treatment, but remained high compared to healthy controls (61). TARC levels were stable before and after treatment at different clinics (52).

Discussion

Main findings

Our systematic search for the effect of alpine climate therapy of patients with AD has identified only observational studies. The largest study is a cohort of 31 480 patients treated in a clinic in Davos, Switzerland, from 1961 to 1995 (46). Disease activity was decreased in 96% of patients at the end of climate therapy. Topical as well as systemic corticosteroid use could be reduced or stopped during treatment in 80% of patients. Up to 12 months after treatment, 64% of patients reported a decreased disease activity; an overall improved course of disease compared to the year before treatment and 72% reported no or reduced topical corticosteroid use. Similar results were reported for children and adults.

Risk of bias

The quality of the body of evidence for the separate outcomes was very low. All identified studies had methodological and other limitations. In most identified studies, clinical improvement was scored by the physician as improved, not improved, or worsened. Physician global assessments are also used nowadays, because they are fast and easy to perform and give a good indication of the course of disease when repeated over time (62). In more recent studies, SCORAD was used to measure clinical activity during climate therapy, allowing for a more objective estimation of the treatment effect (49, 52, 53, 59). However, the measurements were not performed by an independent and blinded physician.

The majority of available data is provided by three alpine clinics, reporting on patients with AD who were treated in these clinics during a certain time period. Selection bias is a problem, because there have been no generally accepted criteria for whom alpine climate therapy should be provided (46). Also, the position of climate therapy in the healthcare system changed over time, decreasing its availability to patients with AD. The relatively low rate of topical corticosteroid use could imply that patients with mild AD or concomitant diagnoses of severe asthma and mild AD were overrepresented in the study sample. However, patient characteristics were not well described, and data on other pharmacological therapy were not provided. In most studies, style of reporting was very global and details were often lacking, making it difficult to interpret the data. Six studies

were designed with a follow-up period, but risk of bias was substantial due to the high dropout rates. Clinical efficacy during follow-up is important for reasons of cost-effectiveness as long-term beneficial effects may show the added value of alpine climate therapy compared to other treatment options.

It has been hypothesized that the lack or low level of respiratory allergens may contribute to the clinical effect of alpine treatment. The results in this systematic review of alpine climate therapy for patients with AD are very similar to what was reported of alpine climate therapy for patients with AA (20). However, the latter was no systematic review and no level of evidence was assigned to the reported findings. Also, beneficial effects of alpine climate therapy irrespective of atopic status have been reported in children and adults with AA (30, 59, 63). But because no trials have been conducted and no control groups were included in the observational studies, there is no reliable data on which elements of alpine climate treatment are responsible for the observed effect. Multidisciplinary evaluation and treatment in a regular outpatient setting for several days also shows reduction of disease activity, corticosteroid use, and improved quality of life up to 2 years after the described treatment program (31, 64). This suggests that apart from the climate, other elements may be important during alpine climate therapy, for example the multidisciplinary approach or the increased adherence to treatment.

Conclusion

To our knowledge, this is the first systematic review on the outcomes of alpine climate treatment of patients with AD using the Cochrane Handbook for assessing risk of bias, GRADE guidelines for assessing level of evidence, and PRISMA guidelines for reporting. The results of this systematic review provide very low quality evidence that alpine climate therapy results in decreased disease activity and reduced corticosteroid requirement direct and up to 1 year after treatment in patients with AD. Randomized controlled trials designed with a follow-up period including well-defined patient populations, detailed description, and measurement of applied interventions during climate therapy and using validated outcomes including cost-effectiveness parameters are required to improve the evidence for alpine climate therapy as an effective treatment for patients with AD.

Author contributions

KF participated in literature search, data collection and analysis, manuscript writing, and final approval of the manuscript. GW participated in literature search, data collection, and final approval of the manuscript. EZ participated in data analysis, critical revision, and final approval of the manuscript. CBK participated in critical revision and final approval of the manuscript. SP participated in literature search, data collection and analysis, critical revision, and final approval of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;**358**:1483–1494.
2. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009;**124**:1251–1258.
3. Ben-Gashir MA, Seed PT, Hay RJ. Quality of life and disease severity are correlated in children with atopic dermatitis. *Br J Dermatol* 2004;**150**:284–290.
4. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006;**60**:984–992.
5. Novak N, Leung DY. Advances in atopic dermatitis. *Curr Opin Immunol* 2011;**23**:778–783.
6. Boguniewicz M, Leung DY. Recent insights into atopic dermatitis and implications for management of infectious complications. *J Allergy Clin Immunol* 2010;**125**:4–13.
7. Kezic S, Novak N, Jakasa I, Jungersted JM, Simon M, Brandner JM et al. Skin barrier in atopic dermatitis. *Front Biosci* (Landmark Ed) 2014;**19**:542–556.
8. de Benedictis FM, Franceschini F, Hill D, Naspitz C, Simons FE, Wahn U et al. The allergic sensitization in infants with atopic eczema from different countries. *Allergy* 2009;**64**:295–303.
9. Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. *J Am Acad Dermatol* 2008;**58**:68–73.
10. van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol* 2007;**120**:565–569.
11. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol* 2013;**132**:1132–1138.
12. Langan SM, Williams HC. What causes worsening of eczema? A systematic review *Br J Dermatol* 2006;**155**:504–514.
13. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol* 2012;**26**:1045–1060.
14. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012;**26**:1176–1193.
15. Hoare C, Li Wan PA, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000;**4**:1–191.
16. Foolad N, Brezinski EA, Chase EP, Armstrong AW. Effect of nutrient supplementation on atopic dermatitis in children: a systematic review of probiotics, prebiotics, formula, and fatty acids. *JAMA Dermatol* 2013;**149**:350–355.
17. Tan HY, Zhang AL, Chen D, Xue CC, Lenon GB. Chinese herbal medicine for atopic dermatitis: a systematic review. *J Am Acad Dermatol* 2013;**69**:295–304.
18. Roll S, Reinhold T, Pach D, Brinkhaus B, Icke K, Staab D et al. Comparative effectiveness of homoeopathic vs. conventional therapy in usual care of atopic eczema in

children: long-term medical and economic outcomes. *PLoS One* 2013;**8**:e54973.
19. DiNicola C, Kekevian A, Chang C. Integrative medicine as adjunct therapy in the treatment of atopic dermatitis–the role of traditional Chinese medicine, dietary supplements, and other modalities. *Clin Rev Allergy Immunol* 2013;**44**:242–253.
20. Rijssenbeek-Nouwens LH, Bel EH. High-altitude treatment: a therapeutic option for patients with severe, refractory asthma? *Clin Exp Allergy* 2011;**41**:775–782.
21. Vocks E. Climatotherapy in atopic eczema. In: Ring J, Przybilla B, Ruzicka T editors. *Handbook of Atopic Eczema*. Berlin, Heidelberg: Springer-Verlag, 2006: 507–523.
22. Fuchs F, Hentschel G. Possibilities and experiences with high altitude-climatotherapy in patients with constitutional neurodermatitis at Fichtelberg. *Dermatol Wochenschr* 1959;**140**:1138–1147.
23. Harms V, Buhles N, Folster-Holst R. Therapy of atopic dermatitis at the seaside of the North Sea and Baltic Sea: therapeutic methods and quantification of the effect: a multicenter study. *Phys Rehab Kur Med* 2002;**12**:89–94.
24. Linser K. Climatotherapy of eczema. *Dtsch Gesundheitsw* 1956;**11**:12–22.
25. Marchionini A, Borelli S. Climatotherapy of neurodermatitis disseminata. *Dtsch Med Wochenschr* 1956;**81**:811–816.
26. Schuh A, Nowak D. Evidence-based acute and long-lasting effects of climatotherapy in moderate altitudes and on the seaside. *Dtsch Med Wochenschr* 2011;**136**:135–139.
27. Grootendorst DC, Dahlen SE, Van Den Bos JW, Duiverman EJ, Veselic-Charvat M, Vrijlandt EJ et al. Benefits of high altitude allergen avoidance in atopic adolescents with moderate to severe asthma, over and above treatment with high dose inhaled steroids. *Clin Exp Allergy* 2001;**31**:400–408.
28. Peroni DG, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1994;**149**:1442–1446.
29. Piacentini GL, Bodini A, Costella S, Vicentini L, Peroni D, Zanolla L et al. Allergen avoidance is associated with a fall in exhaled nitric oxide in asthmatic children. *J Allergy Clin Immunol* 1999;**104**:1323–1324.
30. Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, Hashimoto S, Bel EH, Weersink EJ. High-altitude treatment in atopic and nonatopic patients with severe asthma. *Eur Respir J* 2012;**40**:1374–1380.
31. Boguniewicz M, Nicol N, Kelsay K, Leung DY. A multidisciplinary approach to evaluation and treatment of atopic dermatitis. *Semin Cutan Med Surg* 2008;**27**:115–127.
32. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Last Accessed 2 April 2014.
33. Drzimalla K, Wagner SA, Disch R. Long-term results after high-altitude climatotherapy in Davos - A follow-up study. *Allergologie* 1999;**22**:S29.
34. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**: 924–926.
35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.
36. Lalova A. Follow up of the microcirculatory phenomena in dermatologic patients with urticaria and neurodermitis in alpine conditions (Bulgarian). *Savrem Med* 1973;**24**:22–26.
37. Rakhmanov VA. Effect of climatotherapy on the course of neurodermatitis. *Vestn Dermatol Venerol* 1964;**38**:34–38.
38. Tuleutaeva GA. Dynamics of clinico-immunological indicators in children with neurodermatitis during climatotherapy. *Vopr Kurortol Fizioter Lech Fiz Kult* 1988;**3**:29–31.
39. Borelli S, Duve S, Walker A. Kortisonmedikation bei Neurodermitis constitutionalis atopica nach Hochgebirgsklimatherapie. *Ärzteblatt* 1992;**89**:1365–1367.
40. Borelli S, Brenn H. Zur Rehabilitation der atopischen Neurodermitis. *Zeitschrift für Haut-und Geschlechtskrankheiten* 1969;**44**:819–826.
41. Duengemann H, Borelli S. Climatotherapy in allergic dermatoses. *Therapiewoche* 1975;**25**:478–493.
42. Engst R. Ergebnisse hochalpiner stationÃrer Klimatherapie bei chronischen Hautkranken und Allergikern aus der Klinik für Dermatologie und Allergie Davos (1560 m). *Deutsche Dermatol* 1977;**25**:283–292.
43. Fuchs F, Hentschel G. Experiences with winter climatotherapy of eczema at the Fichtelberg mountain resort. *Dtsch Gesundheitsw* 1958;**13**:1562–1568.
44. Fuchs F. Preliminary experiences with high altitude climate in endogenous eczema. *Dtsch Gesundheitsw* 1958;**13**:253–256.
45. Borelli S. Climatic therapy and catamnesis of neurodermatitis. *Arch Dermatol Forsch* 1972;**244**:356–357.
46. Borelli S. *Chronische Hautkrankheiten und Hochgebirgsklimatherapie*. Frankfurt am Main, Germany: Lichtenwys, 1995.
47. Harnack K. Problems of economy and rehabilitation in climatotherapy of eczema. *Dermatol Wochenschr* 1965;**151**:1080–1095.
48. Hofschneider PH. Climatotherapy of neurodermatitis disseminata. *Die Medizinische* 1958;**43**:1715–1717.
49. Petermann F, Gulyas A, Niebank K, Stubing K, Warschburger P. Effects of rehabilitation on children and adolescents with asthma and atopic dermatitis. *Allergologie* 2000;**23**:492–502.
50. Duve S, Walker A, Borelli S. Verlaufskontrolle bei Neurodermitis constitutionalis atopica bei Hochgebirgsklimatherapie. *Deutsch Derm* 1991;**39**:1418–1428.
51. Kneist W, Rakoski J. Neurodermitis atopica-Klimatherapie im Hochgebirge. *Allergologie* 1987;**10**:531–535.
52. Eberlein B, Gulyas A, Schultz K, Lecheler J, Flogel S, Wolfmeyer C et al. Benefits of alpine mountain climate of Bavaria in patients with allergic diseases and chronic obstructive pulmonary disease: results from the AURA* study. *J Investig Allergol Clin Immunol* 2009;**19**:159–161.
53. Simon D, Weigl L, Disch R. Influence of high-altitude climate therapy on atopic eczema. *Allergologie* 1999;**22**:S26.
54. Walker C, Kagi MK, Ingold P, Braun P, Blaser K, Bruijnzeel-Koomen CA et al. Atopic dermatitis: correlation of peripheral blood T cell activation, eosinophilia and serum factors with clinical severity. *Clin Exp Allergy* 1993;**23**:145–153.
55. A Porta B, Barandun J, Wuthrich B. Therapy of atopic dermatitis in high mountain climate. *Schweiz Rundsch Med Prax* 2000;**89**:1147–1153.
56. Drzimalla K, Wagner SA, Disch R, Borelli S. Long-term results after high-altitude climatotherapy in Davos - A follow-up study. *Prev Rehabil* 1999;**11**:18–27.
57. Heine A. *Verlauf und Cortisonmedikation bei atopischen Erkrankungen im Kindesalter nach einer Hochgebirgsklimatherapie*. München, Germany: Technische Universität München, 1995.
58. Borelli S, Michailov P, Ene-Popescu C. Changes in the environment dependent allergic reactivity in patients with neurodermatitis constitutionalis following high-altitude climate therapy. *Hautarzt* 1967;**18**:456–458.
59. Petermann F, Gulyas AF, Niebank K, Warschburger P. Effects of allergen avoidance at high altitude on children with asthma or atopic dermatitis. *Pediatr Asthma Allergy Immunol* 2004;**17**:15–24.
60. Drosner M. Climate therapy and change in cellular immunity. *Z Hautkr* 1988;**63**(Suppl 4):104–107.
61. Triebskorn A, Guhring H, Gloor M, Borelli S. Hydration of the horny layer and barrier function in atopic dermatitis before and after therapy in high-altitude climate. *Z Hautkr* 1991;**66**:145–147.

62. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol* 2012;**66**:369–375.
63. Huss-Marp J, Kramer U, Eberlein B, Pfab F, Ring J, Behrendt H et al. Reduced exhaled nitric oxide values in children with asthma after inpatient rehabilitation at high altitude. *J Allergy Clin Immunol* 2007;**120**:471–472.
64. Kelsay K, Carel K, Bratton DL, Gelfand EW, Klinnert MD. Functional status following treatment of children with atopic dermatitis. *J Allergy Clin Immunol* 2006;**117**:S233.
65. Schünemann H, Oxman A, Brozek J. *The GRADE Working Group: GRADE Handbook for Grading Quality of Evidence and Strength of Recommendation Version 3.2*. http://tech.cochrane.org/revman/gradepro. Last Accessed 23 March 2014.