Arch Dermatol Res (2016) 308:601–616
DOI 10.1007/s00403-016-1673-4

REVIEW

Health economic analyses of psoriasis management: a systematic literature search

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Received: 14 September 2015 / Revised: 20 May 2016 / Accepted: 27 June 2016 / Published online: 19 July 2016

Abstract In the course of the chronic skin disease psoriasis, where a variety of treatment interventions is available, a strong growth of health economic studies comparing treatment costs and benefits can be noticed. The objective was to identify health economic evaluations of psoriasis treatments that have been published to date. Of particular interest were the mostly used analysis and outcome parameters, the compared treatments, and the question, if available health economic studies may be used to perform a meta-analysis of qualitative findings. A systematic literature search using PubMed Medline, Ovid Medline, and Cochrane Library was performed for articles, published and available until mid of January 2016. Among the key words were the terms "psoriasis" and "cost-effectiveness". The search resulted in 318 articles without duplicates. Thereof 60 health economic analyses in psoriasis management were identified. Most of these are cost-effectiveness evaluations (45). The clinical parameter PASI (Psoriasis Area Severity Index) is the most often used cost-effectiveness outcome (33) followed by the Dermatology Life Quality Index (DLQI) (6). In case of cost-utility analyses, QALYs (quality-adjusted life-years) were mostly generated with the help of EuroQol five dimensions questionnaire (EQ-5D) (12), which was partly based on PASI and DLQI values. The majority of health economic studies is focusing on the direct medical and non-medical costs without consideration of productivity losses. Almost 70 % of 60 publications were conducted in Europe. Overall, most considered systemic treatments were the biological agents etanercept (36), adalimumab (27), and infliximab (26) followed by ustekinumab (17) and phototherapy (incl. UV-B, PUVA/psoralen combined with UV-A) (14). Comparisons including only topical treatments mostly focused on vitamin D treatment (14), corticosteroids (13), and coal tar products (6) followed by dithranol (5) and tazarotene (4). Given the setting, compared treatments, and study conditions, different results can be found for medical decision-making. Thereby, it can be noted that there are no standards on methods and outcomes measures available. This leads to a very limited comparability of health economic studies and presents no comfortable basis to examine a meta-analysis of health economic results. The presented systematic review shows the need for nationwide data and interpretation.

Keywords Cost-effectiveness · Psoriasis · Health economic evaluations · PASI

Introduction

Psoriasis vulgaris is a chronic, non-infectious inflammatory disease, and with a prevalence of 2–3 % one of the most frequent chronic skin diseases worldwide [9, 25, 58, 61].

Moreover, it is associated with numerous comorbidities such as cardiovascular and metabolic diseases as well as chronic immune diseases like rheumatism, chronic bowel disease, and Crohn's disease. Thus, psoriasis is connected with a high disease burden, in particular marked reductions of patient's quality of life.

Treatment of psoriasis consists of topical agents, UV treatment, traditional systemic treatments, and since 2003

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also of biologics. Costs, especially for systemic treatments including biologics can be overwhelming to patients and the health care system [4].

Chronic diseases, which often require a lifelong treatment, cause significant follow-up costs and, therefore, have a high relevance concerning health economic aspects. While treatment costs as a monetary term are relatively easy to determine, different types to evaluate the benefit of a therapy exist. So far, the most often cited measurements to determine the benefit considering economic objectives are clinical outcomes like the Psoriasis Area and Severity Index (PASI) and cost outcomes, for example reduced follow-up costs [9].

In case of comparing the costs and benefits of treatment options, a cost-effectiveness analysis will be conducted. In cost-effectiveness analyses, outcomes are measured in program-specific units such as clinical parameters like the severity of disease or health outcomes like quality of life, cases cured, and days absent averted. When measuring quality of life in terms of a person's health, factors to consider are for example pain level, mobility, and general mood. In case of combining outcome parameters of a treatment into a single aggregated summary outcome, the comparison with costs refers to a cost-utility analysis. There are different methods available to generate outcomes of a treatment in benefit units, for example the concept of quality-adjusted life-years (QALYs) [20]. A QALY gives an idea, how many extra months or years of life with a reasonable health-related quality a patient might gain as a result of treatment. Thereby, quality of life can range from 0 (worst possible health) to 1 (the best possible health). With the consideration of costs, cost–utility analyses present the cost of using a treatment to provide a year of the best quality of life available. Cost–utility analyses as kind of cost-effectiveness analyses using the QALYs to measure the effectiveness are expressed as cost per QALY [20, 34, 46].

Focusing on the costs of a cost-effectiveness/-utility analysis, costs are basically differentiated into direct and indirect ones. Direct costs include all resource consumptions that are associated with the medical treatment (e.g., costs of pharmaceuticals) as well as all resources that are used as a consequence of the treatment or disease, known as direct non-medical costs (e.g., for transportation, for household help, or for the educational system). Indirect costs generate all other costs caused indirectly through the treatment or the disease, including in particular disability days [25].

The variety of benefits and costs, economic analysis methods, and modeling techniques (e.g. decision tree, Markov model) indicate a wide range of different health economic evaluation studies. Many aspects have to be considered in planning a health economic study. Hence, there are several guidelines available [20, 37, 47, 64].

In the course of the chronic skin disease psoriasis, where a variety of interventions is available, a strong growth of health economic studies comparing treatment costs and benefits can be noticed. With the help of a systematic literature search, the researchers aimed to identify health economic evaluations of psoriasis treatments. Of particular interest were the following research questions:

1. Which health economic studies on costs and benefits of psoriasis treatment have been published?
2. Which analytical methods were used?
3. Which outcomes were analyzed?
4. Which models can be identified (decision tree, Markov model, or discrete event simulation)?
5. Which treatments were investigated?
6. What gaps exist in health economic studies of psoriasis care?

Materials and methods

Literature search

A literature search using Medline database (via PubMed and Ovid) and Cochrane Library was performed to identify the current situation of available health economic studies, evaluating treatment interventions for psoriasis patients and the respectively used benefit parameters and costs as well as modeling techniques. Search alerts were generated and reviewed for articles published until the 20 January 2016.

For example, the search algorithm in PubMed Medline was as follows:

> (psoriasis) AND ("cost effectiveness" OR "cost effective" OR "health economic" OR "pharmacoeconomics" OR "pharmacoeconomic" OR "cost benefit" OR "cost utility").

The literature search was limited to articles in English and German languages.

Study identification

Criteria for selecting the available research were: disease state is psoriasis, and the study is a health economic analysis, comparing costs as well as benefits of at least two interventions. Thus, analyses of one treatment only as well as cost-of-illness studies and cost-minimization analyses, in which no differences in the effectiveness of interventions are assumed, were excluded. In addition, only full texts, which were available for the authors, were considered. Pure abstracts based on a congress

Table 1 Resulted hits of studies exclusively comparing topical treatments

Authors	Year	Setting	Analysis	Model	Cost	Effectiveness	Result[a]
Marchetti et al. [44]	1998	USA	Pharmacoeconomic analysis of topical therapies	Decision tree	Direct	PASI, DFD	Tazarotene 0.1 % was more cost-effective than tazarotene 0.05 % (17 %), fluocinonide (85 %), and calcipotriene (144 %). The expected cost of achieving a DFD was USD49.46 for tazarotene 0.1 %, USD57.74 for tazarotene 0.05 %, USD91.73 for fluocinonide, and USD120.56 for calcipotriene
Ashcroft et al. [6]	2000	UK	Cost-effectiveness analysis of topical calcipotriol vs. short-contact dithranol	Decision tree	Direct	Difference in successful days (degree of improvement)	Selecting short-contact dithranol as first-line treatment was the most cost-effective strategy
Bergstrom et al. [10]	2003	USA	Clobetasol propionate foam 0.05 % vs. a combined program of clobetasol cream 0.05 % and solution 0.05 %	No specific model, study based	Direct	PASI	The cost per change of one unit in PASI score was USD21.60 for patients using foam and USD16.42 for those using cream/solution; the difference was not statistically significant
Peeters et al. [53]	2005	France, Germany, Spain, UK	Cost-effectiveness of once-daily treatment with calcipotriol/betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol	No specific model, study based	Direct	PASI	Over 8 weeks, Daivobet was almost twice as cost-effective as tacalcitol (241.22 € per successful treatment vs. 476.70 €)
Augustin et al. [7]	2007	Germany	Cost-effectiveness model of calcipotriol/betamethasone (Daivobet/Dovobet/Taclonex) once daily vs. a morning/evening non-fix combination of calcipotriol and betamethasone	Markov model, incl. decision tree	Direct	DCD	Treatment with Daivobet/Dovobet/Taclonex showed a higher cost-effectiveness compared to the non-fix combination
Bottomley et al. [11]	2007	UK	Cost-effectiveness of the two-compound formulation calcipotriol and betamethasone dipropionate (TCF) compared with commonly used topical treatments	Markov model	Direct	QALY (EQ-5D by PASI)	With reduced costs and superior outcomes, the TCF 'dominated' commonly used topical treatments since the latter were associated with higher cost and lower utility or QALY gain
Augustin et al. [8]	2009	Germany	Cost-effectiveness of calcipotriol vs. tacalcitol	Markov model, incl. decision tree	Direct	DCD	The treatment of mild to moderate psoriasis with a fixed calcipotriol/betamethasone combination is a more cost-effective treatment than a treatment with the single agents or tacalcitol monotherapy
Alora-Palli et al. [4]	2010	USA	Cost-effectiveness of liquor carbonis distillate (LCD) solution vs. calcipotriol cream	Model according to Hankin et al. (34)	Direct	PASI	The LCD solution was a more cost-effective treatment option than calcipotriol cream in this study, demonstrating a superior and longer-lasting therapeutic effect than prescription calcipotriol cream at a lower cost

Table 1 continued

Authors	Year	Setting	Analysis	Model	Cost	Effectiveness	Result[a]
Affleck et al. [1]	2011	UK	Cost-effectiveness of two-compound formulation (TCF) calcipotriol plus betamethasone dipropionate gel used first-, second- or third-line vs. standard topicals	Markov model	Direct	QALY (SF-36)	TCF gel used first-, second- or third-line was projected to increase QALYs (around 0.0025) with cost savings per patient (£20–30) over 1 year
Freeman et al. [26]	2011	UK	Economic analysis of the two-compound formulation (TCF) calcipotriol plus betamethasone dipropionate and other commonly used topical agents	Markov model	Direct	QALY (based on PASI response status)	Topical treatment with high-efficacy first-line therapies is a cost-effective treatment strategy in moderate plaque psoriasis
Colombo et al. [15]	2012	Italy	Cost-effectiveness analysis of a gel containing calcipotriol and betamethasone dipropionate (Dovobet gel) versus the ointment formulation (Dovobet ointment)	Markov model	Direct	PASI	The Dovobet gel strategy appears to be favorable from the pharmacoeconomic point of view than the ointment formulation
Devaux et al. [19]	2012	France	Topical vitamin D analogs alone (VD) vs. in association with topical steroids (VDS)	No specific model, systematic literature search for RCTs	Direct	PASI	The cost/efficacy ratio was evaluated as 1.2-1.8 times higher for VDS than for VD
Papp et al. [51]	2012	Canada	Cost-effectiveness of a maintenance therapy with clobetasol propionate shampoo (CPS) vs. its vehicle	Decision tree	Direct	DFD	The mean costs per DFD are 30–46 % lower with CPS compared with the vehicle
Sawyer et al. [61]	2013	UK	Cost-effectiveness of topical therapies	Markov model (meta-analysis)	Direct	QALY (EQ-5D, SF-36)	Potent corticosteroids, used alone or in combination with vitamin D for patients with trunk or limbs psoriasis, are likely to offer the best value for money, while potent or very potent corticosteroids are likely to be best for patients with scalp psoriasis

DCD disease controlled days, *DFD* disease free days, *EQ-5D* quality of life questionnaire of the EuroQol Group with five dimensions, *PASI* Psoriasis Area Severity Index, *QALY* quality-adjusted life year, *RCT* randomized controlled trial, *SF-36/SF 6D* short form of SF-36

[a] Base-case results of cost-effectiveness

presentation were excluded. Finally, the researchers were only interested in original research articles. Thus, review papers were only included if synthesized data were generated.

Study inclusion was determined at two levels. At the first level, articles resulted from the literature search were screened on the basis of their title and abstract. At the second level, when fulfilling the inclusion criteria, full texts were reviewed to identify the applied method of the health economic study, the treatment options being compared, the kind of costs and outcome parameters as well as the modeling technique. Further characteristics of studies, which have been summarized, were the year of publication and the study setting.

Results

The search with PubMed Medline, Ovid Medline, and Cochrane Library combining "psoriasis" with terms of health economic analyses like "cost effectiveness" and "health economic" resulted in 318 articles without duplicates. Thereof 60 health economic analyses in psoriasis management were identified (see Tables 1 and 2). In total, 258 articles were excluded for not being an health economic study comparing costs and effectiveness of different treatment interventions or disease state other than psoriasis (Fig. 1). The 60 health economic analyses were from countries in Europe (32 including 13 times UK setting), North America (24), Asia (5), and from

Table 2 Resulted hits of studies comparing systemic treatments, including comparisons with topical treatments

Authors	Year	Setting	Analysis	Model	Cost	Effectiveness	Result[a]
Stern [69]	1988	USA	Benefits, costs and risks of topical tar preparations vs. UV-B	No specific model, study based	Direct	Clearing	Using topical tar may increase costs of therapy 3-to 13-fold without substantial clinical benefits
Chen et al. [12]	1998	USA	Cost-effectiveness and cost benefit using methotrexate vs. Goeckerman therapy	Decision tree	Direct	WTP, VAS	Liquid methotrexate should be chosen over the tablet form since it was cheaper and had the same outcome. Goeckerman was cost-effective against liquid methotrexate in severe, but not mild or moderate psoriasis
Shani et al. [65]	1999	Israel	Cost-effectiveness of Dead-Sea climatotherapy versus other modalities	No specific model, literature review	Direct	Clearance, length of treatment, remission	Climatotherapy is well ahead of all other treatments, due to its short treatment period (4 weeks) and long interval until relapse (28 weeks)
Hakkaart-van Roijen et al. [29]	2001	Canada, Spain, Turkey, UK	Cost-effectiveness of tapered versus abrupt discontinuation of oral cyclosporin microemulsion	No specific model, study based	Direct and indirect	TFD	The overall ICER was dominant because tapered discontinuation was associated with both lower costs and improved efficacy in comparison with abrupt discontinuation
Ellis et al. [22]	2002	USA	Cost-effectiveness of a methotrexate-based regimen vs. a rotation regimen of modified cyclosporine and methotrexate	Markov model, incl. decision tree	Direct	Years clear of psoriasis	Over a 10-year treatment period, the methotrexate strategy cost USD33,000 and provided approximately 2 years clear of psoriasis compared with USD38,000 and approximately 4 years clear of psoriasis for the rotational strategy
Hartman et al. [32]	2002	The Netherlands	Cost-effectiveness analysis of dithranol vs. UVB phototherapy and inpatient dithranol treatment	No specific model, study based	Direct and indirect	PASI, number of clearance days	Considering the higher costs, short contact treatment is not a first choice treatment when compared with UVB
Feldman et al. [23]	2003	USA	Strategy to manage the treatment of severe psoriasis	"Cost model"	Direct and indirect	PASI	Methotrexate remained among the least costly (USD5400). UVB (USD5100) and PUVA (USD5700) had similar costs/treatment success. Acitretin monotherapy (USD17,300) was less costly compared to the biological therapies but more costly than methotrexate or the phototherapies
Hankin et al. [31]	2005	USA	Cost comparison of systemic treatments and UV treatment for moderate to severe psoriasis	"Cost model", literature review	Direct	PASI	Oral systemic medications, UV therapy, and UV therapy combined with acitretin appear to be the most cost-effective therapies for moderate to severe psoriasis
Marchetti et al. [43]	2005	USA	Expected clinical and economic outcomes for first-line and second-line care	Decision tree	Direct	TFD, RD	The addition of the 308-nm excimer laser to the rotational mix of treatments commonly utilized as second-line therapies is expected to add incremental clinical benefit for patients without incremental cost for payers

Table 2 continued

Authors	Year	Setting	Analysis	Model	Cost	Effectiveness	Result[a]
Nelson et al. [48]	2006	USA	Cost-effectiveness of biologic agents	No specific model, systematic review	Direct	PASI, DLQI	Adalimumab and infliximab appear to be the most cost-effective biologic agents when utilizing the cost per patient achieving PASI75. When utilizing the cost per patient achieving the DLQI MID, infliximab again appears to be the most cost-effective agent
Pearce et al. [52]	2006	USA	Cost-effectiveness and cost of treatment failures associated with systemic psoriasis therapies	"Treatment model" for each treatment, literature review	Direct	PASI	For continuous-dose agents, the cost-effectiveness results are: methotrexate USD623, acitretin USD2729, cyclosporine USD2969, nUVB USD3,692, PUVA USD4668, etanercept USD16,312, and efalizumab USD17,196
Woolacott et al. [74]	2006	UK	Cost-effectiveness of etanercept and efalizumab	"York model" developed, systematic review of published studies	Direct	QALY (EQ-5D by PASI and DLQI)	Clinical trial data indicate that both etanercept and efalizumab are efficacious in patients who are eligible for systemic therapy, but the economic evaluation demonstrates that these biological therapies are likely to be cost-effective only in patients with poor baseline QoL and who are at risk of hospitalization
Heinen-Kammerer et al. [33]	2007	Germany	Cost-effectiveness of psoriasis therapy with etanercept	Markov model based on "York model" [74]	Direct	QALY (EQ-5D)	For patients with an initial PASI >10 and a DLQI >10 the ICER for etanercept compared to non-systemic therapy was 45,491 €/QALY. For patients with PASI and DLQI >15 costs/QALY were 32,058 € and among patients with severe plaque psoriasis (DLQI and PASI >20) 18,154 €
Nelson et al. [49]	2008	USA	Cost-effectiveness of biologic agents vs. placebo	"Economic model" (meta-analysis)	Direct	DLQI, PASI	Etanercept (25 mg) administered subcutaneously (SQ) once weekly was the most cost-effective agent in cost per patient achieving DLQI minimally important difference. Intravenous infliximab (3 mg/kg) was the most cost-effective agent in terms of cost per patient achieving PASI-75 improvement
Colombo et al. [16]	2009	Italy	Cost-utility analysis of etanercept vs. nonsystemic therapy	Markov model based on "York model" [74]	Direct	QALY (TTO)	Intermittent etanercept is cost-effective compared with nonsystemic therapy. For patients with PASI20, cost-effectiveness of etanercept is even greater
Greiner et al. [28]	2009	Switzerland, Germany	Cost-effectiveness of infliximab, etanercept, adalimumab, efalizumab, and alefacept	Decision tree	Direct	PASI	Infliximab demonstrated lowest ICER per PASI90 responder of CHF 22,995 at 12 weeks. Modeling treatment changes at 12 weeks over 36-week-horizon resulted in lowest ICER per PASI 75responder for adalimumab and infliximab compared to the other biologics

Table 2 continued

Authors	Year	Setting	Analysis	Model	Cost	Effectiveness	Result[a]
Lloyd et al. [41]	2009	UK	Cost-effectiveness of etanercept 50 mg bi-weekly vs. etanercept 25 mg bi-weekly and comp. with no systemic therapy	"Economic model used a Markov process" based on "York model" [74]	Direct	QALY (EQ-5D by DLQI)	The incremental cost per QALY for etanercept 50 mg biw compared with no systemic therapy was found to be 6217 lb sterling
Sizto et al. [66]	2009	UK	Cost-effectiveness of systemic therapies vs. supportive care	Markov model based on "York model" [74]	Direct	QALY (EQ-5D by PASI)	Methotrexate and ciclosporin are cost effective but require monitoring for toxicities. Of the biologics, adalimumab was most cost effective following conventional systemic treatment failure or inadequate response
Hankin et al. [30]	2010	USA	Cost-effectiveness of systemic treatments for moderate to severe psoriasis	"Cost model", systematic review	Direct	PASI	Hankin et al. found a wide range of annualised costs to achieve a PASI75, from a low of USD2611 for methotrexate 7.5 mg weekly to a high of USD35,096 for alefacept 15 mg weekly
Koek et al. [39]	2010	The Netherlands	Cost-effectiveness of ultraviolet B light at home vs. for outpatients	No specific model, primary study	Direct and indirect	DFD, QALY (EQ-5D, SF-6D)	Home ultraviolet B phototherapy for psoriasis is not more expensive than phototherapy in an outpatient setting and proved to be cost effective
de Portu et al. [18]	2010	Italy	Cost-effectiveness of infliximab vs. other anti-tumor necrosis factor-alpha agents	No specific model, literature search	Direct and indirect	PASI, DLQI	Infliximab seems to be cost-effective in the therapy of psoriasis
Schmitt-Rau et al. [63]	2010	Germany	Cost-effectiveness of biological therapy	No specific model, literature search	Direct	PASI	Infliximab at a dose of 3 mg/kg was the most cost-effective agent, directly followed by adalimumab, infliximab 5 mg/kg and ustekinumab
Anis et al. [5]	2011	USA	Determination of most cost-utiliy biological therapy	Markov model based on "York model" [74]	Direct	QALY (EQ-5D)	While infliximab was found to provide the most incremental QALY and etanercept was found to be the least costly, on balance, the incremental cost-effectiveness ratio of adalimumab was the most favorable (ICER = USD544/QALY)
Chern et al. [13]	2011	Taiwan	Cost-effectiveness of modified Goeckerman regimen vs. conventional therapy	No specific model, primary study	Direct	PASI	In comparison with conventional therapy, the modified Goeckerman regime showed similar clinical efficacy, with additional benefits in improving overall quality of life and psychosocial distress, and more cost-effectiveness
Martin et al. [44]	2011	USA	Cost per responder analysis of ustekinumab and etanercept	No specific model, study based	Direct	PASI	The cost per responder was lower for ustekinumab (USD17,842) than for etanercept (USD20,077) through 16 weeks
Pan et al. [50]	2011	Canada, USA	Cost-utility analysis of ustekinumab vs. etanercept	Markov model	Direct	QALY (EQ-5D by DLQI and PASI)	The incremental difference in costs and utilities remained in favor of ustekinumab across a range of sensitivity analyses

Table 2 continued

Authors	Year	Setting	Analysis	Model	Cost	Effectiveness	Result[a]
Staidle et al. [68]	2011	USA	Cost-efficacy of systemic agents, phototherapies and all available biologics	No specific model, literature search	Direct	PASI, DLQI	The lowest cost per achieving DLQI minimally important difference was from phototherapy; the highest was from alefacept. The lowest costs per patient achieving PASI-75 was from methotrexate and the highest was from alefacept
Ferrándiz et al. [25]	2012	Spain	Cost-efficacy of adalimumab, etanercept, infliximab and ustekinumab	Decision tree model (meta-analysis)	Direct	PASI	In terms of cost-efficacy, the most efficient biological drug was adalimumab
Knight et al. [38]	2012	Sweden, UK	Cost-effectiveness of etanercept vs. adalimumab and non-systemic standard of care	Markov model, incl. decision tree	Direct and indirect	QALY (EQ-5D by DLQI and PASI)	The incremental costs per QALY were 1,559,939 kr (165,354 €) for adalimumab 40 mg every other week, compared with intermittent once-weekly etanercept 50 mg, and 93,629 kr (9925 €) for once-weekly intermittent etanercept 50 mg compared with non-systemic standard of care
Liu et al. [40]	2012	USA	Cost-effectiveness of biologic therapies for Crohn's disease, psoriasis, and rheumatoid arthritis	No specific model, meta-analysis	Direct	PASI	Among biologics approved in psoriasis, 3-month cost per responder was lowest for adalimumab (USD9756), infliximab (USD12,828), and ustekinumab 45 mg (USD13,821)
Vanó-Galván et al. [71]	2012	Spain	Cost-effectiveness of home-based phototherapy with narrow-band UV-B radiation compared with biological drugs	Decision tree	Direct	PASI	The direct costs required to achieve PASI75 were 8256 € per patient for biologics and 903 € per patient for home-based phototherapy
Aggarwal et al. [2]	2013	India	Cost-effectiveness of psoralen and ultraviolet A versus psoralen and sunlight	No specific model, primary study	Direct and indirect	PASI	Cost-effectiveness ratio was USD0.72 with PUVA and USD0.37 with PUVAsol. Both PUVA and PUVAsol were equally efficacious, with PUVAsol being twice as cost effective
Ahn et al. [3]	2013	USA	Cost-effectiveness of biologic therapies	"Treatment models", literature search	Direct	DLQI, PASI	Intravenous (IV) infliximab 3 mg/kg was the most cost-effective biologic agent with respect to both the cost per patient achieving PASI-75 and the cost per patient achieving a DLQI MID
Igarashi et al. [35]	2013	Japan	Cost-efficacy comparison of biological therapies	"York model" [74], meta-analysis	Direct	PASI	Ustekinumab was a more cost-efficient biological therapy than adalimumab or infliximab
Ruano et al. [60]	2013	Spain	Long-term cost-effectiveness analysis of etanercept and adalimumab	No specific model, retrospective observational study	Direct and indirect	PASI	Data suggest that etanercept is as cost-effective as adalimumab during the first year of treatment
Villacorta et al. [72]	2013	USA	Cost-effectiveness of etanercept and ustekinumab	Markov model	Direct and indirect	QALY (EQ-5D by DLQI)	Ustekinumab 45 mg dominates etanercept 50 mg therapy for an equivalent patient psoriasis severity and time horizon

Table 2 continued

Authors	Year	Setting	Analysis	Model	Cost	Effectiveness	Result[a]
Chi et al. [14]	2014	USA	Efficacy and cost-efficacy of biologic therapies	Decision tree (meta-analysis)	Direct	PGA, PASI	Based on the ICER as to PASI 75 response, adalimumab had the best cost-efficacy (USD21,315), followed by ustekinumab 45 mg (USD25,055) and infliximab (USD27,782)
Puig et al. [55]	2014	Spain	Cost-effectiveness ratio analysis of biologic treatments	No specific model (meta-analysis)	Direct	PASI	The results for a PASI75 response at week 24 show that the treatment with the lowest ICER is ustekinumab 45 mg (10,371 €), followed by adalimumab (10,549 €), infliximab (14,514 €), etanercept (16,080 €), and ustekinumab 90 mg (20,880 €)
Riveros et al. [59]	2014	Brazil	Cost-effectiveness of Biologic Agents	Markov model, study based	Direct	PASI	Adalimumab was the most cost-effective biologic therapy (RUSD120,981.45/PASI75) for moderate-to-severe psoriasis, followed by ustekinumab (RUSD126,336.67), etanercept (RUSD225,074.71), and infliximab (RUSD377,656.28)
Spandonaro et al. [67]	2014	Italy	Cost-effectiveness of biologic therapy	No specific model, observational study	Direct	PASI, VAS itching and pain, QALY (EQ-5D)	The ICER of the switch to biologic therapies of patients with plaque psoriasis in real practice settings was €28,656 per QALY gained (etanercept €25,840, adalimumab €29,285, infliximab €53,525)
Terranova et al. [70]	2014	Italy	Costs of therapy with biologics	No specific model, analysis of individual studies	Direct	PASI	The analysis of the 52-week PASI75 responder shows that ustekinumab has the lowest cost per responder (21,401 € 45 mg; 20,780 € 90 mg), followed by adalimumab 40 mg (23,516 €), infliximab 100 mg (23,659 €), etanercept 50 mg without induction (27,938 €) and etanercept 50 mg (28,602 €)
Wang et al. [73]	2014	Taiwan	Cost-efficacy of biologic therapies	No specific model, meta-analysis of RCTs	Direct	PASI	One-year ICERs per PASI 75 responder were USD39,709, USD23,711, and USD26,329 for etanercept, adalimumab, and ustekinumab, respectively. Two year ICERs were USD71,973, USD62,665, and USD52,657 for etanercept, adalimumab, and ustekinumab, respectively
D'Souza et al. [21]	2015	USA	Cost efficacy of systemic treatments	No specific model, literature review	Direct	PASI	Methotrexate (USD794.05-1502.51) and cyclosporine (USD1410.14–1843.55) had the lowest monthly costs per number needed to treat to achieve PASI75
Polistena et al. [54]	2015	Italy	Impact of biologic agents on direct and indirect non-medical cost, including cost-effectiveness of biologic therapy	No specific model, study based	Direct and indirect	PASI, VAS itching and pain, QALY (EQ-5D)	The ICER of biologic therapies (etanercept, adalimumab, and infliximab) for treating plaque psoriasis amounted to 18,634.40 € per QALY gained

Table 2 continued

Authors	Year	Setting	Analysis	Model	Cost	Effectiveness	Result[a]
Sawyer et al. [62]	2015	UK	Potential cost effectiveness of sequential biologic therapies in patients with psoriasis who have been exposed to previous biologic therapy	Decision tree with Markov model (meta-analysis)	Direct	QALY by PASI and DLQI	Base case results suggest the ICER of the second biologic compared to best supportive care (e.g. methotrexate, cyclosporine) is £ 17,681 per QALY
Puig et al. [56]	2016	Spain	Model for assessing the efficiency of biologic drugs	Decision tree	Direct	PASI	The mean cost per patient treated successfully at the end of 1 year is lowest in patients who start treatment with ustekinumab (15,209 €), followed by infliximab (16,136 €), adalimumab (16,820 €), and etanercept (20,178 €)

DFD disease-free days, *DLQI* Dermatology Life Quality Index, *DLQI MID* DLQI minimal important difference, *EQ-5D* quality of life questionnaire of the EuroQol Group with 5 dimensions, *ICER* incremental cost-effectiveness ratio, *PASI* Psoriasis Area Severity Index, *PGA* physician global assessment, *QALY* quality-adjusted life year, *QoL* quality of life, *RCT* randomized controlled trial, *RD* remission day, *SF-36/SF 6D* short form of SF-36, *TFD* treatment-free days, *TTO* time-trade off, *VAS* visual analog scale, *WTP* willingness to pay

[a] Base-case results of cost-effectiveness

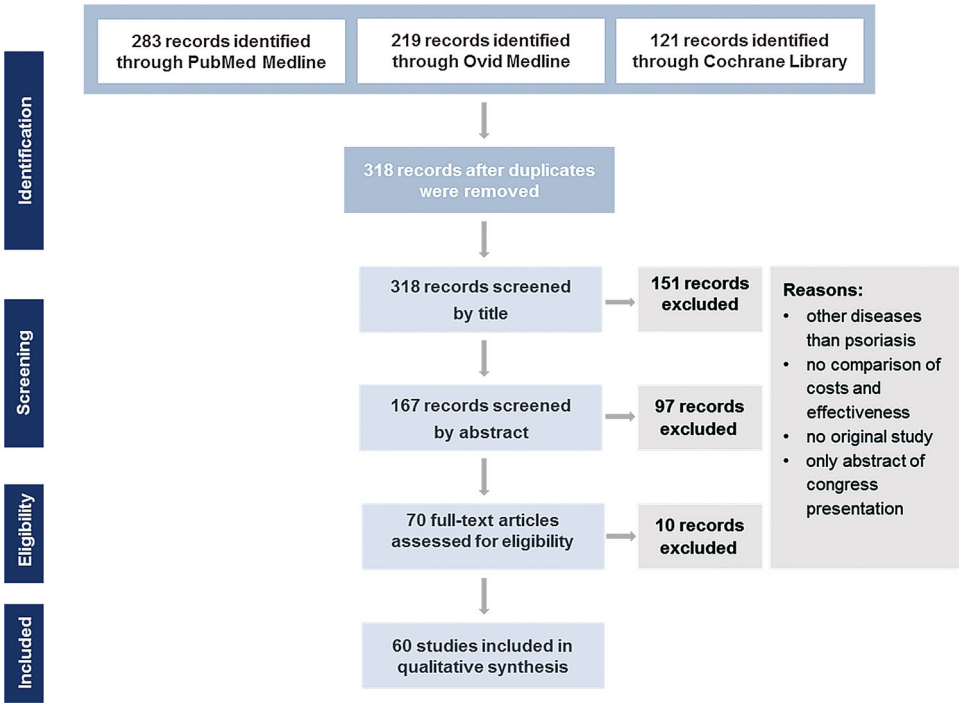

Fig. 1 Search flow showing literature search results

Brazil (1). A few studies were conducted in a multiple setting.

In addition to the extraction of publication year and country, included articles were compared with each other concerning their treatment comparisons, modeling method, and used costs and effectiveness parameters.

The analyses varied in type of treatment, see Figs. 2 and 3. The most considered systemic treatments were the biological agents etanercept (36), adalimumab (27), and infliximab (26) followed by ustekinumab (17) and phototherapy (incl. UV-B, PUVA/psoralen combined with UV-A) (14). Comparisons including topical treatments mostly focused on vitamin D treatment (14), corticosteroids (13), and coal tar products (6) followed by dithranol (5) and tazarotene (4). Some comparisons of systematic treatments with "basal" or "non-systemic" treatments contained no specific information about the topical treatment.

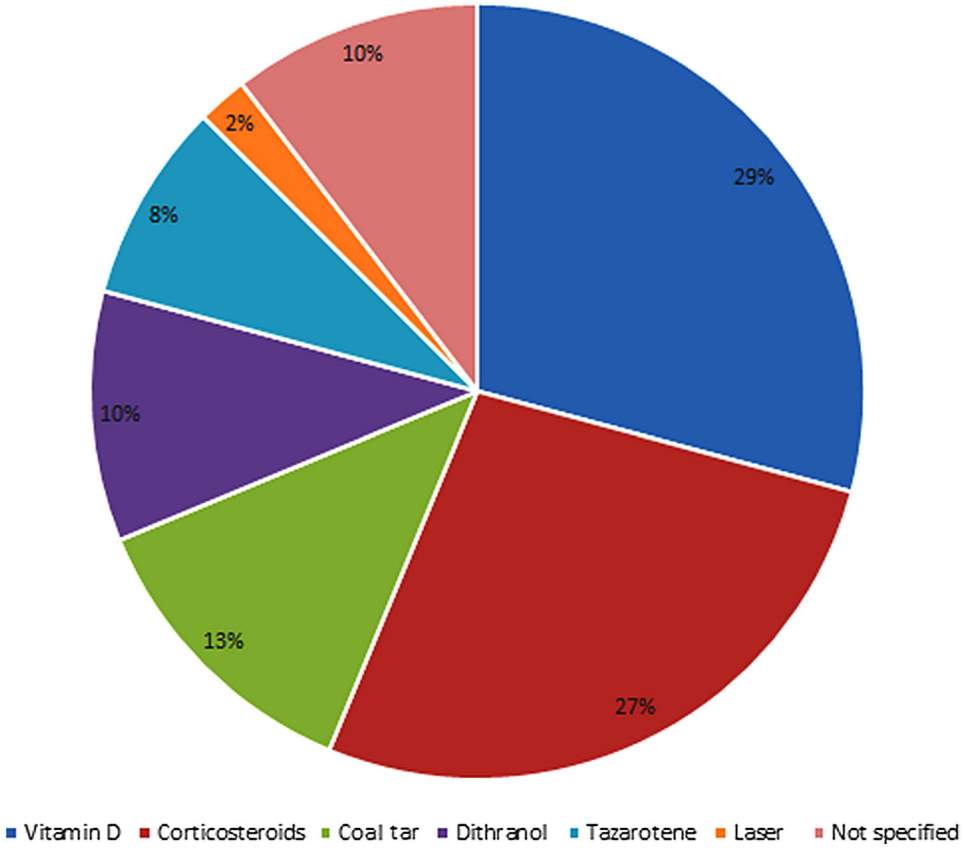

Fig. 2 Distribution of compared topical treatments considered in included articles

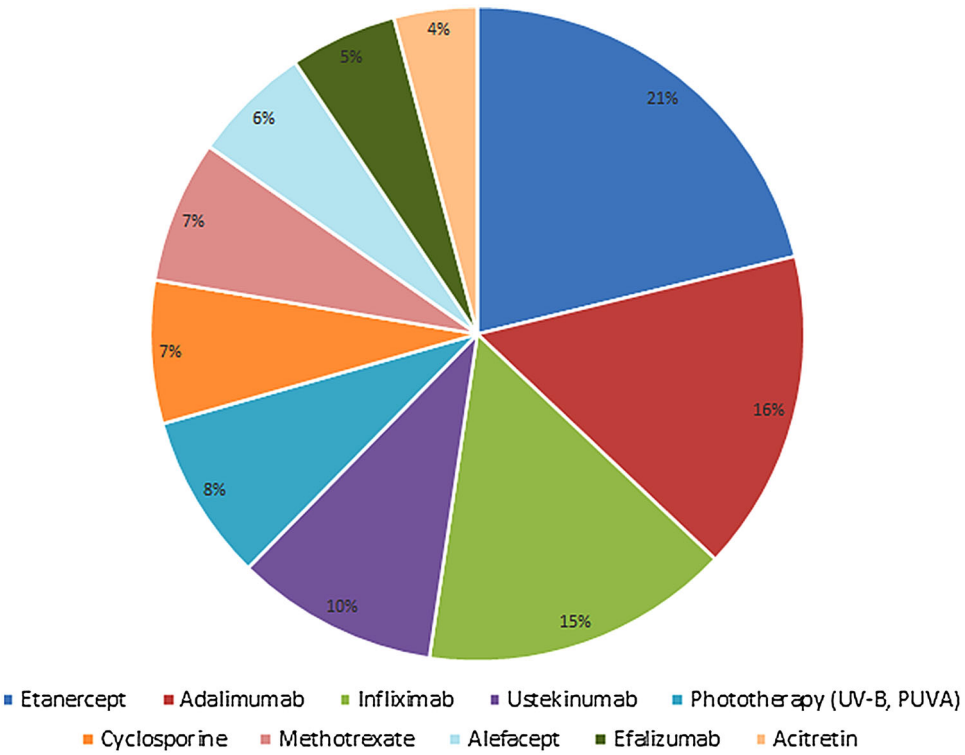

Fig. 3 Distribution of compared systemic treatments considered in included articles

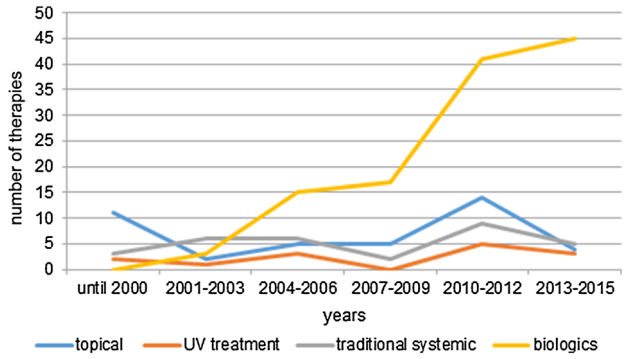

Fig. 4 Overview of the number of topical, UV, and traditional systemic treatments as well as biologics analyzed in cost-effectiveness studies over the years

In addition, the timeline (Fig. 4) shows an overview of the number of topical, UV, and traditional systemic treatments as well as biologics analyzed in cost-effectiveness studies over the years. While the number of UV treatments, topical treatments, and traditional systemic treatments over the years ranges from 0 to 14, the number of biologics considered in health economic studies increases from 3 (2003) to 45 (2015).

A further comparison of included studies shows the distribution of comprised costs and effectiveness parameters in the respective cost-effectiveness and cost-utility analyses (Table 3). If there is a health economic study available, which includes a cost-effectiveness analysis as well as a cost-utility analysis, effectiveness parameters like PASI and DLQI (Dermatology Life Quality Index) were counted in the first row (cost-effectiveness), whereas utility parameters to measure QALYs are shown in the second row (cost-utility). Additionally in this case, modeling type and kind of costs were in a double reporting.

According to Table 3, most health economic analyses in psoriasis management are cost-effectiveness evaluations (45). The clinical parameter PASI is the most often used outcome to compare the costs with the effectiveness of a treatment (33 times in cost-effectiveness analyses). In most articles, the primary outcome was the proportion of patients achieving a 75 % reduction in the PASI score (so-called "PASI 75"). To include the patient-reported health-related quality of life, 5 cost-effectiveness studies used the DLQI. Further effectiveness parameters were disease-free days (DFD) (4), also reported as disease controlled days (DCD), and in 2 cost-effectiveness studies treatment free days (TFD). In the presence of cost-utility studies, the effectiveness is compared with costs in terms of QALYs. The latter were mostly measured by EuroQol five dimensions questionnaire (12), which was partly generated with the help of PASI or DLQI values. For example, a familiar research article to get QALYs with the help of DLQI is the publication of Currie and Conway [17].

Concerning the cost parameters, indirect costs are considered in 9 articles of 60 included hits. The majority of identified health economic studies is focusing on the direct medical and non-medical costs without consideration of productivity losses. As a result, data concerning productivity losses are rarely available in health economic analyses of psoriasis management.

Regarding the modeling type, Markov model is the most often applied kind of model. Discrete-event simulation is not yet applied in psoriasis management.

Discussion

Since it is already known that health economic studies are no new field in psoriasis management [9], the objective of the presented systematic review was to identify health economic analyses concerning psoriasis interventions that have been published to date. Until 20 January 2016, 60 health economic studies comparing costs and benefits were found with the help of the presented systematic literature research. Most of them were examined in Europe, particularly 13 in the UK. There,

Table 3 Distribution of used costs, effectiveness parameters, and model types in all resulted articles ($n = 60$ publications)

	Costs		Effectiveness									Model		
	Direct only	Direct and indirect	PASI	DLQI	DFD/DCD	VAS	TFD	Other	EQ-5D	SF-36/6D	TTO	Decision tree	Markov model[b]	Other models or no model
Cost-effectiveness	39	6	33	5	4	2	2	7	0	0	0	10	5	31
Cost-utility	15	4	8	6	0	0	0	0	12	3	1	1	14	4
Total[a]	53	10	41	11	4	2	2	7	12	3	1	11	19	35

For abbreviations see Tables 1 and 2

[a] Multiple results were possible in case of a study including a cost-effectiveness analysis as well as a cost-utility analysis

[b] Markov models including decision tree were counted only in the column "Markov model"

the National Institute for Health and Care Excellence (NICE) examines independently verified evidence on how well a drug works and whether it provides good value for money. This means whether it is cost-effective. With the use of QALYs as a standard and internationally recognized method to compare different treatments and measure their clinical effectiveness, NICE wants to ensure a fair evaluation of the effectiveness [14]. Therefore, it is not surprising that included evaluations from UK in the present systematic review are in most cases cost-effectiveness analyses using QALYs, known as cost-utility analyses.

It can be noted that since the approvals of the first biological agents by the Federal Drug Association (FDA) in 2003, biologics were directly considered in resulted articles (3). This number increased from 3 in 2003 to 45 in 2015. Biologics are known as considerably more expensive than traditional treatments [24, 55]. Due to their high benefit values for a specific group of psoriasis patients, they are now a permanent standard of treatment [45]. In some years, an update of this review will also yield in cost-effectiveness analyses considering additionally biosimilars. Biosimilars are biotechnologically processed drugs whose amino acid sequence is identical to the original biopharmaceutical [57].

This review of current health economic studies is limited by articles in English and German language with specific keywords. Thus, the search may have missed some relevant articles, published in languages other than English or German and not including selected keywords. Moreover, only full and available publications were considered. Abstracts based on a congress presentation or the like were excluded, given the fact that too little information is presented for this systematic review. Despite these limitations, this article gives an informative overview of health economic analyses, which have been conducted for the comparison of psoriasis treatments.

With regard to all 60 articles and the comparison in Table 3, it was noted that there are no standards on methods and outcome measures available. Even if the review shows that PASI was the most often used measurement in cost-effectiveness analyses of psoriasis interventions, no standardized measurement is used to compare patient-reported quality of life. Therefore, QALYs by EQ-5D or SF-36 (Short Form (36) Health Survey) and the DLQI were used mostly. The literature research yielded also health economic studies, in which no quality of life measurement was used (see Tables 1, 2). According to the increasing importance of the patient perspective, such health economic studies are less comparable with evaluations including patient-reported outcomes.

Concerning the use of costs it was noted that indirect costs are rarely considered in health economic studies of psoriasis treatment. The literature search showed that in only 9 of 60 articles indirect costs were included. However, cost-of-illness studies point out that psoriasis has a high impact on occupational disability [27, 63].

In view of available guidelines [20, 25, 36, 64], a variety of needed content to create a valid health economic evaluation exists. These mostly include details about the study design with objective, methodology, interventions, and target population, the perspective, the validity of data sources, the cost determination as well as the collection of outcome parameters, time horizon, discounting rates, modeling type, sensitivity analyses, and the discussion of outcomes including the presentation of limitations. While focusing on these items, it is possible to assess the quality of an economic analysis. While picking out some articles of the 60 included hits the researchers noted gaps on inter alia data conception, sensitivity analysis, critical discussion of limitations, and inclusion of patient-reported outcomes. Although several articles on topical and systemic agents are published, only a small number of well-conducted health economic studies exists.

In conclusion, the lack of standard on methods and outcome measures leads to a very limited comparability of health economic studies and presents no comfortable basis to examine a meta-analysis of health economic results. Given the setting, compared treatments, and study conditions, different results can be found for medical decision-making. In this context, it should be noted additionally that very heterogeneous requirements by authorities are given. Whereas the NICE requires health outcomes to be expressed in terms of QALYs, the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany refers to the ethical and methodological problems being accompanied by the use of QALYs [36, 49]. The presented systematic review shows the need for nationwide data and interpretation.

Compliance with ethical standards

Funding None.

Conflict of interest Augustin M has served as consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including Abbott, Almirall, Amgen, Biogen, Celgene, Centocor, Janssen-Cilag, Leo, Medac, MSD (formerly Essex, Schering-Plough), Novartis, Pfizer (formerly Wyeth). Gutknecht M and Krensel M don't have any conflicts of interest to declare.

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