Expert Opinion

A pharmacoeconomic analysis of severe psoriasis therapy: a review of treatment choices and cost efficiency

Jonathan P Staidle, Tushar S Dabade & Steven R Feldman†
Wake Forest University School of Medicine, Medical Center Boulevard, Department of Dermatology, Winston-Salem, NC, USA

Introduction: Psoriasis is a chronic, inflammatory disease afflicting 2% of the US population; it results in significant morbidity. The annual healthcare costs related to psoriasis are an estimated $11.3 billion and, with an expanding biologic market, an updated costs analysis is needed.

Areas covered: Current treatments, including systemic agents (acitretin, cyclosporine, methotrexate), phototherapies and all available biologics (adalimumab, etanercept, infliximab, alefacept, ustekinumab) appropriate for severe psoriasis are described mechanistically and with regard to their efficacy, quality-of-life improvements and side effects. A cost-efficacy model considering US health-system-based annual costs, clinical and quality-of-life improvements was created. Reported Psoriasis Area and Severity Index improvement of 75% from baseline (PASI-75) scores, Dermatology Life Quality Index (DLQI) improvements and estimated costs of medications are described. Annual costs ranged from $1330 for methotrexate to $48,731 for high-dose etanercept. 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.

Expert opinion: Phototherapies and methotrexate offer high efficacy for their costs. Therapeutic approaches must be individualized for each patient given all considerations described.

Keywords: acitretin, adalimumab, alefacept, biologics, cyclosporine, etanercept, infliximab, methotrexate, phototherapy, ustekinumab

Expert Opin. Pharmacother. (2011) 12(13):2041-2054

1. Introduction

Psoriasis is a chronic, immune-mediated, inflammatory disease afflicting approximately 2% of the US population; it is the most prevalent autoimmune disease in the US [1]. Many patients suffering from psoriasis experience a significant impact on both their health-related quality of life (HRQOL) and overall psychological and emotional quality of life (QOL) [2-4]. Patients have a decrease in their physical and mental functioning comparable to that of patients with cancer, hypertension, diabetes and depression [5].

The annual healthcare costs related to psoriasis are now estimated at approximately $11.3 billion and the current costs associated with systemic psoriasis therapy are increasing at a rate greater than that of general inflation [6,7]. Since the approval of biologics as a systemic treatment option for moderate-to-severe psoriasis and psoriatic arthritis, they have moved into the limelight as attractive, cost-effective treatment choices [8-10]. However, the price of biologics is higher than more

informa
healthcare

10.1517/14656566.2011.590475 ISSN 1465-6566

Article highlights.

- Therapeutic choices: All current therapies for moderate-to-severe psoriasis are reviewed, with descriptions of their mechanisms of action, clinical trial efficacy and side-effect profiles.
- Cost analysis: An annual cost model and cost-efficacy analysis was performed for all treatments using pooled Psoriasis Area and Severity Index improvement of 75% from baseline (PASI-75) and Dermatology Life Quality Index data.

This box summarizes key points contained in the article.

traditional systemics (e.g., cyclosporine, methotrexate [MTX] or phototherapy), making treatment costs a crucial factor in selecting an appropriate therapy [11].

Cost-effectiveness studies of systemic treatments for moderate-to-severe psoriasis have recently been published [12-14]. These illustrate the rising costs of treating psoriasis but are limited in applicability because newer biologics have already entered the marketplace. Different methods of both subjective and objective evaluation have been used in clinical studies and few head-to-head clinical studies have been performed. The majority of past review articles covered treatment efficacy only with regard to quantitative results such as Psoriasis Area and Severity Index (PASI) clearance and without consideration of QOL measurements [11,15-16].

This study provides an economic review of the literature comparing cost-effectiveness of the current Food and Drug Administration (FDA) approved therapies for moderate-to-severe psoriasis. A cost model is constructed based on the US healthcare system costs, treatment efficacies and QOL data reported in previous studies. Finally, the authors offer an expert opinion proposing a strategy to treat psoriasis while cognizant of the therapeutic and financial consequences.

2. Therapeutic choices

2.1 Introduction

A major factor in treating patients with psoriasis is categorizing them as having either mild-to-moderate (localized) or moderate-to-severe (diffuse or generalized) disease. The National Psoriasis Foundation (NPF) differentiates between moderate and severe disease as affecting between 3 – 10% and > 10% of the body surface, respectively. Nearly 25% of all psoriasis patients have moderate-to-severe disease [1]. This level of severity is also further defined by physical disability or by a severe impact on QOL [17]. The mainstay of treatment for moderate-to-severe psoriasis is systemic therapy. This includes older systemic choices, such as MTX and cyclosporine, phototherapy (ultraviolet B light [UVB]. and ultraviolet A light with psoralen [PUVA]), oral retinoids (such as acitretin) and the newer biologic products including tumor necrosis factor alpha (TNF-α) inhibitors (adalimumab, etanercept, infliximab), interleukin (IL)-12/23 inhibitors (ustekinumab) and the T-cell modulator alefacept. In 2009, the FDA removed efalizumab from the US market and it is not included in our review [18].

2.2 Cyclosporine

Cyclosporine is an oral systemic therapy approved for use in treating severe psoriasis. It is an immune-modulating drug, acting to decrease the activity of T-cell function via inhibition of calcineurin, a molecule that induces transcription factors associated with the production of inflammatory cytokines. Cyclosporine is given at doses of 3 – 5 mg/kg/day by mouth (p.o.) and was reported to achieve a Psoriasis Area and Severity Index improvement of 75% from baseline (PASI-75) in 70% of patients approximately 12 weeks after induction of therapy [19,20]. Long-term use of cyclosporine is associated with nephrotoxicity, so it is best used in patients who are experiencing acute flare-ups of their disease and need a short course of therapy to suppress the disease [14,21-22]. When remission or control of the exacerbation is achieved, cyclosporine therapy is stopped and patients are usually switched to another form of systemic therapy, such as acitretin, for maintenance [23].

2.3 Methotrexate

MTX was the first systemic agent used in the treatment of psoriasis and it is still used today as an effective method for inducing remission and for long-term maintenance therapy for moderate-to-severe psoriasis. MTX is an immunosuppressant that acts by competitively inhibiting dihydrofolate reductase, the enzyme that participates in the synthesis of folate, which is needed in DNA, RNA and protein synthesis. It is commonly administered in doses of 7.5 or 15 mg/week p.o [14]. Among patients using MTX as monotherapy with dose increases as tolerated, 36 – 60% achieve a PASI-75 at 16 weeks [20,24]. MTX is limited by its significant side-effect profile, including hepatic and hematological toxicities. It should also be avoided in women of childbearing age considering pregnancy because it is an abortifacient and causes severe teratogenicity, including mental retardation and craniofacial defects. Consequently, strict laboratory monitoring of both hepatic and hematological parameters is essential, including a liver biopsy after a total cumulative dosage of 1.5 g is received [25].

2.4 Retinoids

2.4.1 Acitretin

Oral retinoids such as acitretin are often used as monotherapy for patients with palmar/plantar, pustular or erythrodermic psoriasis. Acitretin acts by binding to nuclear transcription factors, which induces keratinocyte differentiation and reduces epidermal hyperplasia. Acitretin is normally administered as a daily dose of 25 mg, with approximately 30% of patients achieving PASI-75 [14]. Although it can be used as monotherapy to treat chronic plaque psoriasis at higher doses, acitretin is more efficient when administered at lower doses in

conjunction with UVB or PUVA. Also, the higher doses of acitretin required for monotherapy against plaque psoriasis are limited by the side effects that arise at higher doses, including itchy dry skin, dry mucus membranes and joint pains. Another concern involving oral retinoids is that they are highly teratogenic and should be avoided in women of childbearing age. If acitretin must be used, reports suggest that pregnancy be avoided for at least 2 years following cessation of treatment [12].

2.5 Phototherapy

2.5.1 Ultraviolet type B

Ultraviolet Type B (UVB) light is the oldest treatment for moderate-to-severe psoriasis. It has also been the safest way to maintain control of the disease with regard to long-term therapeutic protocols. Phototherapy can be either broadband (BB; 280 – 315 nm) or narrowband (NB; 311 nm) and it works to improve psoriatic symptoms through immunomodulatory mechanisms in the skin [26]. This includes immediate cytopathic effects and delayed immunosuppressive effects [27]. NB-UVB appears to be more effective than BB-UVB despite a broader safety profile in BB-UVB, especially when dealing with severe disease [28]. The reported efficacy of UVB therapy varies from 41% of patients and up to 80% of patients achieving PASI-75 [19,29-31]. In cases where UVB phototherapy is unsuccessful in controlling a patient's psoriasis, it may be combined with other systemic therapies such as the oral retinoid acitretin to increase efficacy [32]. This is a safe, effective option except in women of childbearing age [33].

UVB therapy can be combined with topical tar or anthralin for patients who have severe psoriatic plaques too thick to be penetrated by UVB light alone [19]. Using UVB as monotherapy or in combination with other topical or systemic agents is safe and effective, but they can be inconvenient and expensive for both patients and physicians. The standard treatment protocol requires patients to receive three or more sessions per week for 6 – 12 weeks [34]. Unfortunately, disincentives for phototherapy on both the patient and physician side have caused this method to decline in frequency in the US [35]. However, much of this temporal and financial inconvenience can be alleviated by using home NB-UVB therapy [36]. Any risk associated with the use of phototherapy includes acute skin reactions similar to that of a sun-burn and a small possibility of an increased risk of skin cancer over long-term, although this risk has not been shown to be any more than that associated with normal sun exposure [12].

2.5.2 Ultraviolet type A with psoralen

Ultraviolet type A with psoralen (PUVA) therapy has the ability to clear psoriatic plaques with more success than NB-UVB and also requires fewer treatment sessions with a higher potential to induce long-term remission in patients, even without maintenance therapy [23,37]. When psoralen is exposed to UVA it enters an excited state and cross-links with DNA, inhibiting DNA replication. It also has anti-inflammatory and immunosuppressive actions. Approximately 80 – 86% of patients receiving PUVA therapy achieve PASI-75 [19,38]. Unlike UVB, however, patients receiving PUVA therapy are at a significantly increased risk of having both melanoma and non-melanoma skin cancer [39-42]. The acute phototoxicity patients may experience is also more severe with PUVA than with UVB [12].

2.6 Tumor necrosis factor alpha antagonists

2.6.1 Introduction

The advent of biologics has expanded the treatment armamentarium for psoriasis, but some of these treatments lack long-term data available on efficacy. This information will soon be revealed through daily practice registries or clinical trials [43]. The TNF-α inhibitors account for the majority of FDA-approved biologic products available for treating chronic severe plaque psoriasis but, although they have favorable safety profiles, they are not devoid of risk. Black-box warnings have been issued for all approved TNF-α inhibitors for their associated risk of serious infections, malignancy and – in the case of infliximab specifically – T-cell lymphoma. The majority of the safety data for TNF inhibitors, however, comes from the rheumatoid arthritis, spondyloarthritis or inflammatory bowel disease literature, which may not generalize to psoriasis patients. Apart from a different disease process, patients in these studies often required concomitant immunosuppressive therapies, which may synergistically increase infectious or malignancy risks [44]. A recent meta-analysis specifically of plaque psoriasis and psoriatic arthritis trials found no increased risk of serious infections or cancer with short-term use of TNF antagonists and the observed small increased risk for overall infections may be due to differences between treatment versus placebo follow-up times [44]. Additionally for this class of drug, purified protein derivative (PPD) skin tests are recommended for each of these agents at the start of therapy [45-47].

2.6.2 Etanercept

Etanercept is a soluble dimeric fusion protein consisting of two TNF receptors fused to the Fc portion of human immunoglobulin G (IgG) that prevents excess TNF from binding and interacting with their cell-bound receptors, thereby acting to competitively inhibit TNF-mediated activity [45]. Etanercept is FDA-approved for the treatment of multiple immune-mediated diseases including rheumatoid arthritis (RA), psoriatic arthritis and moderate-to-severe plaque psoriasis. This TNF-α inhibitor shows variable efficacy ratings with PASI-75 success rates ranging from 33% for a 50 mg/week regimen to approximately 49 – 57% for the 50 mg twice/week treatment regimen [43,48-50]. The FDA-approved dosing schedule of etanercept for psoriasis is a 50 mg subcutaneous (SC) self-administered injection twice/week for an initial induction period of 3 months, followed by a 50% reduction to 25 mg administered twice weekly (or 50 mg/week) for maintenance therapy.

The most significant adverse effect noted with etanercept therapy has been a temporary injection site reaction [52]. Some reports show exacerbation of congestive heart failure and bone marrow suppression during therapy, but the actual causal relationship with this agent has been inconclusive due to the rarity of these events [52,53]. Patients are also at greater risk for developing antinuclear antibodies (ANA), but again it is only in rare cases that patients develop clinical manifestations [53]. There have also been extremely rare reports of CNS demyelinating diseases associated with etanercept and with regard to malignancy, a small number of cases of lymphoma were reported to have occurred following induction of this therapy between 1999 and 2000 [54-56]. However, despite the reported cases of lymphoma, any increased risk for malignancy in patients may be more closely tied to their diagnosis of psoriasis than to etanercept [57].

2.6.3 *Infliximab*

Infliximab is a chimeric monoclonal antibody approved for the treatment of chronic severe psoriasis in September of 2006. This agent binds specifically to soluble and membrane-bound TNF-α and is administered by intravenous (IV) infusion [46]. The standard approved dosing for plaque psoriasis involves induction with 5 mg/kg IV (400 mg daily maximum) over 2 h at weeks 0, 2 and 6, then subsequent infusions every 8 weeks thereafter [46]. Infliximab has shown one of the highest efficacy rates among the TNF-α inhibitors, with studies showing a combined weighted average of nearly 80% of patients achieving PASI-75 [8,13,58-59].

Among the most common adverse events occurring in patients receiving infliximab therapy are infusion reactions, headache, itching and myalgias. However, these events occur at no greater rate than those receiving placebo, with the exception of a reported incidence of infusion reactions occurring in 20% of patients treated with infliximab compared to 2% of those treated with placebo (this included chills, headache, flushing, nausea, dyspnea, injection-site infiltrations and taste perversion) [58]. As is the case with the other TNF-α inhibitors, rare incidents of latent TB reactivation have occurred with infliximab [60,61].

2.6.4 *Adalimumab*

Adalimumab is a fully human monoclonal antibody, another form of a TNF-α inhibitor approved for psoriasis, which also specifically binds to TNF-α, blocking its interaction with TNF cell-surface receptors [47]. In January of 2008, adalimumab was approved for use in moderate-to-severe psoriasis. The approved dosing regimen for this agent includes an 80 mg SC loading dose followed by 40 mg every other week with a reported PASI-75 achieved in 53 – 80% of patients receiving treatment [62-66].

Although the safety of adalimumab has been studied mostly in short-term clinical trials of 10 – 14 weeks, an extended 48-week study of patients treated for psoriasis showed similar rates of adverse events as those seen in the shorter trials. The most common adverse side effects include upper respiratory infections and nasopharyngitis [66]. Like other TNF-α inhibitors, the main concerns associated with adalimumab therapy – aside from infection – include malignancy and the development of ANA positivity. Also, cases of both disseminated and extrapulmonary infections have been reported, most commonly in patients treated with doses of adalimumab that were higher than the recommended dose [67].

2.7 T-cell modulators

2.7.1 *Alefacept*

In January 2003, alefacept became the first biologic agent approved for the treatment of moderate-to-severe psoriasis. Alefacept is a fusion protein that combines a portion of human IgG and the binding site of a lymphocyte function-associated antigen-3 (LFA-3). It binds CD2, its partner molecule on LFA-3, which is located on the surface of T-cells, thereby inhibiting memory T-cell activation and proliferation [68,69]. Alefacept is given in an intramuscular (IM) dose of 15 mg once a week for 12 weeks, which can be repeated after a therapy-free interval of 12 weeks as long as $CD4^+$ counts are within a normal range. According to recent studies, 21% of patients receiving treatment with alefacept achieve PASI-75 2 weeks after completing a 12-week treatment regimen of 15 mg/week [70]. Recent evidence also suggests that the efficacy of alefacept may increase with multiple courses of therapy [71].

The current FDA-recommended monitoring protocol for alefacept involves checking $CD4^+$ and $CD8^+$ T-cell counts on a weekly basis, because this agent does act to eliminate a subset of T-cells [69]. Therapy should be discontinued if $CD4^+$ counts drop below 250 cells/μL for a period of 1 month or more. As with the other biologic agents, there is some concern for lymphopenia, malignancy and serious infections [68]. However, an analysis of clinical trials shows us that the safety of alefacept was maintained over as many as nine courses of therapy, although the number of subjects was limited [72].

2.8 Interleukin-12/interleukin-23 inhibitors

2.8.1 *Ustekinumab*

Approved in September of 2009 for the treatment of moderate-to-severe psoriasis, ustekinumab is the newest biologic agent available to patients. This agent is a fully human monoclonal antibody that targets IL-23 (and IL-12), a key cytokine in the immune response of psoriasis [73,74]. IL-23 is associated with the activation of IL-17-producing T cells. This subset of cytokines is also pro-inflammatory in nature, inducing epidermal proliferation [75-78]. Ustekinumab acts by binding to the p40 subunit shared by IL-12 and IL-23, thereby neutralizing their activity by blocking interactions with their related receptors.

In two Phase III multicenter, double-blind, randomized, placebo-controlled trials – PHOENIX 1 and PHOENIX 2 – patients with psoriasis showed reduction of their disease severity for up to 76 weeks. These studies revealed comparable

efficacy and safety data, with ustekinumab given as an SC injection of 45 or 90 mg at time 0, week 4 and every 12 weeks thereafter. PHOENIX 1 revealed that 67 and 66% of those receiving therapy achieved PASI-75 at the 45 and 90 mg doses, respectively, after 12 weeks of treatment [79]. Similarly, 66 and 75% of patients achieved PASI-75 at week 12 at the 45 and 90 mg doses, respectively, in PHOENIX 2 [80]. Ustekinumab is a novel biological agent and the 2-year safety data are unknown at this point; most biologics require extensive use before the full profile of adverse event possibilities are illustrated [81]. The most commonly reported adverse events include nasopharyngitis and upper respiratory tract infection; there is a potentially increased incidence of malignancy in patients being treated with ustekinumab [82,83].

3. Cost analysis

3.1 Introduction

To determine the most cost-effective systemic treatment within the US setting, we considered efficacy as determined by the PASI-75 rating and the therapeutic effect on HRQOL. Although the PASI-75 rating has been utilized for a long time and is the most commonly used disease-centered measure of treatment efficacy among systemic psoriasis therapies, dermatologists' assessment of disease severity and patients' assessment of the same severity of psoriasis can be inconsistent. Also, the PASI response as a measure for disease severity may have lower accuracy than previously thought because of this interobserver variability when assessing PASI scores [84,85]. QOL measurements may be a more effective way to follow therapeutic response for psoriasis as compared to PASI scores [86,87]. We include both PASI response and a QOL outcome measurement, the Dermatology Life Quality Index (DLQI), in our analysis.

The PASI-75 is the percentage of patients who achieve 75% improvement in their PASI compared to baseline. The PASI combines the assessment of the severity of psoriatic lesions and the area of the body affected into a single score ranging from 0 (no disease) to 72 (maximal disease). The DLQI is a simple, practical, patient-centered tool to measure the effect of dermatologic disease and the efficacy of its treatment on a patient's QOL. It is a 10-item questionnaire to assess any effect or limitation on topics including symptom severity and feelings, daily activities, work and school, leisure, personal relationships and treatment. Each patient chooses among four choices per question: 'not at all', 'a little', 'a lot' or 'very much', which correspond with a score of 0, 1, 2 and 3, respectively. A score of 0 is given for questions that are answered 'not relevant'. Summing the scores for each question gives the DLQI range from 0 to 30, where a higher score corresponds to a more severe impairment of QOL [88]. A 5-point change in the DLQI total score represents the minimally important difference (MID) for patients with severe psoriasis and is particularly important when assessing efficacy regarding QOL.

3.2 Research methods

To identify studies of efficacy, we conducted a literature search on the National Library of Medicine (PubMed) with MeSH terms 'psoriasis', 'economics' and 'therapeutics'. The search was limited to randomized control trials (RCTs) and prior systematic reviews or meta-analysis of RCTs published in English in the past 10 years. We also manually searched the reference lists to find relevant cost-effectiveness studies for review. Titles were screened to identify the following therapies: phototherapy (PUVA, NB-UVB, home UVB) systemic agents (acitretin, cyclosporine, MTX) and biologic agents (adalimumab, alefacept, etanercept, infliximab and ustekinumab). Articles that assessed monotherapy treatment outcomes and efficacy with respect to PASI-75 and DLQI in moderate-to-severe psoriasis were included. Those articles evaluating treatments for psoriatic arthritis, or combined treatment protocols for psoriasis were excluded.

Our cost-effectiveness model was constructed based on a previous base case analysis applied to a continuous treatment regimen for each therapy for 1 year [13]. Cost-effectiveness ratios were determined with respect to consensus DLQI and PASI-75 scores. We included the costs of medication, office visits, laboratory tests and monitoring procedures. The frequency of these variables were based on both clinical experience and published manufacturer's guidelines [64,89,90]. There is variability in the guidelines for laboratory monitoring; the analysis included only tests recommended by the FDA. Treatment costs were assessed from the perspective of third-party payers by use of the medications' average wholesale price (AWP), with phototherapy treatments based on medicare fee schedule and prior reports for equipment [91,92].

When calculating medication costs we assumed a patient weight of 80 kg and, for infliximab, assumed the entire vial of medication was used during treatment. Costs for infliximab were based on a 3-h infusion time. Monitoring costs for MTX included a liver biopsy to present the highest potential cost for this therapy; however, this procedure would be performed less than annually. As most patients with moderate-to-severe psoriasis are established patients within dermatology offices, the model assessed the cost for only maintenance therapy, thus prices for loading doses were not included and office visits were calculated as level 3 return visits. Phototherapy costs did include a three-times-per-week-for-10-weeks regimen preceding a weekly treatment for the remainder of the year. Pricing of outpatient office visits, laboratory testing, infusions and other laboratory and monitoring tests was determined using the 2010 Medicare National Median Physician Reimbursement schedule and Clinical Laboratory Fee schedule (Table 1 and Table 2) [93]. We used Current Procedural Technology (CPT) codes to search for prices of laboratory tests and procedures [94]. All costs were calculated in US dollars and additional direct costs, such as hospital costs or other costs associated with adverse side effects of medication and indirect

Table 1. Laboratory and procedure costs in $2010.

Item/CPT code*	Medicare Reimbursement ($)
R3 visit/99213	66.74
Nurse visit/99211	19.54
Eye exam/92012	75.96
Fundus photographs/92250	68.95
Liver biopsy/47000	321.53
IV Infusion up to 1 hr/96365	67.48
IV Infusion each additional hour/96366	21.02
CXR/71020	30.97
PPD/86580	7.01
Creatinine/82565	9.92
CBC with differential/85025	15.05
Absolute CD4/CD8 cell count/86360	90.94
BMP/80048	16.38
CMP/80053	20.46
AST/84450	10.01
ALT/84460	10.24
Hepatic function panel/80076	15.81
Magnesium/83735	12.97
Potassium/84132	8.89
Triglycerides/84478	11.13
Cholesterol/82465	8.43
Blood urea ntrogen/84520	7.64
Uric acid/84550	8.74
UVB/96910	69.00
PUVA/96912	89.00

Relevant monitoring costs for maintenance therapy of established patients are in **Table 1**, with induction dosages and extra hospital costs associated with adverse drug reactions excluded. Pricing is based on the 2010 Medicare National Median Physician Reimbursement/Fee Schedule and Clinical Laboratory Fee Schedule [93].

*From the American Medical Association website [94].

ALT: Alanine transaminase; AST: Aspartate transaminase; BMP: Basic metabolic profile; CBC: Complete blood count; CMP: Comprehensive metabolic profile; CPT: Current Procedural Terminology; IV: Intravenous; PPD: Purified protein derivative; R3: Level 3 return visit.

costs such as time away from work, were not included. Data were analyzed using Microsoft Excel.

Previously, cost-effectiveness ratios of treatments relative to placebo evaluated RCTs that assessed the efficacy of biologics as a means for treatment comparison. The cost-effectiveness ratio was calculated as the cost difference between therapy and placebo divided by the mean DLQI improvement difference between therapy and placebo. A similar ratio was calculated using the PASI-75 rating, dividing total treatment cost of therapy by the percentage of patients achieving PASI-75. Details are described further elsewhere [13]. The difference between the two constructed ratios is that the DLQI calculation involved multiplication of the ratio by 5, which gives the DLQI MID improvement. This study uses similar cost-effectiveness calculations to all other systemic agents used in the treatment of moderate-to-severe psoriasis (adalimumab, alefacept, etanercept, infliximab, PUVA, UVB and ustekinumab) to determine a cost-effectiveness ratio and make relative comparisons between medications. Relatively higher and lower doses were used for etanercept calculations to display the range of PASI-75 scores reported with moderate-to-severe psoriasis.

3.3 Results

The annual costs for systemic treatments of severe psoriasis ranged from $1330 for MTX 15 mg weekly to $48,731 for high-dose (HD) etanercept (50 mg SC twice weekly). Phototherapy costs ranged from $2768 for home phototherapy to $7697 for PUVA, with UVB costing $6676 annually. Annual costs of biologics ranged from $19,114 per year for infusions of infliximab to $48,731 for high-dose etanercept. The annual cost of the newest FDA-approved biologic, ustekinumab, was lower than all other biologic agents except for infliximab (**Table 3**). On average, phototherapies cost an estimated $5713, oral systemics $11,029 and biologics $26,708 per year for maintenance regimens.

Mean DLQI improvements for biologic agents ranged from 4.9 for alefacept to 9.7 for infliximab. Mean phototherapy DLQI improvements were 8.5 for NB-UVB. PUVA, acitretin, cyclosporine and MTX did not have reported DLQI score estimates for monotherapy (**Table 4**).

The percentage of patients achieving PASI-75 ranged from 21% (alefacept) to ± 80% (PUVA, infliximab). Acitretin (30%), low-dose (LD) etanercept (33%), home UVB (41%), MTX (36 – 60%), NB-UVB (42 – 80%), HD etanercept (49 – 57%), ustekinumab (67%), adalimumab (53 – 80%) and cyclosporine (70%) PASI-75 scores fell within this range (**Table 4**).

To obtain a DLQI MID, costs ranged from $3032 for NB-UVB to $59,564 for alefacept, with home UVB, infliximab, adalimumab, ustekinumab, LD etanercept and HD etanercept lying within this range (lowest to highest cost). Annual cost-efficacy ratio per patient to achieve PASI-75 ranged from $657 – 1094 for MTX to $124,800 for alefacept, with phototherapies being relatively cost-effective based on cost per PASI-75 ratio (**Figure 1**).

4. Discussion

When choosing the best therapy for a patient, the physician must consider therapeutic efficacy, cost effectiveness, safety profiles and – in particular – the treatment impact on QOL and patient preference [90]. Comparisons of costs and quality of life – crucial elements particularly with the increasing use of biologics – are not completely accomplished by observing PASI-75 scores alone. Recognition of this resulted in reported measures of QOL such as the DLQI, which is better documented in the newer studies of biologic therapies compared to older studies of pre-biologic systemic agents and phototherapy. The DLQI questionnaire is easy to use with patients and has high internal and external consistency [95,96]. Changes in the DLQI correlate well with patients' clinical outcomes and reductions in the DLQI correlate with decreases in patients' PASI score [97].

Table 2. Annual monitoring guidelines for systemic psoriasis therapy.*

Therapy	Office visits	Lab work	Other direct costs
Acitretin	6 R3s	4 LFTs, lipids	None
Alefacept	6 R3s	24 CD4 counts	None
Adalimumab	4 R3s	1 PPD	None
Cyclosporine	7 R3s	6 CMPs, CDPs, LFTs, Mg, K	None
Etanercept	4 R3s	1 PPD	None
Infliximab	4 R3s	1 PPD	7 infusions
PUVA	4 R3s	None	2 Eye Exams, 1 Fundoscopy
Methotrexate	6 R3s	6 CDPs, LFTs	1 Liver Biopsy‡
NB-UVB	4 R3s	None	None
Home NB-UVB	4 R3s	None	None
Ustekinumab	4 R3s	1 PPD	None

*Because of variability in guidelines for laboratory monitoring during treatment with each therapy, we list only the monitoring tests recommended by the FDA for each agent [113].

‡Liver biopsy may be done every 2 years, but we have included it here to estimate the highest total cost possible with methotrexate therapy.

CD4 count: T cell $CD4^+$ count; CDP: Complete blood count with differential; CMP: Comprehensive metabolic profile; K: Potassium level; LFT: Liver function tests; Mg: Magnesium level; PPD: Tuberculin skin test; R3: Level 3 return visit.

This analysis first reviews annual treatment costs, which demonstrates the vast difference between older therapies, such as oral systemics and phototherapies and newer biologics. While other incentives or purchasing factors may change the costs of medications, the general differences are approximately two- to five-fold between older treatments and biologics. Although the cost analysis has the highest reliability among the models done in this study, integrating efficacy and DLQI is also important.

The cost-efficacy ratios for patients to achieve a DLQI MID and PASI-75 find phototherapy (home UVB, outpatient NB-UVB and PUVA) and methotrexate to be relatively inexpensive, efficacious agents for moderate-to-severe psoriasis. Phototherapy was the most cost-effective measure when both parameters were available. Although side effect profiles were not directly assessed, NB-UVB adverse events are relatively minor compared to other systemic agents and include sun-burns and a long-term risk of skin cancer, but not significantly increased risks as compared to that of normal sun exposure. This highlights its importance as a first-line treatment for moderate-to-severe psoriasis. Even with the limitations of comparisons across studies, the magnitude of the difference between phototherapy and MTX on the one hand and biologics on the other make the cost effectiveness differences quite clear.

MTX did reveal itself to be the most cost-effective medication from our study in terms of PASI-75 data. However, significant adverse effects associated with long-term MTX use can limit its consideration as a first-line choice. Past studies on cost-effectiveness have also shown home UVB therapy to be the single most cost-effective therapy for eligible patients when considering the safety, efficacy and cost of therapy [36]. Home therapy has similar effectiveness to traditional UVB phototherapy in educated patients [98,99].

When comparing the biologics, infliximab appears to be the most cost-effective method for treating moderate-to-severe psoriasis, but the newest therapeutic choice, ustekinumab, is not far behind and is more convenient as it does not require IV infusions. The relative differences between most TNF inhibitors is not large, however, thus contracting cost differences or even the limitations of the accuracy of relative effectiveness could affect the order of cost-effectiveness of these drugs.

Four head-to-head clinical studies were identified comparing systemic psoriasis therapies, MTX vs. cyclosporine, home vs. outpatient NB-UVB, MTX vs. adalimumab and ustekinumab vs. etanercept, of which cost comparisons have been published based on the first two [20,31,100-101]. Efficacy data of these studies were incorporated in our analysis as appropriate. Opmeer *et al.*'s economic analysis of MTX vs. cyclosporine [102] paralleled their 16-week head-to-head clinical trial and described direct and indirect costs for both the trial period as well as the 36 weeks following (1 year in total). Similar to this analysis, methotrexate was less expensive in their monotherapy treatment phase ($1593 vs. $2144, MTX vs. cyclosporine). Their analysis differed in their incorporation of indirect costs (which were higher for MTX), a higher number of patient visits, lower doses of cyclosporine and incorporation of other treatment modalities after the treatment phase for the remainder of the year. At the 1-year point, MTX was still less costly than cyclosporine; however, it was only marginally so and there were no PASI scores to evaluate efficacy at the 1-year mark [102].

Koek *et al.* similarly published a cost-effectiveness analysis of their home versus outpatient phototherapy trial in the Netherlands (PLUTO study) [31,99]. In their cost analysis they followed patients both during their treatment period and afterwards for 1 year, included direct and indirect costs (time lost from work, etc.) and allowed for treatment variability. By 17.6 weeks, patients had an estimated €727 vs. €464 direct medical costs for home and outpatient phototherapy, respectively, and, by 1 year after trial's end, €1151 vs. €864. Their costs for home phototherapy equipment use, which were estimated based on equipment rental invoice tariffs (and hypothesized by the authors as more expensive than actual costs), made home phototherapy estimates higher than our analysis. Home phototherapy equipment usage costs were more expensive than outpatient usage, which was the reverse of our estimate. Indirect costs in their analysis, however, evened out the financial burden of the therapies. Koek *et al.*'s economic conclusions aligned with our study showing both home and outpatient NV-UVB treatments as relatively cost-effective. They prefer home phototherapy over outpatient, citing patient preference

Table 3. Comparison of annual treatments costs in $2010 for moderate-to-severe psoriasis.

Therapy	Dose and frequency	Medication cost, $*	Lab/monitoring costs, $‡	Office visit cost, $‡	Total annual cost, $
Acitretin	25 mg/day	21005	329	402	21736
Alefacept	Two 12-week courses, 15 mg IM weekly	26208	2183	402	28793
Adalimumab	40 mg SC eow	23774	7	268	24049
Cyclosporine (5 mg/kg/d)	400 mg/day	8916	636	469	10021
Etanercept	50 mg SC weekly	24228	7	268	24503
	50 mg SC twice weekly	48456	7	268	48731
Infliximab	5 mg/kg/day IV; 400 mg daily maximum, every 8 weeks	18072	774	268	19114
PUVA	3×/week for 10 weeks, then weekly	6408	221	1068	7697
Methotrexate	15 mg/week	394	534	402	1330
NB-UVB	3×/week for 10 weeks, then weekly	4968	0	1708	6676
Home NB-UVB	3×/week for 10 weeks, then weekly	2500	0	268	2768
Ustekinumab	45 mg SC every 3 months	22382	7	268	22657

*Medication costs based on brand-name AWP for 2010; PUVA, UVB costs based on national 2010 Medicare Fee Schedule; Home phototherapy cost includes full cost of one phototherapy unit (this typically would be distributed over multiple years); costs in US dollars [91,92].
‡Total lab/monitoring and office visit costs based on data from the 2010 Medicare National Median Physician Reimbursement and Laboratory Fee Schedules [93].
AWP: Average wholesale price; eow: Every other week; IM: Intramuscular; IV: Intravenous infusion; NB-UVB: Narrowband ultraviolet B light therapy; PUVA: Psoralen with ultraviolet A light therapy; SC: Subcutaneous injection.

Table 4. Efficacies of active treatment as measured by DLQI and PASI-75.*

Therapy	Mean unit DLQI improvement [ref. no.]	% of Patients achieving PASI-75 [ref. no.]
Acitretin 25 mg/day	-	30 [14]
Alefacept 15 mg/week IM for 12 weeks	4.9 [13]	21 [114]
Adalimumab 40 mg SC eow	9.5 [13]	53 – 80 [63-65]
Cyclosporine 5 mg/kg/day	-	70 [19]
Etanercept 25 mg twice weekly	7 [13]	33 [43,48-49]
Etanercept 50 mg twice weekly	7.5 [13]	49 – 57 [48,49,115]
Infliximab 5 mg/kg/d, every 8 weeks	9.7 [13]	80 [13]
PUVA 3 – 4 times/week	-	80 – 86 [19,38]
Methotrexate 15 mg/weeek	-	36 – 60 [20,24]
NB-UVB 3 times/week	8.5 [116]	42 – 80 [19,29-31]
Home NB-UVB 3 times/week	8.5 [116]	41 [31]
Ustekinumab 45 mg SC at start, 1 month, then q 3 months	8.0 [117]	67 [79,80]

*DLQI improvement and PASI-75 success rates reflect approximately 12-week treatment durations (range 10 – 16 weeks; light therapies, approximately 30 sessions; MTX, 16 weeks). Note variation between trials exists making comparisons rough estimates.
DLQI: Dermatology Life Quality Index; eow: Every other week;
IM: Intramuscular injection; NB-UVB: Narrowband ultraviolet B light therapy;
PASI-75: Psoriasis Area and Severity Index reduction of 75% from baseline;
PUVA: Psoralen with ultraviolet A light therapy; SC: Subcutaneous injection.

for the modality. Key differences, particularly in the frequencies of therapy and time frame considered, prevent additional direct cost comparisons between our study and theirs.

Our review provides cost-effectiveness data on all current US FDA-approved systemic treatment options for moderate-to-severe psoriasis, including ustekinumab, the most recently added biologic. As with any pharmacoeconomic analysis, this study is challenged by the newer treatment options that may soon become approved and available. This includes another TNF-α inhibitor (golimumab) and a new class of immune-modulating drugs that act to inhibit cell signaling cascades mediated by the Janus-Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) class of proteins. Compared to this author's past studies on cost-effectiveness, we include an assessment of each agent with respect to both PASI-75 scores and DLQI improvement.

A limitation from our retrospective methodology is that treatment efficacy data were gathered from several different clinical trials. As a result, when comparing different cohorts there is no method of standardizing study/patient characteristics across multiple trials and caution must be taken when comparing or extrapolating from PASI or DLQI scores. The study did not include indirect costs and solely addressed the cost from the payer perspective. Although this is the case, interpretation of the data is less likely to be altered given that the variations in medication costs are often high between classes of medications. If the employer is both the payer and inconvenienced by lost time at work the indirect costs may influence the cost-analysis in very high hourly wage jobs.

In actual practice, medications may be used in various combinations or altered based on patient responses,

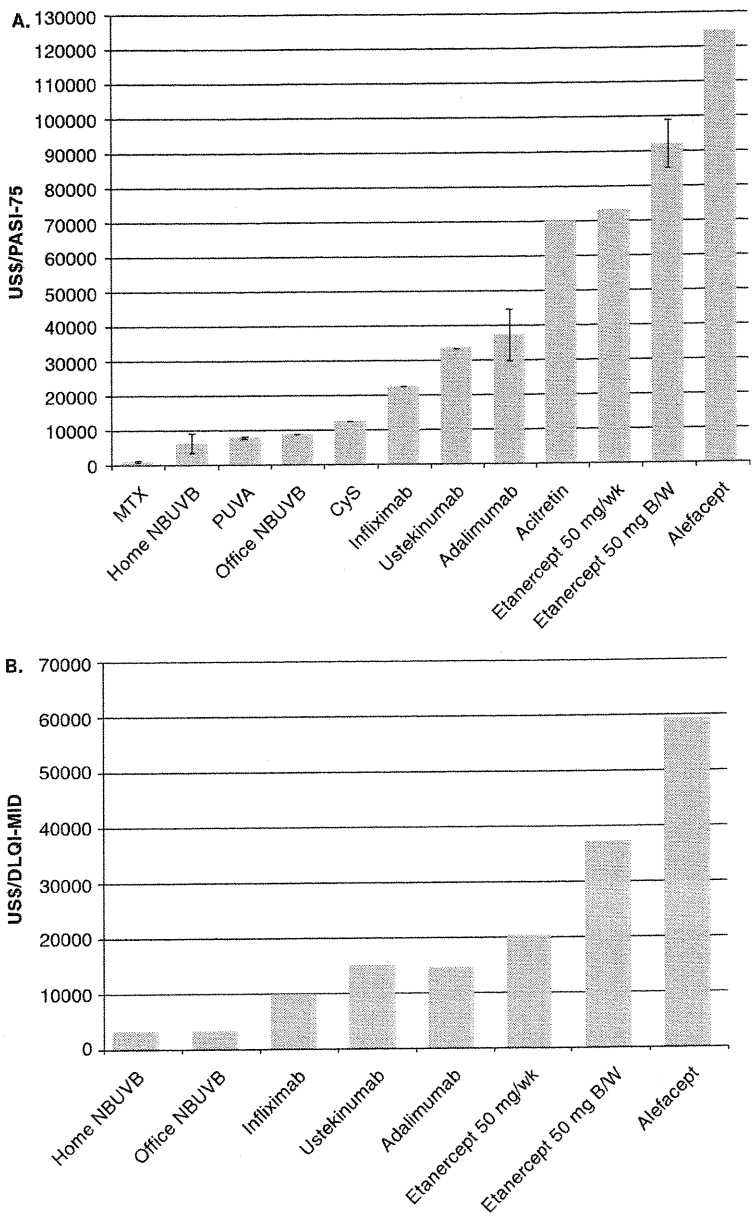

Figure 1. Cost-effectiveness ratios, 2010 US$. Cost-efficacy ratios are extracted from **(A)** PASI-75 and **(B)** DLQI assessments of different studies and should be understood as rough estimates. Consensus efficacies were used; ranges are shown when appropriate. DLQI MID represents a 5-point change in the DLQI total score. This is calculated by multiplying the cost effectiveness ratio for DLQI improvement by 5 [13]. Therapeutic schedule is for 1 year with: acitretin 25 mg/day; alefacept 15 mg/week IM for 12 weeks; adalimumab 40 mg SC eow; cyclosporine 5 mg/kg/day; etanercept 50 mg/week; etanercept 50 mg twice weekly; infliximab 5 mg/kg/day IV; 400 mg daily maximum, every 8 weeks; PUVA 3×/week for 10 weeks, then weekly; methotrexate 15 mg/week; NB-UVB 3×/week for 10 weeks, then weekly; home NB-UVB 3×/week for 10 weeks, then weekly; ustekinumab 45 mg SC every 3 months.

DLQI MID: Dermatology Life Quality Index minimally important difference; DLQI: Dermatology Life Quality Index; eow: Every other week; IM: Intramuscular injection; NB-UVB: Narrowband ultraviolet B light therapy; PASI-75: Psoriasis Area and Severity Index reduction of 75% from baseline; PUVA: Psoralen with ultraviolet A light therapy; SC: Subcutaneous injection.

comorbidities and adverse events, which was not illustrated. Our costs are estimated for maintenance therapy over 1 year; however, PASI-75 scores were available only in the 3 – 4 month range with slight variations in dosing. If a medication has increasing (such as alefacept) or decreasing efficacy after longer time periods this would not be reflected. Also, dosing variations between maintenance therapy and those in clinical trials may influence cost-efficacy ratios. For this reason, ranges are shown when appropriate and conclusions are drawn only from large differences. Additionally, the cost analysis may not apply directly in non-US settings, such as national health systems, as it is based on US cost data. However, given large variation among drug cost in the US market, the general medication cost principles of the study may be considered in other markets.

5. Conclusion

The costs of treating psoriasis are increasing and as a result the economics of psoriasis will continue to be an important focus of discussion [103,104]. Patients, physicians and insurers are now faced with a wider array of therapeutic choices that vary widely in costs. The implications for the patient are in many realms – both as they relate to psoriasis and its comorbidities, and as indirect and direct personal financial burdens [105,106]. Choosing a treatment regimen that provides the most value for its cost will provide savings in healthcare expenditures and, in an age of healthcare dollar scrutiny, shift financial resources appropriately [107,108]. To do so requires a full understanding by both the physician and patient of the safety, efficacy and cost considerations of the many systemic treatment options for severe psoriasis patients.

Ultimately, the best guide for treatment is through patient education and an individual patient's preferences. Patients may interpret the side-effect profiles, advantages and disadvantages differently, so there is no single best agent for all patients, especially as they may also lie anywhere along the moderate-to-severe spectrum [90]. Also, the role of pharmacogenetics should always be considered, because patients will respond differently to certain treatment regimens [109,110]. If patients are to play a role in controlling the cost of treatment, then reasonable incentives should be in place to encourage them to use safe, effective, low-cost ultraviolet light treatment methods over biologic treatments. In many cases, the incentive structures do just the opposite [92,111].

6. Expert opinion

Previous cost-effectiveness articles published in *Expert Opinions in Pharmacotherapy* have reported that phototherapy is a safe, effective and cost-effective form of treatment for moderate-to-severe psoriasis, especially when used as home therapy. Today, in light of current biologic options available on the menu of systemic psoriasis therapies, phototherapy is still among the most cost-effective ways to treat chronic, severe psoriasis. We find this to be true even when considering QOL data by means of the DLQI in addition to PASI scores. The DLQI shows us that the cost of phototherapy per patient to achieve an estimated DLQI MID is far lower than any other currently FDA-approved agent for moderate-to-severe psoriasis, including the new biologics.

Regardless of these large series trials and this study data presented, patient care must be individualized to truly achieve individualized safe, low-cost, high-efficacy therapy. During the course of treatment patients' responses vary. One person may achieve clearance with phototherapy and topical creams, whereas another may develop joint symptoms and require an agent for his/her psoriatic arthritis. By anticipating potential transitions, educating patients and sharing resources (such as the National Psoriasis Foundation) with patients early in treatment, patient satisfaction and sense of control over their disease improves [112]. The difficulties of explaining to the patient the treatment pros, cons and adjustments then becomes less challenging, finding the most appropriate agent becomes a team approach and the most appropriate regimen for each patient can be more easily identified. Keeping this in mind, large-scale review analyses such as this one can serve as an educated starting point for these discussions.

Declaration of interest

SR Feldman has received research, speaking and/or consulting support from Galderma, Abbot Laboratories, Warner Chilcott, Leo Amgen, Astellas, Centacor, National Biological Corp. and Steifel/GSK. The other authors state no conflict of interest and have received no payment in preparation of this manuscript. The Center for Dermatology Research is supported by an educational grant from Galderma Laboratories, L.P.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. About Psoriasis Statistics. Available from: http://www.psoriasis.org/netcommunity/learn/about-psoriasis/statistics 2010; 7-31-2010
2. Russo PA, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: a review. Australas J Dermatol 2004;45:155-9
3. Perrott SB, Murray AH, Lowe J, Mathieson CM. The psychosocial impact of psoriasis: physical severity, quality of life and stigmatization. Physiol Behav 2000;70:567-71
4. Lundberg L, Johannesson M, Silverdahl M, et al. Health-related quality of life in patients with psoriasis and atopic dermatitis measured with SF-36, DLQI and a subjective measure of disease activity. Acta Derm Venereol 2000;80:430-4
5. Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999;41:401-7
6. Fowler JF, Duh MS, Rovba L, et al. The impact of psoriasis on health care costs and patient work loss. J Am Acad Dermatol 2008;59:772-80
7. Beyer V, Wolverton SE. Recent trends in systemic psoriasis treatment costs. Arch Dermatol 2010;146:46-54

• **An extensive review of the recent trend of rising costs in psoriasis therapy.**

8. Menter A, Griffiths CE. Current and future management of psoriasis. Lancet 2007;370:272-84
9. Sizto S, Bansback N, Feldman SR, et al. Economic evaluation of systemic therapies for moderate to severe psoriasis. Br J Dermatol 2009;160:1264-72
10. Olivieri I, de Portu S, Salvarani C, et al. The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy. Rheumatology (Oxford) 2008;47:1664-70
11. Bansback N, Sizto S, Sun H, et al. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. Dermatology 2009;219:209-18
12. Miller DW, Feldman SR. Cost-effectiveness of moderate-to-severe psoriasis treatment. Expert Opin Pharmacother 2006;7:157-67
13. Nelson AA, Pearce DJ, Fleischer AB Jr, et al. Cost-effectiveness of biologic treatments for psoriasis based on subjective and objective efficacy measures assessed over a 12-week treatment period. J Am Acad Dermatol 2008;58:125-35

•• **Cost-effectiveness analysis of biologic psoriasis therapy utilizing both PASI and DLQI data.**

14. Feldman SR, Garton R, Averett W, et al. Strategy to manage the treatment of severe psoriasis: considerations of efficacy, safety and cost. Expert Opin Pharmacother 2003;4:1525-33

•• **Extensive analysis estimating the costs of phototherapy, traditional systemics and biologics in the treatment of moderate-to-severe psoriasis.**

15. Brimhall AK, King LN, Licciardone JC, et al. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol 2008;159:274-85
16. Schmitt J, Zhang Z, Wozel G, et al. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol 2008;159:513-26
17. Feldman S. The psoriasis and psoriatic arthritis pocket guide: treatment algorithms and management options. National Psoriasis Foundation; Portland, OR: 2005
18. Food and Drug Administration. FDA Statement on the Voluntary Withdrawal of Raptiva From the U.S. Market. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149561.htm 2010; 8-10-2010
19. Griffiths CE, Clark CM, Chalmers RJ, et al. A systematic review of treatments for severe psoriasis. Health Technol Assess 2000;4:1-125
20. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med 2003;349:658-65
21. Grossman RM, Chevret S, Abi-Rached J, et al. Long-term safety of cyclosporine in the treatment of psoriasis. Arch Dermatol 1996;132:623-9
22. Zachariae H, Kragballe K, Hansen HE, et al. Renal biopsy findings in long-term cyclosporin treatment of psoriasis. Br J Dermatol 1997;136:531-5
23. Koo J. Systemic sequential therapy of psoriasis: a new paradigm for improved therapeutic results. J Am Acad Dermatol 1999;41:S25-8
24. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158:558-66
25. Roenigk HH Jr, Auerbach R, Maibach H, et al. Methotrexate in psoriasis: consensus conference. J Am Acad Dermatol 1998;38:478-85
26. Krutmann J. Therapeutic photoimmunology: photoimmunological mechanisms in photo(chemo)therapy. J Photochem Photobiol B 1998;44:159-64
27. Zanolli M. Phototherapy treatment of psoriasis today. J Am Acad Dermatol 2003;49:S78-86
28. Coven TR, Burack LH, Gilleaudeau R, et al. Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. Arch Dermatol 1997;133:1514-22
29. van Weelden H, De La Faille HB, Young E, van der Leun JC. A new development in UVB phototherapy of psoriasis. Br J Dermatol 1988;119:11-19
30. Walters IB, Burack LH, Coven TR, et al. Suberythemogenic narrow-band UVB is markedly more effective than conventional UVB in treatment of psoriasis vulgaris. J Am Acad Dermatol 1999;40:893-900

31. Koek MB, Buskens E, van Weelden H, et al. Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study). BMJ 2009;338:b1542

32. Lowe NJ, Prystowsky JH, Bourget T, et al. Acitretin plus UVB therapy for psoriasis. Comparisons with placebo plus UVB and acitretin alone. J Am Acad Dermatol 1991;24:591-4

33. Lebwohl M, Acitretin in combination with UVB or PUVA. J Am Acad Dermatol. 1999;41:S22-4

34. Ashcroft DM, Li Wan PA, Griffiths CE. Therapeutic strategies for psoriasis. J Clin Pharm Ther 2000;25:1-10

35. Housman TS, Rohrback JM, Fleischer AB Jr, Feldman SR. Phototherapy utilization for psoriasis is declining in the United States. J Am Acad Dermatol 2002;46:557-9

36. Yelverton CB, Kulkarni AS, Balkrishnan R, Feldman SR. Home ultraviolet B phototherapy: a cost-effective option for severe psoriasis. Manag Care Interface 2006;19:33-6; 39

37. Gordon PM, Diffey BL, Matthews JN, Farr PM. A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. J Am Acad Dermatol 1999;41:728-32

38. Sivanesan SP, Gattu S, Hong J, et al. Randomized, double-blind, placebo-controlled evaluation of the efficacy of oral psoralen plus ultraviolet A for the treatment of plaque-type psoriasis using the Psoriasis Area Severity Index score (improvement of 75% or greater) at 12 weeks. J Am Acad Dermatol 2009;61:793-8

39. Stern RS, Nichols KT, Vakeva LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study. N Engl J Med 1997;336:1041-5

40. Stern RS. Carcinogenic risk of psoralen plus ultraviolet radiation therapy: evidence in humans. Natl Cancer Inst Monogr 1984;66:211-16

41. Lindelof B, Sigurgeirsson B, Tegner E, et al. PUVA and cancer: a large-scale epidemiological study. Lancet 1991;338:91-3

42. Stern RS, Bolshakov S, Nataraj AJ, Ananthaswamy HN: p53 mutation in nonmelanoma skin cancers occurring in psoralen ultraviolet a-treated patients: evidence for heterogeneity and field cancerization. J Invest Dermatol 2002;119:522-6

43. Papp KA. Potential future therapies for psoriasis. Semin Cutan Med Surg 2005;24:58-63

44. Dommasch ED, Abuabara K, Shin DB, et al. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol 2011;64(6):1035-50

45. Wyeth. Enbrel (etanercept). Available from: http://www.enbrel.com/documents/ENBREL-Prescribing-Information.pdf 2009; 8-11-2010

46. Centocor Ortho Biotech, Inc. Remicade (infliximab). Available from: http://www.remicade.com/remicade/assets/HCP_PPI.pdf 2009; 8-11-2010

47. Abbott. Humira (adalimumab). Available from: http://rxabbott.com/pdf/humira.pdf 2009; 8-11-2010

48. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;349:2014-22

49. Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003;139:1627-32

50. Griffiths CE, Strober BE, van de KP, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118-28

51. Koo J, Lee E, Lee CS, Lebwohl M. Psoriasis. J Am Acad Dermatol 2004;50:613-22

52. Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med 2003;138:807-11

53. Kormeili T, Lowe NJ, Yamauchi PS. Psoriasis: immunopathogenesis and evolving immunomodulators and systemic therapies; U.S. experiences. Br J Dermatol 2004;151:3-15

54. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001;44:2862-9

55. Robinson WH, Genovese MC, Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism: by what mechanisms could tumor necrosis factor alpha antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? Arthritis Rheum 2001;44:1977-83

56. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum 2002;46:3151-8

57. Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. Arch Dermatol 2003;139:1425-9

58. Gottlieb AB, Evans R, Li S, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004;51:534-42

59. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005;366:1367-74

60. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098-104

61. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004;50:372-9

62. Gordon KB, Bonish BK, Patel T, et al. The tumour necrosis factor-alpha inhibitor adalimumab rapidly reverses the decrease in epidermal Langerhans cell density in psoriatic plaques. Br J Dermatol 2005;153:945-53

63. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58:826-50

64. Menter A, Cather JC, Baker D, et al. The efficacy of multiple courses of alefacept in patients with moderate to severe chronic plaque psoriasis. J Am Acad Dermatol 2006;54:61-3

65. Koo J, Khera P. Update on the mechanisms and efficacy of biological therapies for psoriasis. J Dermatol Sci 2005;38:75-87

66. Langley R. Long-term safety and efficacy of adalimumab in the treatment ofmoderate to severe chronic plaque psoriasis. Proceedings of the 63rd Annual Meeting of the American Academy of Dermatology; New Orleans, LA.2005

67. Abbott Laboratories. Humira (adalimumab) package insert. North Chicago, IL; 2004

68. Biogen, Inc. Amevive (alefacept) prescribing information. Cambridge, MA; 2005

69. Krueger GG, Callis KP. Development and use of alefacept to treat psoriasis. J Am Acad Dermatol 2003;49:S87-97

70. Ortonne JP, Lebwohl M, Em GC. Alefacept-induced decreases in circulating blood lymphocyte counts correlate with clinical response in patients with chronic plaque psoriasis. Eur J Dermatol 2003;13:117-23

71. Cather JC, Menter A. Combining traditional agents and biologics for the treatment of psoriasis. Semin Cutan Med Surg 2005;24:37-45

72. Goffe B, Papp K, Gratton D, et al. An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. Clin Ther 2005;27:1912-21

73. Torti DC, Feldman SR. Interleukin-12, interleukin-23 and psoriasis: current prospects. J Am Acad Dermatol 2007;57:1059-68

74. Kauffman CL, Aria N, Toichi E, et al. A phase I study evaluating the safety, pharmacokinetics and clinical response of a human IL-12 p40 antibody in subjects with plaque psoriasis. J Invest Dermatol 2004;123:1037-44

75. Oppmann B, Lesley R, Blom B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity 2000;13:715-25

76. Aggarwal S, Ghilardi N, Xie MH, et al. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J Biol Chem 2003;278:1910-14

77. Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007;356:580-92

78. Centocor Ortho Biotech, Inc. Stelara (ustekinumab). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125261s001lbl.pdf 2009; 8-10-2010

79. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665-74

80. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675-84

81. Schafer JA, Kjesbo NK, Gleason PP. Formulary review of 2 new biologic agents: tocilizumab for rheumatoid arthritis and ustekinumab for plaque psoriasis. J Manag Care Pharm 2010;16:402-16

82. Center for Drug Evaluation and Research. Medical Review of Ustekinumab Application number 125261. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125261s000_MedR.pdf 2010; 8-12-2010

83. Patel RV, Clark LN, Lebwohl M, Weinberg JM. Treatments for psoriasis and the risk of malignancy. J Am Acad Dermatol 2009;60:1001-17

84. Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R. Quality of life in patients with psoriasis. Health Qual Life Outcomes 2006;4:35

85. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. Br J Dermatol 1999;141:185-91

86. Weisman S, Pollack CR, Gottschalk RW. Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. J Dermatolog Treat 2003;14:158-65

87. Krueger G, Koo J, Lebwohl M, et al. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol 2001;137:280-4

88. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-16

• **A thorough presentation on the development and description of the Dermatology Life Quality Index.**

89. Lebwohl M, Ali S. Treatment of psoriasis. Part 2. Systemic therapies. J Am Acad Dermatol 2001;45:649-61

90. Nelson AA, Pearce DJ, Fleischer AB, et al. New treatments for psoriasis: which biologic is best? J Dermatolog Treat 2006;17:96-107

91. Lehman B. The red book. Houghton Mifflin Co; Boston: 2010

92. Yentzer BA, Feldman SR. Trends in home phototherapy adoption in the US: monetary disincentives are only the tip of the iceberg. J Dermatolog Treat 2011;22(1):27-30

93. Centers for Medicare and Medicaid Services. Clinical Laboratory and Physician fee schedules. Available from: http://www.cms.hhs.gov/home/medicare/asp 2010; 7-29-2010

94. American Medical Association. CPT Code Search. Available from: https://catalog.ama-assn.org/Catalog/cpt/cpt_search.jsp?requestid=74979 2010; 7-29-2010

95. Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. The Cavide Research Group. Br J Dermatol 1999;141:698-702

96. Shikiar R, Bresnahan BW, Stone SP, et al. Validity and reliability of patient reported outcomes used in psoriasis: results from two randomized clinical trials. Health Qual Life Outcomes 2003;1:53

97. Mazzotti E, Picardi A, Sampogna F, et al. Sensitivity of the dermatology life quality index to clinical change in

patients with psoriasis. Br J Dermatol 2003;149:318-22

98. Cameron H, Yule S, Moseley H, et al. Taking treatment to the patient: development of a home TL-01 ultraviolet B phototherapy service. Br J Dermatol 2002;147:957-65

99. Koek MB, Sigurdsson V, van Weelden H, et al. Cost effectiveness of home ultraviolet B phototherapy for psoriasis: economic evaluation of a randomised controlled trial (PLUTO study). BMJ 2010;340:c1490

100. Griffiths CE, Strober BE, van de KP, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118-28

101. Opmeer BC, Heydendael VM, De Borgie CA, et al. Costs of treatment in patients with moderate to severe plaque psoriasis: economic analysis in a randomized controlled comparison of methotrexate and cyclosporine. Arch Dermatol 2004;140:685-90

102. Opmeer BC, Heydendael VM, De Borgie CA, et al. Costs of treatment in patients with moderate to severe plaque psoriasis: economic analysis in a randomized controlled comparison of methotrexate and cyclosporine. Arch Dermatol 2004;140:685-90

103. Stein KR, Pearce DJ, Feldman SR. The impact of biologics on the quality of life of psoriasis patients and the economics of psoriasis care. Semin Cutan Med Surg 2005;24:52-7

104. Pearce DJ, Thomas CG, Fleischer AB Jr, Feldman SR. The cost of psoriasis therapies: considerations for therapy selection. Dermatol Nurs 2004;16:421-8; 432

105. Feldman SR, Fleischer AB Jr, Reboussin DM, et al. The economic impact of psoriasis increases with psoriasis severity. J Am Acad Dermatol 1997;37:564-9

106. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. Br J Dermatol 1995;132:236-44

107. Shepard DS. Cost-effectiveness in health and medicine. In: Gold MR, Siegel JE, Russell LB and Weinstein MC (eds). New York: Oxford University Press, 1996. J Ment Health Policy Econ 1999;2:91-2

108. Darst M, Reddan J. Pharmacoeconomics. In: Wolverton S. editor Comprehensive dermatologic drug therapy. Saunder; Philadelphia, PA: 2007

109. Suarez-Farinas M, Shah KR, Haider AS, et al. Personalized medicine in psoriasis: developing a genomic classifier to predict histological response to Alefacept. BMC Dermatol 2010;10:1

110. Ryan C, Menter A, Warren RB. The latest advances in pharmacogenetics and pharmacogenomics in the treatment of psoriasis. Mol Diagn Ther 2010;14:81-93

- **An extensive review of the role of pharmacogenetics and how it may be utilized to establish personalized treatment for psoriasis, thereby offering more cost-effective treatment solutions.**

111. Yentzer BA, Yelverton CB, Simpson GL, et al. Paradoxical effects of cost reduction measures in managed care systems for treatment of severe psoriasis. Dermatol Online J 2009;15:1

112. Nijsten T, Rolstad T, Feldman SR, Stern RS. Members of the national psoriasis foundation: more extensive disease and better informed about treatment options. Arch Dermatol 2005;141:19-26

113. US Food and Drug Administration. Drugs @ FDA. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm 2010; 7-29-2010

114. Lebwohl M, Christophers E, Langley R, et al. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. Arch Dermatol 2003;139:719-27

115. Griffiths CE, Strober BE, van de KP, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118-28

116. Akaraphanth R, Kittipavara Y, Voravutinon N, et al. Efficacy of a far erythemogenic dose of narrow-band ultraviolet B phototherapy in chronic plaque-type psoriasis. J Dermatol 2010;37:140-5

117. Lebwohl M, Papp K, Han C, et al. Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. Br J Dermatol 2010;162:137-46

Affiliation

Jonathan P Staidle MD, Tushar S Dabade MD & Steven R Feldman[†] MD PhD
[†]Author for correspondence
Wake Forest University School of Medicine, Medical Center Boulevard, Department of Dermatology, Winston-Salem, NC 27157-1071, USA
Tel: +1 336 716 1763; Fax: +1 336 716 7732; E-mail: sfeldman@wfubmc.edu