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REVIEW

Burden of Moderate-to-Severe Plaque Psoriasis and New Therapeutic Approaches (Secukinumab): An Italian Perspective

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ABSTRACT

Psoriasis is a chronic immune-mediated inflammatory skin disease commonly categorized as mild, moderate, or severe. Moderate-to-severe psoriasis is associated with significant comorbidity and has been shown to severely impair quality of life. Moreover, psoriasis is associated with high costs, including those associated with treatment, which have increased recently with the inclusion of biological systemic agents (most recently secukinumab) as available treatment options. However, despite clear evidence of their value in the treatment of moderate-to-severe plaque psoriasis, in Italy access to the biological agents remains limited to dermatological centers originally involved in the Psocare network. The impact of secukinumab entry into the market in Italy is still to be determined, but we believe that it will be associated with significant changes in the way in which biological treatments for psoriasis are accessed and prescribed in Italy. It is noteworthy that in January 2015, the European Medicines Agency approved secukinumab as first-line systemic therapy in this indication.

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Keywords: Moderate-to-severe; Psoriasis; Secukinumab

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INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory skin disease [1, 2], with plaque psoriasis accounting for more than 80–90% of cases [1, 3]. Plaque psoriasis appears as well-defined, well-demarcated, erythematous plaques [1]. Psoriasis is one of the most common inflammatory diseases of the skin, with an estimated prevalence in Western countries of between 0.6% and 4.8% [4–7]. Notably, results of a recent study suggest that the incidence of the disease in adults has been steadily increasing [2].

Psoriasis is commonly categorized as mild, moderate, or severe, depending on the Psoriasis Area and Severity Index (PASI), the percentage body surface area (BSA) affected, and the Physician's Global Assessment (PGA) [8]. There is a European consensus decision on the definition of moderate-to-severe psoriasis as BSA >10% or PASI >10 and Dermatology Life Quality Index (DLQI) >10 [9]. Epidemiological studies show that about 25% of patients have moderate-to-severe forms of the disease [10]. Moderate-to-severe psoriasis is associated with significant comorbidity [3, 11, 12] and has been shown to severely impair quality of life (QoL) of affected patients [3, 13–15]. Moreover, psoriasis is associated with high costs, including those associated with treatments. These costs have increased recently, as the treatment options for psoriasis have expanded to include biological systemic agents, most recently secukinumab [16, 17]. However, despite clear evidence of their value in the treatment of moderate-to-severe plaque psoriasis, access to these agents remains limited to centers originally involved in the Psocare network in Italy.

Objective and Methodology

The aim of this review was to present an overview of the current epidemiological data, the clinical and socioeconomic burden of moderate-to-severe psoriasis and its comorbidities, and available treatments in the context of current treatment guidelines and access to treatment. This is a narrative review and so a systematic search strategy was not performed. Ad hoc literature searches were carried out to find the most recent and relevant data and guidelines on this topic. Additional information came from a meeting of an Italian advisory board, which included a pharmacoeconomics expert, clinical dermatologists, and hospital pharmacists, convened to define the impact in terms of organization, management, and costs of secukinumab for the treatment of patients with moderate-to-severe plaque psoriasis who are eligible for systemic therapy. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

BURDEN OF DISEASE

Psoriasis is associated with a substantial burden, due to significant comorbidity, severe impact on QoL, and high costs, both direct and indirect. It is a chronic disease, for which there is no cure and hence patients need lifelong care.

Comorbidities

Patients with psoriasis are likely to suffer from comorbidities such as psoriatic arthritis (approximately 20%) [12]. Moreover, 50% of

patients suffer from fingernail psoriasis and 35% from toenail involvement [18]. Psoriasis has also been shown to be associated with a number of other chronic inflammatory conditions, thought to be due to common pathogenic mechanisms. More specifically, the incidence of inflammatory bowel disease is higher in patients with psoriasis than in the general population [18–20], and there is a suggested link between multiple sclerosis and psoriasis, as psoriasis is more common in those with multiple sclerosis than in control subjects [21].

Patients with psoriasis are more likely to be overweight, have diabetes, hypertension and dyslipidemia, and often have metabolic syndrome, with an associated increase in risk of cardiovascular morbidity and mortality [3, 18, 22–27]. Additionally, patients with psoriasis are at increased risk of stroke [28] and myocardial infarction [29]. Importantly, mortality associated with myocardial infarction or stroke is 2.6-times higher in patients with early and frequent hospital admissions for psoriasis [30]. Severe psoriasis has also been shown to be associated with an increase in overall mortality risk (hazard ratio 1.5; 95% confidence interval 1.3–1.7) [31], as well as reduced life expectancy [31].

Psoriasis also has a significant psychological and emotional impact on patients and is associated with an increased incidence of mood disorders such as anxiety and depression [11, 32–34]. As many as 60% of psoriasis patients receive a diagnosis of depression [11], and psoriasis has also been found to be associated with suicidal ideation [33].

Quality of Life

Studies have shown that the impairment of health-related QoL (HRQoL) in patients with psoriasis is comparable with that due to hypertension, diabetes, cancer, depression, and heart disease [3, 13, 15, 35]. The negative impact of psoriasis on patient QoL can be attributed to the fact that it interferes with many day-to-day activities, activities related to work/school and leisure time, and impacts interpersonal and social relations [14]. Disease symptoms such as itching and pain can interfere with ordinary day-to-day activities such as washing, dressing, and sleeping, and psoriasis on the hands and feet can hinder many activities of daily living [36].

A study performed in Italy in 11 centers of the Psocare program showed that at least 50% of the assessed patients reported a minimum 20% decrease in their QoL related to their health state [15]. Factors associated with these decreases in QoL include frequent medical appointments, hospitalization, missing work, and reduced productivity [37]. The most important determinants of the impact of psoriasis on HRQoL are the sites affected and patients' attitude to their condition [13]. QoL reduction is greater if visible areas, the soles of the feet, and nails are involved [38–41]. Unfortunately, stigmatization is frequently experienced by patients with psoriasis, with associated reductions in QoL [42, 43].

Cost Burden

Psoriasis has high direct, indirect, and intangible costs—the more severe the disease the higher the costs [44]. Direct costs of psoriasis include those related to prescription drugs, hospital admissions, medical examinations, phototherapy, laboratory tests, and the costs of the over-the-counter products [45]. The indirect costs associated with psoriasis include those related to reduced work productivity, due to days of work missed because of the disease, and the time required

for medical examinations and non-pharmacological treatments, such as phototherapy and prescribed diagnostic procedures [45]. Key cost drivers in psoriasis include costs due to hospitalization, pharmaceutical products, and physician visits. Patients with the most severe psoriasis account for a disproportionate amount of total psoriasis costs [46]. Additionally, psoriasis has been shown to have a significant impact on productivity and income [47, 48], and more than half of all patients with psoriasis report missing an average of 26 days of work per year [47].

Costs associated with psoriasis are high worldwide, indicating a continued need for treatments that offer good value for money. In 2004, the annual total cost (direct and indirect) of psoriasis in the US alone was approximately US$1.40 billion [49]. Among European countries, recent studies reported annual total costs per patient of €11,928 in Sweden [50], €8372 in Italy [45], and €2866–6707 in Germany [51]; this cost was estimated to be CDN$7999 in Canada [52].

TREATMENT

The therapeutic approach to psoriasis depends on disease severity. The treatments available include topical drugs, phototherapy, systemic drugs such as methotrexate and, more recently, biological drugs. Treatment of psoriasis on limited areas of skin is initiated with topical therapies or a combination of potent topical steroids and calcipotriene (a form of vitamin D) [53]. Topical therapies for mild psoriasis include coal tar, anthralin, vitamin D analogues, retinoids, and calcineurin inhibitors (tacrolimus and pimecrolimus) [53]. Patients who do not respond to topical therapy, or who have lesions covering >10% of their BSA, are candidates for light therapy, conventional systemic therapy, or biologicals [54, 55]. Conventional systemic treatments include methotrexate, cyclosporine A, acitretin, and fumaric acid esters, which are associated with a number of side effects and organ-specific toxicity [3, 18].

Biological Agents

There are now several biological agents available for the treatment of patients with moderate-to-severe psoriasis (Table 1). Etanercept, infliximab, adalimumab, and ustekinumab have all been shown to be effective, easing symptoms and improving QoL [56]. Secukinumab has recently been added to the list of approved biologicals for the treatment of plaque psoriasis [16, 17]. Compared with conventional systemic treatments, biologic drugs have reduced toxicity, lack of drug interactions, and fewer contraindications [56, 57].

The licensed indication for etanercept, infliximab, adalimumab, and ustekinumab is ‘treatment of patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate, and psoralen with ultraviolet-A light (PUVA)’ [56, 58]. However, as ustekinumab was introduced later than the tumor necrosis factor antagonists, and due to the limited experience with this agent relative to other biologicals, it has been recommended as second-line biologic therapy for psoriasis by the British Association of Dermatologists [58]. There have been three cases of confirmed progressive multifocal leukoencephalopathy with efalizumab, with

Table 1 Summary of biologic agents approved in Europe for use in moderate-to-severe psoriasis [84]

Agent	Approved indication
Adalimumab	Treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultraviolet A
	Also for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies
Efalizumab	Withdrawn
Etanercept	Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including cyclosporine, methotrexate or psoralen and ultraviolet-A light
	Also for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies
Infliximab	Treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultraviolet A
Secukinumab	Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy
Ustekinumab	Treatment of moderate-to-severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and psoralen ultraviolet A

consequent withdrawal of the European marketing authorization for this agent by the European Medicines Agency (EMA) [58].

New Therapeutic Approaches

Until recently, biological drugs were indicated in moderate-to-severe psoriasis where there was no response to, and/or the presence of intolerance or contraindications to, traditional systemic therapies. However, this has now changed with the EMA and US Food and Drug Administration (FDA) approval in January 2015 for secukinumab as first-line systemic treatment of moderate-to-severe plaque psoriasis patients [16, 17].

Secukinumab is a first-in-class fully human anti-interleukin (IL)-17 monoclonal antibody [59–61]. Secukinumab targets the IL-17A ligand and acts by inhibiting the interaction of the IL-17A ligand with its receptor, which is expressed on various cell types [60]. This inhibits release of pro-inflammatory cytokines, chemokines, and mediators of tissue damage, reducing IL-17A-mediated processes involved in autoimmune and inflammatory diseases such as psoriasis. Secukinumab is the first biological drug approved for the first-line treatment of patients eligible for systemic therapy; all other available biological agents for psoriasis are approved as second-line systemic therapy.

The efficacy of secukinumab for moderate to severe plaque psoriasis is supported by the findings of the ERASURE ($n = 738$) and FIXTURE ($n = 1306$) trials (ClinicalTrials.gov identifiers: NCT01365455 and NCT01358578, respectively), both of which were 52-week phase

III trials, the first one placebo-controlled and the second one with an active comparator (etanercept) [62]. In these trials, secukinumab was given as a 300-mg or 150-mg dose once weekly for 5 weeks, then once every 4 weeks. Secukinumab was superior to placebo for the co-primary endpoints of ≥75% reduction in PASI (PASI 75) and a score of 0 or 1 on a 5-point modified investigator global assessment scale (Table 2). Two additional placebo-controlled randomized trials, JUNCTURE ($n = 182$) [63] and FEATURE ($n = 177$; ClinicalTrials.gov identifiers: NCT01636687 and NCT01555125, respectively) [64], evaluated the efficacy of secukinumab 300 mg or 150 mg administered with an autoinjector or prefilled syringe on moderate to severe psoriasis. In these trials, secukinumab was given once weekly up to week 4, then every 4 weeks, with findings again supporting the efficacy of secukinumab (Table 2).

Importantly, in the FIXTURE trial the efficacy of secukinumab was compared with etanercept, and it was found that secukinumab was significantly more effective than subcutaneous etanercept 50 mg administered twice weekly with respect to the co-primary efficacy end points of PASI 75 and a response of 0 or 1 on the modified investigator's global assessment at week 12 [62]. Furthermore, the

Table 2 Summary of key phase III clinical trial data for secukinumab

Study	Outcome measure (week 12)	Secukinumab 300 mg	Secukinumab 150 mg	Placebo	Etanercept 50 mg	Ustekinumab
ERASURE [62]	PASI 75	200/245 (81.6%)	174/243 (71.6%)	11/246 (4.5%)		
	Response of 0 or 1 on modified IGA	160/245 (65.3%)	125/244 (51.2%)	6/246 (2.4%)		
FIXTURE [62]	PASI 75	249/323 (77.1%)*	219/327 (67.0%)	16/324 (4.9%)	142/323 (44.0%)	
	Response of 0 or 1 on modified IGA	202/323 (62.5%)	167/327 (51.1%)	9/324 (2.8%)	88/323 (27.2%)	
FEATURE [64]	PASI 75	44/59 (75%)	41/59 (69%)	0/59 (0%)		
	Clear or almost clear on modified IGA	40/59 (68%)	31/59 (53%)	0/59 (0%)		
JUNCTURE [63]	PASI 75	52/60 (87%)	43/61 (70%)	2/61 (3%)		
	Clear or almost clear on modified IGA	44/60 (73%)	32/61 (52%)	0/61 (0%)		
CLEAR [65]	PASI 90 (week 16)	264/334 (79.0%)**				193/335 (57.6%)

IGA Investigators Global Assessment, *PASI* Psoriasis Area and Severity Index

* $P < 0.001$ vs. etanercept and placebo; ** $P < 0.0001$ vs. ustekinumab

CLEAR trial ($n = 676$; ClinicalTrials.gov identifier: NCT02074982), a 52-week, multicenter, randomized, double-blind study, compared secukinumab 300 mg, administered weekly for up to 4 weeks then every 4 weeks until week 48, with ustekinumab, with results revealing secukinumab to be significantly superior [65]. Overall, the safety profile of secukinumab has been shown to be comparable with those of etanercept and ustekinumab. In the FIXTURE study, the number of adverse events per 100 patient-years was similar in patients receiving secukinumab 300 mg, secukinumab 150 mg, or etanercept (252.0, 236.4, and 243.4 cases per 100 patient-years, respectively), as was the number of serious adverse events (6.8, 6.0 and 7.0 cases per 100 patient-years) and the number of patients who discontinued due to adverse events ($n = 14$, 10, and 12) [62]. In the CLEAR study, 64.2% and 58.3% of patients receiving secukinumab or ustekinumab experienced at least one adverse event, and 3% of each treatment group experienced a serious adverse event [65]. A significantly higher proportion of the secukinumab group versus the ustekinumab group in the CLEAR study self-reported no impairment of HRQoL scores due to skin impairment at week 16 (71.9% vs. 57.4%; $P < 0.0001$) [65].

Other new therapeutic approaches for the treatment of moderate-to-severe plaque psoriasis include apremilast, a phosphodiesterase-4 inhibitor, approved by the US FDA in September 2014 for use in patients who are candidates for systemic therapy [66], with European approval in January 2015 for the treatment of moderate-to-severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA [67]. Apremilast has not yet been addressed in published guidelines. Other agents in development for the treatment of moderate-to-severe plaque psoriasis include brodalumab (monoclonal antibody against IL-17 receptor A), ixekizumab (a humanized anti-IL-17A antibody) [60], guselkumab and tildrakizumab (antagonists of the p19 subunit of IL-23) [68], and tofacitinib (a Janus kinase inhibitor) [69]. In the AMAGINE phase III clinical trials of brodalumab (AMAGINE-I, -II, and -III, ClinicalTrials.gov identifiers: NCT01708590, NCT01708603, and NCT01708629, respectively), there was some suggestion of an increase in suicide/suicide ideation [70, 71]; on May 22, 2015, Amgen announced that it would terminate its participation in the development of brodalumab because of these events [72], and the AMAGINE clinical trials have been terminated.

Cost Effectiveness of the Biological Agents

Biologicals are an important option in moderate-to-severe plaque psoriasis, but are associated with significant costs and are a considerable strain for the national health systems (NHSs) of various countries. For this reason, many countries have strict criteria for refunding the cost of biologicals. In Italy the expenditure for biologicals used in psoriasis, rheumatic diseases, and oncology represents 13.7% of the drug expenditure for the NHS [37].

Various estimates of annual costs of these therapies have been found to range between US$13,000 and US$30,000 in one study [73], with a more recent study providing estimates of annual treatment costs with biological agents ranging from US$6800 for low-dose alefacept (no longer marketed) to US$56,000 for high-dose ustekinumab [74]. Another study estimated the cost of 1 year of induction and

maintenance treatment to be as follows: ustekinumab US$53,909; etanercept US$46,395; and adalimumab US$39,041 [75]. In a recent review of data from high-quality randomized trials ($n = 27$), cost-effectiveness ratios (determined over a 12-week period) were calculated as cost per patient achieving a PASI 75 response and the cost per patient achieving the minimal important difference in the DLQI score [74]. In this study, intravenous infliximab 3 mg/kg was the most cost-effective biologic agent (Table 3). Although costs of biologics are higher, adherence rates are better and patients require fewer hospitalizations with biologic therapy versus non-biologics; a longitudinal cohort study of 186 patients with psoriasis in the US showed that adherence rates were 0.66 with biologics versus 0.35 with other psoriasis medications ($P < 0.001$), and the mean number of hospitalizations was reduced from 0.9 in the 6 months before starting biologics to 0.4 in the 6 months after patients started therapy with biologics ($P < 0.001$) [76]. Italian-based studies have shown that hospitalization costs constitute a significant proportion of total costs; in one study, hospitalization costs were >80% of total costs, and more than 90% of the cost of physician visits, day hospital stays, and hospitalizations were incurred by the 20% of patients who were hospitalized [77]. In another study of Italian patients with moderate-to-severe psoriasis, hospitalization cost was the most significant direct cost associated with treatment, accounting for 30% of total costs [45]. A cost-utility analysis of psoriasis treatment in Italy has shown that etanercept treatment is a cost-effective therapy from the health service perspective and that the cost-effectiveness of etanercept increases with disease severity (incremental cost-effectiveness ratios for moderate-to-severe and severe psoriasis: €33,216 and €25,486 per QoL year, respectively) [78]. A study of adherence to therapy with infliximab, adalimumab, or etanercept in Italian patients with psoriasis, rheumatoid arthritis or Crohn's disease showed that non-pharmacological costs were reduced in patients who were adherent to therapy versus those who were not (€988 vs. €1255). Taken together, these data suggest that the use of biological therapies to treat psoriasis in Italy reduces healthcare costs.

National Institute for Health and Clinical Excellence (NICE) Guidelines on Biological for Psoriasis

The guidance documents produced by the UK National Institute for Health and Clinical Excellence (NICE) provide evidence-based recommendations regarding clinically effective and cost-effective treatments and interventions to improve outcomes for local populations.

At the time of writing, technology appraisal guidance documents were available for adalimumab, etanercept, efalizumab, infliximab, ustekinumab, and secukinumab in the treatment of adults with psoriasis. Regarding etanercept, the NICE guidance recommends etanercept for moderate-to-severe psoriasis not responding to, intolerant to or with contraindications to, standard systemic therapy [79]; efalizumab is no longer included in the NICE guidelines due to its withdrawal from market by the EMA [79]. Evaluation of infliximab found that infliximab was only considered cost effective in the subgroup of patients with very severe disease [80]. Adalimumab is only recommended for people with severe plaque psoriasis when standard systemic therapies have failed [81]; limitations of the clinical effectiveness data and uncertainty around

Table 3 Summary of cost-effectiveness analyses of biological agents for psoriasis based on US pricing [75] Copyright © Cheng J, Feldman SR. Reproduced with permission from Drugs in Context. DOI:10.7573/dic.212266

Study	Number of trials	Cost methodology	Efficacy methodology	Most cost-effective biologic
Hankin et al. [85]	16 studies (1966–2004)	Annual cost (AWP, treatment administration, adverse-event monitoring and treatment, reimbursement rate from Medicare)	PASI% between 6 and 14 weeks	Infliximab 5 mg/kg at weeks 0, 2, and 6
Menter et al. [86]	3 RCTs	18 months of treatment (AWP, office fees, injection fees, costs due to adverse events, laboratory monitoring)	PASI-75 at 18 months	Etanercept 50 mg twice weekly × 12 weeks, then 50 mg weekly
Miller et al. [73]	16 studies	Annual cost (treatment administration, adverse-event monitoring and treatment)	PASI% (treatment period not specified)	Infliximab 5 mg/kg
Pearce et al. [87]	13 RCTs (1998–2004)	12 weeks of treatment (AWP, physician visits, laboratory tests, Medicare fee for schedule of infusions)	PASI-75 after 12 weeks	Infliximab 5 mg/kg
Nelson et al. [88]	11 RCTs (2003–2007)	12 weeks of treatment (AWP, physician visits, laboratory testing, Medicare fee for schedule of infusions)	PASI-75, DLQI after 12 weeks	Etanercept 25 mg once weekly (DLQI MID) Infliximab 3 mg/kg (PASI 75)
Hankin et al. [89]	22 RCTs (1966–2008)	Annual cost (WAC, adverse event monitoring and treatment, Medicare fee for schedule of infusions)	PASI-75, PGA 0/1 after 6–14 weeks of treatment	Infliximab 5 mg/kg at weeks 0, 2, 6, then every 8 weeks
Staidle et al. [90]	22 RCTs (2001–2011)	Annual cost (AWP, office visits, laboratory tests, monitoring procedures)	PASI-75, DLQI MID after 12 weeks of treatment	Infliximab 5 mg/kg every 8 weeks (PASI and DLQI)
Anis et al. [91]	22 RCTs	10–16 weeks of treatment (AWP, treatment administration, monitoring, laboratory tests)	PASI between 10–16 weeks	Adalimumab 40 mg every other week (QALY)
Martin et al. [92]	ACCEPT trial (ustekinumab, etanercept)	16 weeks of treatment (WAC)	PASI-75 after 12 weeks	Ustekinumab (45 mg or 90 mg depending on weight)
Villacorta et al. [93]	ACCEPT trial (ustekinumab, etanercept)	3 years of treatment (Medicare Part B average sales price, treatment of adverse events, physician visits)	PASI after 12 weeks	Ustekinumab 45 mg ($150,000 threshold per QALY)

Table 3 continued

Study	Number of trials	Cost methodology	Efficacy methodology	Most cost-effective biologic
Ahn et al. [74]	27 RCTs (1995–2012)	12 weeks of treatment (AWP, physician visits, laboratory tests, Medicare fee for schedules of IV procedures)	PASI-75, DLQI after 12 weeks	Infliximab 3 mg/kg (PASI 75 and DLQI)
Chi et al. [94]	13 RCTs (2005–2012)	6 months of treatment (AWP)	PASI-75 and PGA 0/1 after 6 months	Adalimumab 80 mg loading dose, then 40 mg every other week (PASI 75 and PGA 0/1)

ACCEPT Active Comparator (CNTO1275/Enbrel) Psoriasis Trial, *AWP* Average wholesale price, *DLQI* Dermatology Life Quality Index, *MID* Minimally important difference, *PASI* Psoriasis Area and Severity Index, *PGA 0/1* Physician Global Assessment clear/minimal, *QALY* Quality-adjusted life year, *RCT* randomized controlled trial, *WAC* wholesale acquisition cost

[a] Study included non-biologic agents (i.e., phototherapy, cyclosporine, methotrexate, acitretin)

cost-effectiveness results mean that adalimumab cannot be recommended in preference to etanercept, with clinicians needing to exercise clinical judgment in choosing the appropriate therapy.

Ustekinumab is recommended for patients with severe plaque psoriasis not responding to, intolerant of, or with contraindications to standard systemic therapies, although it is noted that no robust differences in cost effectiveness between adalimumab and ustekinumab have been shown [82]. Notably, if etanercept is given continuously, rather than intermittently, ustekinumab is, in comparison, less costly and more effective.

Secukinumab is only recommended by NICE for patients with severe plaque psoriasis when the disease has failed to respond to standard systemic therapies, or the standard systemic therapies are contraindicated or the patient is unable to tolerate them and if the company provides secukinumab with the discount agreed in the patient access scheme [83].

The Italian Situation

Access to Biologicals for Psoriasis in Italy

There is a substantial body of evidence demonstrating the value of using effective therapies for psoriasis. Biologicals have changed psoriasis treatment standards, not only effectiveness, but in allowing the management of patients in an out-patient setting. However, the biological therapies are expensive. In the Italian NHS, biological drugs amount to €30.1 per capita (13.7% of the Italian NHS pharmaceutical expenditure), with biological agents for psoriasis representing 28.9% of the expenditure for biologic drugs [37].

Psocare

In 2005, AIFA, the Italian Medical Agency, formalized the Psocare project and defined the operating methods for prescribing biological drugs in Italy. The Psocare project launched as part of a program promoted by AIFA, based on the philosophy that psoriasis treatment

strategies have resulted in the consolidation of habits or behavior amongst doctors rather than in clear outcomes in terms of efficacy [37]. The aim of the project was to evaluate the long-term efficacy and safety of the treatments available, based on comparisons between different care strategies, to obtain realistic estimates of benefits and risks [37]. The Italian Regions identified reference centers for psoriasis, restricting the prescription of biological drugs to Psocare centers. The Psocare project ended in 2009, but despite evidence proving that biologicals are safer and better tolerated than conventional treatments for psoriasis, in Italy, these agents continue to mostly only be prescribed by Psocare centers.

Biological drugs could be managed by territorial specialists who work in collaboration with general practitioners (GPs). A collaboration network between Psocare centers and specialized territorial healthcare units may help achieve Psocare center quality standards in other units. Biologicals could be used in an outpatient setting, while still requiring that the patient be assessed by a dermatologist experienced in internal medicine aspects. Psocare centers could continue with a role in coordinating research activities, in addition to having an organizational, educational, and monitoring role.

Impact of Secukinumab Entry on the Market

The entry of secukinumab among first-line therapy options for psoriasis treatment places the new drug outside currently established treatment paradigms and opens the door for new scenarios. Secukinumab is a potential competitor of cyclosporine and all conventional first-line therapies, with approximately 30–40,000 patients in Italy expected to be eligible for treatment with this agent. The impact and sustainability of secukinumab in the psoriasis treatment market in Italy will largely depend on its position in the cost pyramid, which has methotrexate and cyclosporine at the base, and biotechnological drugs at the top.

The approval of secukinumab as a first-line treatment in moderate-to-severe psoriasis can be seen as the first step in breaking down the fixed therapy pyramid that currently defines the sequence of therapies for psoriasis. The introduction of secukinumab in this position begins to outline a new way of choosing among treatments, according to factors such as effectiveness, tolerability, comorbidity, etc., rather than simply following a set pathway from one treatment to the next. In order to allow for such choice, the well-established 'silo-type' patterns of funding and budgets need to be broken down, but in doing so, there is likely to be conflict between the existing therapy pyramid and the traditional economic pyramid in which the cheaper drug is preferred.

It is important to consider the particular strengths of secukinumab, including the excellent results compared with placebo, the good safety profile, and the demonstrated superiority to both etanercept and ustekinumab. Moreover, an important opportunity arising with the change in psoriasis management that may potentially occur with the entry into the market of secukinumab as first-line systemic therapy is that for increased education on, and increased awareness of, psoriasis as a currently under-diagnosed and under-treated pathology. This could be achieved by collaboration between scientific societies and patient associations. This is of particular importance given the current lack of interest from decision-makers and the public regarding the impact of psoriasis on patient QoL. Moreover,

the excellent results seen for secukinumab using the reduction of PASI of at least 90% (PASI 90) as an efficacy measure may lead to this becoming the new standard of effectiveness for agents useful for the treatment of psoriasis, although many physicians at present are happy with achievement of PASI 75.

However, there are a number of potential hurdles for secukinumab to overcome in Italy so that it reaches its full potential in the treatment of moderate-to-severe psoriasis. An important potential weakness of secukinumab in terms of access to the drug is the possibility that it could be subject to prescribing restrictions. In Italy, sofosbuvir, used in the treatment of chronic hepatitis C, is subject to monitoring, and prescriptions, including renewals, are restricted to hospitals or specialized physicians. Similarly, denosumab, used in the prevention of osteoporosis-induced bone fractures, is subject to restrictions imposed by AIFA and is only allowed to be used by specialized physicians; this situation is in contrast to that in Germany where denosumab is available from GPs as an alternative to bisphosphonates.

It is likely that prescription of secukinumab will be limited to specialized physicians in Italy, although it is possible that permission to prescribe the drug may be extended to accredited public or private non-Psocare health centers. However, it is unlikely that GPs will be authorized to prescribe the agent. Nevertheless, even in the presence of such restrictions, the access to secukinumab should be guaranteed to all patients that are candidates, while balancing the need to maintain sustainability of the treatment and the safety for patients. While the population of patients in Italy who will be able to access secukinumab is likely to be restricted initially, it is possible that the eligible population will gradually increase as more data on the agent becomes available, with associated changes in the prescribing model. Furthermore, it is expected that distribution channels would change over time to include an increased number of hospitals as well as territorial outpatient services. There are already tools available from the AIFA that could be used to monitor and control health costs, while guaranteeing access and sustainability at the same time; these tools could be used with secukinumab to ensure that it is used appropriately.

Factors which may influence the positioning of secukinumab in the Italian marketplace include the fact that refundability may be limited only to Psocare centers, that clinicians have to choose among several drugs in the same budget and that there have been budget cuts in Italian regulatory framework File F, which already has too many drugs and not enough room for dermatology.

CONCLUSIONS

Moderate-to-severe psoriasis is associated with significant comorbidity and has a substantial impact on patient QoL. The introduction of the biological agents for the treatment of moderate-to-severe psoriasis has vastly improved available treatment options for patients, with the addition of secukinumab as a first-line systemic therapy further broadening options. However, the biological agents are costly and pose a significant burden on NHSs. In Italy, the introduction of secukinumab as a first-line therapy should influence a reconsideration of the way dermatological care for psoriasis is organized, moving to a larger involvement of specialists under the coordination of Psocare centers.

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REFERENCES

1. Langley RGB, Krueger GG, Griffiths CEM. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005;64(Suppl 2):ii18–23.

2. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133(2):377–85.

3. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2009;23(Suppl 2):1–70.

4. Wolkenstein P, Revuz J, Roujeau JC, Bonnelye G, Grob JJ, Bastuji-Garin S. Psoriasis in France and associated risk factors: results of a case-control study based on a large community survey. Dermatology. 2009;218(2):103–9.

5. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. Arch Dermatol. 2005;141(12):1537–41.

6. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. J Am Acad Dermatol. 2009;60(2):218–24.

7. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc. 2004;9(2):136–9.

8. Leman J, Burden AD. Treatment of severe psoriasis with infliximab. Ther Clin Risk Manag. 2008;4(6):1165–76.

9. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1–10.

10. Feldman SR, Burudpakdee C, Gala S, Nanavaty M, Mallya UG. The economic burden of psoriasis: a systematic literature review. Expert Rev Pharmacoecon Outcomes Res. 2014;14(5):685–705.

11. Esposito M, Saraceno R, Giunta A, Maccarone M, Chimenti S. An Italian study on psoriasis and depression. Dermatology. 2006;212(2):123–7.

12. Reich K, Kruger K, Mossner R, Augustin M. Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis. Br J Dermatol. 2009;160(5):1040–7.

13. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. Br J Dermatol. 1995;132(2):236–44.

14. Pereira MG, Brito L, Smith T. Dyadic adjustment, family coping, body image, quality of life and psychological morbidity in patients with psoriasis and their partners. Int J Behav Med. 2012;19(3):260–9.

15. Spandonaro F, Altomare G, Berardesca E, et al. Health-related quality of life in psoriasis: an analysis of Psocare project patients. G Ital Dermatol Venereol. 2011;146(3):169–77.

16. European Commission. Commission implementing decision for Cosentyx™ (secukinumab). http://ec.europa.eu/health/documents/community-register/2015/20150115130444/dec_130444_en.pdf. Accessed 26 Apr 2015.

17. US Food and Drug Administration. FDA approves new psoriasis drug Cosentyx. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430969.htm. Accessed 27 Apr 2015.

18. 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(5):826–50.

19. Cohen AD, Dreiher J, Birkenfeld S. Psoriasis associated with ulcerative colitis and Crohn's disease. J Eur Acad Dermatol Venereol. 2009;23(5):561–5.

20. Najarian DJ, Gottlieb AB. Connections between psoriasis and Crohn's disease. J Am Acad Dermatol. 2003;48(6):805–21.

21. Broadley SA, Deans J, Sawcer SJ, Clayton D, Compston DA. Autoimmune disease in first-degree relatives of patients with multiple sclerosis. A UK survey. Brain. 2000;123(Pt 6):1102–11.

22. Tadros A, Vergou T, Stratigos AJ, et al. Psoriasis: is it the tip of the iceberg for the quality of life of patients and their families? J Eur Acad Dermatol Venereol. 2011;25(11):1282–7.

23. Gisondi P, Girolomoni G. Psoriasis and atherothrombotic diseases: disease-specific and non-disease-specific risk factors. Semin Thromb Hemost. 2009;35(3):313–24.

24. Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol. 2006;54(4):614–21.

25. Cohen AD, Gilutz H, Henkin Y, et al. Psoriasis and the metabolic syndrome. Acta Derm Venereol. 2007;87(6):506–9.

26. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006;55(5):829–35.

27. Shapiro J, Cohen AD, David M, et al. The association between psoriasis, diabetes mellitus, and atherosclerosis in Israel: a case-control study. J Am Acad Dermatol. 2007;56(4):629–34.

28. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. J Invest Dermatol. 2009;129(10):2411–8.

29. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296(14):1735–41.

30. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol. 2004;19(3):225–30.

31. Gelfand JM, Troxel AB, Lewis JD, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol. 2007;143(12):1493–9.

32. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol. 2001;137(3):280–4.

33. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. Br J Dermatol. 1998;139(5):846–50.

34. Russo PA, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: a review. Australas J Dermatol. 2004;45(3):155–9.

35. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41(3 Pt 1):401–7.

36. Parrish L. Psoriasis: symptoms, treatments and its impact on quality of life. Br J Community Nurs. 2012;17(11):524.

37. Spandonaro F, Ayala F, Berardesca E, et al. The cost effectiveness of biologic therapy for the treatment of chronic plaque psoriasis in real practice settings in Italy. BioDrugs. 2014;28(3):285–95.

38. Miniszewska J, Juczynski Z, Ograczyk A, Zalewska A. Health-related quality of life in psoriasis: important role of personal resources. Acta Derm Venereol. 2013;93(5):551–6.

39. Sojevic Timotijevic Z, Jankovic S, Trajkovic G, et al. Identification of psoriatic patients at risk of high quality of life impairment. J Dermatol. 2013;40(10):797–804.

40. Klaassen KM, van de Kerkhof PC, Pasch MC. Nail psoriasis, the unknown burden of disease. J Eur Acad Dermatol Venereol. 2014;28(12):1690–5.

41. Baran R. The burden of nail psoriasis: an introduction. Dermatology. 2010;221(Suppl 1):1–5.

42. Vardy D, Besser A, Amir M, Gesthalter B, Biton A, Buskila D. Experiences of stigmatization play a role in mediating the impact of disease severity on quality of life in psoriasis patients. Br J Dermatol. 2002;147(4):736–42.

43. Schmid-Ott G, Schallmayer S, Calliess IT. Quality of life in patients with psoriasis and psoriasis arthritis with a special focus on stigmatization experience. Clin Dermatol. 2007;25(6):547–54.

44. Raho G, Koleva DM, Garattini L, Naldi L. The burden of moderate to severe psoriasis: an overview. Pharmacoeconomics. 2012;30(11):1005–13.

45. Colombo G, Altomare G, Peris K, et al. Moderate and severe plaque psoriasis: cost-of-illness study in Italy. Ther Clin Risk Manag. 2008;4(2):559–68.

46. Yu AP, Tang J, Xie J, et al. Economic burden of psoriasis compared to the general population and stratified by disease severity. Curr Med Res Opin. 2009;25(10):2429–38.

47. Horn EJ, Fox KM, Patel V, Chiou C-F, Dann F, Lebwohl M. Association of patient-reported psoriasis severity with income and employment. J Am Acad Dermatol. 2007;57(6):963–71.

48. Chan B, Hales B, Shear N, et al. Work-related lost productivity and its economic impact on Canadian patients with moderate to severe psoriasis. J Cutan Med Surg. 2009;13(4):192–7.

49. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. J Am Acad Dermatol. 2006;55(3):490–500.

50. Ghatnekar O, Ljungberg A, Wirestrand LE, Svensson A. Costs and quality of life for psoriatic patients at different degrees of severity in southern Sweden—a cross-sectional study. Eur J Dermatol. 2012;22(2):238–45.

51. Berger K, Ehlken B, Kugland B, Augustin M. Cost-of-illness in patients with moderate and severe chronic psoriasis vulgaris in Germany. J Dtsch Dermatol Ges. 2005;3(7):511–8.

52. Levy AR, Davie AM, Brazier NC, et al. Economic burden of moderate to severe plaque psoriasis in Canada. Int J Dermatol. 2012;51(12):1432–40.

53. Luba KM, Stulberg DL. Chronic plaque psoriasis. Am Fam Physician. 2006;73(4):636–44.

54. Zeichner JA, Lebwohl M. Potential complications associated with the use of biologic agents for psoriasis. Dermatol Clin. 2007;25(2):207–13.

55. Herrier RN. Advances in the treatment of moderate-to-severe plaque psoriasis. Am J Health Syst Pharm. 2011;68(9):795–806.

56. Nast A, Boehncke WH, Mrowietz U, et al. S3—guidelines on the treatment of psoriasis vulgaris (English version). Update. J Dtsch Dermatol Ges. 2012;10(Suppl 2):S1–95.

57. Levine D, Gottlieb A. Evaluation and management of psoriasis: an internist's guide. Med Clin North Am. 2009;93(6):1291–303.

58. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987–1019.

59. Novartis Pharmaceuticals Corporation. Advisory Committee briefing materials: secukinumab (AIN457). http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM419023.pdf. Accessed 26 Apr 2015.

60. Lønnberg AS, Zachariae C, Skov L. Targeting of interleukin-17 in the treatment of psoriasis. Clin Cosmet Investig Dermatol. 2014;7:251–9.

61. Garnock-Jones KP. Secukinumab: a review in moderate to severe plaque psoriasis. Am J Clin Dermatol. 2015;16(4):323–30.

62. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med. 2014;371(4):326–38.

63. Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015;29(6):1082–90.

64. Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015;172(2):484–93.

65. Thaçi D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol. 2015;73(3):400–9.

66. Celgene Corporation. Oral OTEZLA® (apremilast) approved by the U.S. Food and Drug Administration for the treatment of patients with moderate to severe plaque psoriasis [media release]. http://ir.celgene.com/releasedetail.cfm?ReleaseID=872240. Accessed 28 Apr 2015.

67. Celgene Corporation. Oral OTEZLA® (apremilast) approved by the European Commission for the treatment of both patients with psoriasis and psoriatic arthritis [media release]. http://ir.celgene.com/releasedetail.cfm?ReleaseID=891728. Accessed 16 May 2015.

68. Campa M, Mansouri B, Warren R, Menter A. A review of biologic therapies targeting IL-23 and IL-17 for use in moderate-to-severe plaque psoriasis. Dermatol Ther (Heidelb). 2016;6(1):1–12.

69. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. Br J Dermatol. 2012;167(3):668–77.

70. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med. 2015;373(14):1318–28.

71. Papp KA, Reich K, Paul C, et al. A prospective phase 3, randomised, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016;. doi:10.1111/bjd.14493.

72. Amgen. Amgen to Terminate Participation in Co-development and Commercialization of Brodalumab [media release]. 2015. http://www.amgen.com/media/news-releases/2015/05/amgen-to-terminate-participation-in-co-development-and-commercialization-of-brodalumab/. Accessed 22 May 2015.

73. Miller DW, Feldman SR. Cost-effectiveness of moderate-to-severe psoriasis treatment. Expert Opin Pharmacother. 2006;7(2):157–67.

74. Ahn CS, Gustafson CJ, Sandoval LF, Davis SA, Feldman SR. Cost effectiveness of biologic therapies for plaque psoriasis. Am J Clin Dermatol. 2013;14(4):315–26.

75. Cheng J, Feldman SR. The cost of biologics for psoriasis is increasing. Drugs Context. 2014;3:212266.

76. Bhosle MJ, Feldman SR, Camacho FT, Timothy Whitmire J, Nahata MC, Balkrishnan R. Medication adherence and health care costs associated with biologics in Medicaid-enrolled patients with psoriasis. J Dermatolog Treat. 2006;17(5):294–301.

77. Finzi AF, Mantovani LG, Belisari A. The cost of hospital-related care of patients with psoriasis in Italy based on the AISP study. Associazione Italiana Studi Psoriasi. J Eur Acad Dermatol Venereol. 2001;15(4):320–4.

78. Colombo GL, Di Matteo S, Peris K, et al. A cost-utility analysis of etanercept for the treatment of moderate-to-severe psoriasis in Italy. Clinicoecon Outcomes Res. 2009;1:53–9.

79. National Institute for Health and Clinical Excellence (NICE). Etanercept and efalizumab for the treatment of adults with psoriasis. http://www.nice.org.uk/guidance/ta103/resources/guidance-etanercept-and-efalizumab-for-the-treatment-of-adults-with-psoriasis-pdf. Accessed 28 Apr 2015.

80. National Institute for Health and Clinical Excellence (NICE). Infliximab for the treatment of adults with psoriasis. http://www.nice.org.uk/guidance/ta134/resources/guidance-infliximab-for-the-treatment-of-adults-with-psoriasis-pdf. Accessed 28 Apr 2015.

81. National Institute for Health and Clinical Excellence (NICE). Adalimumab for the treatment of adults with psoriasis. http://www.nice.org.uk/guidance/ta146/resources/guidance-adalimumab-for-the-treatment-of-adults-with-psoriasis-pdf. Accessed 28 Apr 2015.

82. National Institute for Health and Clinical Excellence (NICE). Ustekinumab for the treatment of adults with moderate to severe psoriasis. http://www.nice.org.uk/guidance/ta180/resources/guidance-ustekinumab-for-the-treatment-of-adults-with-moderate-to-severe-psoriasis-pdf. Accessed 28 Apr 2015.

83. National Institute for Health and Clinical Excellence (NICE). Secukinumab for treating moderate to severe plaque psoriasis. http://www.nice.org.uk/guidance/ta350/resources/guidance-secukinumab-for-treating-moderate-to-severe-plaque-psoriasis-pdf. Accessed 16 Sept 2015.

84. European Medicines Agency. European public assessment reports. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124. Accessed 16 May 2015.

85. Hankin CS, Feldman SR, Szczotka A, Stinger RS, Fish L, Hankin DL. A cost comparison of treatments of moderate to severe psoriasis. Drug Benefit Trends. 2005;17(5):200–14.

86. Menter A, Baker T. Cost-efficacy analysis of biological treatments in psoriasis: an 18-month assessment. J Med Econ. 2005;8(1–4):139–46.

87. Pearce DJ, Nelson AA, Fleischer AB, Balkrishnan R, Feldman SR. The cost-effectiveness and cost of treatment failures associated with systemic psoriasis therapies. J Dermatol Treat. 2006;17(1):29–37.

88. Nelson AA, Pearce DJ, Fleischer AB Jr, Balkrishnan R, Feldman SR. 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(1):125–35.

89. Hankin CS, Bhatia ND, Goldenhert G, et al. A comparison of the clinical effectiveness and cost-effectiveness of treatments for moderate to severe psoriasis. Drug Benefit Trends. 2010;22(1):17–27.

90. Staidle JP, Dabade TS, Feldman SR. A pharmacoeconomic analysis of severe psoriasis therapy: a review of treatment choices and cost efficiency. Expert Opin Pharmacother. 2011;12(13):2041–54.

91. Anis AH, Bansback N, Sizto S, Gupta SR, Willian MK, Feldman SR. Economic evaluation of biologic therapies for the treatment of moderate to severe psoriasis in the United States. J Dermatol Treat. 2011;22(2):65–74.

92. Martin S, Feldman SR, Augustin M, Szapary P, Schenkel B. Cost per responder analysis of ustekinumab and etanercept for moderate to severe plaque psoriasis. J Dermatol Treat. 2011;22(3):138–43.

93. Villacorta R, Hay JW, Messali A. Cost effectiveness of moderate to severe psoriasis therapy with etanercept and ustekinumab in the United States. Pharmacoeconomics. 2013;31(9):823–39.

94. Chi CC, Wang SH. Efficacy and cost-efficacy of biologic therapies for moderate to severe psoriasis: a meta-analysis and cost-efficacy analysis using the intention-to-treat principle. Biomed Res Int. 2014;2014:862851.