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INVESTIGATIVE REPORT

Economic Burden of Psoriasis and Potential Cost Offsets with Biologic Treatment: A Swedish Register Analysis

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Estimates of direct and indirect costs of psoriasis are limited. The aim of this study was to estimate: (*i*) costs in patients with psoriasis compared with controls; and (*ii*) impact on costs from initiating biologics. The study extracted data from Swedish administrative registers and compared 31,043 patients with 111,645 sex-, age- and residency-matched referents. Mean direct and indirect costs were estimated as US dollars (USD) 1,365 (62%) and USD 3,319 (50%) higher in patients compared with referents, respectively. The study included 352 patients treated with biologics who had at least 1-year follow-up before and after initiation of biologics. Among the 193 patients persistent with biologics for one year, 1-year costs of biologics were estimated at USD 23,293 (95% confidence interval (95% CI) 22,372−24,199). This cost was partially offset, with savings in direct costs estimated to range from USD –1,135 (95% CI –2,050 to –328) to USD –4,422 (95% CI –6,552 to –2,771), depending on assumptions. The corresponding estimates for indirect costs savings were from USD –774 (95% CI –2,019−535) to USD –1,875 (95% CI –3,650 to –188). The study suggests that psoriasis is associated with substantial costs, which may be modifiable with treatment. *Key words: psoriasis; cost-of-illness; cost savings; biologics.*

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Psoriasis is an immune-mediated inflammatory disease of the skin (1). The prevalence of the disease varies globally, with the highest rates observed in Northern Europe at 2–4% (2). Psoriasis is associated with increased risk of comorbidities, including psoriatic arthritis (PSA), obesity, cardiovascular disease and cancer (3); impaired health-related quality of life (HRQoL) (4); increased healthcare resource utilization (HCRU) (5); reduced productivity (6); and premature mortality (7).

Given that no curative therapy for psoriasis exists, the objective of treatment is to lower disease activity and alleviate symptoms (8). In increasing order of potency, the treatment modalities for psoriasis are topicals, phototherapy, traditional systemics and biologics (8).

Estimating the costs of a disease in relation to the general population may allow for identification of unmet needs. It is also an important step in quantifying the burden of the disease; information that may allow decision-makers to anticipate public interest and enable the prioritization of research funding (9). Furthermore, subgroup stratification; for example, by disease severity, may identify patient segments that warrant specific attention.

It is comparatively straight-forward to estimate costs of biologics in psoriasis given information on pricing, dosage and adherence. Cost offsets attributable to biologics are more difficult to derive, reflecting that they necessitate estimation of counterfactual costs; the costs that would have been incurred had the biologic not been initiated. Nevertheless, estimates of cost offsets with biologic treatment are central in the estimation of cost-effectiveness of biologics in psoriasis (10) and the magnitude of cost offsets is a key area of uncertainty for reimbursement decisions taken by Health Technology Assessment (HTA) agencies. Therefore research on the matter has repeatedly been deemed a priority (11, 12).

A number of studies have estimated the costs of psoriasis and a recent systematic review on this research area identified 35 publications (5). However, the studies conducted in Europe to date have not included a control population, rendering interpretation of the cost estimates difficult (13). Whilst biologics have improved treatment outcomes for patients with moderate-to-severe psoriasis, biologics are associated with substantial costs. To our knowledge, only 5 studies have described the impact of initiation of biologics on direct costs (HCRU costs) (14–18), and a single study (17) has described the impact on indirect costs (costs of productivity losses). Therefore this study has 2 aims: (*i*) to estimate the direct and indirect annual costs in patients with psoriasis compared with a sex-, age- and residency-matched reference population; and (*ii*) to estimate the potential direct and indirect cost offsets with biologics in patients with psoriasis.

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METHODS

Data sources

The Skåne Health Care Register (SHCR) and the VEGA register are regional registers with a total population coverage of 2.8 million individuals from 2001 and 2005, respectively. The SHCR and VEGA registers have been used in population-based health outcomes studies (19–23) and are described elsewhere.

The Total Population Register (TPR) includes information on vital status, residency, emigration status, and immigration status at any point in time for all permanent residents in Sweden (24).

The Swedish Prescribed Drug Register (SPDR) captures data on all prescriptions dispensed at all Swedish pharmacies from 2005. The SPDR includes date of prescription, dispense date, Anatomical Therapeutic Chemical (ATC)-code, prescriber information, and costs to the patient and the government (25).

MikroData för Analys av Socialförsäkringen (MiDAS) is a nationwide register with data since 1994 on sickness benefit, activity compensation, and sickness compensation for all permanent residents in Sweden.

Study population and stratification

Patients with a registered diagnosis of psoriasis (L40.x) were identified in the VEGA register and SHCR throughout the data availability for each register at the time of data extraction (1 January 2001 to 31 December 2010 for SHCR, and 1 January 2005 to 31 March 2010 for VEGA). For each patient with psoriasis, 4 subjects without psoriasis but of similar age (±1 year), same sex, and same residency (municipality) were identified. Individuals fulfilling the matching criteria were randomly drawn without replacement from the general population on December 31 of the year before the corresponding patient's first registered diagnosis of psoriasis.

For the analysis of costs of psoriasis in 2010, all patients with a primary diagnosis of psoriasis who were alive during the entire calendar year were identified. Among those patients, individuals who, based on dispensed prescriptions and diagnoses, were difficult to assign to a treatment class were removed from the analysis. For the analysis of indirect costs, patients and referents below 19 or over 64 years of age on 1 January 2010 were excluded, reflecting that those individuals may not have been eligible for sickness benefit, sickness compensation, or activity compensation throughout 2010. Further details of the sample selection are provided in Appendix S1[1].

Patients were stratified according to the most potent treatment modality they were treated with during 2010 in the following order: no therapy, topicals, phototherapy (excluding psoralen combined with ultraviolet A (PUVA)), traditional systemics (including PUVA), biologics, and hospitalization with psoriasis as a primary diagnosis (see Appendix S1[1] for corresponding treatment codes).

For the analysis of potential cost offsets with biologics, among all patients with a diagnosis of psoriasis (51,085, Appendix S1[1]) individuals who dispensed at least one prescription of a relevant biologic (adalimumab, etanercept, or ustekinumab) from 1 July 2006 to 31 December 2010 were identified. Infliximab was not included in the analysis, reflecting that this drug is administered in an outpatient setting and therefore typically not dispensed in pharmacies (26), resulting in it being not well-captured in the SPDR. The index date for the analysis was set as the date of the first dispensed prescription of a biologic. The following patients were excluded: those who had less than 12 months follow-up before or after the index date; and those who had at least one biologic prescription issued by a non-dermatologist and had a registered diagnosis for which the treatments are licensed (see Appendix S1[1]). Furthermore, patients who were persistent with the biologic less than 12 months, with persistency derived using previously described methods (21), were excluded from the analyses of cost offsets; however, for comparative purposes, data on patient characteristics were presented for this group. For the analysis of indirect costs, patients below 19 or above 64 years at the index date were excluded.

Data analysis

Patient characteristics. Patients were characterized with respect to sex, age, and comorbidity profile using the Quan-Charlson comorbidity index (CCI) (27). The index score is the sum of weights (1, 2, 3, or 6) assigned to 19 specific comorbidities (28). Higher index scores imply a more severe comorbidity profile.

In analyses of costs in 2010, age was estimated on 1 January 2010, and comorbidities were extracted from 1 January 2009 to 31 December 2009. In analyses of the cost impact of biologics, age was estimated at the index date, and comorbidities and most potent prior therapy were extracted for the 12 months leading up to the index date.

Resource use and unit costs. In the analysis of costs in 2010, HCRU costs were grouped into outpatient care, inpatient care, psoriasis medication, and other medication. Costs of productivity losses were grouped by sickness benefit (used for short absences) and by sickness or activity compensation (early retirement). Further details on the cost categories and unit costs are given in Appendix S1[1].

The cost categories for the cost offsets analysis were the same as the cost categories in the analysis of costs in 2010, with the exception of psoriasis medications, which excluded traditional systemics and biologics, and hence consisted only of topicals. In addition, to contextualize the cost offsets, the costs of biologics were derived as a separate category. Potential costs offsets with biologics were estimated by comparing the actual accumulated costs (excluding biologics) 12 months after biologic initiation with 3 counterfactual scenarios on development of costs: (*i*) costs and productivity losses remaining the same as in the 12-month period before initiation; (*ii*) costs and productivity losses remaining the same as in the final month prior to biologic initiation; and (*iii*) costs and productivity losses remaining the same as in the penultimate month before biologic initiation. These 3 counterfactuals were chosen reflecting possible scenarios of cost-development in the absence of biologics: the first scenario assumes that costs remain the same on a yearly basis irrespective of biologic initiation. The second scenario assumes that the costs the year after initiation reflect the health status at the time the biologic was initiated (i.e. the month directly before initiation). The assumption underlying the third scenario is that some of the costs in the final month before initiation are driven by the decision to initiate the biologic and instead extrapolate the costs based on the penultimate month, where costs related to the initiation of biologic are less likely to be incurred. In order to facilitate evaluation of the 3 scenarios for cost offsets, the costs of biologics were not included in the figures presenting cost development 12 months before and after initiation of biologics.

Statistical methods

In analyses of patient characteristics, patients in each therapy stratum were compared with the corresponding referents. For continuous variables, *t*-tests were implemented for comparisons of means between groups; for categorical variables, Pearson's χ^2 was used to test for differences of proportions between groups.

Given that cost data may be heavily skewed, bootstrapping was conducted for comparisons of mean costs involving strata with less than 1,000 patients, as recommended by Desgagné et al. (29). In comparisons of mean costs involving strata with at least 1,000

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patients, *t*-tests were implemented. When bootstrapping was conducted, *p*-values were derived using the bootstrap *t*, and CIs were derived using the bias corrected percentile method (30). For each bootstrap analysis, 10,000 bootstrap replications were run.

In order to control for the potential confounding effect of comorbidities on the mean cost differences between patients and referents in each therapy strata, bootstrapped generalized linear models (GLMs) assuming gamma-distributed costs (31) were fitted to the data. The dependent variables in these models were total direct and indirect costs, and the independent variables were CCI and patient/referent indicators. The point estimates of the indicator variables from the GLMs were divided by the crude point estimates to estimate the proportion of the excess costs attributable to differences in comorbidity status between patients and referents. In order to explore differences in mean total direct and indirect costs among patients across therapy strata, similar GLM models were implemented. The difference consisted of that referents were excluded from the analyses; that age and sex were added as independent variables; and that the patient/referent indicator variables were replaced with indicator variables for therapy strata, with "no treatment" used as the reference stratum.

All statistical tests were conducted using a 2-sided level of significance (probability of rejecting a true null-hypothesis) of 0.05. Data management was conducted in SAS 9.2 and STATA 14 was used for statistical analyses.

RESULTS

In the analysis of costs in 2010, 31,043 patients and 111,645 referents were eligible for analysis see (Appendix S1; SFig. 1[1]). Given the study design, differences in age and sex distributions between patients and referents within severity strata were small, as expected (Table I). However, the comorbidity burden measured using the CCI was significantly higher in patients than in referents in all strata ($p < 0.01$ for all comparisons).

Total HCRU costs were significantly higher in patients than in referents in all strata (Table II). In the crude analysis, the differences in mean total HCRU costs between patients and referents ranged from USD 461 (22%) in the no-treatment stratum to USD 18,077 (674%) in the hospitalized stratum. When the CCI was used to control for differences in mean total HCRU costs between patients and referents, the cost differences were attenuated by 2% to 33%, for the different strata. For all patients and corresponding referents, mean total HCRU costs were estimated at USD 3,555 and USD 2,190 ($p < 0.001$), respectively. In the comparison of HCRU costs among patients in different strata, costs generally increased with potency of therapy, albeit the increase was not monotonic (Table SI[1]).

Mean total costs of productivity losses were significantly higher in patients than in referents in all strata (Table III). The difference in mean total costs of productivity losses between patients and referents ranged from USD 2,226 (36%) in patients without treatment to USD 21,832 (225%) in patients hospitalized for psoriasis. When the CCI was used to control for differences in mean total costs of productivity losses between patients and referents, the cost differences were attenuated by 12–34%, for the different strata. For all patients and corresponding referents, mean total costs of productivity losses were estimated at USD 9,898 and USD 6,579 ($p < 0.001$), respectively. In the comparison of mean total costs of productivity losses among patients in different strata, compared with patients without therapy, mean costs were significantly higher in patients who received topicals, biologics, or who were hospitalized for psoriasis (Table SI[1]).

In the analysis of cost offsets with biologics, 352 patients had a minimum of 12 months follow-up before and after initiation of biologics, and were classified as being treated with biologics for psoriasis. Among those 352 patients, 193 (55%) were persistent for at least 12 months with treatment and were included in the analysis. Patient characteristics stratified by persistence status are

Table I. *Baseline characteristics of the study population, by most potent treatment modality in patients and corresponding referents (Ref.)*

	No treatment	Topicals	Phototherapy	Traditional systemics	Biologics	Hospitalized
Subjects, *n* (%)						
Patients	17,856 (57.5)	9,327 (30.0)	1,352 (4.4)	1,972 (6.4)	459 (1.5)	77 (0.2)
Ref.	64,392 (57.7)	33,353 (29.9)	4,837 (4.3)	7,130 (6.4)	1,667 (1.5)	266 (0.2)
Male, *n* (%)						
Patients	8,126 (45.5)	4,332 (46.4)	781 (57.8)	1,021 (51.8)	276 (60.1)	47 (61.0)
Ref.	29,136 (45.2)	15,364 (46.1)	2,769 (57.2)	3,658 (51.3)	1,011 (60.6)	161 (60.5)
Age, mean (standard deviation [SD])						
Patients	50.3 (18.7)	56.9 (18.0)	51.4 (17.5)	57.3 (15.0)	49.1 (13.4)	59.1 (14.8)
Ref.	50.0 (18.3)	56.2 (17.3)	51.4 (17.2)	56.8 (14.5)	49.2 (13.0)	58.6 (13.9)
0–18 years, *n* (%)						
Patients	850 (4.8)	210 (2.3)	44 (3.3)	11 (0.6)	2 (0.4)	0 (0)
Ref.	3,281 (5.1)	817 (2.4)	166 (3.4)	44 (0.6)	8 (0.5)	0 (0)
19–64 years, *n* (%)						
Patients	12,598 (70.6)	5,672 (60.8)	972 (71.9)	1,304 (66.1)	401 (87.4)	53 (68.8)
Ref.	45,980 (71.4)	20,938 (62.8)	3,508 (72.5)	4,843 (67.9)	1,467 (88.0)	189 (71.1)
>65 years, *n* (%)						
Patients	4,408 (24.7)	3,445 (36.9)	336 (24.9)	657 (33.3)	56 (12.2)	24 (31.2)
Ref.	15,131 (23.5)	11,598 (34.8)	1,163 (24.0)	2,243 (31.5)	192 (11.5)	77 (28.9)
Quan-Charlson comorbidity index score, mean (SD)						
Patients	0.39 (1.25)	0.63 (1.58)	0.57 (1.61)	0.52 (1.28)	0.38 (1.08)	1.05 (1.93)
Ref.	0.32 (1.16)	0.42 (1.35)	0.40 (1.35)	0.42 (1.35)	0.22 (0.91)	0.43 (1.47)

Table II. *Mean (standard deviation [SD]) healthcare resource utilization (HCRU) costs by category and most potent treatment modality in patients (Pat.) and corresponding referents (Ref.), US dollars (USD) (2010)*

	No treatment Pat./Ref.	Topicals Pat./Ref.	Phototherapy Pat./Ref.	Traditional systemics Pat./Ref.	Biologics Pat./Ref.	Hospitalized Pat./Ref.
Outpatient costs, mean (SD)	968[a] (1,443)/ 799 (1,225)	1,449[a] (1,716)/ 864 (1,193)	3,050[a] (1,855)/ 804 (1,249)	1,822[a] (1,671)/ 851 (1,245)	1,775[a] (1,654)/ 687 (1,113)	2,910[a] (2,275)/ 852 (1,345)
Inpatient costs, mean (SD)	1,080[a] (5,075)/ 834 (4,462)	1,623[a] (6,436)/ 1,019 (4,823)	1,151 (5,436)/ 947 (5,230)	1,459[a] (5,771)/ 943 (4,356)	1,222[b] (4,379)/ 654 (3,680)	14,156[a] (13,094)/ 1,314 (5,438)
Psoriasis medication costs, mean (SD)	0[a] (0)/ 28 (629)	196[a] (331)/ 23 (562)	279[a] (375)/ 16 (424)	314[a] (539)/ 34 (657)	15,588[a] (7,131)/ 18 (554)	1,929[a] (4,423)/ 9 (50)
Other medication costs, mean (SD)	488[a] (1,750)/ 414 (1,461)	915[a] (4,497)/ 493 (2,069)	664[a] (1,744)/ 433 (1,486)	784[a] (1,320)/ 505 (1,707)	735[a] (1,367)/ 382 (1,372)	1,765[a] (2,850)/ 507 (1,235)
Total HCRU, mean (SD)	2,536[a] (6,297)/ 2,075 (5,564)	4,183[a] (8,970)/ 2,400 (6,134)	5,145[a] (6,702)/ 2,200 (6,362)	4,378[a] (6,998)/ 2,333 (5,805)	19,320[a] (9,025)/ 1,742 (4,980)	20,759[a] (13,778)/ 2,682 (6,783)
Difference in total HCRU*, mean (95% CI)	326 (243–409)	1,203 (1,031–1,375)	2,816 (2,222–3,410)	1,845 (1,422–2,269)	17,246 (16,416–18,076)	16,947 (13,813–20,082)

[a]$p<0.001$, [b]$p<0.01$, *Obtained from regression model controlling for Quan-Charlson comorbidity index. CI: confidence interval.

provided in Table IV. There were no statistically significant differences between the 2 patient groups.

In the 12 months after biologic initiation, mean costs of the biologics were estimated at USD 23,293 (95% CI 22,372−24,199). Development of mean HCRU costs (excluding systemics and biologics) and costs of productivity losses 12 months before and after initiation are presented in Fig. 1. In the counterfactual scenario where costs 12 months after biologic initiation were assumed to have remained the same as in the 12 months before initiation, mean HCRU costs offsets and mean costs of productivity loss offsets were estimated at USD –1,135 (95% CI –2,050 to –328) and –774 (95% CI –2,019–535), respectively. In the scenario where costs were assumed to have remained the same as in the final month before biologic initiation, mean HCRU and productivity costs loss offsets were estimated at USD –4,422 (95% CI –6,552 to –2,771) and –1,794 (95% CI –3,377 to –537), respectively. When costs were assumed to have remained at the same level as in the penultimate month before biologic initiation, mean HCRU and productivity loss cost offsets were estimated at USD –1,944 (95% CI –3,749 to –587) and –1,875 (–3,650 to –188), respectively.

DISCUSSION

This study estimated direct and indirect annual costs associated with psoriasis and potential cost offsets with biologics in patients with psoriasis. Compared with age, sex and residency-matched referents, patients with psoriasis incurred higher HCRU costs and costs of productivity losses. The majority (58%) of patients did not have a record of any psoriasis treatment in 2010 and, in those patients, HCRU costs and costs of productivity losses were moderately increased compared with referents, at USD 461 (22%) and USD 2,226 (36%), respectively. Both HCRU costs and costs of productivity losses generally increased with potency of therapy, and patients hospitalized for psoriasis had the highest HCRU costs and costs of productivity losses compared with referents, with the increments estimated at USD 18,077 (674%) and USD 21,832 (225%), respectively. Controlling for comorbidity status attenuated the difference in costs between patients and referents, especially in patients without treatment or on topicals, albeit the differences in both mean total HCRU and mean total costs due to productivity losses remained statistically significant in all strata.

In patients persistent at least 12 months with biologics, HCRU costs and productivity losses increased in the months prior to biologic initiation. After initiation, both cost categories decreased to, or even below, the levels observed before the increase. Potential mean HCRU cost offsets were estimated between USD –1,135 (95% CI –2,050 to –328) and USD –4,422 (95% CI –6,552 to –2,771), depending on assumptions on development of

Table III. *Mean (standard deviation [SD] costs of lost productivity by category and most potent treatment modality in patients (Pat.) and corresponding referents (Ref.), US dollars (USD) (2010)*

	No treatment Pat./Ref.	Topicals Pat./Ref.	Phototherapy Pat./Ref.	Traditional systemics Pat./Ref.	Biologics Pat./Ref.	Hospitalized Pat./Ref.
Sickness benefit, mean (SD)	1,556[a] (6,731)/ 1,148 (5,618)	1,844[a] (7,305)/ 1,276 (6,122)	1,354 (6,042)/ 1,309 (6,567)	2,630[a] (8,585)/ 1,397 (6,585)	1,806 (6,178)/ 1,178 (6,406)	5,575[b] (13,914)/ 1,408 (6,869)
Sickness or activity compensation, mean (SD)	6,935[a] (18,245)/ 5,117 (15,954)	10,209[a] (21,555)/ 5,898 (17,027)	7,948[a] (19,370)/ 5,205 (16,097)	9,894[a] (20,752)/ 6,025 (17,070)	12,060[a] (22,261)/ 3,782 (13,604)	25,964[a] (27,979)/ 8,300 (19,811)
Total productivity loss, mean (SD)	8,491[a] (19,295)/ 6,265 (16,791)	12,053[a] (22,354)/ 7,174 (17,980)	9,302[a] (19,979)/ 6,514 (17,174)	12,523[a] (22,002)/ 7,421 (18,183)	13,866[a] (22,899)/ 4,961 (15,049)	31,539[a] (30,051)/ 9,707 (20,600)
Difference in total productivity loss* mean (95% CI)	1,781 (1,395–2,168)	3,697 (2,973–4,421)	1,844 (424–3,264)	4,523 (2,912–6,133)	7,874 (5,482–10,265)	18,935 (2,494–35,376)

[a]$p<0.001$, [b]$p<0.05$. *Obtained from regression model controlling for Quan-Charlson comorbidity index. CI: confidence interval.

Table IV. *Baseline characteristics for patients on biologics stratified by 12 months persistence status*

	Patients persistent for 12 months ($n=193$)	Patients not persistent for 12 months ($n=159$)
Male, *n* (%)	120 (62.2)	99 (62.3)
Age, mean (SD)	47.7 (13.7)	49.5 (12.7)
0–18 years, *n* (%)	0 (0)	0 (0)
19–64 years, *n* (%)	175 (90.7)	140 (88.1)
>64 years, *n* (%)	18 (9.3)	19 (11.9)
Comorbidities		
CCI score, mean (SD)	0.22 (0.79)	0.38 (1.15)
Most potent treatment modality 1 year prior to biologic initiation, *n* (%)		
No treatment	25 (13.0)	15 (9.4)
Topicals	41 (21.2)	43 (27.0)
Phototherapy	7 (3.6)	7 (4.4)
Traditional systemics	108 (56.0)	83 (52.2)
Hospitalized	12 (6.2)	11 (6.9)

SD: standard deviation.

costs had the biologic not been initiated, whereas estimated mean productivity loss offsets ranged from USD –774 (95% CI –2,019 to 535) to USD –1,875 (95% CI –3,650 to –188) for the same scenarios. Given the costs of biologics estimated in this study, USD 23,293 (95% CI 22,372 to 24,199), total costs increased in all 3 scenarios.

The development of non-biologic and non-systemic HCRU costs over one year before and after initiation of biologics, presented in Fig. 1A, shows an increase in costs that starts several months before treatment initiation, suggesting that patients' disease worsened a number of months before initiation. The peak in the month prior to initiation reflects that patients need to visit a physician to be prescribed the biologic; hence the peak is partially a result of the study design. The trajectory of cost development suggests that a direct comparison of costs one year before and one year after biologic initiation may underestimate the potential cost offsets with biologics: given the upward slope in costs that starts several months prior to biologic initiation (Fig. 1A), it may be difficult to argue that 1-year costs would remain the same if the biologic had not been initiated.

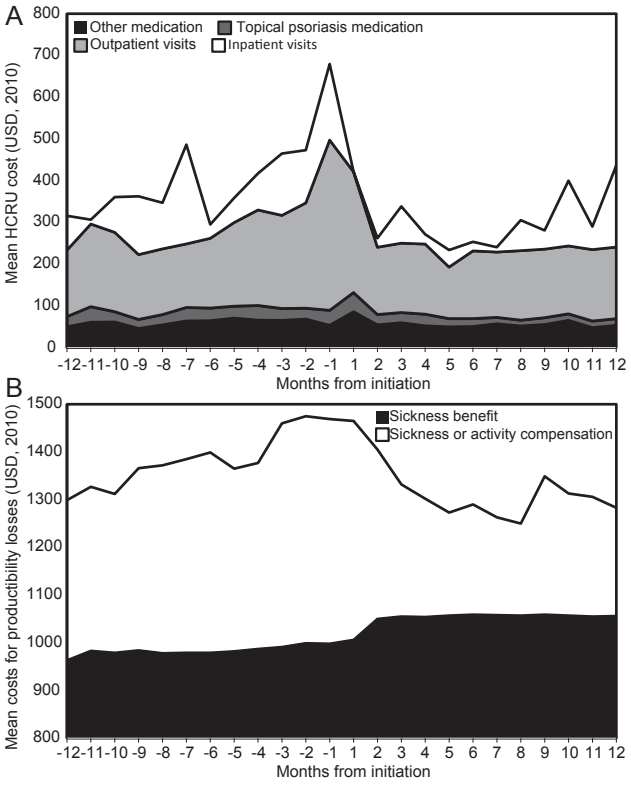

Fig. 1. (A) Development of healthcare resource utilization (HCRU) costs (excluding traditional systemics and biologics). (B) Development of costs of productivity losses 12 months before and after initiation of biologics in patients persistent for at least 12 months.

For costs of productivity losses, there appears to be an upward trend in sick leave the year before biologic initiation (Fig. 1B). The first month after biologic initiation, costs for productivity losses are relatively stable, with a subsequent decrease. The lag between initiation of biologic treatment and decrease in costs of productivity losses may reflect that changes in sick leave status are likely to follow changes in patients' health.

Three US studies have reported estimates of HCRU costs in patients with psoriasis compared with a reference population. Given the challenges in comparing absolute costs across healthcare systems and countries, it may be more meaningful to compare the relative estimates. In relative terms, the excess costs in patients with psoriasis presented in this study are similar to the estimates derived in 2 of the studies (32, 33), but are smaller than in the third study (6). The difference may reflect that that patients in the third study required at least 2 diagnoses of psoriasis and had incurred both direct and indirect costs.

Three Swedish studies have presented estimates of costs in patients with psoriasis. On an annualized basis, HCRU cost estimates in the 3 studies were USD 1,043 (34), USD 2,645 (35), and USD 11,356 (36). Annualized estimates of cost of productivity losses in the 3 studies were USD 1,500 (35), 3,190 (36), and approximately USD 13,500 (34). The differences may reflect patient recruitment strategy, inclusion/exclusion criteria, and differences in definition of costs.

Five studies have compared costs before and after initiation of biologics (14–18). All but one US study (14) reported increased mean total HCRU costs. When the costs of biologics were excluded in the 4 other studies, results differed: a UK study reported that mean annual costs (excluding psoriasis specific medications) decreased by GBP 1,682 (95% CI –3,182 to –182) (16); an Italian study reported that mean costs (excluding psoriasis specific medication) decreased by 33% (approximately EUR 650), albeit the statistical significance of the difference was not reported (18); a Dutch study reported a statistically significant decrease in mean per patient year costs for day care admissions, but not for hospitalizations (15); a French study reported that costs increased across a broad range of cost categories (17). The cost offsets in the present study are similar to the ones presented in the

UK (16) and Italian (18) studies; appear smaller than in the US study (14), but higher than in the French study (18). The divergence in findings may reflect differences in patient populations, country settings, categories of HCRU included in the studies, and time periods analysed.

There are general limitations in estimating cost of illness using administrative healthcare data produced for reimbursement purposes. For example, it is not possible to verify diagnoses clinically and the registered diagnoses may be affected by reimbursement rates. Another limitation is that all relevant resources are not captured in administrative registers. Examples include out of pocket payments and impaired ability to work (such as presenteeism).

Limitations specific to this study include that, in the majority of cases, productivity losses were assigned only to sick leave episodes lasting longer than 14 consecutive days. Hence a substantial proportion of all sick leave episodes were not accounted for, for example, 1 or 2 days of absence from work would not have been captured, resulting in underestimation of costs of productivity losses. Another limitation is that costs were estimated by assigning unit costs to resources reflecting that data on actual payments were not available for the whole time-period.

This study estimated annual costs in patients with psoriasis compared with a reference population. This approach facilitates estimation of the burden of psoriasis, including costs attributable to comorbidities associated with the disease. However, to the extent that the excess comorbidity burden does not result from psoriasis, this approach may overestimate the costs of psoriasis. Although analyses controlling for differences in comorbidity profiles between patients and referents were conducted, there may be residual confounding due to unmeasured comorbidities. Hence, the results may be interpreted as the costs incurred in patients with psoriasis compared with patients without psoriasis, rather than the costs of psoriasis. It may be important to note that only a proportion of the excess cost burden in patients with psoriasis may be modifiable by effective psoriasis treatment. This proportion is difficult to estimate, reflecting that the impact of effective psoriasis control on comorbidities is not known.

For the estimation of potential cost offsets, it should be noted that the relevant counterfactual (the costs the patient would have incurred had she not been treated with biologics) is unknown. For example, if patients had not been treated with biologics, they may have needed to be hospitalized, substantially increasing HCRU costs. Furthermore, the limited sample size renders monthly estimates of mean costs uncertain, necessitating additional caution in the interpretation of the development of costs over time and in the counterfactual scenarios where 1-year costs are projected based on 1-month estimates. This is particularly important for inpatient care which is infrequent but costly.

This study also has several strengths. Firstly, the number of patients in the analysis of costs in 2010 was substantial, allowing for analysis stratified by most potent treatment modality. Furthermore, the inclusion of a reference population allowed for a contextualization of the disease burden that would otherwise not have been possible. It may also be noted that this study included patients with a diagnosis of psoriasis in primary care, potentially providing more representative data on patients with psoriasis compared with studies that identify patients based on filled prescriptions. The analysis of cost offsets benefit from including all types of healthcare resulting in that cost offsets that accrue outside the dermatology department are also accounted for. Furthermore, analysis of cost offsets on a monthly basis may also provide a more comprehensive picture of potential cost offsets than studies that only compare yearly costs before and after initiation of biologics.

Further research in this area is needed. Studies with broader definition of costs would be valuable, In addition, studies defining the proportion of non-psoriasis costs attributable to psoriasis and treatment would also add to the understanding of the disease burden. In terms of costs offsets associated with biologics in psoriasis, studies identifying the costs of the true counterfactual would advance the field and allow for more accurate estimation of the cost-effectiveness of biologics in psoriasis.

In summary, this study suggests that psoriasis is associated with substantial economic burden and that the burden can be affected by treatment. Whilst the cost burden increases with potency of treatment, and hence presumably with disease severity, patients classified as having mild disease also incur substantially higher costs than age-, sex- and residency-matched referents, highlighting the need for novel treatment options across the disease severity spectrum.

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Conflicts of interest. CM and JC are employees and shareholders of Pfizer Inc; at the time of manuscript development LM was an employee and shareholder of Pfizer Inc; as employees of Mapi, JD and AS have provided consultancy services to numerous companies involved in the marketing of treatment for psoriasis; IP has received honoraria for educational lectures from Pfizer, Abbvie, UCB Pharma; MS has received honoraria for serving as advisor and for participating in symposia arranged by Abbvie, Novartis, Pfizer, Eli Lilly and Janssen-Cilag.

REFERENCES

1. Ortonne JP. Aetiology and pathogenesis of psoriasis. Br J Dermatol 1996; Suppl 49: 1–5.
2. Christophers E. Psoriasis – epidemiology and clinical spectrum. Clin Exp Dermatol 2001; 26: 314–320.

3. Kimball AB, Gladman D, Gelfand JM, Gordon K, Horn EJ, Korman NJ, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol 2008; 58: 1031–1042.
4. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999; 41: 401–407.
5. 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: 685–705.
6. Fowler JF, Duh MS, Rovba L, Buteau S, Pinheiro L, Lobo F, et al. The impact of psoriasis on health care costs and patient work loss. J Am Acad Dermatol 2008; 59: 772–780.
7. Ahlehoff O, Gislason GH, Charlot M, Jorgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. J Intern Med 2011; 270: 147–157.
8. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, 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: 826–850.
9. Rice DP. Cost of illness studies: what is good about them? Inj Prev 2000; 6: 177–179.
10. Zhang W, Islam N, Ma C, Anis AH. Systematic review of cost-effectiveness analyses of treatments for psoriasis. PharmacoEconomics 2015; 33: 327–340.
11. Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Asses 2006; 10: iii–iv, xiii–xvi, 1–239.
12. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis: final appraisal determination. [Accessed 2016 Jan 16] Available from: http://www.nice.org.uk/guidance/ta350/history.
13. Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. Pharmacoeconomics 2011; 29: 653–671.
14. Bhosle MJ, Feldman SR, Camacho FT, Timothy WJ, Nahata MC, Balkrishnan R. Medication adherence and health care costs associated with biologics in Medicaid-enrolled patients with psoriasis. J Dermatolog Treat 2006; 17: 294–301.
15. Driessen RJ, Bisschops LA, Adang EM, Evers AW, Van De Kerkhof PC, De Jong EM. The economic impact of high-need psoriasis in daily clinical practice before and after the introduction of biologics. Br J Dermatol 2010; 162: 1324–1329.
16. Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. Br J Dermatol 2010; 163: 807–816.
17. Le Moigne M, Sommet A, Lapeyre-Mestre M, Bourrel R, Molinier L, Paul C, et al. Healthcare cost impact of biological drugs compared with traditional systemic treatments in psoriasis: a cohort analysis in the French insurance database. J Eur Acad Dermatol Venereol 2014; 28: 1235–1244.
18. Spandonaro F, Ayala F, Berardesca E, Chimenti S, Girolomoni G, Martini P, et al. The cost effectiveness of biologic therapy for the treatment of chronic plaque psoriasis in real practice settings in Italy. Bio Drugs 2014; 28: 285–295.
19. Gustavsson A, Bjorkman J, Ljungcrantz C, Rhodin A, Rivano-Fischer M, Sjolund KF, et al. Socio-economic burden of patients with a diagnosis related to chronic pain – register data of 840,000 Swedish patients. Eur J Pain 2012; 16: 289–299.
20. Hubertsson J, Petersson IF, Thorstensson CA, Englund M. Risk of sick leave and disability pension in working-age women and men with knee osteoarthritis. Ann Rheum Dis 2013; 72: 401–405.
21. Svedbom A, Dalen J, Mamolo C, Cappelleri JC, Petersson IF, Stahle M. Treatment patterns with topicals, traditional systemics and biologics in psoriasis – a Swedish database analysis. J Eur Acad Dermatol Venereol 2015; 29: 215–223.
22. Svedbom A, Dalen J, Mamolo C, Cappelleri JC, Mallbris L, Petersson IF, et al. Increased cause-specific mortality in patients with mild and severe psoriasis: a population-based Swedish register study. Acta DermVenereol 2015; 95: 809–815.
23. Lofvendahl S, Theander E, Svensson A, Carlsson KS, Englund M, Petersson IF. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden – a population-based register study. PLoS One 2014; 9: e98024.
24. Johannesson I. The total population register of statistics Sweden. New possibilities and better quality. Örebro: Statistics Sweden. 2002: p. 1–18.
25. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad OP, Bergman U, et al. The new Swedish Prescribed Drug Register – opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007; 16: 726–735.
26. Neovius M, Sundstrom A, Simard J, Wettermark B, Cars T, Feltelius N, et al. Small-area variations in sales of TNF inhibitors in Sweden between 2000 and 2009. Scand J Rheumatol 2011; 40: 8–15.
27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–383.
28. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43: 1130–1139.
29. Desgagne A, Castilloux AM, Angers JF, LeLorier J. The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data. Pharmaco Economics 1998; 13: 487–497.
30. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Stat Med 2000; 19: 3219–3236.
31. Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. J Health Serv Res Policy 2004; 9: 197–204.
32. Crown WH, Bresnahan BW, Orsini LS, Kennedy S, Leonardi C. The burden of illness associated with psoriasis: cost of treatment with systemic therapy and phototherapy in the US. Curr Med Res Opin 2004; 20: 1929–1936.
33. Yu AP, Tang J, Xie J, Wu EQ, Gupta SR, Bao Y, et al. Economic burden of psoriasis compared to the general population and stratified by disease severity. Curr Med Res Opin 2009; 25: 2429–2438.
34. Norlin JM, Steen Carlsson K, Persson U, Schmitt-Egenolf M. Resource use in patients with psoriasis after the introduction of biologics in Sweden. Acta Derm Venereol 2015; 95: 156–161.
35. Ekelund M, Mallbris L, Qvitzau S, Stenberg B. A higher score on the dermatology life quality index, being on systemic treatment and having a diagnosis of psoriatic arthritis is associated with increased costs in patients with plaque psoriasis. Acta Derm Venereol 2013; 93: 684–688.
36. 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: 238–245.