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ORIGINAL RESEARCH

Economic Evaluation of Timely Versus Delayed Use of Tumor Necrosis Factor Inhibitors for Treatment of Psoriatic Arthritis in the US

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ABSTRACT

Introduction: The present study aimed to evaluate clinical outcomes and costs associated with timely versus delayed use of tumor necrosis factor inhibitors (TNFis) among patients with moderately to severely active psoriatic arthritis (PsA) with and without moderate/severe psoriasis (Ps) from a US payer's perspective.

Methods: An economic model evaluated PsA patients initially treated with a TNFi (timely TNFi use) or apremilast (delayed TNFi use). Patients without joint (American College of Rheumatology 20%, [ACR20]) improvement either switched TNFis or initiated one. ACR20 responses were evaluated for all patients and skin responses by Psoriasis Area Severity Index 75% (PASI75) for those with concomitant PsA and Ps. Published randomized controlled trials and publicly available databases provided model inputs. Effectiveness measures included 1-year responses and number needed to treat (NNT). Direct costs, costs per responder, and incremental costs per responder were calculated.

Results: After 1 year, timely TNFi-treated patients had higher ACR20 responses (70.4% vs. 59.6%) and lower NNTs (1.42 vs. 1.68) compared with delayed use. Among PsA + Ps patients, timely TNFi use was associated with higher ACR20 + PASI75 responses (41.0% vs. 30.0%) and lower NNTs (2.44 vs. 3.33). Cost per ACR20 responder was higher ($56,492 vs. $52,835) among PsA patients without Ps; with concomitant Ps, cost per ACR20 + PASI75 responder was lower for timely TNFi use ($100,954 vs. $111,686). Incremental costs per responder for timely versus delayed TNFi were $76,823 in PsA and $71,791 in PsA and Ps.

Conclusion: Timely use of TNFis is a cost-effective strategy for the management of

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INTRODUCTION

Psoriasis (Ps) affects an estimated 7.4 million adults (3.2% of the total population) in the US [1]. Nearly one in three psoriasis patients will develop psoriatic arthritis (PsA) [2, 3], a chronic inflammatory arthropathy typically associated with Ps of the skin or nails and includes other manifestations such as enthesitis, dactylitis, uveitis, and spondylitis [4]. Given the progressive nature of the disease, nearly half of PsA patients will develop irreversible bone erosions/joint destruction [5], leading to impaired physical function [6], higher likelihood of presenteeism and work disability [7–9], and, consequently, high direct and indirect costs [10–12]. Several treatment options are available to manage symptoms and inhibit structural disease progression. The recently published Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations (2016) strongly recommend disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX), leflunomide, sulfasalazine and tumor necrosis factor inhibitors (TNFis) as initial treatment for patients with PsA [13]. For patients who fail to respond to DMARDs, biologics (TNFis, interleukin [IL] 12/23 or IL 17 inhibitors) or a phosphodiesterase-4 inhibitor (PDE4i) are suggested [13].

Recently, apremilast, a PDE4i, was approved for treatment of active PsA [14] based on demonstrated improvement in the signs and symptoms of active PsA relative to placebo in several randomized controlled trials (RCTs) that did not evaluate structural joint damage [15–19]. While there are no head-to-head RCTs comparing the efficacy of apremilast versus a TNFi, treatment responses were substantially lower in individual recent Phase III RCTs with apremilast [16, 20] than with TNFis in patients with moderately to severely active PsA [21, 22], despite generally similar inclusion criteria. By week 16 in phase III RCTs (PALACE 1–3; NCT01172938, NCT01212757, NCT01212770), 30–41% of apremilast-treated DMARD incomplete responders (DMARD-IR) achieved American College of Rheumatology 20% responses (ACR20) [16–19], and 21–22% patients achieved Psoriasis Area Severity Index 75 (PASI75) responses (PALACE-3; NCT01212770) [18]. In contrast, 58–68% of DMARD-IR patients treated with TNFis achieved ACR20 and 51–59% PASI75 responses in 12–16 weeks [21, 22]. Additionally, an indirect comparison of RCT data found that apremilast has similar efficacy to MTX in treating a MTX-naïve population [23].

Both TNFis and the PDE4i have been recommended by GRAPPA as treatment options after initial DMARD failure. However, it is not clear whether using apremilast or a TNFi first may have different clinical and/or economic impacts on patient outcomes. Use of apremilast after DMARD failure may result in a delay in prescribing TNFis known to reduce structural progression. The current study was designed to robustly model the economic impact of timely versus delayed use of TNFis in patients with moderately to severely active PsA with/without moderate/severe Ps from a US payer's perspective.

METHODS

Model Overview

This economic evaluation was performed using a Markov state transition model to simulate costs and outcomes over a 1-year time horizon in patients with moderately to severely active PsA (defined as presenting with ≥3 swollen and ≥3 tender joints). Two treatment sequences were compared: timely use of TNFi (initiating treatment with adalimumab, etanercept, infliximab, or golimumab; insufficient data were available for certolizumab pegol) versus delayed use (initiating treatment with apremilast), followed by a TNFi in non-responders or those who lost responses.

The model structure (Fig. 1) builds on the probabilistic decision-analytic models used in the Health Technology Assessment of TNFis (York Model), with some adaptations that incorporate the impact of timely versus delayed TNFi use [24]. The length of each Markov cycle was 3 months (i.e., 13 weeks, not including week 0), consistent with labeling recommendations to assess treatment responses at 12–16 weeks and with the British Society of Rheumatology guidelines [25]. The current model was built from a US third-party payer's perspective. Direct costs, including treatment-related and other medical costs, were calculated for each treatment sequence based on Health Assessment Questionnaire

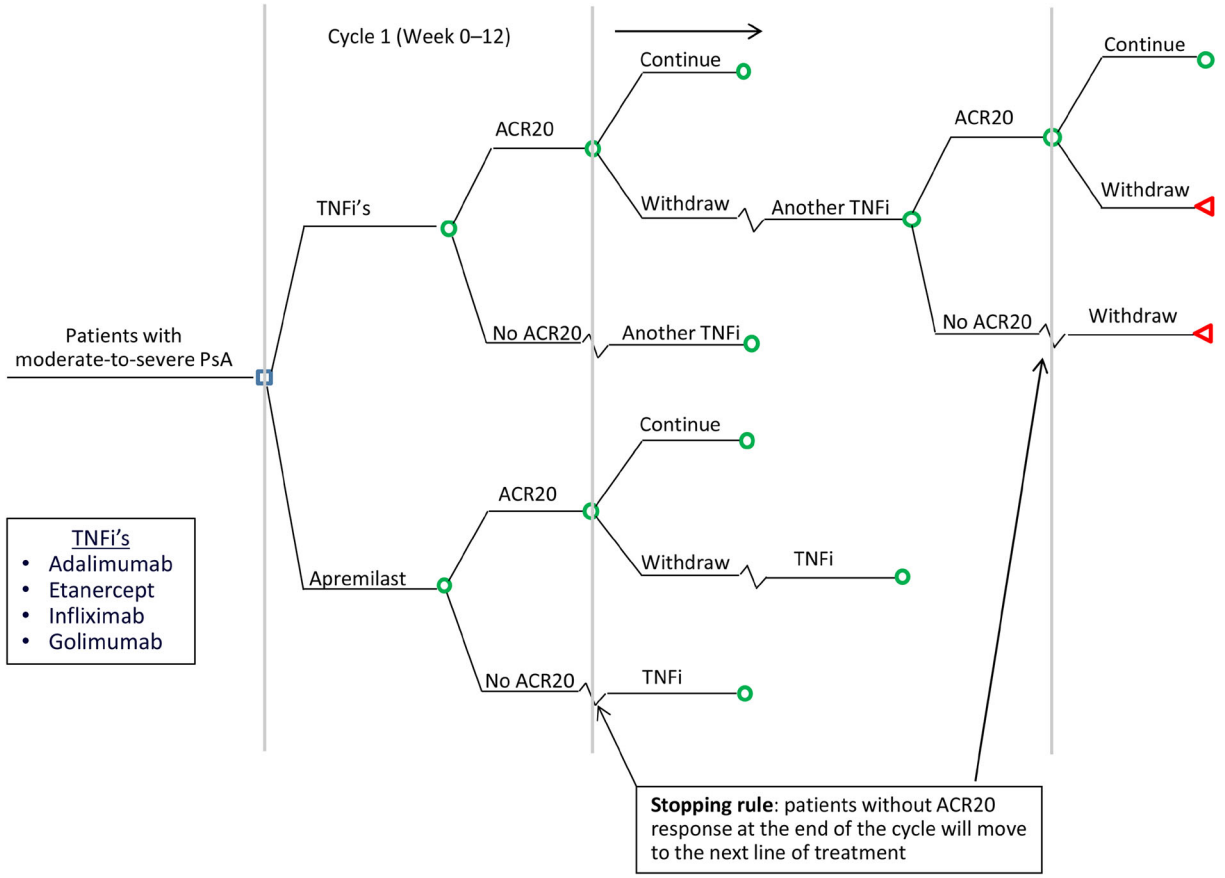


Fig. 1 Model structure. *ACR20* American College of Rheumatology 20% response; *PsA* psoriatic arthritis; *TNFi* Tumor Necrosis Factor inhibitors

(HAQ) or PASI scores. In addition, the analysis was conducted in the subpopulation with concomitant moderate-to-severe Ps, defined as having ≥3% body surface area involvement.

Model Parameters

Treatment Effectiveness

First-Line Effectiveness Patient characteristics at treatment initiation were based on the population enrolled in the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT; NCT00195689) (Table 1) [26, 27]. Treatment responses were defined as ACR20 responses at month 3 (first cycle), the primary outcome in most PsA RCTs [28]. For first-line mixed TNFis, efficacy data by ACR20, ACR50, and ACR70 responses (i.e. by achieving ACR 20, 50, and 70% responses) in the intention-to-treat (ITT) population were pooled from Phase III RCTs, weighted by each TNFi market share (Table 2) [29]. The efficacy of apremilast 30 mg twice daily in the per-protocol population of Phase III RCTs (i.e., PALACE 1–3) was pooled and weighted by the sample size in each trial. Approximately 20% of patients in these trials had previously received TNFis, while all patients in ADEPT; NCT00195689 were biologic-naive [30]. Because limited information was available regarding efficacy in a biologic-naïve population, the base case model was conducted based on the efficacy noted in all patients in PALACE 1–3, and sensitivity analyses were conducted using ACR20 responses among biologic-naïve patients reported in PALACE 1 [16] and 3 [20].

Clinical efficacy at month 3 was then translated into improvements in HAQ scores relative to baseline (Table 2). This HAQ calculation was developed using patient-level data from the ADEPT trial, reported in the adalimumab manufacturer submission to the National Institute for Health and Care Excellence (NICE) in the UK [31]. Initial HAQ improvement was conditional on the level of ACR responses achieved (i.e., ACR20, 50, 70) and patient's age, gender, HAQ score, MTX use, and PsA duration at baseline. The algorithm calculated HAQ changes for treatment responders as weighted averages of ACR20, 50 and 70 as well as non-responders. In patients with ACR20 responses at month 3, average decreases in HAQ from baseline were 0.73 and 0.65 for TNFi and apremilast, respectively. Responders were considered to have maintained their initial improvement in HAQ until they withdrew. Patients continued current treatment after month 3 as long as they maintained their initial joint response, regardless of skin response, until discontinuation. Non-responders were assumed to have limited improvements in joint disease at an average decrease in HAQ of 0.13 with both TNFis and apremilast at month 3. Non-responders moved to the next line of therapy at the beginning of the second cycle.

Subsequent-Line Effectiveness In non-responders or patients who lost ACR20

Table 1 Patient characteristics of the target population

Description	Value
Age, year	49
Male, %	56%
PsA duration, year	10
Baseline HAQ	1.3
Ps defined as BSA involvement ≥3%	40%
Baseline PASI (patients with BSA ≥3%)	7.4
MTX use at baseline, %	51%

PsA psoriatic arthritis; *HAQ* Health Assessment Questionnaire; *Ps* psoriasis; *BSA* body surface area; *PASI* Psoriasis Area Severity Index; *MTX* methotrexate

responses after 3 months, the model considered subsequent treatment with a different TNFi (timely use of TNFi arm) or initiation of a TNFi (delayed use arm).

Responses for subsequent lines of treatment in the timely use of TNFi arm were assumed to be lower than first-line responses, based on findings of lower efficacy with a 2nd and 3rd TNFi in patients with rheumatoid arthritis (RA) [32]. Reduction in short-term responses were estimated as 25, 27 and 37% relative to first-line ACR20, ACR50 and ACR70 responses, respectively [32]. On the other hand, there is no evidence regarding the effectiveness of delayed TNFi use following apremilast failure—a decrease in efficacy was assumed. This was based on observations from rescue treatment in the ADEPT trial and its open-label 48-week extension, which suggested that patients who initially received TNFis experienced better outcomes than those originally randomized to receive placebo and then received the TNFis [26, 27]. The efficacy of TNFi after apremilast was assumed to decrease by 21, 14 and 8% for ACR20, ACR50 and ACR70 respectively, again based on the rescue arm of the ADEPT RCT [26, 27].

Treatment Withdrawal Based on real-world observations of treatment discontinuation and switching, the model assumed a certain risk of withdrawal from TNFi therapy after each cycle, due to loss of efficacy, adverse events or other reasons. Withdrawal rates for first and subsequent line TNFi use were obtained from a British registry study and assumed to be constant over time (Table 2) [33]. As long-term real-world withdrawal rates have not yet been reported for apremilast, they were assumed to be the same as for TNFis. When patients withdrew from treatment, HAQ scores were assumed to rebound to baseline levels and patients were moved to the next line of treatment at the beginning of the next cycle.

Outcomes for Symptomatic Care For patients who failed a subsequent-line TNFi, the model placed these patients in symptomatic care. This was based on the York model [24], given that treatment guidelines at the time of this analysis did not have recommendations past second-line treatment with TNFi biologics [25, 34, 35]. For patients who failed TNFi treatment, the model assumed that their HAQ score would continue to deteriorate from the last value assigned on subsequent-line treatment at a rate of 0.018 per cycle—based on an assumption of inefficacy with subsequent DMARD treatment for PsA symptoms, as suggested by clinical expert opinion [31].

Mortality Since PsA patients are known to have an increased risk of death compared with the general population [36], an additional mortality risk of 65% for males and 59% for females [36] was considered for PsA when estimating mortality and the model assumed no difference in mortality rates between treatments.

Effectiveness in Treating Psoriasis TNFis are approved to treat both joint and skin disease. A subgroup analysis examined clinical improvement, measured by 75% improvement in PASI as well as ACR20 at each Markov cycle. Effectiveness for both skin and joint manifestations was modeled in this previously defined subgroup. Since there is a positive correlation between responses (e.g., ACR responders are more likely to be PASI responders [37–40]), a bivariate evidence synthesis was performed. Correlations between PASI75 and ACR20 responses were again derived

Table 2 Effectiveness inputs

Description	Timely TNFi use	Delayed TNFi use
Initial treatment	1st TNFi[a]	Apremilast
Effectiveness at Month 3 among PsA patients		
Probability of achieving ACR20 response	0.580	0.371
Probability of achieving ACR50 response	0.364	0.140
Probability of achieving ACR70 response	0.155	0.030
Effectiveness at Month 3 among the subgroup with Ps		
Probability of achieving PASI50 response	0.630	0.419
Probability of achieving PASI75 response	0.438	0.220
Probability of achieving PASI90 response	0.260	0.110
Probability of achieving ACR20 + PASI75 response[∓]	0.331	0.158
Effectiveness at Month 3 among biologic naïve patients (sensitivity analyses)		
Probability of achieving ACR20 response	NA	0.435
Probability of achieving ACR50 response	NA	0.171
Probability of achieving ACR70 response	NA	0.044
Withdrawal rate per cycle after the first cycle	0.023	0.023
Subsequent treatment	2nd TNFi[a]	1st TNFia (delayed)
Effectiveness at Month 3 among PsA patients		
Probability of achieving ACR20 response	0.435	0.458
Probability of achieving ACR50 response	0.266	0.314
Probability of achieving ACR70 response	0.096	0.143
Effectiveness at Month 3 among the subgroup with Ps		
Probability of achieving PASI50 response	0.638	0.630
Probability of achieving PASI75 response	0.448	0.438
Probability of achieving PASI90 response	0.267	0.260
Probability of achieving ACR20 + PASI75 response[b]	0.271	0.277
Withdrawal rate per cycle after the first cycle	0.073	0.073
Change in HAQ given an ACR20 response at month 3[c]		
ACR20 responder	−0.716	−0.747
ACR20 non-responder	−0.130	−0.130
HAQ change per cycle while on symptomatic care	0.018	0.018
Standardized mortality rate for PsA vs. general population		
Male	1.65	1.65

Table 2 continued

Description	Timely TNFi use	Delayed TNFi use
Female	1.59	1.59

ACR20, 50, 70 American College of Rheumatology 20, 50, and 70% response; *HAQ* Health Assessment Questionnaire; *PASI 50, 75,* and *90* Psoriasis area severity index reduction of 50, 75, and 90%; *PsA* psoriatic arthritis; *Ps* psoriasis; *TNFi* tumor necrosis factor inhibitor

[a] The treatment effectiveness for mixed TNFi biologics in first and subsequent line were estimated based on the market shares of biologic use in patients with PsA [29]. The proportions of first-line biologics were estimated to be 37.0% for adalimumab, 35.1% for etanercept, 22.4% for infliximab, and 5.5% golimumab, while the shares for the subsequent line were 32.8, 32.8, 26.6, and 7.8%, respectively

[b] The probability of achieving PASI75 response in the first cycle was modeled using a joint distribution with ACR20 using Bayesian bivariate analysis

[c] PASI score and HAQ score changes in the first cycle of treatment were estimated based on PASI (50/75/90) and ACR (20/50/70) response rates. The maximum HAQ score was 3

from the ADEPT trial [26] and used to estimate the probability a patient would have both joint and skin responses (Table 2). This same correlation was used across all treatment groups, assuming the relationship between joint and skin responses are independent of the treatment patients received (as known for TNFis) [24].

Costs

Based on a third-party payer's perspectives, the base case model considered only direct costs, including treatment-related (product, administration, and monitoring costs) and other medical costs (Table 3). Treatment-related costs were calculated for TNFis based on market share [29], unit prices, and dose per cycle of each therapy. Unit prices for TNFis and apremilast were based on wholesale acquisition costs obtained from ReadyPrice (assessed April 2014) [41]. Dose per cycle was calculated based on product label recommended dosing schedules. Patients receiving TNFis also incurred monitoring costs [42] and patients receiving infliximab incurred administration costs for intravenous infusions administered by a healthcare professional. No monitoring or administration costs were assumed for apremilast. No treatment-related costs were assumed for symptomatic care in the base case model. Costs for using MTX were tested in sensitivity analyses.

The model assumed that PsA patients incurred other medical costs for inpatient and outpatient visits and that costs would increase with severity of arthritis and/or psoriasis [43]. Due to the lack of economic studies on medical costs by HAQ in PsA, the health service costs of treating arthritis were derived from a US-based study that estimated the effect of HAQ on direct costs in patients with RA [43]. The study reported total direct costs corresponding to quartiles of HAQ scores, with 75% attributed to medical services. A weighted linear regression was fitted using the mid-point of the HAQ score as an independent variable and other medical costs as the dependent variable, weighted by the number of patients in each quartile. This coefficient was estimated to be $1040, the mean change in 3-month cost for a 1-unit change in HAQ. Medical costs of treating PsA were estimated as a function of HAQ score at

Table 3 Cost inputs

Description	Cost per cycle (3 months)
Drug[a] and drug administration costs	
Adalimumab	$8132
Etanercept	$8211
Golimumab	$8132
Infliximab[b]	$17,660 for the first cycle; $7406 after the first cycle
Apremilast	$5531 for the first cycle; $5688 after the first cycle
Monitoring costs	
Mixed TNFi	$143 for the first cycle; $45 after the first cycle
Apremilast	$0
Medical costs[c,d]	
HAQ 0.000–0.625	$1325
HAQ 0.626–1.250	$1590
HAQ 1.126–1.750	$2375
HAQ 1.751–3.000	$3375
Medical costs related to Ps	
PASI75 responder	$22
PASI75 non-responder	$1150
Indirect costs (modeled in the sensitivity analyses)[c]	
HAQ < 0.5	$2265
HAQ 0.5 to <1.1	$4111
HAQ 1.1 to <1.6	$6931
HAQ 1.6 to <2.1	$9992
HAQ 2.1 to <2.6	$13,639
HAQ ≥ 2.6	$9141

TNFi Tumor necrosis factor inhibitor; *HAQ* Health Assessment Questionnaire; *Ps* psoriasis; *PASI* Psoriasis Area Severity Index

[a] Treatment costs for mixed TNFi biologics in first and subsequent line were estimated based on the market shares of biologic use in patients with PsA [29]. The proportions of first-line biologics were estimated to be 37.0% for adalimumab, 35.1% for etanercept, 22.4% for infliximab, and 5.5% golimumab, while the shares for the subsequent line were 32.8, 32.8, 26.6, and 7.8%, respectively

[b] The drug and drug administration costs for infliximab included costs for intravenous infusion administered by a healthcare professional ($85.8 per infusion based on the CMS physician fee schedule 2014)

[c] Direct costs extracted from the source included inpatient costs, outpatient costs, drug costs and ancillary costs. Medical costs were assumed to be 75% of the direct costs

[d] Linear interpolation was used to estimate the association between costs and HAQ score

each cycle. For the subgroup of patients with concomitant psoriasis at baseline, patients achieving PASI75 responses were assumed to receive phototherapy once a year. Those who did not achieve PASI75 responses incurred Ps-related medical costs [24], obtained from a real-world claims study of Ps-associated treatment costs [44].

All costs were inflated to 2014 United States Dollar (USD). No discounting was applied to the base case model, due to the short time horizon of the analysis; 3% discounting rates for both effectiveness and costs were considered when varying time horizon to 5 years in the sensitivity analyses.

Model Outputs

The base case model estimated total direct costs and effectiveness for each treatment sequence at 1 year after treatment initiation. Among patients with PsA, effectiveness was measured by joint responses (ACR20) and mean time as an ACR20 responder at year 1. Among patients with both joint and skin manifestations, treatment effectiveness was measured by combined ACR20 + PASI75 responses and mean time as ACR20 + PASI75 responders. Numbers needed to treat (NNT) for achievement of ACR20 or ACR20 + PASI75 responses were also reported.

Based on effectiveness and costs outputs, costs per responder for each treatment sequence were calculated. Incremental costs per responder measured the costs per ACR20 (or ACR20 + PASI75) responders with timely vs. delayed use of TNFi.

Sensitivity Analyses

One-way sensitivity analyses were conducted to examine the impact of change in one key model input or assumption, while holding others at base case values. Model inputs that were varied include treatment costs, other medical costs, efficacy, treatment withdrawal rate, baseline patient characteristics, mortality rate, and time horizon. In addition, the societal perspective, considering both direct and indirect costs, was modeled in sensitivity analyses—indirect costs were estimated as a function of HAQ, based on the similar approach for medical costs. Since no US studies were found to estimate indirect costs associated with PsA, the number of working days missed due to RA were obtained from a German study [45] and the average wage per day in the US [46] was applied to estimate total indirect costs associated with given HAQ scores.

A detailed list of parameters and corresponding ranges/assumptions of the one-way sensitivity analyses are provided in Fig. 2.

The model and sensitivity analyses were conducted using Excel 2010 (Microsoft Corporation, Redmond, WA).

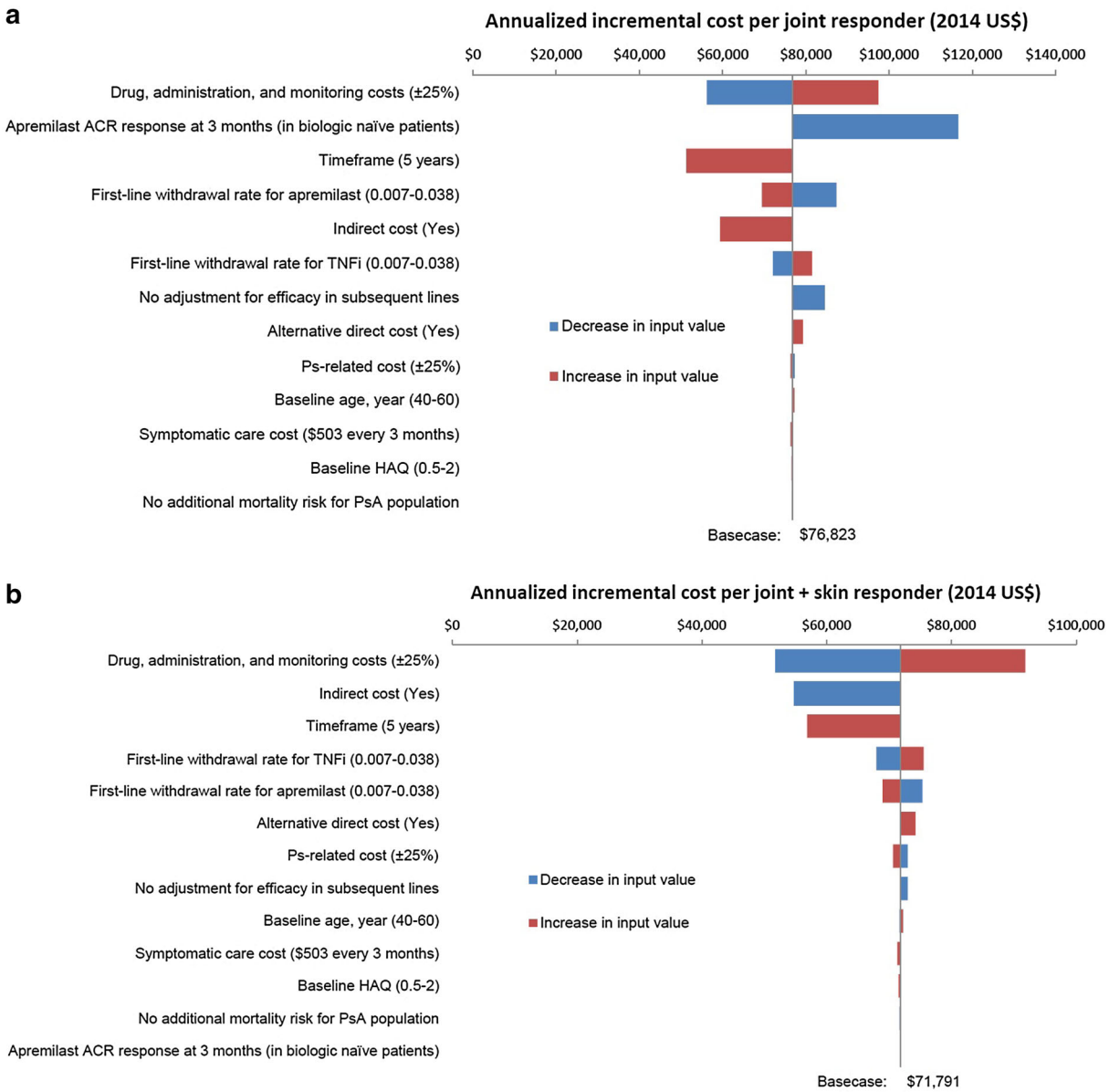
Compliance with Ethics Guidelines

This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Base Case Analysis

After 1 year, patients with moderately to severely active PsA who started a TNFi in a timely manner had higher ACR20 responses (70.4% vs. 59.6%), and corresponding lower NNTs (1.42 vs. 1.68), than those first treated with apremilast and later receiving a TNFi. Mean times with responses were also longer for timely vs. delayed use of TNFi (7.2 months



Top panel: Patients with PsA (Incremental cost per ACR20 responder)

Bottom Panel: Patients with PsA and psoriasis (Incremental cost per ACR20 + PASI75 responder)

ACR, American College of Rheumatology; HAQ, Health Assessment Questionnaire; PsA, psoriatic arthritis; PsO, psoriasis; TNFi, Tumor Necrosis Factor inhibitors

Notes: Alternative medical costs inputs were obtained from Kobelt et al. 2002 [63]. The costs were inflated to 2014 USD.

◀ **Fig. 2** Tornado diagram of one-way sensitivity analyses for incremental costs per responder. *Top panel* patients with PsA (Incremental cost per ACR20 responder). *Bottom panel* Patients with PsA and psoriasis (Incremental cost per ACR20 + PASI75 responder). *ACR* American College of Rheumatology; *HAQ* Health Assessment Questionnaire; *PsA* psoriatic arthritis; *PsO* psoriasis; *TNFi* Tumor Necrosis Factor inhibitors Alternative medical costs inputs were obtained from Kobelt et al. 2002 [63]. The costs were inflated to 2014 USD

vs. 5.8 months). Patients with timely TNFi treatment incurred higher costs ($39,754 vs. $31,513). The cost per ACR20 responder was similar between the two treatment groups ($56,492 vs. $52,835, respectively) and the 1-year incremental cost per ACR20 responder was $76,823 for timely vs delayed TNFi use (Table 4a).

Among patients with concomitant moderate to severe Ps, timely TNFi use was associated with higher combined ACR20 + PASI75 responses (41.0% vs. 30.0%), corresponding to lower NNTs (2.44 vs. 3.33), with longer durations of response (4.2 months vs. 2.8 months). Timely TNFi treatment was also associated with higher costs during the 1st year ($41,437 vs. $33,510), resulting in the incremental cost per ACR20 + PASI75 responder as $71,791 for timely vs delayed use. However, cost per ACR20 + PASI75 responder was lower for initial treatment with TNFi than apremilast ($100,954 vs. $111,686) (Table 4b).

One-Way Sensitivity Analyses

In the one-way sensitivity analyses, incremental cost per ACR20 responder ranged from $51,274 to $116,624. Factors with the largest impact on incremental costs were treatment-related costs, apremilast ACR20 responses at 12 weeks, and a longer time horizon (i.e., 5 years). Incremental costs per ACR20 + PASI75 responders ranged from $51,760 to $91,822 and were most sensitive to treatment-related costs, indirect costs, and a longer time horizon (Fig. 2).

DISCUSSION

Recently, several new therapies have been approved for PsA, prompting further assessments of treatment options [47, 48] and their cost-effectiveness [24, 49–51], as well as issuance of new treatment recommendations [13]. In patients with active PsA, TNFis have proven highly effective in treating PsA symptoms and inhibiting structural progression [52–54]. A newly introduced agent, apremilast, has been shown to be effective in treating the signs and symptoms of PsA. A few other studies have attempted to investigate the economic impact of using apremilast before or instead of TNFi treatment and concluded that apremilast is a more cost-effective option over a lifetime horizon [55], with lower costs per responder relative to TNFis in a one-year treatment model [56]. However, from the available published information, these previously published models did not consider concomitant Ps or structural progression in PsA, and still produced only modest cost savings with the use of apremilast.

In the present economic model, patients initially treated with a TNFi had higher responses and lower NNTs than those initially receiving apremilast. Although patients with timely use of a TNFi had higher treatment-related costs than the delayed use group after 1 year, these costs were partially offset by lower other medical costs. Based on costs-per-responder estimates, total annual costs for ACR20 responders were similar in both groups, although slightly higher with

Table 4 Based case results (2014 USD)

	Timely TNFi use (Arm A)	Delayed TNFi use (Arm B)	Difference (Arm A–Arm B)
A. Patients with PsA			
Costs			
Direct costs	$39,754	$31,513	$8241
Treatment-related costs	$31,751	$22,904	$8847
Other medical costs	$8003	$8609	−$606
Effectiveness			
% of ACR20 responder	70.4%	59.6%	10.7%
Number needed to treat[a]	1.42	1.68	*9.32*
Mean time with joint response (month)	7.2	5.8	1.4
Cost per responder			
Cost per ACR20 responder	$56,492	$52,835	$3657
Incremental cost per joint responder			Arm A vs. Arm B $76,823
B. Subgroup of patients with PsA and psoriasis			
Costs			
Direct costs	$41,437	$33,510	$7927
Treatment-related costs	$31,751	$22,904	$8847
Other medical costs	$9686	$10,606	−$920
Effectiveness			
% of ACR20 + PASI75 responder	41.0%	30.0%	11.0%
Number needed to treat[a]	2.44	3.33	*9.06*
Cost per responder			
Cost per ACR20 + PASI75 responder	$100,954	$111,686	−$10,732
Incremental cost per joint and skin responder			Arm A vs. Arm B $71,791

ACR20 American College of Rheumatology 20% response; *PASI* Psoriasis Area Severity Index; *PsA* psoriatic arthritis; *TNFi* Tumor Necrosis Factor inhibitors

[a] Number needed to treat is defined as the average number of patients who need to be treated for one responder. The comparison results (in *italics*) between the two arms should be interpreted as the number of patients who need to be treated to observe one responder in arm A versus arm B

timely use. When both joint and skin responses were accounted for, responses and cost trends were similar to analyses that were based on joint responses only, but total costs were much lower for timely use vs. delayed use of TNFis. These results indicate that, overall, timely treatment with TNFis is more expensive than delayed treatment, but for those patients with both skin and joint manifestations, cost savings can be substantial. Since 46–83% patients enrolled in TNFi RCTs [57] have manifestations of Ps, this finding underscores the need to consider effectiveness for both joint and skin disease when assessing treatments for PsA.

This study provides important information on economic and clinical outcomes associated with choice of TNFis versus apremilast as 1st-line treatment for moderately to severely active PsA, with careful attention to presenting an accurate model of the disease. Nonetheless, this still remains a model, which cannot account for the natural history of the disease or all aspects of its treatment. Sensitivity analyses were performed to identify largest areas of uncertainty [58] in the model—indicating that, among other factors, ACR20 responses with apremilast treatment and 1st-line withdrawal rates following apremilast had a large impact on the model results. Due to lack of available information, some assumptions were necessary to incorporate into the model: ACR20 responses were derived from RCTs with apremilast that included mixed populations of treatment-naïve and TNFi-exposed patients. Based on reported efficacy, it is possible that treatment-naïve patients receiving apremilast might achieve higher responses than in the mixed population trials—although ACR20 rates at week 14 were 28–31% in the PALACE 4 trial (NCT01307423) in DMARD (synthetic and biologic)-naïve patients [59], below those observed in PALACE 1–3 (which were used in the present analysis). Therefore, sensitivity analyses were conducted to include a compensatory factor for ACR20 responses with apremilast, increasing response rates from the observed 37% to an estimated 43%, based on the subgroup analysis in biologic-naïve patients, as reported in PALACE 1 and 3. Furthermore, since there is no information regarding the degree to which the effectiveness of TNFis may be impacted by prior use of apremilast, the model used rescue data from RCTs to estimate the difference between timely vs. delayed initiation of a TNFi. Nonetheless, the effect of this latter adjustment on the primary findings was not substantial, and the model assumed the same withdrawal rates for the two treatment sequences, as there were no long-term observational data with apremilast.

Despite these sensitivity analyses, several limitations of the current model must be acknowledged. The effectiveness mode inputs were mainly based on RCTs, but patients enrolled in trials differ from those treated in routine clinical practice, and trial design may impose additional treatment restrictions not generally observed in clinical practice. Results may therefore not be generalizable to the greater PsA patient population.

There are no head-to-head trials comparing the two modeled treatment sequences; therefore, effectiveness data were obtained from a mix of several RCTs and observational studies, and the comparative results may be biased by differences between populations and study design. For example, while all RCTs for TNFis included in the present study were based on the ITT population, all RCTs for apremilast were based on the per-protocol population. In addition, RCTs with apremilast (PALACE 1–3 [16, 20, 60, 61]) included both TNFi-naïve and -experienced patients, and a subgroup analysis of all modeled outcomes was not available for TNFi-naïve patients. The present analysis may

have underestimated ACR20 responses in TNFi-naïve patients, which could have biased results against initial use of apremilast. On the other hand, as there are no data that apremilast can inhibit the progression of structural damage, the current analysis may be conservative relative the cost-efficacy of apremilast vs a TNFi.

The model included several assumptions regarding the effectiveness of 1st versus 2nd-line TNFi use, and early vs. delayed treatment; these assumptions were tested in sensitivity analyses and the model was not sensitive to the assumption of decreased efficacy with prior exposure. While sequential use of TNFis is common in clinical practice, the model assumes that patients receive no treatment (i.e., symptomatic care) after subsequent TNFi therapy—as assumed by other models of PsA treatment [24]. However, the newly published GRAPPA recommendations suggest possible rescue of response with IL-12/23 or IL-17 inhibitors and PDE4i in patients who have TNFi failure [13]. At the time of model development, the IL-17 inhibitors had not yet been approved for this indication and their clinical evidence after two TNFis or one TNFi and one PDE4i failure are lacking. Therefore, the current model did not consider these treatment options after subsequent TNFi failure.

Finally, uncertainty [62] remains regarding progression of HAQ scores with and without TNFi and apremilast treatment and their short-term effectiveness in PsA. Further research is needed on these topics, as all current cost-effectiveness models of treatment for PsA rely on assumptions for these inputs [24].

CONCLUSION

Timely use of TNFis is a cost-effective strategy for management of moderately to severely active PsA, due to greater improvements in joint and skin manifestations than observed with delayed initiation of TNFis. Furthermore, timely use of TNFis can reduce medical costs, which can partially offset the higher treatment-related costs compared with delayed TNFi treatment. Future research on the impact of delayed use of TNFis on patients' health-related quality of life is warranted.

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