



## Cost-utility and budget impact analysis of adding-on apremilast to biologic therapy in the treatment of moderate to severe plaque psoriasis, an Iranian payer perspective

Marzieh Zargaran<sup>1</sup>, Fatemeh Soleymani<sup>1</sup>, Saman Ahmad Nasrollahi<sup>2</sup>, Meysam Seyedifar<sup>1,\*</sup>, and Mohammad Mehdi Ashrafian Rahaghi<sup>3</sup>

<sup>1</sup>Pharmaceutical Management and Economic Research Center, The Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences, Tehran, I.R. Iran.

<sup>2</sup>Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, I.R. Iran.

<sup>3</sup>Department of Commercial Management, Faculty of Management, Iranian University, Tehran, I.R. Iran.

### Abstract

**Background and purpose:** Plaque psoriasis is a chronic inflammatory disease with skin manifestations that affect the patients' quality of life negatively. The prevalence of psoriasis is approximately 2-3% worldwide and appears to be still on the increase. Due to the stigma problems, psoriasis has a significant effect on one's life that is often overlooked. The current study aimed to conduct the cost-utility evaluation and budget impact analysis of adding-on apremilast ahead of biologic therapy in the treatment of moderate to severe plaque psoriasis. The psoriatic patients who did not undergo the conventional systemic therapy were eligible to enter the defined sequences.

**Experimental approach:** An excel-based Markov model with 40 cycles of 3 months, each of which was adopted to compare the outcomes of each exclusively administered sequence in the treatment of moderate to severe plaque psoriasis. Two exclusive therapeutic sequences were considered. In the first sequence, apremilast was followed by biologics and in the second one, biologics were administered initially without apremilast. The results were extrapolated up to 10 years. The designed Markov model was also used in budget impact analysis. The cost-saving potential of the new treatment was accounted for the next 5 years.

**Findings/Results:** Incremental cost and incremental effect were reported in the base case scenario. Using the sequence consisting apremilast provided an additional 0.10 quality-adjusted life years and decreased total costs by about 11,100 USD per patient. These results were in line with the findings from sensitivity analysis. The cost-saving over 5 years is estimated to be around 30 million dollars for the Iran market following the use of the new treatment.

**Conclusion and implications:** In the treatment of moderate to severe plaque psoriasis, apremilast supplementation prior to biological treatments is more cost-effective than biological treatment alone.

**Keywords:** Budget impact; Cost-utility; Payer perspective; Plaque psoriasis.

### INTRODUCTION

Psoriasis is a chronic, immunological, and debilitating disease accompanied by inflammatory dermal-epidermal plaques that have negative effects on patients' physical appearance and quality of life. This hardly-curable disease can occur at any age but is more common in the age group of 50-69 years (1). The prevalence of psoriasis

varies from 2-3% worldwide (2,3) among people of different ages and races (1,4). In addition, there is evidence that the prevalence of psoriasis is increasing (5).

#### Access this article online



Website: <http://rps.mui.ac.ir>

DOI: 10.4103/1735-5362.319576

\*Corresponding author: M. Seyedifar  
Tel: +98-9122781827, Fax: +98216695606  
Email: seyedifar@gmail.com

According to some studies, psoriasis is a high-burden disease, with an estimated average global disability-adjusted life year (DALY) of 1050660 in 2010 (6). The reported prevalence of psoriasis in Iran is 1.3 to 2.5% (7,8).

Plaque psoriasis is the most common phenotype accounting for about 80 to 90% of patients (9). Plaque psoriasis severity can be restricted by a range of well-established treatment methods, including topical therapies, phototherapy, oral, and biological medicines. Developments in biologic medicine to treat plaque psoriasis have made them the most effective alternatives for intolerant or unresponsive cases who have received the conventional therapies (*e.g.* methotrexate and cyclosporine) (10). Despite the verified efficacy of the biologic agents in the treatment of plaque psoriasis, their tolerability and safety concerns have made some challenges (11,12). In addition, the effectiveness of biologics decreased over time (13). Time-dependent decrease in the biologic effectiveness leading to increase in the required doses and treatment switch or withdrawal are other reasons that limited the biologic therapy in psoriatic patients (13,14). To treat psoriasis, biologic sequential therapy is recommended by National Institute for Health and Care Excellence (NICE) to reduce the mentioned restrictive factors in biologic administration (15). In sequential therapy, a second or third subsequent biologic may be administered in the case of failure (15).

High costs of biologic medicines impose an increasing economic burden annually. In addition, alternative treatments are required for the contraindicated or intolerant cases. Apremilast is an oral phosphodiesterase-4 inhibitor shown to be effective in moderate to severe plaque psoriasis in patients who are contraindicated or intolerant to traditional systemic therapy (16). According to the NHS recommendation, the administration of apremilast, as a non-biologic medicine, could reduce the time on biologic therapy and best supportive care, leading to a more cost-effective treatment in comparison with the biologic therapy alone (17). The purpose of this study was to evaluate the costs and effects of oral apremilast prior to the biological treatment in patients with moderate to severe plaque

psoriasis in whom routine systemic treatment has failed. Also, a budget impact model has been designed and the analysis results have been reported. This study has been performed from the perspective of Iranian payers.

## MATERIALS AND METHODS

### *Study design*

A cost-utility analysis was performed in which the costs were expressed in US dollars and the utilities, regarding the changes in quality of life, were affected by the psoriasis area and severity index (PASI). Rial/USD exchange rate (using the exchange rate of each US dollar equalling 42,000 Rials in 2019) was obtained from the Central Bank of Iran as the most reliable reference (18).

The Markov model was constructed with 40 cycles of 3 months each to evaluate the results of two designed hypothetical cohort studies of patients with moderate-to-severe plaque psoriasis, intolerant or unresponsive to conventional plaque psoriasis therapies. It was also utilized to determine the imposed-budgetary impact of adding apremilast to the previous biologic therapy in comparison with the previously administered biologic sequence in the context of the Iranian health system.

The developed model includes the assumptions accepted by the University of York and UK models for psoriasis (17). Two Iranian dermatologist experts validated this modeling method that accurately could indicate the treatment pathways in Iranian patients.

### *Markov model description*

An excel-based Markov model was designed in Microsoft Excel 2003 to compare the results of each exclusively administered sequence in the treatment of moderate to severe plaque psoriasis. As shown in Fig. 1, two sequential treatment pathways were developed where all the 10,000 hypothetical patients entered a 3-months trial period of the first medicine in each sequence. In one of the pathways, apremilast was followed by biologics and in the other one, biologics were administered initially without apremilast. The 3-months trial period, designed for all drugs based on pharmacoeconomic studies and clinical trials

(19-21). The PASI is a measurement criterion of psoriasis area involvement and severity in which greater scores indicate more severe disease. The PASI-75 and PASI-90 responses are the reported scores to define the reduction from baseline PASI and signifying the disease improvement (19). Achieving a PASI-75 score at the end of each trial period was defined as the target point to stay in or pass to the next state (19). Patients who had recovered more than or equal to 75% of their initial PASI scores were eligible for transition to maintenance modes. The patients who did not achieve the target score left this treatment and were transferred to the trial period of the next medicine. The Best Supportive Care (BSC) state was defined at the end of each therapeutic sequence for the patients who did not respond to the sequential therapy or who left the parenteral biologic treatment. Patients in the BSC state receive topical medicines or Narrow Band Ultra Violet B (NBUVB) as supportive care. In high needed cases, patients are hospitalized in BSC state (22).

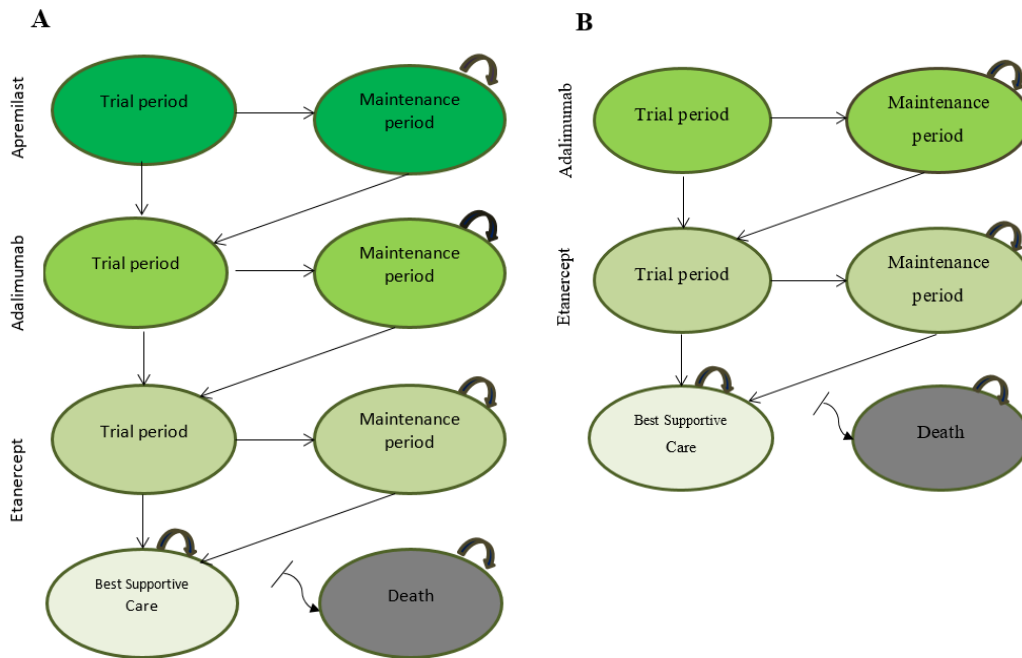
The probability of leaving the treatment due to complications or non-response to the treatment was ignored in this model. Death as the absorbing state was defined in both treatment sequences to which patients in all states could be transferred. Modelled patients

were 10,000 hypothetical persons with 50 years of age in the first cycle and considering the 10-year follow-up in this model, the probability of death in all patients aged 50-60 years was considered as constant. A 10-year time horizon was applied in this pharmacoeconomic evaluation (22,23) as the appropriate time horizon accepted by NICE (23). Figure 1 shows the developed Markov model.

**Probabilities**

The probability of achieving a PASI-75 score at the end of each trial period was defined as the transition probability estimated for remaining in these states. Table 1 highlighted the transition probabilities obtained from a Network Meta-Analysis (NMA) (18). Patients receiving biologics experience an annual dropout due to adverse events or treatment failure (23). Annual dropout probability for the patients in maintenance period states was 20% and was applied for apremilast and biologics (23,24).

The death probability in the trial period and BSC state were estimated based on the all-cause mortality due to moderate to severe plaque psoriasis (25). In the maintenance period states, it was assumed based on the Iranian published life table (26).



**Fig. 1.** The Developed Markov model for treatment of moderate to severe plaque psoriasis. (A) Treatment sequence with apremilast, (B) treatment sequence without apremilast.

**Table 1.** Treatment responses by PASI categories at the end of 3 months trial periods.

Trial period	Apremilast		Adalimumab		Etanercept	
	Probability	Range	Probability	Range	Probability	Range
PASI-75 Achieving probability	0.29	(0.21-0.38)	0.62	(0.51-0.72)	0.43	(0.33-0.54)

PASI, Psoriasis area and severity index.

**Table 2.** Baseline utility and utility changes in the model states.

Model states	Baseline utility QALY	Changes in EQ-5D score, Mean (95% CI) ( $\geq$ PASI-75 to $<$ PASI-90)	Range
Trial periods (Apremilast/adalimumab/etanercept)	0.65	0	-
Maintenance (Apremilast/ Adalimumab/etanercept)	0.65	+0.16	(0.11-0.21)
Best supportive care	0.65	0	-

PASI, Psoriasis area and severity index.

**Table 3.** Implementations and monitoring tests required in different model states.

Medicine /implementation	Apremilast		Adalimumab		Etanercept	
	Time per cycles in each state					
	Trial period (30 mg BD)	Maintenance period (30 mg BD)	Trial period (40 mg every other wk after an initial single 80-mg dose)	Maintenance Period (40 mg every other wk after an initial single 80-mg dose)	Trial period (50 mg/wk)	Maintenance period (50 mg/wk)
Referral to Dermatologist Administration	1	1	1	1	1	1
Liver function panel test	0	0	7	6	12	12
CBC check	1	0	1	1	1	1
Urea and electrolyte check	1	0	1	1	1	1

**Table 4.** Implementations in best supportive care state.

Implementation	Time (year)	Remarks
Referral to dermatologist	5	-
Narrow-band ultra violet B	3.84	1 course including 24 sessions (for 16% of patients) High needed (82% with 1 admission)
Hospitalization	27	Very high needed (18% with 2.5 admissions)
Administration of calcipotriol 0/005%	126	3 Times annually of 6 weeks each
Administration of fluocinolone 0/025%	126	3 Times annually of 6 weeks each

### Utilities

A 0.65 baseline utility was considered for the patients with moderate to severe plaque psoriasis (26). Utility increase associated with PASI response has been defined based on changes in EQ-5D score, reported in pooled apremilast trials (27,28). Table 2 shows the utility changes in the states of the model.

### Resource and costs

The direct medical costs were accounted for according to the payer's perspective. The official price was used to obtain the drug acquisition costs based on Iran Food and Drug Administration (IFDA) website. The monitoring tests and their required times were

taken from previous related studies and approved by two dermatologist experts. All of the costs originated from Iran's relative tariffs for health services books, published annually by the Iranian Ministry of Health (29). Table 3 lists the related implementations in different states of the model. The imposed costs in BSC state were estimated according to the defined-required implementations including physician visits, administration of topical therapeutics, narrow-band ultraviolet B (NBUVB) procedure, and hospitalization. Table 4 demonstrates the necessary implementations in the BSC state obtained from previous studies (23) and confirmed by dermatologists. The costs of each cycle is shown in Table 5.

**Table 5.** Costs of the designed model (base case).

Medicine/state	State	Cost/cycle (US dollar)
Apremilast	Trial period	84
	Maintenance period	69
Adalimumab	Trial period	1,193
	Maintenance period	1,025
Etanercept	Trial period	1,102
	Maintenance period	1,102
Best supportive care		3,193

**Outcomes**

The current analysis resulted in quality-adjusted-life-years (QALYs), total costs and incremental cost-effectiveness ratio (ICER). According to the Iranian guidelines, the discount rates for costs and utility were set at 5% and 3%, respectively (30).

**Sensitivity analysis**

A one-way (deterministic) sensitivity analysis was conducted due to the uncertainties in collected data, the probabilities, and assumptions in the economic evaluation. Medicine costs, PASI response rates, discount rates, the annual dropout rate for the maintenance period, mortality rates, and the hospitalization rate of BSC were the evaluated parameters in a sensitivity analysis. Upper and lower limits of confidence intervals were used in the available cases. Medicine prices were varied by ± 20% and the annual dropout rate by ± 10%. According to the Iranian guideline, the discount rates were modified from 0% to 5% for utilities and 0% to 7% for costs.

**Budget impact analysis**

Budget impact analysis (BIA) was conducted to estimate the financial budgetary impact of adding apremilast before biologic therapy in the treatment of moderate to severe plaque psoriasis from the payer perspective in Iran. The designed Markov model was also used for BIA (Fig. 1). The patients with moderate to severe plaque psoriasis who did not undergo conventional therapy were eligibly modeled in this analysis, based on the existing epidemiologic data on the prevalence of plaque psoriasis.

To analyze the impact of the budget according to Iranian guidelines, a 5-year time horizon with direct medical costs was used. The average prevalence of psoriasis in Iran was 1.9% (7,8). Plaque psoriasis averaged about 85% of all psoriasis patients (9). The prevalence

of moderate to severe plaque psoriasis was considered to be 25% of all the patients with plaque psoriasis (31). Due to the lack of epidemiologic data in Iran, the incidence rate of moderate to severe plaque psoriasis was estimated at about 1.7 in 100,000 annually based on the other global epidemiologic reports (32).

Based on the prevalence rate (at the beginning of the first year) and the annual incidence rate, the annual number of Iranian eligible patients was calculated at the beginning of the next 5 years. The Markov model was run 5 times for both of the sequences. The total annual cost was calculated by adding the current year's cost to the previous years' costs.

**RESULTS**

**Cost-utility analysis**

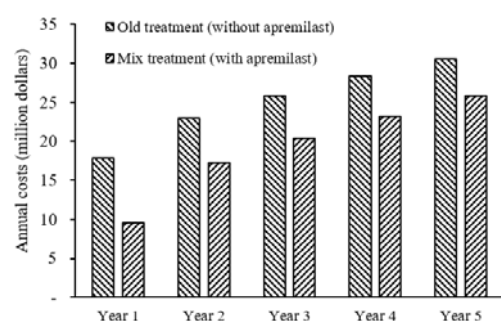
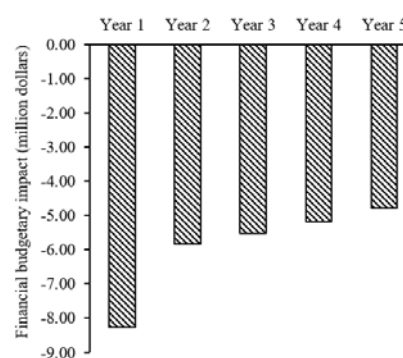
The base case analysis findings showed that the sequence consisted of apremilast and adalimumab followed by etanercept which was more effective and less costly in comparison with the sequence consisting of adalimumab followed by etanercept. The current analysis demonstrated that using the first sequence of therapy in the treatment of moderate to severe plaque psoriasis provided an additional 0.10 QALYs and decreased total costs by about 11250 USD per patient in 10 years.

**Sensitivity analysis findings**

The findings showed that the designed model was not sensitive to the evaluated parameters in the modified ranges. Table 6 presents the cost-effectiveness result of two therapeutic pathways for the base case and sensitivity analysis. As explained in Table 6, based on incremental cost and incremental effect overall, adding apremilast was the dominant choice in the base case scenario and all the assumed scenarios in sensitivity analysis which indicates the robustness of the developed model.

**Table 6.** Sensitivity analysis outcomes.

Parameters and modified ranges	Incremental costs (US dollar)	Incremental utility	Result
Base case			
10-year time horizon			
20% Annual dropout	-111,015,756	1028	Dominant
5% Discount rate for Costs			
3% Discount rate for utilities			
Maintenance state Utility (-0.11,+0.21)	-111,015,756	(716 and 1349)	Dominant
Discount rate cost (0, 7%)	(-142, 761,656, -104, 994, 829)	1028	Dominant
Apremilast price (-20%, +20%)	(-112, 878, 238, -111, 630, 229)	1028	Dominant
Discount rate utility (0, 5%)	-111, 015, 756	(1246 and 864)	Dominant
Prob Hospitalization	(-106, 841, 054, -150, 056, 391)	1028	Dominant
Prob Annual Dropout (-10%, +10%)	(-115, 670, 506, -110, 051, 778)	(1033 and 1014)	Dominant
Prob Achieving PASI 75 Etanercept(0.33,0.54)	(-115, 379, 108, -108, 816, 872)	(1105 and 953)	Dominant
Prob Achieving PASI75 Adalimumab (0.51,0.72)	(-118, 726, 232, -108, 916, 842)	(1113 and 959)	Dominant
Prob Death (0.0011, .00017)	(-110, 321, 984, -114, 228, 764)	(1157 and 865)	Dominant
Prob Achieving PASI75 Apremilast (0.21,0.38)	(-89, 414, 835, -142, 975, 416)	(720 and 1386)	Dominant

**Fig. 2.** Annual costs of old treatment and add-on-therapy.**Fig. 3.** Annual financial budgetary impact of adding apremilast to the previous treatment.

### Budget impact analysis findings

Two scenarios were defined for budget impact analysis. In the old treatment scenario, the sequential therapy consisted of adalimumab, etanercept, and the BSC in eligible patients. The add-on-therapy scenario was defined as the same sequence in addition to the apremilast administered before the biological therapy. Figures 2 and 3 present the annual costs of the scenarios and the financial impact of adding apremilast to the old treatment, respectively.

## DISCUSSION

The result showed that the addition of apremilast orally (30 mg twice daily) prior to biological treatments would lead to higher utility with lower costs. This is the first pharmacoeconomic study to evaluate the sequential therapy in the treatment of moderate

to severe plaque psoriasis in the Iranian Health System. The Markov model was developed to assess the ICER over a 10-year time horizon in a cohort of 10,000 patients. The modelled patients with moderate to severe plaque psoriasis did not undergo conventional drug therapy. The Markov model has been derived from the York model with a strongly validated structure (23). The designed model and assumptions were confirmed by two dermatologist experts to minimize the differences and make the outcomes more applicable in the Iranian setting. Due to the high probability of treatment failure in biologic therapy, sequential biologic therapy is a recommended strategy to manage psoriatic patients properly (15).

High costs of biologic medicines and hospitalizations in the BSC period are the most important components that highlight the benefits of adding apremilast to the biologic regimen in long term.

Apremilast, as a small molecule phosphodiesterase 4 inhibitor, increases the intracellular cyclic adenosine 3',5'-monophosphate levels by blocking the intracellular degradation of this substance, resulting in the reduction in proinflammatory mediators expression. This anti-inflammatory mechanism of action makes the apremilast different from immunosuppressive medicines (33).

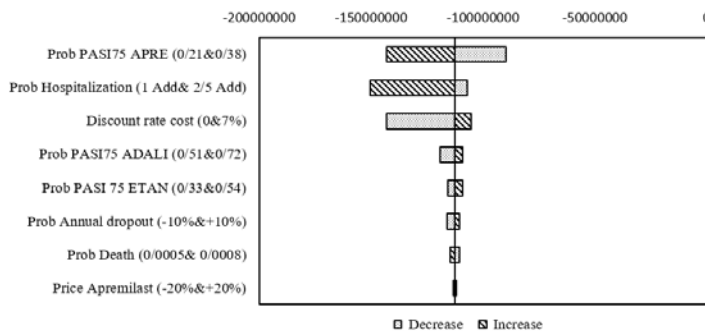
A Canadian multicenter retrospective study has reported that apremilast can lead to significant control of chronic moderate to severe plaque psoriasis, both in monotherapy and combination therapy strategies (34). Long-term maintenance of therapeutic response in an appropriate proportion of psoriatic patients is another well-established clinical characteristic of apremilast (35).

An important point regarding the model development is the positioning of apremilast in the treatment pathway. Other studies have indicated that the pathway with apremilast positioned ahead of the sequence is the most cost-effective scenario (36,37).

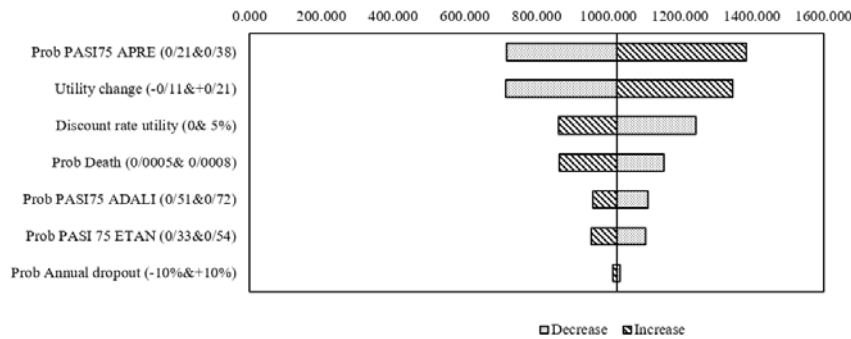
The findings showed that our designed model was robust and not sensitive to the changing of parameter values in the defined ranges. In Fig. 4, the effective parameters were ranked based on the cost variation in the alternative scenarios of sensitivity analysis.

Increasing the probability of hospitalization is the most effective component in increasing the cost difference between the two treatment pathways in favor of the addition of apremilast. Decreasing in the probability of achieving a PASI-75 score in the trial period of apremilast is the most impressive factor to reduce the cost differences between two treatment pathways which occur in favor of the previous treatment pathway, although the new pathway remains dominant in all of the scenarios.

Figure 5 shows the utility changes related to different scenarios. As can be seen in this tornado plot, the most effective parameter to increase the utility differences between two treatment sequences is increasing in the probability of achieving a PASI-75 score in the trial period of apremilast which is in favor of the new treatment pathway.



**Fig. 4.** Effects of parameter value changes on the cost difference between the treatment sequences. X-axis, Changes in the cost differences; Y-axis, affected parameters; APRE, apremilast; PASI, psoriasis area and severity index; ADLI, adalimumab; ETAN, etanercept.



**Fig. 5.** Effects of parameter value changes on the utility difference between the treatment sequences. X-axis, Changes in the cost differences; Y-axis, affected parameters; APRE, apremilast; PASI, psoriasis area and severity index; ADLI, adalimumab; ETAN, etanercept.

The decrease in the utility change and probability of achieving PASI-75 score in the trial period of apremilast is the most influential parameter variation affecting the utility differences between the pathways in favor of the old treatment.

According to the Iranian health system regulations, conducting the budget impact analysis is a necessary step to submit a newly registered drug in the reimbursement schemes. The developed model for cost-utility analysis was also used in BIA. Our findings would seem to show the budgetary saving potential of the new treatment. According to the calculations, adding orally administered apremilast ahead of biologic therapy can reduce the annual financial burden on the Iranian health system. The cost saved over the 5 years is estimated to be around 30 million USD following the addition of apremilast before biologic therapy in the eligible Iranian population.

This study encountered a number of limitations. First, it was devoid of head-to-head clinical trials comparing adalimumab and etanercept with or without apremilast. Second, it overlooked the costs and disutilities related to adverse effects, and finally, there was the narrow epidemiologic data about moderate to severe plaque psoriasis which could affect the accuracy of the outcomes especially in BIA.

## CONCLUSION

From the pharmacoeconomic point of view, adding-on apremilast before biologic therapy is a dominant strategy in the treatment of moderate to severe plaque psoriasis. Decreasing healthcare expenditure for the Iranian health system is another effect of apremilast administration verified in this study by budget impact analysis.

## Acknowledgements

This work was carried out within the framework of the Iranian health care project and was partly sponsored by the Zist Takhmir pharmaceutical company. We also thank Research Editor Institution team for their ongoing collaboration in the English editing of this paper.

## Conflict of interest statement

There are no conflicts of interest in this study.

## Authors' contribution

M. Zargaran, F. Soleymani, M. Seyedifar, and S.A. Nasrollahi contributed in the study conception and design; M. Zargaran collected the data; analysis and interpretation of results: M. Zargaran, F. Soleymani, M. Seyedifar, and M.M. Ashrafiyan Rahaghi analyzed and interpreted the data; M. Zargaran and M. Seyedifar wrote the manuscript. All authors reviewed the results and approved the final version of the manuscript.

## REFERENCES

1. Institute for Health Metrics and Evaluation (IHME). Global Burden of Disease Study 2010 Results by Cause 1990-2010. 2012. Available from: <http://ghdx.healthdata.org/record/ihme-data/gbd-2010-results-cause-1990-2010>.
2. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(2):205-212. DOI: 10.1111/jdv.13854.
3. Cannavò SP, Guarneri F, Giuffrida R, Aragona E, Guarneri C. Evaluation of cutaneous surface parameters in psoriatic patients. *Skin Res Technol*. 2017;23(1):41-47. DOI: 10.1111/srt.12299.
4. Enamandram M, Kimball AB. Psoriasis epidemiology: the interplay of genes and the environment. *J Invest Dermatol*. 2013;133(2):278-289. DOI: 10.1038/jid.2012.434.
5. Danielsen K, Olsen AO, Wilsgaard T, Furberg AS. Is the prevalence of psoriasis increasing? A 30-year follow-up of a population-based cohort. *Br J Dermatol*. 2013;168(6):1303-1310. DOI: 10.1111/bjd.12230.
6. World Health Organization. Global Report on Psoriasis. 2016. Available from: <https://apps.who.int/iris/handle/10665/204417>.
7. Baghestani S, Zare S, Mahboobi AA. Skin disease patterns in Hormozgan, Iran. *Int J Dermatol*. 2005;44(8):641-645. DOI: 10.1111/j.1365-4632.2004.02140.x.
8. Noorbala MT, Kafaie P. Pattern of skin disease in the central Iran, Yazd province. *J Pak Assoc Dermatol*. 2010;20:137-141.
9. 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(5):826-850. DOI: 10.1016/j.jaad.2008.02.039.
10. Sivamani RK, Goodarzi H, Garcia MS, Raychaudhuri SP, Wehrli LN, Ono Y, *et al.* Biologic therapies in the treatment of psoriasis: a comprehensive evidence-based basic science and clinical review and a practical guide to tuberculosis monitoring. *Clin Rev Allergy Immunol.* 2013;44(2):121-140. DOI: 10.1007/s12016-012-8301-7.
  11. Carretero G, Ferrandiz C, Dauden E, Vanaclocha Sebastian F, Gomez-Garcia FJ, Herrera-Ceballos E, *et al.* Risk of adverse events in psoriasis patients receiving classic systemic drugs and biologics in a 5-year observational study of clinical practice: 2008-2013 results of the Biobadaderm registry. *J Eur Acad Dermatol Venereol.* 2015;29(1):156-163. DOI: 10.1111/jdv.12492.
  12. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol.* 2015;172(1):244-252. DOI: 10.1111/bjd.13343.
  13. Warren RB, Smith CH, Yiu ZZ, Ashcroft DM, Barker JN, Burden AD, *et al.* Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol.* 2015;135(11):2632-2640. DOI: 10.1038/jid.2015.208.
  14. Levin AA, Gottlieb AB, Au SC. A comparison of psoriasis drug failure rates and reasons for discontinuation in biologics vs conventional systemic therapies. *J Drugs Dermatol.* 2014;13(7):848-853.
  15. Greater Manchester Medicines Management Group (GMMM), New Therapies Subgroup. The Sequential Use of Biologic Agents in the Treatment of Chronic or Plaque Psoriasis, for Those Patients, Fulfilling NICE Criteria for a Biologic. 2015. Available from: <https://studyres.com/doc/19079427/biologic-agents---sequential-use-in-psoriasis>.
  16. Gisondi P, Girolomoni G. Apremilast in the therapy of moderate-to-severe chronic plaque psoriasis. *Drug Des Devel Ther.* 2016;10:1763-1770. DOI: 10.2147/DDDT.S108115.
  17. Bewley A, Barker J, Mughal F, Cawston H, Damera V, Morris J, *et al.* Cost-effectiveness of apremilast in moderate to severe psoriasis in the United Kingdom. *Cogent Medicine.* 2018;5:1495593,1-24. DOI: 10.1080/2331205X.2018.1495593.
  18. Central Bank of Iran. Available from: [https://www.cbi.ir/exrates/rates\\_fa.aspx](https://www.cbi.ir/exrates/rates_fa.aspx).
  19. Bansback N, Sizto S, Sun H, Feldman S, Willian MK, Anis A. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. *Dermatology.* 2009;219(3):209-218. DOI: 10.1159/000233234.
  20. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, *et al.* Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med.* 2010;362(2):118-128. DOI: 10.1056/NEJMoa0810652.
  21. Pan F, Brazier NC, Shear NH, Jivraj F, Schenkel B, Brown R. Cost utility analysis based on a head-to-head Phase 3 trial comparing ustekinumab and etanercept in patients with moderate-to-severe plaque psoriasis: a Canadian perspective. *Value Health.* 2011;14(5):652-656. DOI: 10.1016/j.jval.2011.01.006.
  22. Royal College of Physicians (UK). National Clinical Guideline Centre (UK). Appendix P: Review to define 'best supportive care' for NCGC economic model. 2012. Available from: <https://www.nice.org.uk/guidance/cg153/evidence/appendices-jupdf-188351538>.
  23. Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB, *et al.* Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess.* 2006;10(46):1-233, i-iv. DOI: 10.3310/hta10460.
  24. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, *et al.* Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol.* 2006;55(4):598-606. DOI: 10.1016/j.jaad.2006.05.027.
  25. Dhana A, Yen H, Yen H, Cho E. All-cause and cause-specific mortality in psoriasis: a systematic review and meta-analysis. *J Am Acad Dermatol.* 2019;80(5):1332-1343. DOI: 10.1016/j.jaad.2018.12.037.
  26. World Health Organization. Life tables by country, Iran (Islamic Republic of). Available from: <https://apps.who.int/gho/data/?theme=main&vid=60760>.
  27. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, *et al.* Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (efficacy and safety trial evaluating the effects of apremilast in psoriasis [ESTEEM] 1). *J Am Acad Dermatol.* 2015;73(1):37-49. DOI: 10.1016/j.jaad.2015.03.049.
  28. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, *et al.* Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe plaque psoriasis over 52 weeks: a phase III, randomized, controlled trial (ESTEEM 2). *Br J Dermatol.* 2015;173(6):1387-1399. DOI: 10.1111/bjd.14164.
  29. Tariff Book for Health Services. 3rd ed. Ministry of Health. Islamic Republic of Iran; 2017. Available from: <https://www.tamin.ir/file/file/64332>.
  30. Abdoli G. Estimation of social discount rate for Iran. *J Econ Res.* 2009;9(34):135-156.

31. Armstrong AW, Koning JW, Rowse S, Tan H, Mamolo C, Kaur M. Under-treatment of patients with moderate to severe psoriasis in the United States: analysis of medication usage with health plan data. *Dermatol Ther (Heidelb)*. 2017;7(1):97-109. DOI: 10.1007/s13555-016-0153-2.
32. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol*. 2013;133(2):377-385. DOI: 10.1038/jid.2012.339.
33. Torres T, Puig L. Apremilast: a novel oral treatment for psoriasis and psoriatic arthritis. *Am J Clin Dermatol*. 2018;19(1):23-32. DOI: 10.1007/s40257-017-0302-0.
34. Ighani A, Georgakopoulos JR, Walsh S, Shear NH, Yeung J. A comparison of apremilast monotherapy and combination therapy for plaque psoriasis in clinical practice: a Canadian multicenter retrospective study. *J Am Acad Dermatol*. 2018;78(3):623-626. DOI: 10.1016/j.jaad.2017.09.060.
35. Ighani A, Georgakopoulos JR, Shear NH, Walsh S, Yeung J. Maintenance of therapeutic response after 1 year of apremilast combination therapy compared with monotherapy for the treatment of plaque psoriasis: a multicenter, retrospective study. *J Am Acad Dermatol*. 2018;79(5):953-956. DOI: 10.1016/j.jaad.2018.04.043.
36. Mughal F, Cawston H, Kinahan D, Morris J, Tencer T, Zhang F. Cost-effectiveness of apremilast in moderate to severe psoriasis in Scotland. *Value Health*. 2015;18(7):A335-A766. DOI: 10.1016/j.jval.2015.09.553.
37. Cawston H, Damera V, Ektare V, Shear NH, Tencer T, Liu FF. Cost-effectiveness of apremilast in moderate-to-severe psoriasis in Canada. *Value Health*. 2016;19(7):A587. DOI: 10.1016/j.jval.2016.09.1386.