Journal of the Turkish Academy of Dermatology
eISSN 1307-394X

Research DOI: 10.6003/jtad.16104a1

Biological Agents on Psoriasis Treatment in Greece

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Published:
J Turk Acad Dermatol 2016; **10 (4)**: 16104a1.
This article is available from: http://www.jtad.org/2016/4/jtad16104a1.pdf
Keywords: Psoriasis, PASI score, biological agents, cost effectiveness

Abstract

Background: Psoriasis is an autoimmune chronic inflammatory disorder of the skin with a 2 - 4% frequency of occurrence worldwide. The plaque psoriasis appears to be the most common form of the disease with an 85% frequency of occurrence. The biological drugs are considered as a revolutionary therapeutical treatment of the chronic inflammatory disease common as gastroenterology, rheumatology and dermatology in the last decade.

Material and Methods: The objective of this study was, firstly the estimation of the Psoriasis Area and Severity Index (PASI) score of the Greek patients.

Results: The sample consisted of 65 patients (32 men and 33 women) with mean age as 50.2 years. 36.9% of patients (n=24) received the Adalimumab drug for the treatment of psoriasis. Adalimumab received by 33.8% of patients (n = 22) who used the agent Ustekinumab, and finally 29.2% (n=19) of patients used Etanercept. PASI score for the first visit was 5.22, and for the second visit was 3.02.

Conclusion: Consequently, different treatments affect in a different way the PASI score of the patient. The agent Adalimumab had the greatest statistically significant difference between the PASI score of the first and second visit (first visit's PASI: 5.12, second visit's PASI 2.28).

Introduction

Studies aimed to estimate in field in the prevention and treatment of diseases is a well recognized tool for the overall evaluation of the economic burden of patient in a country. Based on these studies, various subgroups of disease can be differentiated based on relatively very high cost reimbursed for prevention and treatment [**1**].

Psoriasis is an autoimmune chronic inflammatory disorder of the skin with a 2 - 4% frequency of occurrence worldwide. The plaque psoriasis appears to be the most common form of the disease with a 85% frequency of occurrence [**2, 3, 4**] It is estimated that 125 million people have already the disease worldwide, with a higher prevalence in Americans and Caucasians, and a smaller one in Chinese and black people [**5**]. Based on US sta-

Table 1. Demographic Characteristics of Patients

Demographic Characteristics		N	%
Sex	Men	32	49.2
	Women	33	50.8
Age	18-40	18	27.7
	41-62	30	46.2
	63-83	15	23.0
	No answer	2	3.1
Marital Status	Married	29	44.7
	Single	12	18.5
	Divorced / Widower	2	3.0
	No answer	22	33.8
Profession	Civil Servant	6	9.2
	Private Employee	17	26.1
	Freelancer	12	18.4
	Student	2	3.0
	House worker	7	10.8
	Retired	7	10.8
	Unemployed	3	4.6
	No answer	11	27.1

tistics 7,5 million Americans have the disease tendering it one of the most common autoimmune disease. No one single case ever appeared in the Samoa population, meanwhile a very high percentage of 12% appeared in the Arctic Kasach'ye race [**6, 7, 8**]. A 10 – 15% of all the cases involves children under the age of 10, meanwhile the 75% of the cases involve people under the age of 40. In Greece, there are approximately 165.000 – 350.000 (average 200.000 cases) of psoriasis. Two possible justifications may be involved to explain this matter. The first one refers to the incomplete defection of the existing cases and the second one refers to the general ignorance of the patient regarding the pathophysiology of the disease [**9, 10, 11**]

The exact causes of the diseases appear not to be clear yet. It is estimated that in the 1/3 of the patients the disease is genetically transmitted. Based on a family history of the disease, genetic, environmental and immunological factors are involved in the emergence of psoriasis [**12, 13**]. In a study performed by *Swanbeck* et al. [**14**], the risk of occurrence of the disease in the cases that relatively none of the parents, one of the parents or both of them have psoriasis is approximately 0.04, 0.28 and 0.65 respectively. Additionally, if one sick child exists at the family the risk of the disease is respectively 0.24, 0.5 and 0.83. Based on the specific form of the disease, the appropriate therapeutically treatment is selected, namely local therapy, phototherapy and systematic therapy. Lately, novel biological agents are used as therapeutical drugs with prominent results [**15**]. These agents (Etanercept, Alefacept, Efalizumab, Infliximab, Adalimumab main used in Greece) have a targeted impact on the immune system, ameliorating the patient quality of life [**16**].

The biological drugs are considered as a revolutionary therapeutical treatment of the chronic inflammatory disease common as gastroenterology, rheumatology and dermatology in the last decade. With the use of these drugs huge cost savings can be done without jeopardizing the quality of the health services provided [**17**]. The overall direct and indirect costs for psoriasis patient in the USA are approximately 11.250 billion dollars annually. The cost involved in the therapeutical

Table 2. PASI According to the Demographic and Clinical Characteristics of Patients

Demographic Characteristics		PASI score		
		Mean (SD)	Median (min–max)	P-value
Sex	Men	2.53 (2.605)	1.8 (0-10.10)	.969
	Women	3.27 (4.771)	1.8 (0-22.50)	
Age	18-40	2.52 (2.771)	1.6 (0-9)	.100
	41-62	3.57 (4.609)	2.0 (0-22.5)	
	63-83	1.68 (2.760)	0.0 (0-9.2)	
Marital Status	Married	3.48 (4.534)	1.9 (0-22.5)	.878
	Single	2.61 (2.387)	3.15 (0-20.4)	
	Divorced / Widower	5.50 (7.040)	2.4 (1.2-16)	
Profession	Civil Servant	5.28 (8.460)	1.9 (1.2-22.5)	.962
	Private Employee	3.39 (3.614)	1.8 (0-10.10)	
	Freelancer	2.99 (2.728)	1.8 (0-8.4)	
	Other	3.00 (3.872)	1.8 (0-16)	
Clinical Characteristics		**PASI score**		
		Mean (Standard Deviation)	**Median (min – max)**	**P-value**
Disease duration (on years)	<20	2.636 (2.881)	1.6 (0-10.10)	.100
	20-40	3.42 (3.702)	2.2 (0-16)	
	>40	3.70 (7.150)	1.8 (0-22.5)	
Family History	YES	3.48 (5.398)	3.2 (0-22.5)	.969
	NO	2.61 (2.387)	2.10 (0-9)	
Accompanying Diseases	YES	2.03 (2.285)	1.55 (0-9.2)	.076
	NO	4.02 (4.991)	1.8 (0-22.5)	
Drugs	YES	2.17 (2.404)	1.65 (0-9.2)	.264

treatment of psoriasis with biological agents is approximately $10.000 - 20.000 per biological agent per year [**18**]. In a research performed by *Wu* et al. [**19**], the total cost of the therapeutical treatment with Adalimumab was between $23,427 to $26,304, for Infliximab, from $22,824 to $28,907, and for Etanercept, from $21,468 to $27,748. Similar results are found in researches performed in US, in which the cost of therapeutical treatment fluctuates between $18,384 to $27,577 [**20**]. In Sweden, the monthly costs of the therapeutical treatment with the use of biological agents was approximately $1709 per patient ($20.508 annually) [**21**]. Contrary, in Spain this cost amounts to 6.992,12 Euros per year [**22**]. Finally, in Greece, there are very few studies referring to the cost of the disease. Samoutis [**23**], presents in his research the finding that the cost per patient amounts 1.038 Euros per month (€ 12.455,91 annually). In numerous research papers, the use of biological agents in the therapeutical treatment of psoriasis is proved to be very effective and less toxic [**24, 25, 26, 27**]. In a research presented by *Cawson* et al. [**28**], the Etanercept is the less costly therapeutical treatment with the use of Infliximab, Adalimumab and Golimumab. Other researches though, presented non important statistical

Table 3. Comparison of PASI Scores of 1st and 2nd Visit

Medication		Mean (Standard Deviation)	N	P-value
Etanercept	PASI- 1st visit	6.06 (6.196)	19	.091
	PASI- 2nd visit	3.27 (3.709)	19	
Adalimumab	PASI- 1st visit	5.12 (6.413)	24	.018
	PASI- 2nd visit	2.28 (4.716)	24	
Ustekinumab	PASI- 1st visit	4.62 (5.032)	22	.211
	PASI- 2nd visit	3.61 (3.986)	22	

Table 4. Pharmaceuticals Costs of Patient For 2013

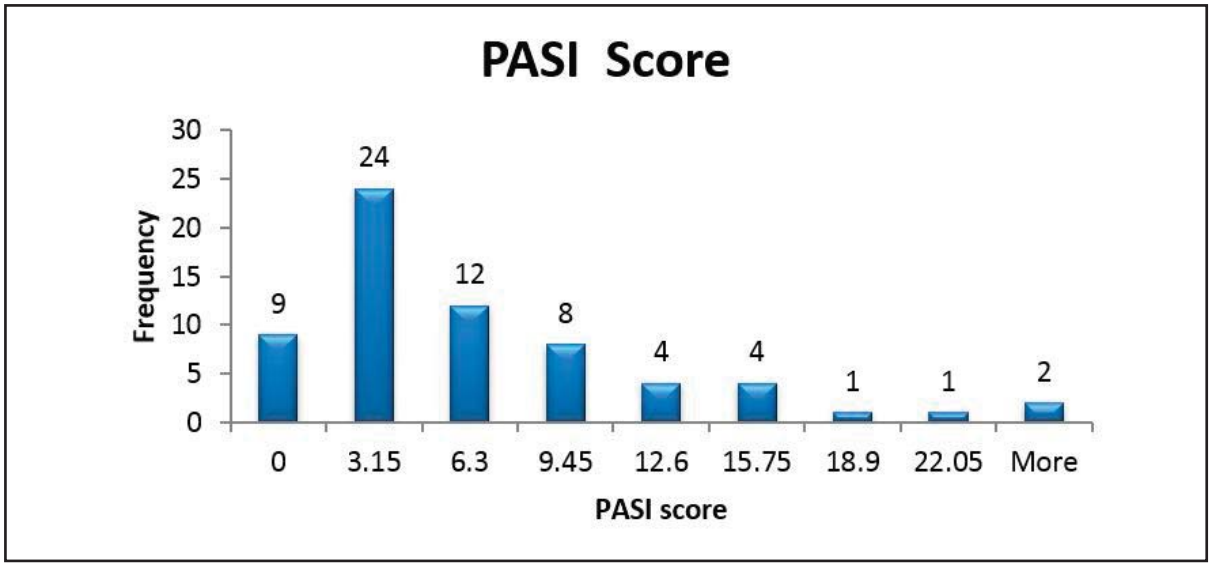
Medication		N	Total Hospital Costs
Latest Treatment	Etanercept	19	230.115,84 €
	Adalimumab	24	256.294,08 €
	Ustekinumab	22	396.869,22 €

differences between the usage of Etanercept and Adalimumab [29]. According to *Ahn* et al. [30], Infliximab was the most effective biological agent used in psoriasis treatment, followed by Adalimumab. *Gladman* et al. [31], showed that Ustekinumab, Adalimumab and Infliximab were statistically superior than the treatment with Etanercept. *Schmitt* et al. [32], found also that Infliximab in a dose of 3 mg / kg was the most effective for the therapeutical treatment of psoriasis followed by the Adalimumab, the Infliximab in a dose of 5 mg / kg and finally the Ustekinumab. The Infliximab in a dose of 50 mg twice a week was more effective and less costly than the Etanercept. Unfortunately, this fact, did not occur when the Infliximab was given in another dose [33]. Similar are the results given in a research performed by *Cummins* et al. [34], showing that Infliximab was the most effective and less costly therapeutical treatment in comparison to Etanercept and Adalimumab. Finally, *Ateno* et al. [35], approved that patients using the Infliximab and Adalimumab presented a better PASI score.

The investigation of the effectiveness of the therapeutical treatment of psoriasis in Greece is minimal. The objective of this research is firstly the estimation of the Psoriasis Area and Severity Index (PASI) score of the Greek patients having either a mild or severe form of the disease, with the cost – effectiveness of the therapeutical treatment and secondly the estimation of the economic burden of the disease in the Greek society as whole. Moreover, the evaluation of the findings of the research either by dermatologist especially area to observe the pathway of the disease or by the Ministry of Health and Social Affairs could be additional objective.

Material and Methods

In this study, for recording the history of patients suffering from psoriasis, the data were collected from the "Hospital Venereal and Skin Diseases, Andreas Syggros" of Attica. More specifically, for the recording of the clinical profile of the patient at that time the clinical index PASI score was measured. The demographic data included gender, age, marital status and occupation. Also, data were gathered for height and weight of patients, and the frequency of alcohol consumption and smoking behaviors. The parameters that were recorded and were related to the disease included the duration of the disease, family history, current treatment, and also the index PASI score (severity assessment of the disease). However, potential confounding diseases of psoriatic patients and their respective



Şekil 1. PASI score distribution of 1st visit

treatments administered by competent doctors were recorded too.

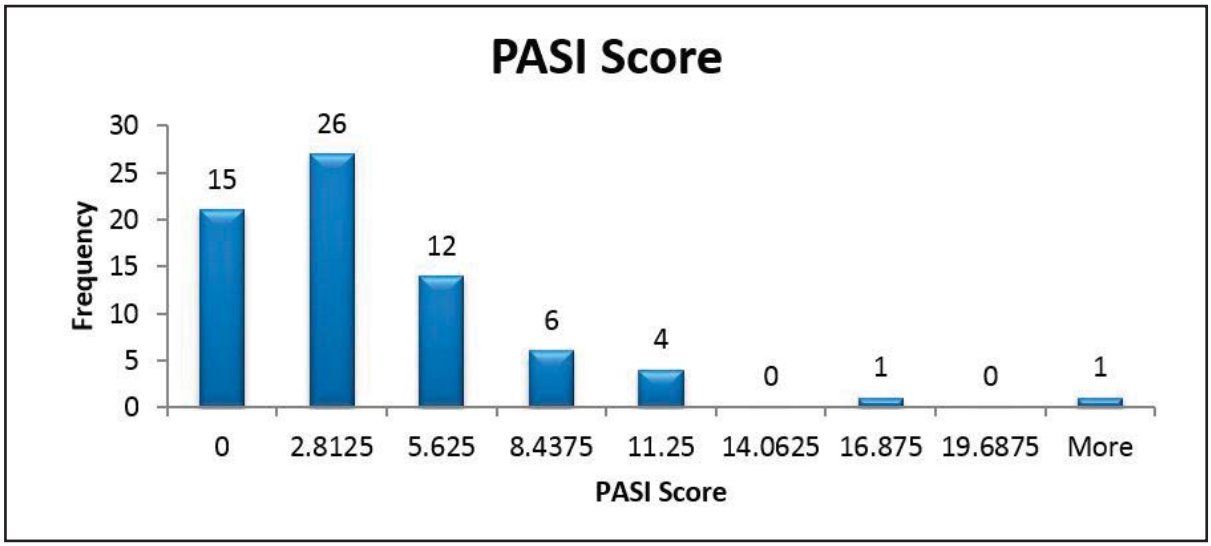
The study was conducted in patients examined in Psoriasis Clinic's' Hospital Venereal and Skin Diseases, "Andreas Syggros" of Attica, during the period January 2013 / 01 - December 2013 / 31. Initially, it was decided to check the history of 85 patients who had come to the psoriasis clinic the previous year. Patients were randomly selected. Historical of patient were randomly selected from three possible choices (three different active substances used for treating the disease). The limitations placed on the selection of the sample were the participants to be over 18 years old, to have already joined to biological agents (Etanercept, Adalimumab, Ustekinumab) and to have visited at least 2 times the psoriatic clinic during 2013. After placing restrictions, our final sample was 65 people. The evaluation of the PASI score was related to the first time receiving treatment (we called it: the first visit) and the second evaluation was made again in the same patients after a time interval of 3-6 months (we called it: second visit). The data collection was carried out at all stages of this study oriented to the medical ethics and maintains the confidentiality of the data of persons that participate at the survey.

For the statistical analysis of data the statistical program SPSS 21.0 was used. For the description of categorical variables absolute and relative frequencies were used by the researchers. The mean value standard deviation and median (minimum and maximum values) were used for describing the quantitative variables. Normality distribution of variables was assessed with Kolmogorov-Smirnov test. If data followed the normal distribution, t-test control was applied, but if they did not follow the normal distribution, Mann-Whitney and Kruskal-Wallis were applied. To test the difference in average prices of the quantitative variables, paired t-test was used.

The estimation of the effectiveness of the treatment regimen was done using the clinical profile of the disease, the PASI score. This indicator was recorded in both the first and second visit of patients to the hospital, and used the biological agent. To draw exacts conclusions about the effectiveness of treatment, it was therefore essential that patients to have participated in both phases, and therefore for this purpose we only used the sample of 65 patients (final sample of the study).

Results

The sample consisted of 65 patients, 32 men and 33 women. The mean age was 50.2 years (standard deviation 14.58). The majority of patient were between 41 – 62 years old (47.2%). The 44.6% of patients did not consume alcohol, versus 40.5% of patients who consumed. The 26.7% consumed alcohol daily (76% 1-2 glasses, 24%> 2 cups), with the overwhelming proportion of 40.0% stating that consumed alcohol weekly (64% 1-2 glasses, 36%>



Şekil 2. PASI score distribution of 2nd visit

2 glasses). Regarding smoking habits almost half patients (44.6%) were non smokers, of whom 27.8% declared former smokers. The 55.4% of patients reported smokers, with 51.7% of them smoking more than a pack per day, and 44.8% of patients to smoke less than a pack. On average, patients in the sample diseased approximately 25.36 years (standard deviation 13.77 years). Moreover, 58.4% did not have a family history of the disease; while in 35.3% of patients appear to have a history of psoriasis in the family environment. Finally, 56.8% suffered simultaneously from other diseases, except psoriasis, while 43.2% did not note another companion illness (**Table 1**).

The majority of patients (36.9%, n = 24) used the Adalimumab drug for the treatment of psoriasis. Adalimumab received by 33.8% of patients (n = 22) who used the agent Ustekinumab, and finally 29.2% (n = 19) of patients used Etanercept. The scale PASI score was recorded on both patients visits. As the first visit, we considered the first time that patients began using the biological agent. The PASI score was found to have an average value of 5.22 (standard deviation 5.85) and median 3 (threshold value: 0 (no damage foci) - maximum value: 25.20 (severe psoriasis)). The PASI score did not follow the normal distribution under Kolmogorov- Smirnov control (p<0.001) (**Şekil 1**).

In accordance with the non-parametric control Mann-Whitney, no difference in PASI score between different demographic characteristics of the patients as the clinical features of patients was found. As the second visit, we considered the next measurement which has been made after a period of 3-6 months. This is the time that can be seen, if there is any improvement in the antifungal given therapy.

The PASI score was found to have an average value of 2.89 (standard deviation = 3.81) and median of 1.8 (minimum value: 0 (no damage foci) - maximum value: 22.50 (severe psoriasis)). The PASI score did not follow the normal distribution under Kolmogorov- Smirnov control (p<0.001) (**Şekil 2**). We observed that the PASI score of patients who participated in this research is relatively low with mean score 2.89. The majority of patients have PASI score below 6 score. We should also mention a statistically significant reduction of PASI from the first visit to the second visit. In the first visit, the PASI score was 5.22 and 3.02 in the second. As in the first visit, we observed no difference in PASI score between different demographic characteristics of the patients as well as the clinical features too at a confidence level of 5% in the second visit (**Table 2**). We arrived in a conclusion that there was a difference in the PASI score of the second visit between the three different biological agents administered to patients as therapeutical treatment for psoriasis (**Table 3**). Consequently, different treatments affect in a different way the PASI score of the patient. Therefore, it is observed that depending on the PASI score and different plurality of values between the two patient visits, the effectiveness of drugs either differentiated or not. According to Table 4, the agent Adalimumab has had the greatest statistically significant difference between the PASI score of the first and second visit at a significance level of 5%. To a lesser extent was Etanercept and last with the smallest change in the PASI score was Ustekinumab.

Regarding the costs of these patients for their biological drugs computing, that reaches to an amount of 883.279,14 € for the year 2013 (**Table 4**). The cost of treating patients using Etanercept re-

ached the € 12.111,36 a year per patient, while the cost for those who used the Adalimumab and Ustekinumab reaches € 10.678,92 and 18.039,46 respectively. Finally, concerning the average annual cost of each treating patients with biological agents that reaches at € 13.588,90.

Discussion

The reason for the current conduct of study on the cost of psoriasis and especially the effectiveness of biological agents by the medical discipline, as well as by the health system administration is that psoriasis, being a chronic, incurable disease, occupies a significant part of healthcare. Psoriasis, is an irremediable disease with a great impact on the quality of life, comparable to the experience which patients with type 2 diabetes or with chronic pulmonary disease undergo. Therefore, the clinical efficacy and the cost-effectiveness ratio are important for the medical resources distribution. The main aim of this research was to evaluate the Psoriasis Area Index and the Severity Index (PASI) of Greek patients who suffer from Psoriasis. The chances of development are the same for both sexes, while it affects people of all ages. However, there are two age groups of high impact: 20-30 years and 50-60 years of age. Respecting the first age group, an early outbreak is usually reported, as well as family medical history, while the disease is of a more serious form [**36**]. According to the research findings, the majority of the patients belonged to the age group of 41-62 years old, matching the peak age group according to the existing bibliography [**36, 37, 38**].

Biological agents were introduced as a novel and effective treatment for treating moderate to severe Psoriasis. In the aggregate, the evaluation of the natural medicines effects revealed a significant recovery of the patients, within the time they were monitored. Natural treatment reduced the symptoms notably (first visit's PASI: 5.22, second visit's PASI 3.02.) On average, the 65 patients displayed moderate Psoriasis, with a PASI score of 5.22 (SD=5.85) by their first visit. The lowest PASI index score that was reported was 0(without inflammations), with the highest being 25.20 (severe psoriasis). Regarding the second visit, the 65 patients displayed an average lower PASI score of 2.89 (SD=3.81). The lowest incident on the PASI index was 0, with the highest being 25.20. The results concluded that by the first visit the severity level that the patients display does not differ in connection with the medical treatment they receive. On the contrary, it seems that in the course of time the medical treatment alters the disease's level of severity. Taking into account solely the PASI index rates of the second visit, a difference between the three medications was observed.

According to the results, Adalimumab was identified as the most effective treatment (with the PASI of the first visit being 5.12 and the one of the second visit being 2.28). With respect to the cost of the treatment with biological agents, this ranges from 10.678,92 (Adalimumab) up to 18.039,46 Euros (Ustekinumab). The findings of a Spanish research on the cost evaluation, rated the price of the treatment as slightly different. The annual cost of treatment with Adalimumab went up to 12.120 Euros, while the one with Etanercept and Ustekinumab went up to 14.420 and 15.500 Euros respectively [**22**] Adalimumab was also the most cost effective, in comparison to the remaining biological medicines, followed by Infliximab, Ustekinumab 45 mg, Etanercept and Ustekinumab 90 mg [**38**]. This difference is probably due to the fact that these researches studied incidents of moderate to severe psoriasis, while our study incidents of mild to severe levels of the disease. Different results are also published by a research conducted in the USA, where the price of the annual treatment per patient is different. Etanercept costs 15.836 dollars, while Adalimumab and Infliximab cost 19.457 and 25.748 dollars respectively.

As *Liu* et al. [**39**] report Adalimumab was the one with both the lowest cost and the greatest effectiveness, compared to the other biological medicines. Moreover, according to a study by *Bojke* et al. [**40**] Adalimumab dominates over the other natural medicines, with regard to the cost and the effectiveness. After relatively estimating the natural medicines, cost analysis revealed that the most value for money product is the Adalimumab (ICER 30.000 pounds per QALYs). It is succeeded by Etanercept (ICER 37.000 pounds per QALYs), Efalizumab (ICER 40.000 pounds per QALYs), and Infliximab (ICER 42.000 pounds per

QALYs). In a cost-effectiveness study regarding biological medicines, *Wang* et al. [**41**] revealed that the annual treatment cost of Etanercept, Adalimumab, and Ustekinumab was 39.709, 23.711 and 26.329 dollars respectively. Adalimumab and Ustekinumab had a lower annual cost than Etanercept. The studies by *Chi* and *Wang* [**42**], *Puig* [**43**], *Ferrandiz* et al. [**44**] and *Anis* et al. [**45**] present findings approximate to our results, where Adalimumab has the best cost-effectiveness ratio, being ahead of Ustekinumab 45 mg and Infliximab. A study by *Blasco* et al. [**46**] comes up with results similar to ours (in relation to cost-effectiveness ratio), with the treatment cost with Adalimumab being however lower, costing 8.013 euros, and the cost of the other treatments ranging between 9.370 and 17.112 Euros.

On the contrary, according to a study by *Nelson* et al. [**47**], Etanercept 25 mg has the better cost-effectiveness ratio, with Adalimumab 40 mg ranked third, after Infliximab. *Terranova* et al. [**48, 49**] reported that Ustekinumab has the lowest corresponding price, always being an economically effective treatment of the disease. Adalimumab, Etanercept and Infliximab were significantly more effective in treating Psoriasis, compared to the placebo. Of these medicines, Etanercept was the most efficient treatment (cost-effectiveness ratio). Similar results are found in the study of *Bravo Vergel* et al. [**50**], where Infliximab in comparison to Etanercept was more effective (165.363 and 205.345 QALY respectively). At the same time, according to *Ruano* et al. [**29**], no statistically notable differences in cost and effectiveness were observed between Etanercept and Adalimumab.

We notice the existence of some contradictory results, regarding the cost and effectiveness of various biological factors. There are researches which are in sync with our own results, while there are others which are contradictory. A very important influential factor may be the monitoring time of the patients undergoing the treatment, which varies from study to study. Some last for 12-24 weeks, some (including ours) for one year and finally others for over a year. In addition, all studies suggest that the use of biological elements improves the patients' PASI score and are inherently more effective in curing the disease. Our research agrees with this finding.

Like previous financial analyses, the current cost-effectiveness ratio analysis investigates exclusively the cost of biological agents, taking into consideration no other costs, including indirect costs, loss of productivity, absence from job etc. treatments are as a rule more expensive than conventional ones. Nevertheless, research has shown that introducing biological agents lowers the total cost of healthcare for patients who formerly needed to undergo long term treatment for dealing with the disease, since the sessions are either reduced or no longer necessary [**51**].

Conclusions

During the last decades, the large knowledge acquisition on the pathophysiology of psoriasis has leaded to regarding the discovery of innovative drugs the so called biological agents. These agents are proved very efficient in the therapeutical treatment of psoriasis. Dermatologists and patients foresee excellent perspectives in the adoption of such type of treatment. Psoriasis is a chronic disease to skin burning out them having a considerable impact on the quality of life. The decision to adopt the proper therapeutical treatment is one of the biggest dilemmas faced by medical doctors due to the fact that the use of biological agents has been proven very efficient so far. The estimation of the costs involved in the therapeutical treatment of psoriasis based on biological agents has been proven to be quite high and this consist one of major impediments posed for their wide usage. Finally, regarding the overall treatment protocol one of the most important disease measures should be adopted by the patient himself, the family environment, the health personnel, the Ministry of Health and finally in general the whole society.

Conflict of interests

The author state explicitly that there is no conflict of interest regarding the publication of the present research.

Funding

No funding was received in order to conduct this study.

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