Cost-Effectiveness of Biologic Agents in the Treatment of Moderate-to-Severe Psoriasis: A Brazilian Public Health Service Perspective

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ABSTRACT

Background: Psoriasis is a chronic disease that affects public health and budget payers. In Brazil, biologic therapy for psoriasis is mostly provided by means of lawsuit with no strategy for efficient allocation of resources. Objective: This study aimed to identify which of the available biologic alternatives for psoriasis is the most efficient from the perspective of the Brazilian Public Health Service (SUS). Methods: Direct costs and efficacy were expressed in Brazilian currency (real [R$]; US $1 = R$1.97) and Psoriasis Area Severity Index 75 (PASI75), respectively. The Markov model process included 12 cycles of 3 months each, comprising 3 years of horizon. Adalimumab (80 mg at week 0 followed by a maintenance dose of 40 mg at week 1 and then every other week), etanercept (50 mg twice weekly for 12 weeks followed by a maintenance dose of 25 mg weekly), infliximab (5 mg/kg at weeks 0, 2, and 6 and then every 8 weeks), and ustekinumab (45 mg at weeks 0 and 4 and then every 12 weeks) were assessed. One-way and horizon sensitivity analyses were performed. Moreover, probabilistic sensitivity analysis was applied to evaluate model robustness. The final result was interpreted as the cost for each patient who achieved and maintained PASI75 for at least 3 years. Results: Adalimumab was the most cost-effective biologic therapy (R$120,981.45/PASI75) for moderate-to-severe psoriasis, followed by ustekinumab (R$126,336.67/PASI75), etanercept (R$225,074.71/PASI75), and infliximab (R$377,656.28/PASI75). One-way sensitivity analysis determined that the acquisition cost of biologics was the most sensitive parameter of the model. Horizon analysis suggests that the result was the same when the horizon was varied from 1 year to a lifetime. Probabilistic sensitivity analysis showed that adalimumab has 80% to 10% probability of being the most cost-effective biologic considering a willingness-to-pay value ranging from R$50,000 to R$500,000, whereas ustekinumab presented a probability of 20% to 90% for the same range. Conclusions: From the pharmacoeconomics point of view, adalimumab 80 mg at week 0 followed by a maintenance dose of 40 mg at week 1 and then every other week should be the first-line therapy for patients with plaque psoriasis concomitant or not to psoriatic arthritis or nail psoriasis. This study does not have the potential to evaluate the impact of incorporating a specific biologic agent on the final budget. Its goal is to point out which of the technologies is the most efficient, that is, the one that adds more value to the financial resource invested. Keywords: biological agents, cost effectiveness, drug therapy, pharmacoeconomics, psoriasis.

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Introduction

Psoriasis is a chronic autoimmune disease that affects mainly the skin. Its prevalence around the world varies between 0.6% and 4.8% [1]. There are different phenotypes for this disease, with plaque psoriasis (or psoriasis vulgaris) being the most common and affecting 80% of all patients with such a clinical condition [2]. Concomitant phenotypes are possible, such as psoriatic arthritis and plaque psoriasis (40%), with or without nail psoriasis (35%-50%) [3]. Other morphological combinations are less common, but possible as well.

Treatment is based on disease severity (mild, moderate, or severe). There is no consensus in the way to classify it, but most guidelines [4-13] suggest the “rule of 10” as an acceptable tool. The aforementioned clinical approach considers patients with 1) more than 10% of body surface area (BSA) affected by the disease, 2) a score of 10 or more for the Dermatology Life Quality Index (DLQI), or 3) Psoriasis Area Severity Index (PASI) as patients with moderate-to-severe psoriasis. Some authors consider those with a PASI value of 20 as suffering from a clinically severe condition [7]. In cases of mild psoriasis, topical treatment is generally effective [14]. In cases of moderate-to-severe psoriasis, systemic treatment is based on phototherapy, methotrexate, acetylsalicylic acid, or cyclosporine. For patients who do not respond to any of these therapeutic options or develop adverse reactions, biologic agents are an option [15].

In the Brazilian Public Health System (SUS), the clinical protocol for psoriasis does not indicate the best approach regarding the use of biologics. One of the reasons for this might be that there is a lack of economic evaluations that consider the SUS...
perspective [7]. Moreover, biologics for the treatment of psoriasis remain unavailable in the SUS [16], making lawsuit the only way for patients to access such expensive treatment.

Therefore, we aimed to identify the most cost-effective biologic agent for moderate-to-severe psoriasis according to the perspective of the SUS.

Methods
This is a cost-effectiveness analysis in which costs were expressed in real (R$, Brazilian currency) and efficacy in PASI75 response (PASI75). The exchange rate between real and US dollar was US$ 1 = R$1.97 at the time of the study. This outcome corresponds to an improvement of 75% to 100% in the basal PASI score. Because the chosen outcome corresponds to efficacy and not effectiveness, it is important to highlight that data extracted from clinical trials were obtained in a controlled environment and not in a real-world scenario.

The result was interpreted as the amount of money spent for a patient who achieve and maintain PASI75 for at least 3 years. The adopted perspective is that of the SUS. A Markov model process with 12 cycles of 3 months each was built to assess the scenario of patients with moderate-to-severe psoriasis, eligible for treatment based on biologics, following Brazilian Consensus of Psoriasis [6].

This pharmaco-economic study is part of a broader project that involved systematic reviews of clinical efficacy and safety [17] and patient-related outcomes. Moreover, a mixed treatment comparison for these three outcomes and a benefit-risk multi-criteria decision analysis were carried out. These studies are under review in scientific journals.

Population
Patients with moderate-to-severe psoriasis treated within the SUS who had an indication to start a biologic agent were our targeted population. Efficacy data of each biologic agent were obtained from the literature [18–22]. Thus, our results are applicable to patients with characteristics described in Table 1, which corresponds to the weighted average of the population evaluated in each clinical trial.

Technologies Assessed
The evaluated biologic agents were the ones approved by the National Health Surveillance Agency (ANVISA) for marketing up to the end of 2012, and selected dosages were the ones indicated by Brazilian Consensus of Psoriasis [6]. Thus, adalimumab (80 mg at week 0 followed by a maintenance dose of 40 mg at week 1 and then every other week), etanercept (50 mg twice weekly for 12 weeks followed by a maintenance dose of 25 mg weekly), infliximab (5 mg/kg at weeks 0, 2, and 6 and then every 8 weeks), and ustekinumab (45 mg at weeks 0 and 4 and then every 12 weeks) were assessed.

Markov Model
The proposed model, which consisted of four health states, was based on Woolacott et al. [23]: (Fig. 1):

- PASI75—patients who achieved an improvement of 75% to 100% in their basal PASI score.
- PASI50-75—patients who achieved an improvement of 50% to 75% in their basal PASI score.
- Failure—patients who did not achieve an improvement of 50% to 75% in their basal PASI score nor achieved better scores, patients who achieved an improvement of 50% to 75% in their basal PASI score but after 12 weeks did not improve their response to PASI75, or patients who developed an adverse event preventing the maintenance of biologic therapy.
- Death—includes all death cases regardless of cause.

Each Markov cycle corresponds to 12 weeks, and the study time horizon was 3 years. Discounting of 5% [24] was applied following Brazilian statements. The outcome was assessed considering the number of patients with PASI75 health state at the end of the model.

The first 12 weeks of treatment is not shown in the model. It was, however, represented in cycle 0, and costs were expressed as initial costs. Thus, stage = 0 corresponds to a period between 12 and 24 weeks after treatment initiation.

Because all models are a simplified way to understand a complex situation, all of them have assumptions [25]. The present model assumes the following:

1. After therapeutic failure with any biologic agent, patient did not use any other biologic.
2. Temporary interruptions of biologics were not considered in this model.
3. Patients who achieved PASI75 interrupted biologic therapy only if they a. got a clinical response worse than 50% of improvement or b. developed adverse reaction or any adverse event that increased the risks over the benefits.
4. Patients with an improvement of 50% to 75% in their basal PASI score for more than 12 weeks had their biologics interrupted.
5. Only the clinical efficacy of biologics was taken into account, regardless of association with topic or systemic drugs or phototherapy treatment.

Probabilities
Data of PASI75 were extracted from the literature to serve as foundations for transition probabilities (Table 2). The selected randomized controlled trials (RCTs) were the ones that 1) assessed the same dose regimen as us, 2) showed low risk of bias by means of Cochrane Collaboration’s tool, 3) presented long-term results (at least 1 year of follow-up), and 4) had a number of participants weighing more than 500 lb. Probabilities related to the short-term treatment were retrieved from an network meta-analysis involving the four biologics assessed [18].

From the second year of treatment, efficacy data were extrapolated from the last known result. This assumption was based on literature findings [19,20,22].

Death probability was extracted from the Life Table published by the Brazilian Institute of Geography and Statistics (IBGE) [26].

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>44.8 ± 1.31</td>
</tr>
<tr>
<td>Men (%)</td>
<td>67.8 ± 2.14</td>
</tr>
<tr>
<td>Patients with PsA (%)</td>
<td>29.7 ± 3.54</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>19.5 ± 1.18</td>
</tr>
<tr>
<td>PASI score</td>
<td>19.6 ± 1.9</td>
</tr>
<tr>
<td>DLQI score</td>
<td>11.7 ± 0.66</td>
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</table>

DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis.
Considering the absence of data for patients treated with infliximab after 1 year, a linear regression based on available data was developed and the linear equation was predicted considering unknown responses. External validation and graphs are available in full detail in Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.09.002.

First, extracted data (epidemiological values) had to be calibrated, and then inserted in the model. The calibration method aimed to predict transition probabilities among health states to respect both epidemiological evidence and natural history of the disease. Probabilities applied to the model and other details are available in Appendix 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.09.002.

According to the International Society of Pharmacoeconomics and Outcomes Research, external validation is essential to establishing the credibility of any model [27]. Thus, we validated it considering the epidemiologic data regarding PASI75 response (Table 2) and the reproducibility of these results by the model. In other words, we sought to identify whether the model was capable of retrieving the same PASI75 response as shown in the RCT [19–22].

Costs
Direct costs were assessed from the perspective of the SUS, including costs for biologics, conventional therapy, drug administration, laboratory and imaging tests, hospitalization, consultations, and adverse event management. First, the main costs were identified, then measured, and finally valued. Costs varied according to the technology involved, cycle, and health state. In

<table>
<thead>
<tr>
<th>Table 2 – PASI75 efficacy data extracted from the literature.</th>
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<tr>
<td><strong>Cycle</strong></td>
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<tr>
<td>Months <em>stage</em></td>
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<tr>
<td>Drug</td>
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</table>

Note. Italic values correspond to data obtained through linear regression.
PASI, Psoriasis Area Severity Index.
* Reich et al. [18].
† Gordon et al. [20].
‡ Tyring et al. [22].
§ Reich et al. [21].
Calculated by the author.
Kimball et al. [19].
Appendix 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.09.002, all these data were thoroughly described. The sources used for valuing each cost component were the SIGTAP [28] (a database of procedures performed by the SUS) and the CMED [29] (the Regulation Chamber Drug Market in Brazil). For biologic agents, the costs were retrieved from Sistema Brasileiro de Informação sobre Medicamentos (Brazilian System of Informations about Medications), a database for drugs obtained through lawsuit. Adalimumab 40-μg vial costs R$1,792.56, whereas etanercept 25 and 50 mg, infliximab 100 mg, and ustekinumab 45 mg cost R$1093.22 and R$571.22, R$1896.32, and R$7527.15, respectively. In addition, for adverse events management and hospitalizations, we extrapolated and adjusted findings from cost-of-illness studies [30–32]. First, we identified how much a given health problem costs yearly. Then, we updated this value to the present days by means of Índice Nacional de Preços ao Consumidor Amplo (National Consumer Price Index) Board and we adjusted its annual cost for each Markov cycle.

Efficacy
The outcome considered is PASI75. It is interpreted as an improvement of 75% to 100% in the basal score measured by the PASI questionnaire, which assesses the area, erythema, induration, and desquamation of psoriasis injuries around the body [33]. The model was built to use the percentage of patients at PASI75 health state at the end of 3 years as the measure of efficacy.

Sensitivity Analysis
Following the statements provided by Brazilian Guideline for Economic Evaluations [24], one-way sensitivity analysis and probabilistic sensitivity analysis were performed. Moreover, the impact of time horizon was assessed in the final result.

All the parameters of the model were submitted to one-way sensitivity analysis. The range used for each parameter corresponds to the 95% confidence intervals. Time-horizon analysis considered scenarios ranging from 1 year up to the lifetime period; thus, probabilities from 2 years were extrapolated to the lifetime period. In addition, probabilistic sensitivity analysis was performed considering all variables of the model. Costs were distributed using gamma distributions in which hyperparameters for biologic agents were calibrated so that lowest and highest prices registered in Sistema Brasileiro de Informação sobre Medicamentos corresponded to 0.95 probability interval. Probability parameters were distributed using beta (nodes with two branches) or Dirichlet (nodes with more than two branches) distributions. The hyperparameters for these distributions were calibrated considering the number of participants in each study by which PASI responses were extracted. A total of 10,000 iterations were applied. Hyperparameters of each distribution as well as the ranges used for one-way analysis are available in Appendix 4 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2014.09.002.

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Results
Table 3 presents base-case results of a cost-effectiveness model with a 3-year time horizon using direct costs in the SUS perspective. Adalimumab is the most cost-effective technology because each patient who achieves and maintains PASI75 for at least 3 years cost R$120,981.45. It is followed by ustekinumab (R$126,336.67/PASI75), etanercept (R$225,074.71/PASI75), and infliximab (R$377,656.28/PASI75). Our findings suggest that adalimumab is dominant over etanercept and infliximab and show an incremental cost-effectiveness ratio (ICER) of R$169,283.28/incremental PASI75 between adalimumab and ustekinumab. Considering the threshold for each incremental PASI75 response, the lowest paid value for each response (R$120,981.45/PASI75), the ICER between ustekinumab and adalimumab suggests adalimumab (80 mg at week 0 followed by a maintenance dose of 40 mg at week 1 and then every other week) as the most cost-effective technology.

Sensitivity Analysis Findings
Figure 2 shows a Tornado diagram expressed in ICER considering adalimumab as the common comparator. Dotted lines correspond to the ICER value in the base-case scenario. One-way sensitivity analysis pointed out the acquisition cost of biologics (c_ADA, c_ETA, c_INF, c_UST) as the most sensitive parameter of the model. None of the other variables was able to alter the final interpretation of base-case results.

Important information regarding one-way sensitivity analysis is the identification of threshold values. Decreasing the acquisition cost of ustekinumab by 16.7% makes this technology dominant over all other drugs, whereas a reduction of 5.3% matches efficiency (cost-effectiveness ratio) with adalimumab. The acquisition cost for etanercept should decrease 50% to have the same efficiency as well. There were no scenarios in which infliximab was as efficient as adalimumab.

The impact of the time horizon on the cost-effectiveness ratio was assessed varying the number of cycles of the model. Scenarios from 1 year up to the lifetime period were simulated. Figure 3 shows the final result up to 5 years. It is seen that cost-effectiveness ratios for adalimumab and ustekinumab are very similar through the years, whereas etanercept and infliximab increase their ratio compared with other biologics. Analysis with a longer time horizon maintained that tendency. In the first 6 months of treatment, infliximab is the most effective treatment, with 82% of PASI75 response [21] (see Table 2). In this time horizon, adalimumab is the most cost-effective treatment (R$27,847.92/PASI75) followed by ustekinumab (R$30,559.99/PASI75), infliximab (R$41,684.74/PASI75), and etanercept (R$63,572.69/PASI75). A reduction in the acquisition cost of ustekinumab, infliximab, and etanercept by 11%, 36%, and 67%, respectively, would change their cost-effectiveness ratio to that shown by adalimumab.

Probabilistic sensitivity analysis was undertaken as recommended by the Brazilian Guideline for Economic Evaluations [24].

Table 3 – Results from 3 y of treatment with biologics.

<table>
<thead>
<tr>
<th>Biologic agent</th>
<th>Cost (R$)</th>
<th>Effectiveness (PASI75)</th>
<th>Cost-effectiveness (R$/PASI75)</th>
<th>Incremental cost-effectiveness ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>64,422.62</td>
<td>0.5325</td>
<td>120,981.45</td>
<td>–</td>
</tr>
<tr>
<td>Infliximab</td>
<td>74,813.71</td>
<td>0.1981</td>
<td>377,656.28</td>
<td>Dominated</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>75,663.03</td>
<td>0.5989</td>
<td>126,336.67</td>
<td>169,283.28</td>
</tr>
<tr>
<td>Etanercept</td>
<td>116,678.73</td>
<td>0.5184</td>
<td>225,074.71</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

PASI, Psoriasis Area Severity Index.
A cost-effectiveness acceptability curve was obtained from the simulation whereby distributions were applied for all parameters in the model (Fig. 4). This graph shows the probability of a given treatment being the most cost-effective (or efficient) alternative for a range of willingness-to-pay (WTP) values. On varying the WTP value from R$50,000 to R$500,000, the probability of adalimumab being the most cost-effective treatment varies from 80% to 10%, respectively. For the same WTP range, the probability of ustekinumab being the most cost-effective treatment varies from 20% to 90%, respectively. When the WTP is R$240,000, both biologics have 50% probability of being the most cost-effective treatment. For the assessed WTP range, etanercept and infliximab have probabilities close to 0%. The ICER between adalimumab and ustekinumab showed a mean of R$197,000/incremental PASI75, and the most likely values are between R$100,000 and R$200,000/incremental PASI75. Nevertheless, the aforementioned ICER shows a probability of 62% to be above the considered WTP.

Discussion

This is the first pharmacoeconomic analysis that assessed biologics in the treatment of moderate-to-severe psoriasis in the Brazilian Public Health Service (SUS). In this context, the following five issues deserve special attention, and, thus, discussion was carried out by considering the following.

Why Not Cost-Utility Analysis?

Until the present date, pharmacoeconomic studies assessing biologic agents in the long-term treatment of moderate-to-severe psoriasis have not considered PASI75 response as an outcome. This is the first study that considered PASI75 response as an outcome. Previous studies used cost-utility analysis [34–41] or cost-effectiveness for assessing short-term treatment [42,43]. Studies that have used Markov models were based on the one proposed by Woolacott et al. [23], which consists of health states defined by PASI response, in which a value of the DLQI is attributed to each health state and then changed by the EuroQol five-dimensional questionnaire (EQ-5D) utility through a linear equation. It is already known that psoriasis has a high-level impact on quality of life [44]. Thus, cost-utility analyses comparing biologic agents are of great relevance to analyze psoriasis treatment in a broader way. Norlin et al. [45], however, demonstrated that PASI response and the EQ-5D instrument have low correlation ($r = -0.25, P < 0.001$), and, thus, suggest that defining utility values by means of PASI response seems to have a high level of bias. Moreover, the Markov model proposed by Woolacott et al. may not be feasible for cost-utility analysis assessed by the EQ-5D. Considering this new evidence, we chose to develop a cost-effectiveness analysis considering PASI75 as a clinical outcome because it is the tool used most often to assess psoriasis.

Patients Benefited from This Study

People with moderate-to-severe psoriasis treating their disease in the SUS were the target population for our study. Because efficacy data were extrapolated by clinical trials up to now, their characteristics remained unknown. These results should ideally be applied to patients with clinical particularities given in Table 1. Thus, children with psoriasis are not covered by our results. Our team developed a psoriasis cost-of-illness model and determined the characteristics of patients with moderate-to-severe psoriasis using biologics [52]. The profile of these patients is different from that of patients included in RCTs, especially regarding age and time of disease. We understand, however, that these patients are representative of the real ones benefited when the SUS start dispensing such biologic drugs. For the moment, patients with psoriasis get access to these drugs by the SUS; they will start the treatment earlier, and so their profile will tend to be similar to that of patients included in RCTs.
Study Horizon

Because psoriasis is a chronic disease, its treatment lasts for lifetime. So, the ideal scenario to evaluate it would be a model capable of predicting changes and interruptions during the treatment, as well as its effectiveness for many years. The main limitation to such a model is the lack of data to support long-term transition probabilities.

The horizon defined in different studies varies. Knight et al. [37], Marcellusi et al. [38], and Lloyd et al. [41] defined 10 years, extrapolating the last known data through the next cycles up to the end of the study. Verma and Dharmarajan [46] defined 5 years, Villacorta et al. [40] 3 years, Ahn et al. [47] 1 year, and Ferrándiz et al. [42] 6 months. Our choice of 3 years was sustained by the available evidence [19,20,22] and its feasibility with the real world. In other words, it is frequently seen that patients treat psoriasis with biologic agents up to 3 years, but not 10 years, for instance. It is important to highlight that a 3-year time horizon is unable to capture costs, benefits, and adverse events that occurred after these 3 years of treatment.

Our horizon analysis shows the same tendency for a very broad horizon range. This evidence provides more reliability for our results, though there are some biases around the results from 3 years to lifetime because probabilities were extrapolated to make this analysis possible.

Sensitivity Analysis

Although one-way sensitivity analysis pointed out the acquisition cost of biologics as a sensitive parameter for the model, we consider the final results robust. It can be explained by the nature of this critical parameter. The uncertainty around it can be known and measured because a decision maker knows exactly how much will each vial of a biologic agent cost. Other parameters such as discounting, hospitalization, and adverse event costs and short- and long-term probabilities were not able to change the final result. Important data provided by this analysis were the required costs for each biologic agent vial to change the found results (described in the Results section). These data can be useful for stakeholders when defining a specific price for a determined market.

Regarding probabilistic sensitivity analysis, 10,000 iterations were performed and the interpretation was based on the cost-effectiveness acceptability curve. Because the perspective’s WTP is unknown, the cost-effectiveness acceptability curve provides a range of values, defined by us from R$50,000 to R$500,000. In scenarios with limited financial resources—WTP values up to R$240,000—adalimumab had the highest probability to be the most efficient. By considering greater values, ustekinumab is the best option. Considering the least cost-effectiveness ratio ($120,891.45/PASI75) as the WTP for each incremental patient who achieves and maintains PASI75 for at least 3 years, adalimumab (80 mg at week 0 followed by a maintenance dose of 40 mg at week 1 and then every other week) is the most likely biologic agent to be cost-effective. Moreover, probabilistic sensitivity analysis showed that the ICER between adalimumab and ustekinumab is more likely to be above the proposed WTP value.

First-Line Therapy Definition

Choosing a biologic agent to be used as first-line therapy for psoriasis is not easy. After all, many variables such as
Psoriasis can assume many phenotypes, such as plaque (or vulgar), nail, erythrodermic, guttate, inverse, and pustular psoriasis. For most of the patients, more than one phenotype can occur concomitantly, including joint involvement called psoriatic arthritis [2]. PASI75 response is the main outcome for psoriasis because it is the criterion standard used to evaluate plaque psoriasis, which is the most common phenotype affecting 80% [2] of the patients. This outcome, however, cannot properly evaluate all the phenotypes. Although in clinical trials there were individuals with other phenotypes, we recommend these results for those with plaque psoriasis, with or without concomitant psoriatic arthritis and nail psoriasis, in which the main objective of the treatment is to control the disease in the skin. It is important to highlight that for some cases, such as pustular psoriasis, anti–TNF-α agents are contraindicated [8].

Conclusions

From the pharmacoeconomic point of view, in Brazilian SUS, adalimumab (80 mg at week 0 followed by a maintenance dose of 40 mg at week 1 and then every other week) should be the first-line therapy among the biologics used for the treatment of patients with moderate to severe psoriasis. We recommend adalimumab (80 mg at week 0 followed by a maintenance dose of 40 mg at week 1 and then every other week) for patients with plaque psoriasis with or without concomitant psoriatic arthritis, or nail psoriasis, whereas those with contraindication to anti–TNF-α agents should be treated with ustekinumab (45 mg at weeks 0 and 4 and then every 12 weeks).

This study does not have the potential to evaluate the impact of incorporating a specific biologic agent on the budget. Its goal was to point out which of the assessed technologies is the most efficient, that is, the one that adds more value to the financial resources invested.

Supplementary Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.vhri.2014.09.002 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

References
