

Cost-effectiveness of moderate-to-severe psoriasis biologic treatments in Brazilian private healthcare system: cost-per-responder results derived from a network metanalysis

Custo-efetividade do tratamento biológico para psoríase moderada a grave no sistema brasileiro de saúde suplementar: resultados de custo por resposta obtidos por meio de uma metanálise em rede

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DOI: 10.21115/JBES.v12.n3.p231-40

Keywords

psoriasis, biological products, costs and cost analysis, supplemental health

ABSTRACT

Objective: To assess the cost-per-responder (CpR) of biologic therapies available in Brazil to treat moderate-to-severe plaque psoriasis (PsO) from the private healthcare system's perspective. **Methods:** Number needed to treat (NNT) and (CpR) analyses were performed to evaluate biologic therapies' cost-effectiveness for moderate-to-severe PsO available in Brazil. The effectiveness of biologic treatments for moderate-to-severe PsO was assessed based on a previously published metanalysis, which included studies considering PsO patients and outcomes of interest (PASI 75, 90, and 100). The clinical efficacy data in terms of estimated NNT based on the network metanalysis (NMA) results were combined with drug treatment costs to determine the CpR for each treatment arm in 3-time horizons: the primary response period, 1-year, and 2-years. **Results:** Risankizumab was the most cost-effective option when NMA base case scenario data was used to calculate NNT in all PASI response for both the primary response period and 1- and 2-years follow-up durations. Differences in CpR between risankizumab and other biologic drugs increased with more significant PASI improvements. CpR sensitivity analysis also confirmed these findings, indicating that risankizumab has a better performance for PASI 100, and both risankizumab and guselkumab are very similar in terms of cost per additional PASI 75 and PASI 90 responder. **Conclusions:** Risankizumab was estimated to have a lower cost per PASI 75, 90, and 100 responders in most simulated scenarios (primary response period [12-16 weeks], 1-year and 2-years), among the evaluated biologic therapies.

Received on: 11/13/2020. Approved for publication on: 11/19/2020.

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Institution where the work was performed: AbbVie Brazil.

Congresses where the study was presented: Not applicable.

Funding: This work was funded by AbbVie. AbbVie participated in the design, work conduct, interpretation of data, review, and publication approval.

Disclosures: André Vicente Esteves de Carvalho has served as an advisory board member and speaker for Abbvie, Jansen, Leo Pharma, Novartis, Lilly, and UCB; Gleison Vieira Duarte is a speaker for Abbvie, Janssen, Lilly, Novartis, Pfizer, Biolab, Leo Pharma, Galderma, Bayer, and Sanofi-Genzyme; Mayra Ianhez is a speaker for Abbvie, Janssen, Novartis, UCB, Sanofi-Genzyme, Galderma, Leo Pharma, and Biolab, and served as an advisory board member for Abbvie, Janssen, Novartis, and UCB, and Sanofi-Genzyme; Bruno Leonardo Silva, Carla de Agostino Biella, and Rafael Freitas dos Santos: AbbVie employees and may hold AbbVie stocks and/or stock options.

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Palavras-chave:

psoríase, produtos biológicos, custos e análise de custo, saúde suplementar

RESUMO

Objetivo: Avaliar o custo por respondedor (CpR) das terapias biológicas disponíveis no Brasil para tratamento da psoríase em placas (PsO) moderada a grave, na perspectiva do sistema brasileiro de saúde suplementar. **Métodos:** Foram realizadas análises de número necessário para tratar (NNT) e CpR para avaliar o custo-efetividade das terapias biológicas para PsO moderada a grave disponíveis no Brasil. A eficácia foi avaliada por meio de dados de uma metanálise em rede (NMA), que incluiu estudos considerando pacientes com PsO moderada a grave e os desfechos de interesse (PASI 75, 90 e 100). Dados de eficácia em termos de NNT foram combinados com custos do tratamento medicamentoso para determinar o CpR para cada braço de tratamento em três horizontes temporais: período de resposta primária, 1 ano e 2 anos. **Resultados:** Risanquizumabe foi mais econômico quando utilizados os dados do caso-base para calcular o NNT, considerando todos os escores PASI para o período de resposta primária e em 1 e 2 anos. As diferenças no CpR entre o risanquizumabe e os outros medicamentos biológicos aumentaram com maiores ganhos de PASI. O CpR calculado pela análise de sensibilidade confirmou esses achados, indicando que risanquizumabe tem um melhor desempenho para PASI 100, e risanquizumabe e guselcumabe são muito semelhantes em termos de CpR por PASI 75 e PASI 90 adicionais. **Conclusões:** Risanquizumabe apresentou um custo mais baixo por respondedor PASI 75, 90 e 100 na maioria dos cenários analisados (período de resposta primária [12-16 semanas], 1 ano e 2 anos), entre as terapias biológicas avaliadas.

Introduction

Psoriasis (PsO) is a chronic inflammatory, painful and disabling systemic condition, currently considered of public health concern by the World Health Organization (WHO) (World Health Organization (WHO), 2016). High-quality evidence has observed that PsO patients are at increased risk of several comorbidities such as diabetes mellitus cardiovascular conditions, inflammatory bowel disease, chronic obstructive pulmonary disease, and psychiatric disorders (Ferreira *et al.*, 2016; Fu *et al.*, 2018; Li *et al.*, 2015; Mamizadeh *et al.*, 2019; Richard *et al.*, 2013).

PsO has a relevant impact on the quality of life (QoL) due to its high disabling potential given by skin involvement and the consequent isolation and/or social discrimination and the eventual joint involvement (Menter *et al.*, 2019). Health-related QoL can also be impaired in PsO patients due to comorbidities associated with the disease, such as metabolic syndrome (Souza *et al.*, 2019).

The most common PsO type is plaque PsO, usually characterized by well-demarcated red plaques with silvery scales (Menter *et al.*, 2019). In the past 15 years, management of plaque psoriasis has evolved towards biologic medications, targeting various cytokines in PsO pathogenesis such as tumor necrosis factor- α (TNF- α), interleukin-12, interleukin-23, and interleukin-17. More recently, other biologic drug classes as the interleukin 23 (IL-23) antagonists have demonstrated a more pronounced reduction in patients' Psoriasis Area and Severity Index (PASI) scores (Gordon *et al.*, 2018).

In this context, studies simultaneously investigating the clinical benefits and incremental costs of PsO therapies are relevant to inform decision-makers about the impact of new drugs on patients' clinical benefits. Health economic evaluations based on cost-per-responder (CpR) have been

used to answer this real-world question. They suggest that incremental (CpR) is a valid measure to assess cost-effectiveness in PsO, presenting both clinical and economic significance for care providers and healthcare system managers. Considering the established relationship between PASI response and the impact on patient quality of life, this outcome has been used as an adequate surrogate endpoint to simplify health economic analysis (Armstrong *et al.*, 2018; Ravasio *et al.*, 2019).

Most biologics clinical trials use PASI outcomes as primary endpoints. PASI combines both qualitative and quantitative dimensions of PsO manifestations in a single measure. PASI score varies from 0 (no lesions) to 72 (disease highest degree). Clinical trials usually report the reduction in patient's PASI scores from baseline values after treatment – i.e., a clinical improvement of 75% (PASI 75), 90% (PASI 90), or 100% (PASI 100) (Amatore *et al.*, 2019). Regardless of PASI 75 historically substantial presence as a primary endpoint in PsO randomized controlled trials (RCT), updates to clinical guidelines have reinforced that PASI 90 response may represent a better efficacy outcome for moderate-to-severe disease. Its achievement is related to higher clinically significant improvements in quality of life, providing patients with greater satisfaction with treatment (Arnone *et al.*, 2019; Puig, 2015). For example, in a posthoc analysis of a phase 2 PsO trial, only 33% of patients achieving a PASI 75 response reached a DLQI score of 0 or 1 (meaning the lower impact on QoL). In comparison, this proportion was 79% among PASI 90 responders (Edson-Heredia *et al.*, 2016).

This study aimed to assess the cost-per-responder of biologic therapies available in Brazil to treat moderate-to-severe plaque PsO, under the private healthcare system's perspective, using PASI responses (75, 90, and 100) as efficacy outcomes.

Methods

Study design

The cost-effectiveness of biologic therapies for moderate-to-severe PsO available in Brazil was evaluated in terms of the number needed to treat (NNT) and cost-per-responder (CpR). The following comparators were included in the analysis (considering marketing authorization in Brazil and available data on the NMA): Adalimumab, Etanercept, Guselkumab, Infliximab, Ixekizumab, Risankizumab, Secukinumab, and Ustekinumab. A responder was defined based on PASI score reduction, with a focus on PASI 90 or higher, as with this response, more than three-quarters of patients have low or no impact on QoL (Edson-Heredia *et al.*, 2016).

Clinical data

The effectiveness of biologic therapies for PsO was assessed based on a previously published meta-analysis. A Bayesian network meta-analysis, comparing each drug with others having a placebo as a common comparator, was conducted to estimate short-term (10-16 weeks) PASI response rates. The long-term (44-60 weeks) PASI rates were estimated via a traditional meta-analysis (Armstrong *et al.*, 2020). The NMA included short-term randomized controlled trials and long-term trials identified from a systematic literature review (Armstrong *et al.*, 2020). Studies included were phase II and III clinical trials enrolling adults with moderate-to-severe PsO, and that reported the outcomes of interest (PASI 75, 90, and 100). Due to a lack of long term comparative data on the studies, a long-term analysis was performed in two different perspectives: a base case NMA that included Etanercept, Ixekizumab, Risankizumab, Secukinumab, and Ustekinumab (comparators with robust long-term evidence), and a pairwise meta-analysis that comprised all phase III studies found in the systematic review as a sensitivity analysis. Thus, five and eight comparators were included in the base case and sensitivity analysis, respectively. In this cost-per-responder (CpR) analysis, most of biologic therapies available in Brazil were included.

Numbers needed to treat (NNT) for additional responder were calculated for each treatment during the primary response period (10-16 weeks) and over one year (44-60 weeks), as the inverse of the absolute risk difference between each active agent and placebo based on the NMA. For two-years analysis, it was assumed the same NNT derived from 1-year period responses, as a conservative approach, considering data was not available in the NMA.

Cost inputs

The cost per patient in each treatment arm was calculated for short (10-16 weeks) and long-term (up to 2 years) periods. Dosing schedules for some comparators during the primary response period are different from the dosing schedules

during the maintenance period. First-year cost and maintenance period costs were considered for cost calculation to get an accurate estimate. The mean weight attributed to patients in the model was 70.0 kg. The proportion of patients with weight ≤ 100 kg for ustekinumab cost estimation was assumed as 70.0%, following previous models developed for HTA in Brazil (Edson-Heredia *et al.*, 2016). This study was designed from the Brazilian private health care system's perspective (*Sistema de Saúde Suplementar [SSS]*). Unit costs included pharmacy costs only and were sourced from the official Brazilian database (*Câmara de Regulação do Mercado de Medicamentos [CMED]*), considering the ex-factory price added by 18% of value-added tax (Ministério da Saúde (Brazil), 2019). Monitoring costs (laboratory tests, physician visits, etc.) were not included in the cost estimation once they are not significantly different between biologic drugs considered in the decision model.

Cost per responder calculation

The clinical efficacy data in terms of estimated NNT based on the NMA results were combined with drug treatment costs to determine each treatment arm's cost-per-responder in 3-time horizons: the primary response period, 1-year, and 2-years. It was computed by multiplying period-specific treatment costs per patient by calculating NNT for the three endpoints of interest (PASI 75, PASI 90, and PASI 100). For the short-term analysis, NNT and their estimated 95% credible intervals (CrIs) as reported by Armstrong *et al.* (Armstrong *et al.*, 2020) were used to provide a sensitivity range for the CpR, assuming constant unit costs. NNT and their 95% confidence intervals (CIs) were used for the long-term analysis.

Results

The NMA in terms of PASI response probabilities and their 95% CrIs (for short-term efficacy) and CIs (for long-term efficacy) are presented in Table 1.

NNT for additional responders were calculated for each treatment during the primary response period (10-16 weeks) and over one year, since the inverse of the absolute risk difference between each active agent and placebo is based on the NMA. For two-year analysis, it was assumed the same NNT derived from 1-year period responses, as a conservative approach, considering data was not available in the NMA. NNT and their 95% CrI or CI are shown in Table 2.

Costs

Details on dosing schedules, unit costs, and cost estimations are presented in Table 3. Mean drug acquisition costs over 1 and 2 years are calculated based on the assumption that all patients remain on treatment during this timeframe with full compliance.

Table 1. Probability of PASI response for each comparator

Treatment	Probability of PASI 75			Probability of PASI 90			Probability of PASI 100		
Results from the NMA – short-term trials (10-16 week) - Estimate (95% CrI)									
Placebo	5.3%	(4.8%,	5.9%)	1.1%	(1.0%,	1.3%)	0.1%	(0.1%,	0.1%)
Adalimumab	69.5%	(66.0%,	72.6%)	43.7%	(40.0%,	47.4%)	16.5%	(14.2%,	19.0%)
Etanercept	40.1%	(35.4%,	45.1%)	17.9%	(14.9%,	21.4%)	4.2%	(3.1%,	5.4%)
Guselkumab	86.8%	(83.8%,	89.4%)	67.3%	(62.5%,	71.9%)	35.7%	(30.9%,	40.7%)
Infliximab	80.4%	(76.5%,	84.0%)	57.4%	(52.2%,	62.8%)	26.5%	(22.3%,	31.4%)
Ixekizumab	88.8%	(86.5%,	90.9%)	70.8%	(66.8%,	74.6%)	39.5%	(35.2%,	44.0%)
Risankizumab	89.2%	(86.9%,	91.3%)	71.6%	(67.5%,	75.4%)	40.4%	(35.9%,	45.0%)
Secukinumab	83.1%	(80.2%,	85.7%)	61.4%	(57.2%,	65.6%)	29.9%	(26.3%,	33.9%)
Ustekinumab	69.7%	(66.3%,	73.1%)	43.9%	(40.2%,	47.9%)	16.7%	(14.4%,	19.3%)
Results from the NMA – long-term trials (44-60 week) – Base Case – Estimate (95% CI)									
Etanercept	53.8%	(44.1%,	63.5%)	35.9%	(27.1%,	45.6%)	15.7%	(10.4%,	22.6%)
Ixekizumab	83.5%	(76.2%,	89.2%)	69.8%	(60.1%,	78.3%)	45.0%	(34.8%,	55.6%)
Risankizumab	91.1%	(87.6%,	93.8%)	81.3%	(75.7%,	86.1%)	59.7%	(52.1%,	67.1%)
Secukinumab	80.1%	(74.7%,	84.8%)	65.2%	(58.1%,	71.6%)	39.9%	(32.9%,	47.3%)
Ustekinumab	69.8%	(67.3%,	72.3%)	52.5%	(49.3%,	55.7%)	28.0%	(25.2%,	31.0%)
Results from the NMA – long-term trials (44-60 week) – Sensitivity Analysis – Estimate (95% CI)									
Adalimumab	71.4%	(52.1%,	85.1%)	48.7%	(44.1%,	53.3%)	25.6%	(20.2%,	31.9%)
Etanercept	55.5%	(50.1%,	60.9%)	33.4%	(28.5%,	38.7%)	10.1%	(7.3%,	13.9%)
Guselkumab	88.2%	(84.6%,	91.1%)	76.5%	(72.1%,	80.5%)	47.4%	(42.5%,	52.4%)
Infliximab	58.3%	(52.5%,	63.8%)	40.1%	(30.0%,	51.1%)	-	-	-
Ixekizumab	85.0%	(79.5%,	89.4%)	73.9%	(69.9%,	77.5%)	54.3%	(50.0%,	58.5%)
Risankizumab	90.1%	(86.3%,	92.9%)	79.4%	(75.5%,	82.9%)	56.2%	(52.4%,	59.9%)
Secukinumab	88.6%	(80.6%,	93.6%)	71.3%	(64.2%,	77.5%)	42.4%	(38.5%,	46.4%)
Ustekinumab	72.5%	(65.9%,	78.2%)	52.4%	(47.1%,	57.7%)	31.0%	(27.2%,	35.2%)

PASI: Psoriasis Area and Severity Index; 95% CrI: 95% credible interval; NMA: network meta-analysis.

Table 2. NNT for PASI response for each comparator

Treatment	NNT for PASI 75			NNT for PASI 90			NNT for PASI 100		
Results calculated based on the NMA – short-term trials (10-16 week) – Estimate (95% CrI)									
Adalimumab	1.56	(1.49,	1.64)	2.35	(2.16,	2.57)	6.10	(5.29,	7.09)
Etanercept	2.87	(2.52,	3.32)	5.95	(4.93,	7.25)	24.39	(18.87,	32.26)
Guselkumab	1.23	(1.19,	1.27)	1.51	(1.41,	1.63)	2.81	(2.46,	3.25)
Infliximab	1.33	(1.27,	1.40)	1.78	(1.62,	1.96)	3.79	(3.21,	4.50)
Ixekizumab	1.20	(1.17,	1.23)	1.43	(1.36,	1.52)	2.54	(2.28,	2.85)
Risankizumab	1.19	(1.16,	1.23)	1.42	(1.35,	1.51)	2.48	(2.23,	2.79)
Secukinumab	1.29	(1.24,	1.34)	1.66	(1.55,	1.78)	3.36	(2.96,	3.82)
Ustekinumab	1.55	(1.48,	1.64)	2.34	(2.14,	2.56)	6.02	(5.21,	6.99)
Results calculated based on the NMA – long-term trials (44-60 week) – Base Case – Estimate (95% CI)									
Etanercept	1.86	(1.57,	2.27)	2.79	(2.19,	3.69)	6.37	(4.42,	9.62)
Ixekizumab	1.20	(1.12,	1.31)	1.43	(1.28,	1.66)	2.22	(1.80,	2.87)
Risankizumab	1.10	(1.07,	1.14)	1.23	(1.16,	1.32)	1.68	(1.49,	1.92)
Secukinumab	1.25	(1.18,	1.34)	1.53	(1.40,	1.72)	2.51	(2.11,	3.04)
Ustekinumab	1.43	(1.38,	1.49)	1.90	(1.80,	2.03)	3.57	(3.23,	3.97)
Results calculated based on the NMA – long-term trials (44-60 week) – Sensitivity Analysis – Estimate (95% CI)									
Adalimumab	1.40	(1.18,	1.92)	2.05	(1.88,	2.27)	3.91	(3.13,	4.95)
Etanercept	1.80	(1.64,	2.00)	2.99	(2.58,	3.51)	9.90	(7.19,	13.70)
Guselkumab	1.13	(1.10,	1.18)	1.31	(1.24,	1.39)	2.11	(1.91,	2.35)
Infliximab	1.72	(1.57,	1.91)	2.49	(1.96,	3.33)	-	-	-
Ixekizumab	1.18	(1.12,	1.26)	1.35	(1.29,	1.43)	1.84	(1.71,	2.00)
Risankizumab	1.11	(1.08,	1.16)	1.26	(1.21,	1.32)	1.78	(1.67,	1.91)
Secukinumab	1.13	(1.07,	1.24)	1.40	(1.29,	1.56)	2.36	(2.16,	2.60)
Ustekinumab	1.38	(1.28,	1.52)	1.91	(1.73,	2.12)	3.23	(2.84,	3.68)

NNT: number needed to treat; 95% CrI: 95% credible interval; NNT for each active drug were calculated versus placebo, respectively.

Table 3. Cost input data and cost estimate per treatment period for each comparator

	Adalimumab	Etanercept	Guselkumab	Infliximab	Ixekizumab	Risankizumab	Secukinumab	Ustekinumab
Dosing schedule	80 mg at week 0, 40 mg EOW starting at week 1	25 mg BIW/50 mg QW	100 mg at weeks 0, 4, then Q8W	5 mg/kg at weeks 0, 2 and 6, then Q8W	160 mg at week 0, then 80 mg Q2W until week 12, followed by 80 mg Q4W	150 mg at weeks 0 and 4, then Q12W	300 mg at weeks 0, 1, 2, 3, and 4, then monthly	45 mg ≤ 100 kg, 90 mg > 100 kg at weeks 0 and 4, then Q12W
Unit drug costs	If ≤ 100 kg If > 100 kg							
Concentration per unit (mg)	40	25	100	100	80	150	300	45 90
Cost per unit (BRL)*	4,008.29	921.72	11,216.39	4,011.36	5,271.74	16,824.54	6,727.53	12,580.95 25,161.90
Primary response period								
Duration (weeks)	16	12	16	14	12	16	12	16
No. of units	10	24	3	12.0	7	2	6	2.6 2.6
Cost in the period (BRL)	40,082.90	22,121.16	33,649.17	48,136.32	36,902.18	33,649.08	40,365.18	32,710.47
Remainder of the first year								
Duration (weeks)	36	40	36	38	40	36	40	36
No. of units	18	80	4.5	19.0	10	3	10	3.9 3.9
Cost in the period (BRL)	72,149.22	73,737.20	50,473.76	76,215.84	52,717.40	50,473.62	67,275.30	49,065.71
Cost in the first year (BRL)	112,232.12	95,858.36	84,122.93	124,352.16	89,619.58	84,122.70	107,640.48	81,776.18
Second year								
Duration (weeks)	52	52	52	52	52	52	52	52
No. of units	26	104	6.5	26.0	13	4.33	13	5.63 5.63
Cost in the period (BRL)	104,215.54	95,858.36	72,906.54	104,295.36	68,532.62	72,906.34	87,457.89	70,872.69
Cost in the first 2 years (BRL)	216,447.66	191,716.72	157,029.46	228,647.52	158,152.20	157,029.04	195,098.37	152,648.86

PASI: Psoriasis Area and Severity Index; EOW: every other week; BIW: twice weekly; Q2W: every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks.

* Ex-factory price added by 18% of value added tax.

Cost per responder in the NMA base-case scenario

Table 4 presents the CpR analysis results per each PASI response and comparator for the three-time horizons, considering NMA base-case results. In all time frames and PASI response criteria (75, 90, and 100), the lower CpR observed was for risankizumab and guselkumab. In the primary response period, the second lower CpR was ixekizumab for PASI 100. For 1- and 2-year time horizons, the second CpR was observed for ixekizumab. The highest CpR was observed for etanercept in PASI 90 and PASI 100 responses in the primary response period. The most increased CpR in the long-term analysis (1-and 2-years) was seen in all PASI response criteria. The highest CpR in the short-term was observed for infliximab in PASI 75 response (Figure 1).

Cost per responder in NMA sensitivity analysis

Estimated response rates from the NMA of short-term PASI sensitivity analyses included global trials and phase III trials only and expanded treatment space. Considering the NMA sensitivity analysis (Armstrong *et al.*, 2020), which included all eight medications in 1- and 2-year time horizons, the lowest

CpR for PASI 75 and PASI 90 was achieved by risankizumab and guselkumab. Risankizumab showed the lowest CpR for PASI 100. The highest CpRs are observed for infliximab for PASI 75 and etanercept for PASI 90 and PASI 100. A similar pattern was observed in 2 years of treatment (Table 5, Figure 2).

Figure 3 shows the sensitivity analysis results using the lower and upper limits of the respective 95% CrI to provide a range interval for cost per PASI 75, 90, and 100 responders in the primary response period. In all comparisons, risankizumab had a lower mean CpR. The same pattern was observed in 1- and 2- years PASI 100 response. For other PASI thresholds in 2-years, risankizumab and guselkumab had very similar cost-per-responder 95% CrI ranges for both PASI 75 (BRL 169,030 to 181,957 and BRL 172,432 to 185,532, respectively) and PASI 90 (BRL 189,420 to 207,985 and BRL 195,163 to 217,872, respectively).

Discussion

The current cost-per-responder analysis adopted a methodologically rigorous network meta-analysis of biologic medications for moderate-to-severe PsO to identify the effectiveness of each therapeutic option (Armstrong *et al.*, 2020).

Table 4. Cost per responder according to PASI response and treatment duration – NMA base case results

Treatment	Drug costs*	iCpR - PASI75**	iCpR - PASI90**	iCpR - PASI100**
Primary response period – Estimate (95% CrI)				
Adalimumab	40,083	62,434 (59,559 – 65,926)	94,091 (86,572 – 103,041)	244,408 (212,079 – 284,276)
Etanercept	22,121	63,567 (55,721 – 73,492)	131,674 (108,971 – 160,298)	539,540 (417,380 – 713,586)
Guselkumab	33,649	41,338 (40,011 – 42,865)	50,906 (47,594 – 54,803)	94,520 (82,880 – 109,251)
Infliximab	48,136	64,096 (61,164 – 67,607)	85,500 (78,017 – 94,200)	182,335 (154,283 – 216,830)
Ixekizumab	36,902	44,194 (43,160 – 45,502)	52,944 (50,207 – 56,168)	93,660 (84,060 – 105,134)
Risankizumab	33,649	40,106 (39,127 – 41,237)	47,729 (45,288 – 50,676)	83,496 (74,942 – 93,992)
Secukinumab	40,365	51,950 (50,205 – 53,892)	67,052 (62,679 – 71,952)	135,454 (119,424 – 154,066)
Ustekinumab	32,710	50,793 (48,676 – 53,188)	76,426 (70,194 – 83,445)	197,051 (170,367 – 228,745)
1 year of treatment – Estimate (95% CI)				
Etanercept	95,858	178,175 (150,958 – 217,366)	267,015 (210,216 – 353,721)	610,563 (424,152 – 921,715)
Ixekizumab	89,620	107,329 (100,470 – 117,611)	128,395 (114,457 – 149,117)	199,155 (161,186 – 257,528)
Risankizumab	84,123	92,341 (89,683 – 96,030)	103,472 (97,703 – 111,126)	140,909 (125,369 – 161,464)
Secukinumab	107,640	134,383 (126,935 – 144,097)	165,093 (150,336 – 185,268)	269,776 (227,570 – 327,175)
Ustekinumab	81,776	117,158 (113,107 – 121,510)	155,764 (146,815 – 165,875)	292,058 (263,794 – 324,509)
2 years of treatment – Estimate (95% CI)				
Etanercept	191,717	356,351 (301,916 – 434,732)	534,030 (420,431 – 707,442)	1,221,126 (848,304 – 1,843,430)
Ixekizumab	158,152	189,404 (177,301 – 207,549)	226,579 (201,982 – 263,148)	351,449 (284,446 – 454,460)
Risankizumab	157,029	172,370 (167,408 – 179,257)	193,148 (182,380 – 207,436)	263,030 (234,022 – 301,399)
Secukinumab	195,098	243,569 (230,069 – 261,176)	299,231 (272,484 – 335,798)	488,968 (412,470 – 593,004)
Ustekinumab	152,649	218,695 (211,133 – 226,819)	290,760 (274,055 – 309,633)	545,175 (492,416 – 605,749)

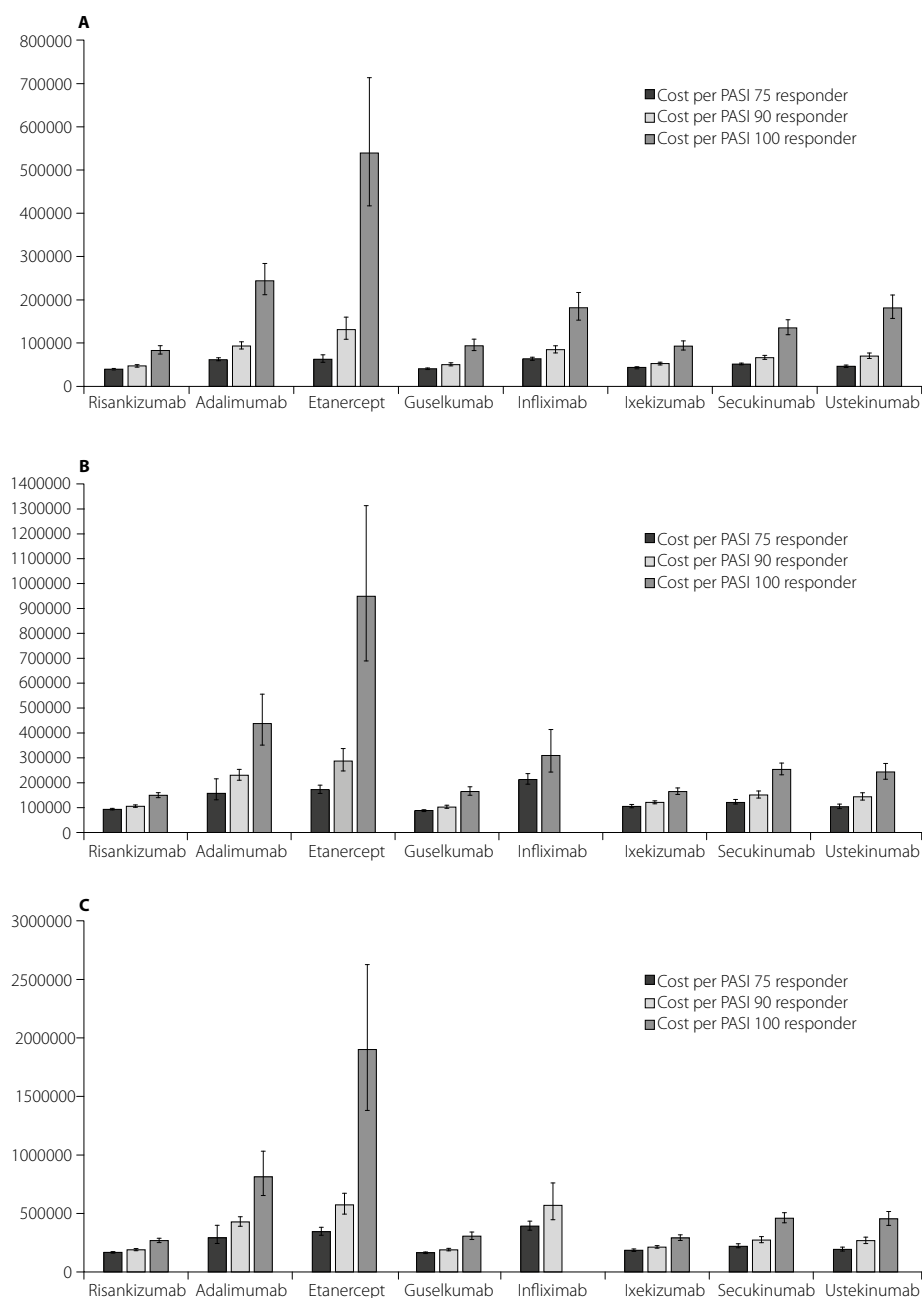
iCpR: incremental cost-per-responder; PASI: Psoriasis Area and Severity Index; CrI: credible interval.

* Drug acquisition costs within the period expressed in BRL (Brazilian real [currency]); Brazilian official database (Câmara de Regulação do Mercado de Medicamentos [CME]), considering the ex-factory price added by 18% of value added tax. ** BRL.

Table 5. Cost per responder according to PASI response and treatment duration using NMA sensitivity analysis results

Treatment	Drug acquisition cost within the period (BRL)	iCpR – PASI75 (BRL)	iCpR – PASI90 (BRL)	iCpR – PASI100 (BRL)
First year of treatment				
Adalimumab	112,232	157,188	230,456	438,407
Etanercept	95,858	172,718	287,001	949,093
Guselkumab	84,123	95,347	109,927	177,291
Infliximab	124,352	213,418	309,898	-
Ixekizumab	89,620	105,435	121,271	165,045
Risankizumab	84,123	93,366	105,948	149,685
Secukinumab	107,640	121,490	150,968	253,869
Ustekinumab	81,776	112,795	156,061	263,794
2 years of treatment				
Adalimumab	216,448	303,148	444,451	845,499
Etanercept	191,717	345,436	574,002	1,898,185
Guselkumab	157,029	177,982	205,197	330,944
Infliximab	228,648	392,414	569,812	-
Ixekizumab	158,152	186,061	214,008	291,256
Risankizumab	157,029	174,283	197,770	279,411
Secukinumab	195,098	220,201	273,630	460,138
Ustekinumab	152,649	210,550	291,315	492,416

iCpR: incremental cost-per-responder; PASI: Psoriasis Area and Severity Index.

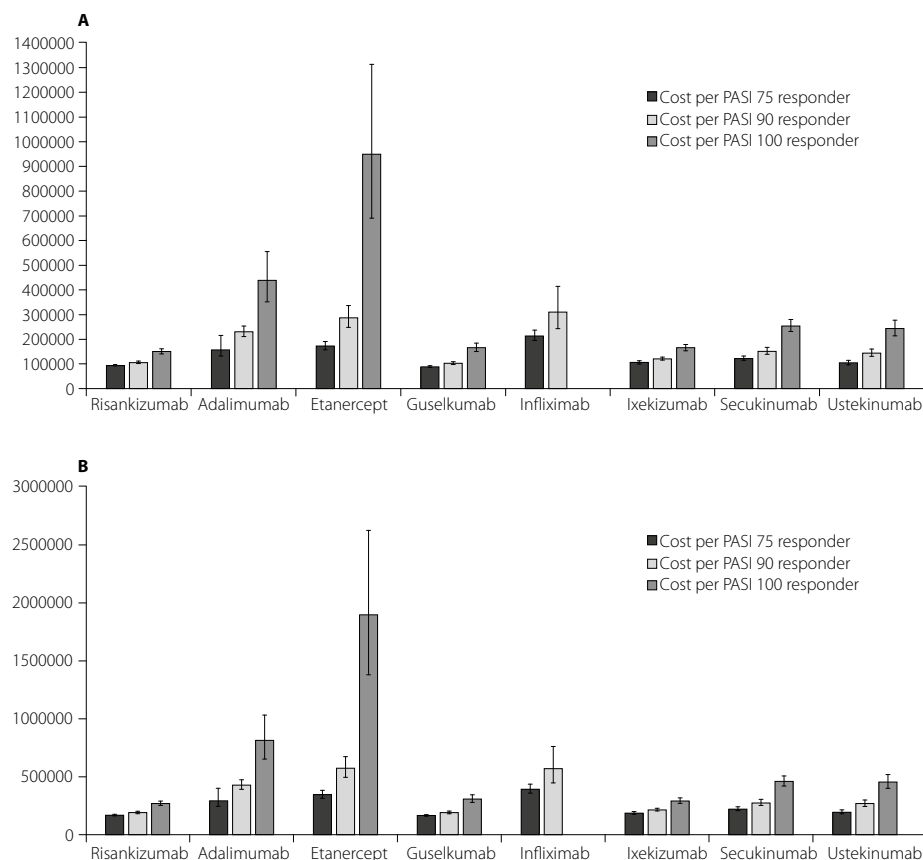


95% CI: 95% confidence interval; NMA: network metanalysis; PASI: psoriasis area severity index.

Figure 1. Cost per responder and 95% CI for each biologic considering NMA base case results: A) primary response period; B) first year of treatment; C) 2 years of treatment.

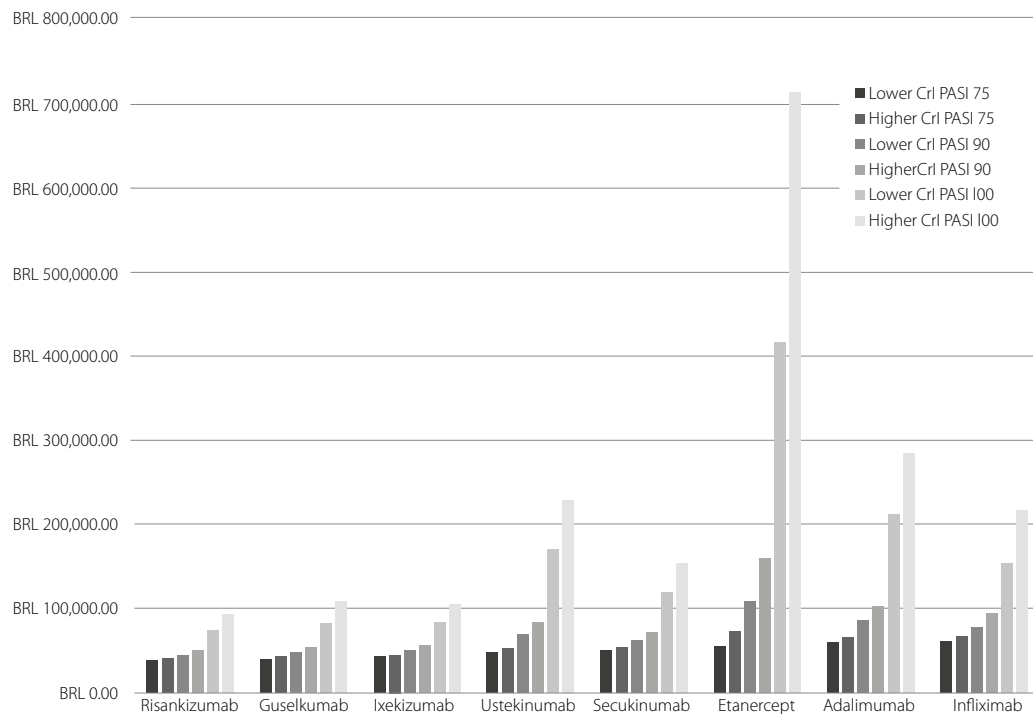
The analysis allowed a simultaneous comparison of 5 to 8 biologic drugs (depending on the time horizon and scenario) and three different PASI outcomes, providing a comprehensive overview of clinical benefits and costs associated with PsO biologic therapy. Given the introduction of novel biologic treatments in the therapeutic armamentarium for moderate-to-severe PsO in Brazil, this long-term analysis can help guide resource allocation decision-making.

Risankizumab was the most cost-effective option when NMA base case scenario data was used to calculate NNT, using all PASI thresholds for both the primary response period and 1- and 2-year follow-up durations. Overall, differences in the cost-per-responder between risankizumab and the other biologic drugs increased with more significant PASI improvements. The cost-per-responder sensitivity analysis also confirmed these findings, indicating that risankizumab has a better performance



95% CI: 95% confidence interval; PASI: psoriasis area severity index.

Figure 2. Cost per responder and 95% CI for each biologic considering the sensitivity analysis: A) first year of treatment; B) 2 years of treatment.



95% CrI: 95% credible intervals; BRL: Brazilian real [currency]; NMA: network metanalysis; PASI: psoriasis area severity index

Figure 3. Cost per responder results using lower and upper limits of 95% CrI reported in the NMA.

for PASI 100 and risankizumab and guselkumab are very similar in cost per additional PASI 75 and PASI 90 responder.

Estimated response results in the CpR analysis are consistent with findings from a recent Cochrane network meta-analysis simultaneously comparing several drug classes and unique drugs for moderate-to-severe PsO in follow-up durations ranging from 8-24 weeks (Sbidian *et al.*, 2017). To achieve a short-term PASI 90 response, the authors identified that the anti-IL23 drugs risankizumab and guselkumab were significantly more effective than ustekinumab, adalimumab, certolizumab and etanercept, as well as were infliximab and all of the anti-IL17 drugs. The efficacy point estimates for these drugs were compatible. Similar conclusions were reached by other authors (Sawyer *et al.*, 2019).

Key strengths of this cost-per-responder analysis include the longer time horizon, the robustness of the NMA providing clinical data, and the inclusion of all biologic drug classes available to PsO patients in Brazil. However, the analysis is subject to some limitations. For instance, CpR did not consider safety and tolerability issues as other cost-effectiveness analyses. This factor may have underestimated all comparators' treatment costs, particularly for those presenting a less favorable safety profile. Additionally, real-world data about costs and efficacy in Brazil were not available, impairing our ability to have a more in-depth understanding of drug effectiveness outside clinical trials and more comprehensive estimate of treatment costs. Infliximab CpR potential underestimation due to weight estimate may be considered a limitation of the present analysis. Furthermore, biosimilars and certolizumab pegol (licensed in Brazil for PsO) were not included in the CpR analysis. Further research is warranted to assess the economic burden of adverse events and to estimate real-world data to improve the external validity of PsO biologic drugs economic evaluations.

Conclusion

Among the evaluated biologic therapies, risankizumab was estimated to have a lower cost per PASI 75, 90, and 100 responders in most simulated scenarios (primary response period [12-16 weeks], 1-year and 2-years). Its clinical and economic benefits were remarkably consistent in PASI 100 threshold. As some of these drugs had recent approval in the country, the analysis provided relevant and innovative data about the clinical and economic impact of new therapeutic options for Brazilian PsO patients, care providers, and the healthcare system.

Acknowledgements

We would like to recognize the assistance of ANOVA Health Consulting Group and Maíra Takemoto from ANOVA that provided medical writing assistance in this manuscript, funded by AbbVie.

We would like to acknowledge Leilane P. Danze, of AbbVie, for her internal publication process and medical writing assistance.

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