

1 ECONOMIC EVALUATION OF TACROLIMUS AND HYDROCORTISONE IN ACUTE
2 FLARE OF ATOPIC DERMATITIS

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21 ABSTRACT

22 Introduction: Atopic dermatitis (AD) is a chronic, remitting-relapsing, and inflammatory
23 dermatosis. It occurs in patients of all ages, with a peak in children and young adults.
24 Immunomodulator treatment improves the quality of life by reducing the intensity and frequency
25 of symptomatic periods, number of physician visits and cost of the treatment for patients and the
26 health system.

27 Methodology: A cost-effectiveness analysis, comparing tacrolimus and hydrocortisone butyrate
28 1% to treat an acute flare of moderate to severe AD in Colombia for patients aged two years or
29 older. A decision tree model was designed in this analysis, and we used a health system perspective
30 and evaluated only direct costs, during 2019.

31 Results: The treatment of a symptomatic exacerbation episode of moderate to severe AD is cost-
32 effective with tacrolimus compared to hydrocortisone.

33 Discussion: tacrolimus is dominant and can be cost-saving because its use reduces complications
34 and adverse events that increase treatment costs.

35 Conclusion: The use of tacrolimus will benefit both patients and the health care system.

36

37 INTRODUCTION

38 Atopic dermatitis (AD) is a chronic, remitting-relapsing, and inflammatory dermatosis. It occurs
39 in patients of all ages, with a peak in children and young adults.^{1,2} AD is the most common chronic
40 skin condition globally, with a reported prevalence between 8.7 and 18.1%^{2,3}, a cumulative
41 prevalence of 5 to 20% in 11 years old⁴, and an increasing incidence.⁵ In Colombia, the evidence
42 suggests that the prevalence of DA was around 14% of the population in 2009-2010.⁶ In tropical

43 regions of Latin America, such as Colombia, perennial exposure to high concentrations of
44 allergens and mites favours the appearance of DA. ^{5,7,8}

45 AD has a presentation characterized by a remitting-relapsing cycle, with a symptom-free period,
46 followed by an acute flare or relapse period, in which patients need the use of immune response
47 modulators. Over one year, an AD patient has an average of three episodes in adults and 1.9
48 episodes in children (under 16 years old) for moderate AD, and five episodes in adults, and 2.6
49 episodes in children for severe AD ⁹. Immunomodulator treatment improves the quality of life by
50 reducing the intensity and frequency of symptomatic periods, number of physician visits and cost
51 of the treatment for patients and the health system ¹⁰. The cost of the AD treatment can increase
52 because of recurring doctor visits, special clothing, and the use of topical medications such as
53 moisturizers and skin barrier protectors. These costs increase greatly impact the health-related
54 quality of life (HRQoL) of patients and a considerable economic impact on the health system ^{11,12}.
55 In severe cases, the psychosocial impact may be more significant than in other chronic diseases
56 due to persistent itching, sleeping and self-image problems ².

57
58 Currently, the first-line treatments for AD are topical corticosteroids. These medicines are
59 associated with the appearance of adverse effects when they are chronically used, such as
60 tachyphylaxis, growth retardation, rebound effect, irreversible local effects, and skin atrophy. ¹³⁻
61 ¹⁶ Because AD is a recurrent disease, which requires longstanding treatment, it is to evaluate
62 different alternatives for treatment, which might reduce the number of adverse events usually
63 found when long-term medicines are used. ¹³ Topical tacrolimus is a suitable alternative for the
64 first-line treatment for AD, the use of this medicine has been approved for moderate and severe

65 AD, and it has been found it is an effective and save option for adult and paediatric populations
66 ^{13,17,18}.

67 Compared with the corticosteroids, tacrolimus is cost-effective in treating moderate to severe AD,
68 both for the first and second-line treatment ^{4,9,19}. According to Hjelmgren et al., for the European
69 population in 2007, the gain in HRQoL for patients treated with tacrolimus was 0.033 QALYs,
70 which corresponds to 1.7 quality weeks gained per year in patients with moderate AD, and 0.042
71 QALYs approximately 2.2 weeks in severe disease. ⁹

72 In Colombia, tacrolimus was included for the treatment of AD in the health benefits package since
73 February of 2021. However, its cost-effectiveness has not been studied yet in the context of
74 Colombia and until now. Thus, it becomes fundamental to understand if, in the context of
75 Colombia, an Upper Middle-Income Country, tacrolimus for the treatment of AD is cost-effective.
76 The objective of this paper is to estimate the cost-effectiveness of using tacrolimus versus t a
77 medium-strength corticosteroid, such as hydrocortisone, for the treatment of an acute flare of
78 moderate to severe AD.

79

80 METHODS

81 We proposed a cost-effectiveness analysis, comparing tacrolimus 0.03% (paediatric patients) or
82 0.1% (adult patients) and hydrocortisone butyrate 1% to treat an acute flare of moderate to severe
83 AD in Colombia for patients aged two years or older. A decision tree model was designed in this
84 analysis, and we used a health system perspective and evaluated only direct costs (Figure 1).

85

86 *Analytical framework*

87 We conducted a systematic search of systematic reviews with meta-analyses (SR-MA) to
88 determine the effectiveness of the treatments using both therapeutic alternatives. We used
89 MEDLINE and EMBASE through the OVID platform; search terms included “atopic dermatitis”,
90 “eczema”, “systematic review”, “metanalysis”, “tacrolimus”, “hydrocortisone”, “corticoids”. The
91 diagnosis of AD was made according to the diagnostic criteria considered by the authors of each
92 article. SR-MA including topical tacrolimus in individual interventions compared to
93 hydrocortisone butyrate at any dose were included. 11 studies were found since 2001 to
94 2021^{13,15,20-29}. Finally, the most recent SR-MA that analyse the interventions of interest was
95 selected and the quality of evidence was evaluated.

96
97 As a flare of AD is an acute event, a decision model was proposed (Figure 1). It includes two
98 branches of decision (tacrolimus and hydrocortisone). For each branch, we considered transition
99 probabilities for effectiveness, cost generating and non-cost generating adverse events and the
100 most common cost associated with each event.^{13,17,18} Cost generation adverse events were the
101 negative events that require additional treatment, such as skin infections (Herpes zoster, herpes
102 simplex or folliculitis). Non-cost generating adverse events do not require further treatment and
103 are treated with medicine discontinuation, such as irritation, local discomfort and burning.^{17,18}. All
104 no responding patients need second line systemic treatment with immunosuppressors
105 (Prednisolone, cyclosporine, azathioprine, mycophenolate or methotrexate). Using data from
106 Poole et al. (2009, 2010) we defined the transition utilities^{30,31}.

107
108 We used a macro-costing strategy to create the model base case, including direct costs such as
109 medicines, medical devices, procedures, and physician appointments. The recommended dose of

110 creams was calculated with data from the Clinical Practice Guide (CPG) to diagnose and treat AD
111 in Colombia³². Costs were extracted from the circulars of the national commission of medicines
112 and medical devices and the System of Information of Prices of Medicines (SISMED). The average
113 costs were obtained for the period of interest.³³ Minimal and maximal cost were calculated for
114 costs of interventions in the year 2019. The cost of procedures of interest was obtained using the
115 Individual Health Service Provision Records (RIPS) for the same year³⁴. The most common
116 procedures found in the RIPS database were used in the model (20% of the patients required the
117 procedure or the procedures were recommended in the Colombian clinical practice guideline for
118 AD) treatment (2. The costs are presented in Colombian pesos (COP) and US Dollars (USD) (1
119 USD = 3,277.14 COP for 2019). This study followed the recommendations of the Institute for the
120 Evaluation of Health Technologies (IETS) for Colombia³⁵.

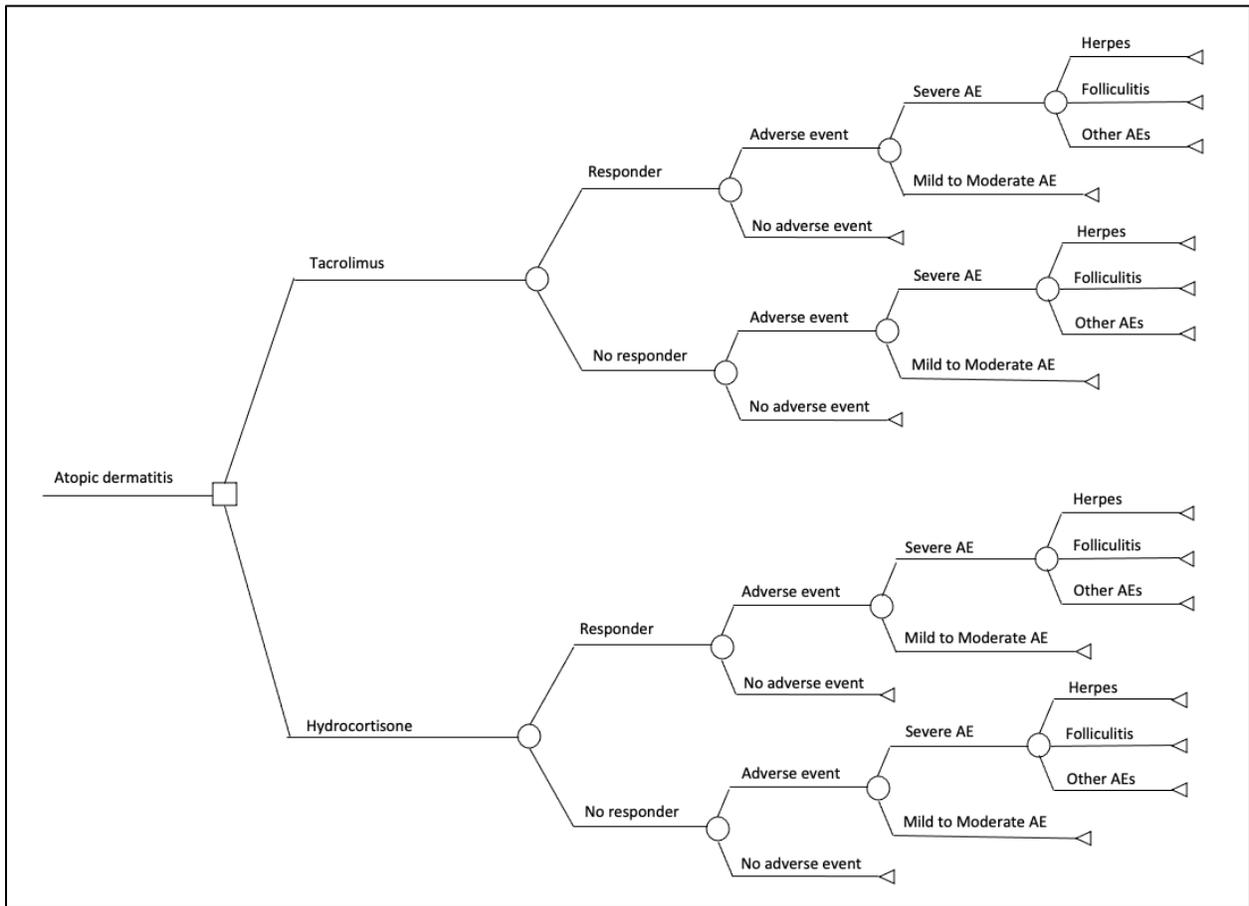
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122 The analysis was conducted using a time frame of 1 year since this period reflects the nature of
123 AD¹⁵. Given this time frame, no discount rate was used. We compute the incremental cost-
124 effectiveness ratio (ICER), comparing costs and effectiveness of receiving treatment for AD with
125 tacrolimus versus hydrocortisone. Finally, to analyze the sensitivity of the results to changes in the
126 cost and the effectiveness, we compute a deterministic sensitivity analysis with a tornado diagram
127 and a probabilistic sensitivity analysis using Montecarlo simulations using Microsoft Excel and
128 TreeAge Pro. The sensitivity analysis was performed for costs, interventions, and outcomes to
129 assess the uncertainty of the model. The cost-effectiveness threshold was calculated according to
130 the IETS guideline³⁵.

131

132 This model is based on two assumptions. First, the effectiveness of international studies for
133 tacrolimus and hydrocortisone is comparable to the effectiveness of these treatments in the
134 Colombian context. Second, the proportion of adverse effects is similar between patients who
135 respond and not respond to the treatment.

136 Figure 1. Decision tree for the analysis of the cost-effectiveness of tacrolimus and hydrocortisone
137



138

139

140 RESULTS

141 EFFECTIVENESS

142 Based on the results of the systematic search, the model presented in this paper is based on the
143 results of a meta-analysis conducted by Łabędź and Pawliczak (2019). This article evaluated the

144 efficacy and safety of tacrolimus and pimecrolimus to treat moderate to severe AD in comparison
 145 with glucocorticosteroids.^{13,17,18} The outcomes to assess effectiveness are natural units such as
 146 disease-free days, days with significant improvement of symptoms, and the number of flares. We
 147 did not include preferences in the analysis.

148
 149 Tacrolimus is the most effective technology, with a global response of improvement: clear or
 150 excellent in 72.6% of patients^{13,17,36}. The recommended dose was 201.25 g/year, according to data
 151 from the CPG for the diagnosis and treatment of atopic dermatitis in Colombia³². Hydrocortisone
 152 is less effective than tacrolimus, with a global response of improvement: clear or excellent in
 153 52.3% of patients^{13,17,36} (see Table 1). For hydrocortisone, the recommended dose per year was
 154 326.16 g/year³².

155 Table 1. Transition probabilities

| Effectiveness and safety | | Probability | Min | Max | Reference |
|--------------------------|-------------------------|-------------|-------|-------|-----------|
| Tacrolimus | Effectiveness | 0.726 | 0.712 | 0.731 | 13 |
| | Combined adverse events | 0.686 | 0.508 | 0.851 | 17,18 |
| | Severe adverse events | 0.01 | 0.001 | 0.048 | 17,18 |
| | Herpes | 0.043 | 0.032 | 0.051 | 17,18 |
| | Foliculitis | 0.120 | 0.088 | 0.139 | 17,18 |
| Hydrocortisone | Effectiveness | 0.523 | 0.390 | 0.620 | 13 |
| | Combined adverse events | 0.719 | 0.539 | 0.854 | 17,18 |
| | Severe adverse events | 0.17 | 0.013 | 0.020 | 17,18 |
| | Herpes | 0.019 | 0.014 | 0.023 | 17,18 |
| | Foliculitis | 0.100 | 0.076 | 0.120 | 17,18 |

156

157 COST

158 The costs of the technologies are described in Table 2. Patients need a lower amount of tacrolimus
159 compared to hydrocortisone (201.25g vs 326.16g). Equal procedure costs were calculated for both
160 technologies. The total annual cost for 2019 for tacrolimus treatment was \$754.41 USD
161 (\$2,472,821 COP) and hydrocortisone treatment was approximately \$800.21 USD (\$2,622,399
162 COP).

Table 2. Base case costs.

| Item | Units | Freq. | Min cost USD (COP) | Mean cost USD (COP) | Max cost USD (COP) | Ref. |
|------------------------------|-------|-------|------------------------|------------------------|------------------------|--------|
| Drugs | | | | | | |
| Tacrolimus 0,1% Ointment | 14 | 1 | \$228.88 (\$750,084) | \$326.98 (\$1,071,548) | \$425.07 (\$1,393,013) | SISMED |
| Ciclosporin capsule 100 mg | 1080 | 0,25 | \$194.59 (\$637,686) | \$277.98 (\$910,980) | \$361.37 (\$1,184,274) | 2019 |
| Azathioprine tablet 50 mg | 1460 | 0,25 | \$87.09 (\$285,394) | \$124.41 (\$407,705) | \$161.73 (\$530,017) | |
| Methotrexate tablet 2,5 mg | 520 | 0,25 | \$40.87 (\$133,952) | \$58.39 (\$191,360) | \$75.91 (\$248,768) | |
| Mycophenolate Mofetil 500 mg | 1095 | 0,25 | \$376.57 (\$1,234,065) | \$537.95 (\$1,762,950) | \$699.34 (\$2,291,835) | |
| Acyclovir 800 mg | 50 | 1 | \$13.88 (\$45,500) | \$19.83 (\$65,000) | \$25.78 (\$84,500) | |
| Procedures | | | | | | |
| Complete blood count | 4 | 1 | \$71.00 (\$232,641) | \$101.41(\$332,345) | \$131.84 (\$432,048) | RIPS |
| Creatinine | 4 | 1 | \$10.93 (\$35,827) | \$15.62 (\$51,182) | \$20.30 (\$66,537) | 2019 |
| Glucose | 1 | 1 | \$16.8 (\$55,103) | \$24.02 (\$78,719) | \$31.23 (\$102,334) | |
| VIIH test | 1 | 1 | \$1.15 (\$3,751) | \$1.64 (\$5,359) | \$2.13 (\$6,967) | |
| Tuberculin | 1 | 1 | \$43.88 (\$143,803) | \$62.69 (\$205,433) | \$81.49 (\$267,063) | |
| ALT | 2 | 1 | \$12.61 (\$41,317) | \$18.01 (\$59,024) | \$23.41 (\$76,731) | |
| AST | 2 | 1 | \$13.90 (\$45,566) | \$19.86 (\$65,094) | \$25.82 (\$84,622) | |
| Dermic sensitization test | 1 | 1 | \$25.93 (\$84,984) | \$37.05 (\$121,405) | \$48.16 (\$157,827) | |

Table 2. Base case costs.

| Item | Units | Freq. | Min cost USD (COP) | Mean cost USD (COP) | Max cost USD (COP) | Ref. |
|----------------------------|-------|-------|--------------------|---------------------|--------------------|------|
| Consultations | 1 | 1 | \$1.71 (\$5,602) | \$2.44 (\$8,002) | \$3.17 (\$10,403) | RIPS |
| General medicine | 1 | 1 | \$1.78 (\$5,844) | \$2.55 (\$8,349) | \$3.31 (\$10,853) | 2019 |
| General medicine follow-up | 1 | 0,319 | \$3.30 (\$10,812) | \$4.71 (\$15,446) | \$6.13 (\$20,079) | |
| Paediatrics | 3 | 0,319 | \$4.41 (\$14,460) | \$6.30 (\$20,657) | \$8.20 (\$26,855) | |
| Paediatric follow up | 1 | 0,5 | \$8.18 (\$26,789) | \$11.68 (\$38,270) | \$15.18 (\$49,750) | |
| Dermatology | 3 | 0,5 | \$8.97 (\$29,403) | \$12.82 (\$42,005) | \$16.66 (\$54,606) | |
| Dermatology follow up | 1 | 0,5 | \$5.02 (\$16,453) | \$7.17 (\$23,504) | \$9.32 (\$30,556) | |
| Allergology | 3 | 0,5 | \$13.94 (\$45,690) | \$19.92 (\$65,272) | \$25.89 (\$84,853) | |
| Allergology follow up | | | | | | |

165 *Incremental cost-effectiveness*

166 Tacrolimus treatment is less expensive and more effective than hydrocortisone treatment. The
167 incremental cost for 2019 was \$45.64 USD (\$149,578 COP), favouring tacrolimus, with an
168 incremental effectiveness of 1.3% in favour of tacrolimus ICER equal to \$-4,752.08 USD (\$-
169 15,573.237 COP). Tacrolimus is a cost-saving technology compared to hydrocortisone. Therefore,
170 tacrolimus was a dominant technology compared to hydrocortisone for an acute exacerbation
171 episode of atopic dermatitis (Table 3).

172 Table 3. Incremental cost effectiveness ratio Tacrolimus vs. hydrocortisone, 2019

| Technology | Cost USD (COP) | Incremental cost USD (COP) | Effectiveness | Incremental effectiveness | ICER USD (COP) | NMB USD (COP) |
|----------------|------------------------|-------------------------------|---------------|------------------------------|-----------------------------|----------------------|
| Tacrolimus | \$754.57 (\$2,472,821) | \$-45.64 (\$-149,578) | 0,721 | 0,013 | \$-4,752.08 (\$-15,573,237) | \$127.65 (\$418,334) |
| Hydrocortisone | \$800.21 (\$2,622,399) | | 0,708 | | | |

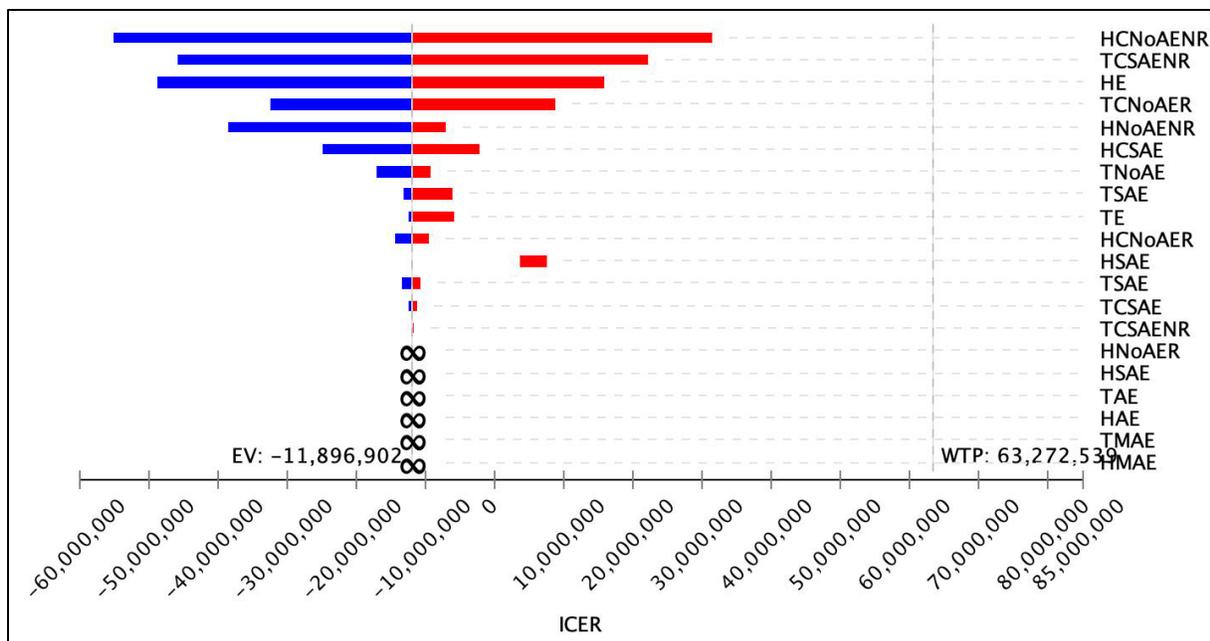
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174 *Sensitivity analysis*

175 The deterministic sensitivity analysis for this model found that the uncertainty is mainly explained
176 by the cost of treating adverse effects associated with hydrocortisone and tacrolimus treatment,
177 also with the variability of the effectiveness of hydrocortisone, and the cost of the second-line
178 treatment in non-responders (See Figure 2, no responder branch). Additionally, in the multivariate
179 analysis with the Montecarlo simulation, treatment with tacrolimus is favoured compared to
180 hydrocortisone for all values for willingness to pay (Figure 3).

181

182 Figure 2. Deterministic sensitivity analysis.



183

184 Tornado diagram.

185 HAE (Hydrocortisone: Probability of AE)

186 HCNAENR (Hydrocortisone: cost of treatment in no responders with no AE)

187 HCNAER (Hydrocortisone: Cost of treatment in responders with no AE)

188 HCSAE (Hydrocortisone: Cost of treatment of severe AE)

189 HE (Hydrocortisone: effectiveness)

190 HMAE (Hydrocortisone: Probability of mild to moderate AE)

191 HNAENR (Hydrocortisone: Probability of no AE in no responders),

192 HNAER (Hydrocortisone: Probability of no AE in responder)

193 HSAE (Hydrocortisone: Probability of severe AE)

194 TAE (Tacrolimus: Probability of AE)

195 TCNAENR (Tacrolimus: cost of treatment in no responders with no AE),

196 TCSAE (Tacrolimus: Cost of treatment of severe AE)

197 TCSAENR (Tacrolimus: cost of treatment in no responders with severe AE)

198 TE (Tacrolimus: Effectiveness)

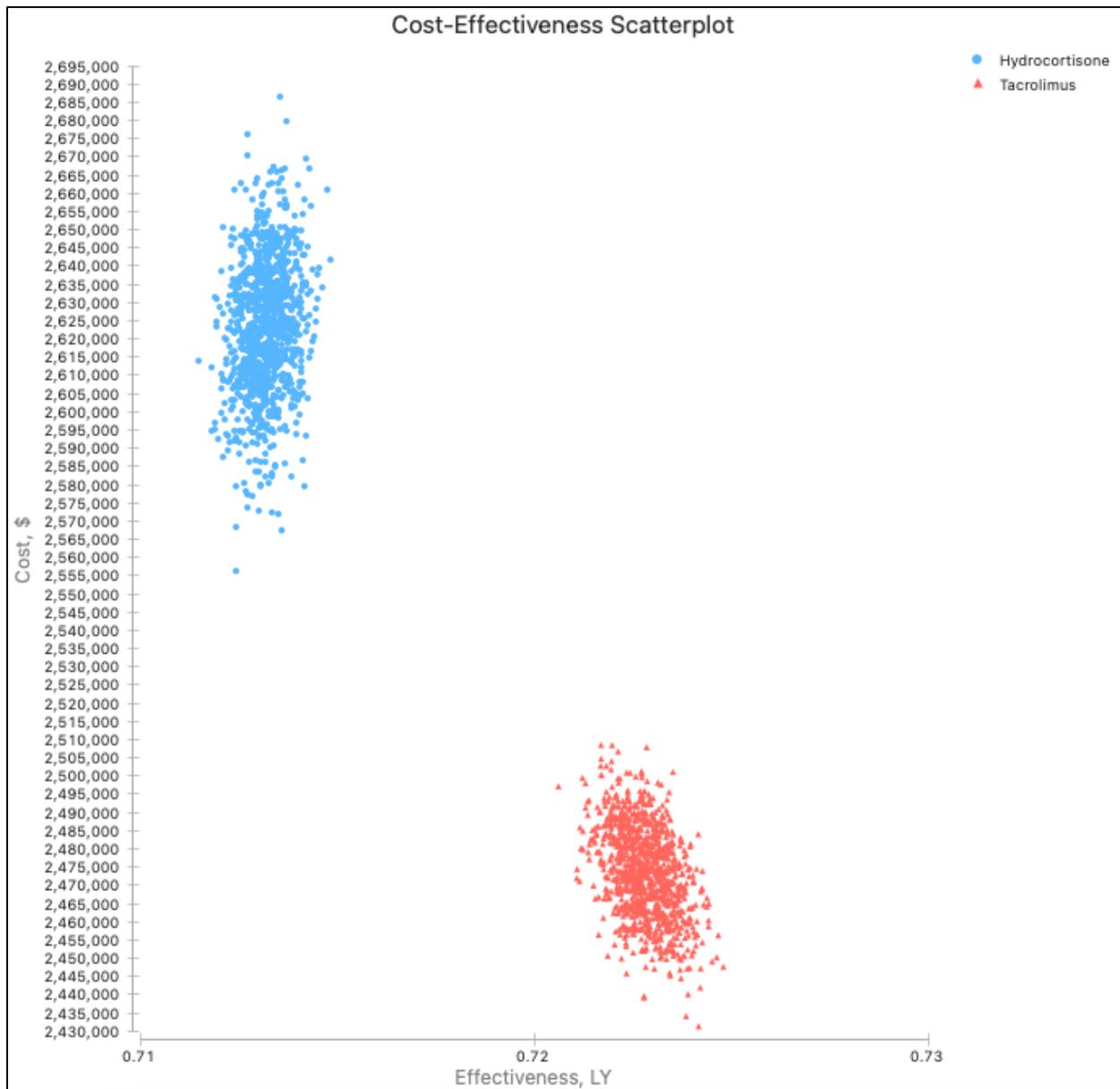
199 TMAE (Tacrolimus: Probability of mild to moderate AE)

200 TNAE (Tacrolimus: Probability of no AE)

201 TSAE (Tacrolimus: Probability of severe AE)

202

203 Figure 3. Incremental cost-effectiveness scatterplot.



204

205

206 DISCUSSION

207 This is the first economic analysis of AD acute treatment in Colombia, comparing tacrolimus and
 208 hydrocortisone. A decision tree was proposed to evaluate a single episode of AD relapse (Figure
 209 1). We conducted a systematic search of SR-MA to determine the effectiveness of the treatments
 210 using both therapeutic alternatives. A macro-costing strategy was used to create the model base

211 case, including direct costs such as medicines, medical devices, procedures, and physician
212 appointments from Health ministry databases. Incremental cost-effectiveness ratio (ICER) was
213 calculated for treatment for AD with tacrolimus versus hydrocortisone, and deterministic and
214 probabilistic sensitivity analyses were performed.

215 The results revealed that tacrolimus is a more effective option compared to hydrocortisone in
216 patients with moderate to severe AD. These findings are consistent with those found in cost-
217 effectiveness studies of calcineurin inhibitors for AD^{2,4,15,20}. However, data used in the decision
218 tree model was not obtained from the Latin American population, which poses challenges when
219 interpreting the results. Then it is recommended that these results not be generalized without
220 considering the particular context of the patients.

221
222 In addition, the main costs are represented by treatment medicines for the first-line (tacrolimus and
223 hydrocortisone) and second-line systemic treatment, such as cyclosporine and azathioprine
224 mycophenolate and methotrexate^{32,33}. The second highest costs included procedures and
225 laboratories needed for the second line of treatment. Finally, the less expensive items were
226 physicians' consultations³⁴. This finding differs from other analysis in European countries, where
227 physicians' visits were more costly than other items such as medicines and other procedures^{1,10}.
228 These differences between our results and previous studies may be explained by the Colombian
229 context, where the remuneration of health professionals is low and the costs of procedures and
230 medicines are high. It can show the need to increase the regulation of prices of technologies. It is
231 crucial to consider the differences between health systems and insurance in Latin-American
232 countries and High-income countries that may explain these differences.

233

234 The model proposed in this study shows that treating a symptomatic exacerbation episode of
235 moderate to severe AD is cost-effective with tacrolimus compared to hydrocortisone. These results
236 are similar to the ones in European economic analyzes evaluating tacrolimus in comparison with
237 corticosteroids.^{4,9,15} According to the analysis, treatment with tacrolimus is dominant and can be
238 cost-saving because its use reduces complications and adverse events that increase treatment costs.
239 The sensitivity analysis confirms these findings. The model is sensitive to the cost of treatment of
240 patients who do not respond to tacrolimus or hydrocortisone first line treatment and treat adverse
241 events. This can be explained by the need for additional second-line treatment that is more
242 expensive and requires tests and physicians' follow-ups when the patient does not respond to first-
243 line treatment.

244

245 It is important to note that this analysis was performed for a single acute episode of the disease,
246 but patients with moderate to severe AD present multiple exacerbations per year¹⁶. Therefore, this
247 model underestimates the cost-effectiveness of tacrolimus, and the differences between treatments
248 can be even greater than the ones presented here. In addition, a social perspective was not adopted
249 because of data limitations and lack of evidence in this subject. As an alternative, we chose the
250 health system perspective and expected to provide a starting point for new analyses in this context.
251 Some aspects of treatment were silenced, such as moisturizers, cleansers and other products used
252 in the treatment recommended by International and Colombian clinical practice guidelines^{32,37,38}.
253 Also, productivity losses of patients and parents could not be considered. Overall analysis data
254 come from health system databases and recommendation from AD clinical practice guidelines.
255 Results found are limited, and generalization is difficult.

256

257 This analysis supports the use of tacrolimus over hydrocortisone in pediatric and adult patients
258 with moderate and severe AD as first-line treatment. The use of this medicine will benefit both
259 patients and the health care system. Nevertheless, more studies on the subject are necessary to
260 make a definitive recommendation.

261

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