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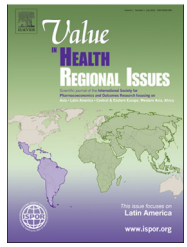

Cost-Effectiveness of Dulaglutide Compared with Liraglutide and Glargine in Type 2 Diabetes Mellitus Patients in Colombia

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ABSTRACT

Background: Diabetes treatment includes very diverse drugs. It is essential to identify which drugs offer the best value for their costs. **Objectives:** To estimate comparative cost-effectiveness for treating diabetes mellitus with dulaglutide, liraglutide, or glargine in Colombia. **Methods:** A Markov model including diabetic microvascular and macrovascular complications was used to estimate cost-effectiveness. We used annual cycles, a 5-year time horizon, 5% discount rate, and third-party payer's perspective. Main outcomes were quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs). Transition probabilities were obtained from primary studies and costs from local databases and studies. We used a threshold of 3 times the Colombian per capita gross domestic product (US $17,270 for 2015; US $1 = 2,743 Colombian pesos) to assess cost-effectiveness. **Results:** Total costs related to dulaglutide, liraglutide, and glargine were US $8,633, US $10,756, and US $5,783, yielding 3.311 QALYs, 3.229 QALYs, and 3.156 QALYs, respectively. Dulaglutide dominated liraglutide given lower total costs and higher QALYs. The estimated ICER for dulaglutide compared with glargine was US $18,385, greater than the accepted threshold. Sensibility analysis shows that decreased dulaglutide cost, increased consumption of glargine, nondaily injection, and number and cost of glucometry could result in ICERs lower than the threshold. Probabilistic sensitivity analysis showed consistent results. **Conclusions:** This estimation indicates that dulaglutide dominates liraglutide. Its ICER is, however, greater than the accepted threshold for Colombia in base case compared with glargine. By increasing population weight or glargine consumption, dulaglutide becomes cost-effective compared with glargine, which could identify a niche where dulaglutide is the best option.

Keywords: Colombia, cost-effectiveness analysis, diabetes, dulaglutide, insulin glargine, liraglutide, quality-adjusted life-years.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease associated with high morbidity and mortality [1]. Its incidence and prevalence will rise in the near future, especially in developing countries [2]. International treatment guidelines suggest several therapeutic options with diverse adverse effects and ways of administration [3]. Insulin directly lowers glycemic levels and is the mainstay of treatment for many patients. Glargine is a widely used basal insulin that requires daily administration [3]. Glucagon-like peptide 1 (GLP-1) analogues affect insulin homeostasis through endogenous pathways [4]. Dulaglutide is a GLP-1 analogue with prolonged action and half-life because of its resistance to degradation and its low renal clearance, allowing once-weekly administration. Liraglutide is another GLP-1 analogue similar to dulaglutide but it requires daily injection. Available studies show some benefits in terms of glycemic control, hypoglycemia events, and weight change when compared with glargine [5–7] and similar results when compared with liraglutide [8,9]. The cost of dulaglutide is, however, an issue, especially when compared with glargine.

The purpose of this study was to estimate the cost-effectiveness of dulaglutide compared with glargine and liraglutide in Colombian patients with T2DM, considering differences in health benefits and costs.

Methods

We performed a cost-effectiveness estimation of treating Colombian patients with T2DM with no microvascular complications with dulaglutide compared with liraglutide or with glargine. Liraglutide was selected as the most representative GLP-1 analogue in the Colombian market. We created a Markov model using TreeAge Pro 2009 (TreeAge Software, Inc., Williamstown, MA) and following official Colombian health technology

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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assessment recommendations [10]. A countable state space for the Markov chain was considered.

We estimated direct medical costs from a third-party payer's perspective (Colombian health care system) with a 5-year time horizon, with sensitivity analysis at 3 and 10 years. We deemed these time horizons to be long enough to show differences between interventions. A 5% annual discount rate was used in the base case, with sensitivity analysis ranging from 0% to 12%. Main effectiveness outcomes were quality-adjusted life-years (QALY) and incremental cost-effectiveness ratio (ICER) of dulaglutide compared with liraglutide and glargine. We also estimated the number of patients developing nephropathy, retinopathy, acute myocardial infarction, stroke, hypoglycemia, or experiencing death in a hypothetical cohort of 10,000 patients with T2DM with no previous microvascular complication and an average age of 55 years. All costs refer to 2015 and are expressed in US dollars with a mean conversion rate for 2015 of US $1 = 2743 Colombian pesos. The ICER threshold was defined as US $17,270 (3 times the Columbian per capita gross domestic product). This is the upper limit of the cost-effectiveness threshold accepted by local agencies.

Patients are assumed to start using dulaglutide, liraglutide, or glargine and continue with the same treatment until the end of the simulation. No restriction on previous diabetes treatment is assumed. The model (Fig. 1) uses 6-month cycles. We assumed this time to be sufficient to show differences in glycemic control and appearance of microvascular complication. For this model, we contemplated only those health states that are relevant to the clinical management of T2DM and could be directly impacted by glycemic control, and assumed that all patients start without any microvascular or macrovascular complications. Patients can then transition to having nephropathy, retinopathy, both, or die. Mortality was dependent on age, on the basis of official Colombian data, adjusted by a relative risk (RR) for diabetic patients [11].

Table 1 presents the main variables introduced in the model. Patients on each treatment differ in the probability of achieving the goal of less than 7% of glycated hemoglobin (HbA_{1c}), as well as in hypoglycemia rate and in weight change. These data were obtained from clinical trials comparing dulaglutide with liraglutide or with glargine [5–9]. We started by either reporting data contained in or calculating them from available information from primary studies for the comparison between glargine and dulaglutide. Because no statistically significant differences between dulaglutide and liraglutide were found in HbA_{1c} and hypoglycemia [8,9], we assumed their values to be equal in the model. Differences in glycemic control influence transition probabilities to microvascular complications. The presence of one microvascular complication also increases the risk of having another one [12].

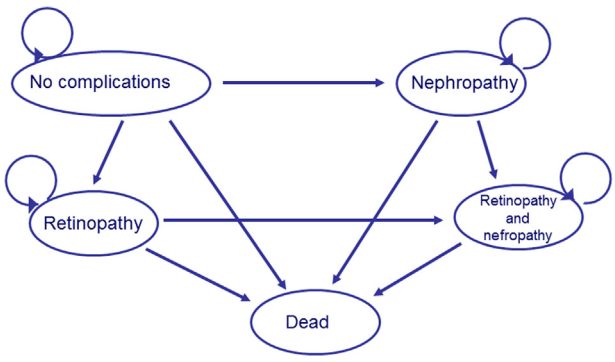

Fig. 1 – Markov model used in the estimation. All patients are assumed to start in the "No complications" state.

Acute myocardial infarction (AMI) and stroke can occur in all patients. Risks for these events were extracted from literature and are influenced by glycemic status [13]. Hypoglycemia can also occur in all patients, and probabilities were based on clinical trials [5–9]. Weight change obtained from primary studies was also integrated [5–9].

Another important transition probability is mortality. Baseline mortality was obtained by multiplying the Colombian general population mortality rate for 55-year-old adults obtained from life tables [14] by the RR of death in patients with T2DM [11]. This mortality was then multiplied by additional death RRs associated with microvascular complications of T2DM.

We considered only direct medical costs. Costs of glargine and liraglutide for 2015 were obtained from SISMED (*Sistema de información de precios de medicamentos*), the official database for drug sale volumes and prices. Dulaglutide was not available in the Colombian market and so the producer provided the expected launch price. We assumed a daily 1.8 mg dose of liraglutide and a weekly 1.5 mg dose of dulaglutide. We assumed a 0.2 international unit/kg dose of glargine and 70 kg mean body weight. This weight implies a body mass index (BMI) of 25 in a population with an average height of 1.65 m. Glargine users were also charged daily with the cost of a needle [15] and one glucometry. Patients affected by microvascular complications had an additional cost associated with follow-up. Resources were identified by creating a base case with experts and their cost was estimated from the national tariff manual established in 2001, with a 30% increase [16]. Patients with retinopathy were charged for outpatient visits (two per year) and, in advanced cases (estimated to be 30%), for optical coherent tomography (one per patient), fluorescein angiography (one per patient), photocoagulation (one per patient), and antivascular endothelial growth factor injections (three per year). Patients with nephropathy were charged for outpatient visits (three per year), renal and cardiac sonograms (one per year), 24-hour proteinuria (two per year), creatinuria (two per year), complete blood cell count (three per year), renal function (three per year), parathyroid hormone test (four per year), vitamin D level (four per year), uric acid (four per year), lipid profile (four per year), and daily intake of losartan and atorvastatin. This was meant to represent average patients with nephropathy and retinopathy considering the great degree of variability in clinical severity and resource consumption they may have. AMI and stroke costs were estimated for the acute event and the subsequent necessary follow-up by using data from a local economic evaluation [15]. Because hypoglycemia cost can vary from being null to being extremely high, we assumed a conservative episode cost comprised by a single visit and basic laboratory examinations once a year.

Utilities were obtained from electronic registries and other diabetes evaluations. T2DM with no complications was attributed a 0.79 utility, on the basis of an analysis on 3867 British patients from the UK Prospective Diabetes Study [17]. Patients with a single microvascular complication were attributed lower utilities obtained from literature (retinopathy, 0.61; nephropathy, 0.551) [18] We assumed a lower utility (0.5) for those having both complications. Each 1 point reduction in BMI was attributed a 0.006 utility [19]. Patients experiencing hypoglycemia, AMI, and stroke presented a reduction in utility of 0.0142, 0.26, and 0.06, respectively [20,21]. Patients on dulaglutide were attributed a nondaily injection utility of 0.022 per year, considering the alternative treatment in which all patients had daily injections [22]. These values were introduced with beta distributions.

Sensitivity Analysis

We assessed the effect of modifying the time horizon (from 3 years to 10 years) and the discount rate (from 0% to 12%). We

Table 1 – Transition probabilities, base risks, and costs.

Variable	Value	Distributions	Parameters	Reference
Patients achieving <7% HbA_{1c}				
Dulaglutide	0.532	Beta	$\alpha = 47; \beta = 41$	[7–9,15,16]
Liraglutide	0.532	Beta	$\alpha = 47; \beta = 41$	[8,9]
Glargine	0.326	Beta	$\alpha = 19; \beta = 41$	[7,15,16]
Monthly hypoglycemia rate				
Dulaglutide	0.00433	Beta	$\alpha = 1; \beta = 229$	[7–9,15,16]
Liraglutide	0.00433	Beta	$\alpha = 1; \beta = 229$	[8,9]
Glargine	0.00658	Beta	$\alpha = 1; \beta = 150$	[7,15,16]
Annual nephropathy rate				
HbA_{1c} >7%	0.0280	Uniform	Min. = 0.0180; max. = 0.0380	[17]
HbA_{1c} <7%	0.0135	Uniform	Min. = 0.0074; max. = 0.0196	[17]
Annual retinopathy rate				
HbA_{1c} >7%	0.038	Uniform	Min. = 0.0324; max. = 0.0436	[17]
HbA_{1c} <7%	0.0193	Uniform	Min. = 0.0150; max. = 0.0246	[17]
Annual AMI rate				
HbA_{1c} >7%	0.0158	Uniform	Min. = 0.0108; max. = 0.0208	[13]
HbA_{1c} <7%	0.0093	Uniform	Min. = 0.0053; max. = 0.0133	[13]
Annual stroke rate	1.311			
HbA_{1c} >7%	0.0041	Uniform	Min. = 0.0031; max. = 0.0050	[13]
HbA_{1c} <7%	0.0028	Uniform	Min. = 0.0018; max. = 0.0038	[13]
Mortality RR given T2DM*	1.91	Uniform	Min. = 1.685; max. = 2.135	[11]
Mortality RR given nephropathy	1.52	Uniform	Min. = 1.335; max. = 1.705	[18]
Mortality RR given retinopathy	1.02	Uniform	Min. = 0.705; max. = 1.335	[18]
Mortality RR given both	2.39	Uniform	Min. = 1.665; max. = 3.115	[18]
RR presenting retinopathy given nephropathy	1.981	Uniform	Min. = 1.056; max. = 2.906	[12]
RR presenting nephropathy given retinopathy	1.508	Uniform	Min. = 0.597; max. = 2.419	[12]
Monthly dulaglutide cost	$113.70	Uniform	Min. = 106.4; max. = 121.0	Provided by the producer
Monthly liraglutide cost	$156.00	Uniform	Min. = 154.2; max. = 157.7	SISMED
Cost/IU glargine	$0.028	Uniform	Min. = 0.021; max. = 0.035	SISMED
Glargine needle cost	$0.048	Uniform	Min. = 0.036; max. = 0.060	[19]
Outpatient visit	$7.91	Uniform	Min. = 6.53; max. = 9.29	[19]
Laboratories cost	$22.80	Uniform	Min. = 21.2; max. = 24.4	[19]
Cost/hypoglycemia	$30.70	Uniform	Min. = 27.4; max. = 34.0	Estimated by authors
Glucometry cost	$0.96	Lognormal	$\mu = 8.1; \sum = 0.16$	[20]
Monthly nephropathy cost	$57.00	Lognormal	$\mu = 2.9; \sum = 1.5$	Base case, SISMED [20]
Monthly retinopathy cost	$60.20	Lognormal	$\mu = 3.6; \sum = 1.0$	Base case, SISMED [20]
AMI, acute event	$3,336.50	Lognormal	$\mu = 8.08; \sum = 0.24$	[19]
Stroke, acute event	$2,043.50	Lognormal	$\mu = 7.51; \sum = 0.48$	[19]
AMI, annual follow-up cost	$302.80	Lognormal	$\mu = 5.67; \sum = 0.27$	[19]
Stroke, annual follow-up cost	$126.20	Lognormal	$\mu = 4.29; \sum = 1.05$	[19]

AMI, acute myocardial infarction; HbA_{1c}, glycated hemoglobin; IU, international unit; RR, relative risk; SISMED, from Spanish *Sistema de información de precios de medicamentos* (information system of drug prices), a Colombian drug price database; T2DM, type 2 diabetes mellitus.
* This RR is multiplied by the baseline mortality risk of Colombian general population 55 y old [14].

performed a univariate sensitivity analysis with all the variables. A tornado diagram was used to show these results. Probabilistic sensitivity analysis was also performed and represented as a scatterplot.

Results

The results from the base case are presented in Table 2. Glargine yielded the lowest costs and QALYs. Dulaglutide yielded the most number of QALYs and liraglutide was the most expensive option.

When compared with glargine, dulaglutide had incremental costs of $2850 and incremental QALYs of 0.155. Calculated ICER was $18,385, which is slightly higher than the accepted threshold. Discount rate variation did not produce a significant change. ICER varied between $19,369 at 3 years and $16,301 at 10 years, which is slightly lower than the threshold. The model estimated reduction in number of patients with nephropathy, retinopathy, hypoglycemia, AMI, stroke, and deaths averted with dulaglutide.

Dulaglutide and liraglutide produced similar clinical results; dulaglutide's lower costs and slightly higher QALYs make it the dominant option.

The tornado diagram in Figure 2 shows the univariate sensitivity analysis. When compared with glargine, dulaglutide is cost-effective when annual nondaily injection utility is more than 0.024, monthly dulaglutide cost is less than $110, percent of patients achieving less than 7% HbA_{1c} with glargine is more than 22%, glucometries per month are more than 33.6, glucometry cost

Table 2 – Costs per person, QALY per person, and outcomes (expressed in events per 10,000 patients) estimated by the model at 5 y with 5% discount rate.

Results	Glargine	Liraglutide	Dulaglutide	vs glargine (incremental)	vs liraglutide (incremental)
Cost ($)	5,783	10,756	8,633	2,850	−2,123
QALY	3.156	3.229	3.311	0.155	0.082
Nephropathy	115	100	100	−15	0
Retinopathy	151	133	133	−18	0
Hypoglycemia	3,948	1,678	1,678	−2,270	0
AMI	137	123	123	−14	0
Stroke	37	34	34	−3	0
Deaths	64	63	63	−1	0

AMI, acute myocardial infarction; QALY, quality-adjusted life-year.

is more than $1.07, international unit per kilogram of glargine is more than 0.26, utility per BMI unit change is more than 0.0073, daily glargine use is more than 18.2 IU, weight is more than 90.9 kg, and percent of patients achieving less than 7% HbA_{1c} with glargine is more than 59%. Liraglutide stops being dominated when its price is equal to that of dulaglutide, and it becomes more cost-effective than dulaglutide when its cost is less than $85.30.

Probabilistic sensitivity analysis is consistent with base-case results, showing dulaglutide as more expensive and more effective than glargine, and liraglutide being dominated. The cost-effectiveness scatterplot between dulaglutide and glargine in Figure 3 shows that 42.5% of simulations yielded ICERs lower than the accepted threshold.

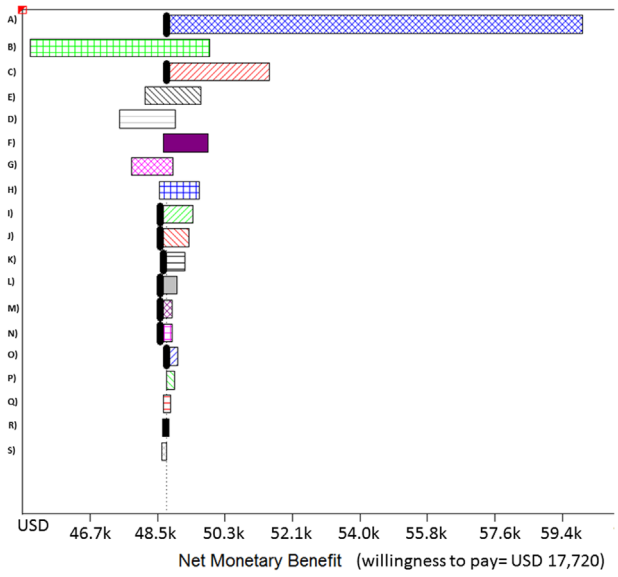

Fig. 2 – Tornado diagram showing univariate sensitivity analysis for base-case scenario. A: nondaily injection utility; B: age; C: monthly dulaglutide cost; D: retinopathy utility; E: monthly retinopathy cost; F: % achieving <7% HbA_{1c} with glargine; G: monthly nephropathy cost; H: nephropathy utility; I: monthly glucometries; J: cost per glucometry; K: utility per BMI unit change; L: IU/kg of glargine; M: daily glargine IU; N: weight; O: % achieving <7% HbA_{1c} with dulaglutide; P: nephropathy and retinopathy utility; Q: cost per IU of glargine; R: hypoglycemia utility; S: hypoglycemia cost. BMI, body mass index; HbA_{1c}, glycated hemoglobin; IU, international unit; USD, US dollars.

Discussion

This cost-effectiveness analysis of dulaglutide compared with liraglutide and glargine in Colombian diabetic patients with no previous microvascular complication is based in a relatively simple Markov model that incorporates only those outcomes known to be different in patients treated with these three therapeutic options, including hypoglycemia rate, and including a QALY value for a once-weekly instead of a daily injection. Transition probabilities were obtained from available literature, whereas costs were estimated using local databases, literature, and expert panels. Our base-case estimation at 5 years with 5% discount rate showed that glargine was the cheapest but less effective option, whereas dulaglutide was the most effective and liraglutide the most expensive. Dulaglutide dominates liraglutide, and its ICER versus glargine is slightly greater than the accepted

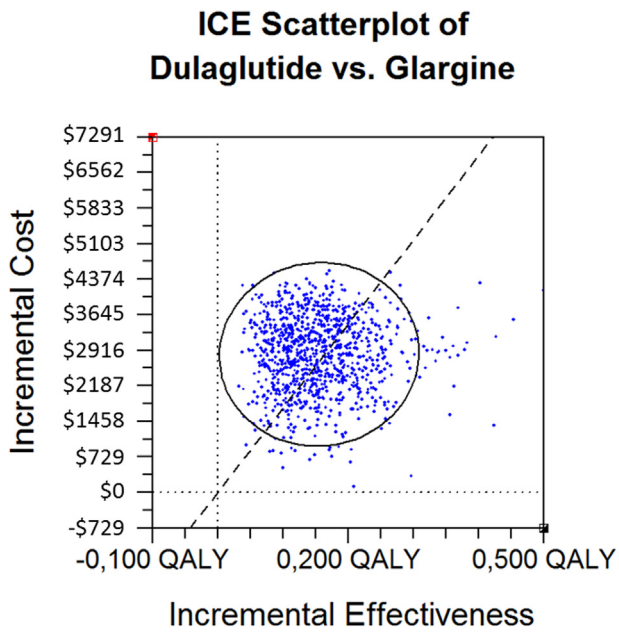

Fig. 3 – Scatterplot showing probabilistic analysis performed by running 1000 Monte-Carlo simulations for the comparison between dulaglutide and glargine. The diagonal line indicates the cost-effectiveness threshold of $17,270 (3 times the Colombian per capita gross domestic product). ICE, incremental cost-effectiveness; QALY, quality-adjusted life-year.

threshold. Sensitivity analysis shows that a longer time horizon yields ICERs lower than the threshold. It is, however, important to remember that this is the upper limit of cost-effectiveness acceptable for local agencies. This issue might be important when deciding which technology to prioritize. Univariate sensitivity analysis evidenced many variables that, by having some variations, could make dulaglutide cost-effective. The conservative values used in the model for international unit of daily glargine, body weight, and glucometries are especially interesting, because they depict real situations for many patients. This could highlight a population niche where dulaglutide could definitely be cost-effective when compared with glargine.

We found two similar economic evaluations. The first one compares exenatide, dulaglutide, liraglutide, and lixisenatide from the British health care system perspective [23]. This study concludes that once-weekly exenatide outperforms all other alternatives. Provided acceptability curves versus exenatide evidence that dulaglutide has higher probabilities of being cost-effective compared with exenatide and with liraglutide at willingness-to-pay thresholds similar to the Colombian one. The second one is a cost-effectiveness evaluation comparing dulaglutide and liraglutide in Sweden [24]. They find that dulaglutide dominates liraglutide and that the result is maintained in sensitivity analysis. These findings are consistent with the results from our study.

Data sources used for the model are a strength of this study. Transition probabilities were obtained from best available clinical data, both clinical trials [5–9,25,26] and large cohorts of patients with longer follow-ups, grouped by their glycemic control [11–13,27,28]. Costs were taken from local databases. There are, however, some weaknesses. Our model is somewhat simplistic. We did not consider every complication of T2DM. We included the more relevant ones while trying to avoid introducing an excessive number of health states that would increase the uncertainty. We did not explore microvascular complications in full depth. For example, glycemic control influenced only the risk of getting a complication, but it did not affect its progression or resource consumption through time. Weight change was also considered only for its impact on utilities, with no interaction with mortality or complications. We also ignored any kind of comorbidity such as arterial hypertension that usually exists in these patients. The actual total number of clinical outcomes estimated by our model may then be inaccurate when compared with a real cohort, affecting internal validity. Nevertheless, we believe that comparative performance of alternative therapeutic strategies may have been more adequately estimated, accomplishing the goal of this study with a certain degree of validity. Extrapolation of clinical data and utilities obtained in diverse contexts to Colombian patients may be inaccurate, but these are the best data available. Using a nondaily injection utility may also be considered a weakness for this study, because it clearly favors dulaglutide compared with other alternatives. We believe it is reasonable to assume that a decrease in injections may represent an improvement in quality of life in some way. There is evidence that certain features of drug dispenser devices may be associated with additional utility loss, which were not considered in this model [29]. These utilities were not considered in our model but could determine some additional differences between interventions. Finally, assuming an initial population with no microvascular complications may also be debatable, because the real population of patients with T2DM have variable degrees of complication in different stages.

Future research could further explore possible benefits of less frequent injections in terms of quality of life, adherence, and, eventually, on clinical outcomes. Clearly identifying the population that could potentially benefit the most from dulaglutide in terms of clinical outcomes and cost-effectiveness would be another interesting topic.

Conclusions

Our study estimated that dulaglutide dominates liraglutide but is not cost-effective compared with glargine in our base-case scenario. Sensitivity analysis shows that a longer time horizon and some population characteristics, such as increased body weight, glargine consumption, or number of glucometries, could make dulaglutide cost-effective. A niche where dulaglutide outperforms glargine could then exist. Further exploration of the effect of less frequent injections on quality of life and adherence is necessary.

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