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CLINICAL EFFICACY AND SAFETY OF TRIPLE COMBINATION CREAM CONTAINING MOMETASONE FUROATE, MICONAZOLE NITRATE, AND GENTAMICIN AS A TOPICAL TREATMENT FOR MIXED SKIN INFECTIONS WITH FUNGI AND BACTERIA

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ABSTRACT

Background: Fixed dose combinations of corticosteroids, antibacterials and antifungals are known to alleviate inflammatory skin conditions. This study aimed to evaluate the safety and clinical efficacy of the topical application of a triple combination of mometasone furoate, miconazole nitrate and gentamicin in a cream base for mixed skin infections. **Materials and Methods:** Patients with mixed skin infections were prescribed Momenta™ cream, at the sole discretion of their physicians, for 7 to 14 days. **Results:** A total of 416 patients were enrolled from 4 sites in this study; of which, 375 were eligible for primary efficacy analysis. The median (IQR) total score of all signs and symptoms was significantly decreased from 11 (7) at baseline to 1 (3) at the end of treatment duration, with a median reduction of 10 points ($p < 0.0001$). At the end of treatment, 89.9% of patients achieved ≥ 50% relative improvement in total score of all signs and symptoms. A total of 4 patients experienced 7 adverse events during the study period. Pruritus was reported by 4 patients while burning sensation was reported by 3 patients. None of the events was serious. **Conclusion:** The triple combination cream of mometasone furoate, miconazole nitrate and gentamicin have acceptable efficacy and safety profile in the treatment of mixed skin infections with bacteria and fungi.

KEYWORDS: skin conditions, antibacterials, antifungals, corticosteroids, mixed infections

INTRODUCTION

Skin, the largest human organ, is an ecosystem that can be invaded by various types of microorganisms. These include bacteria and fungi and vary according to the location and composition of skin on the body. These organisms are usually harmless and may even be symbiotic.[1] However, some of these organisms are opportunistic or harmful and cause infections [2]. These infections may be primary infections (occurring in otherwise normal skin) or secondary infections that complicate chronic skin conditions (e.g., eczema or atopic dermatitis).[3] The most common organisms that attack the skin include Candida species, *Staphylococcus aureus*, nonhemolytic Streptococci, and Coryneform bacteria.[2]

Although clinical manifestations vary from one condition to another, most skin infections involve erythema, edema, and other signs of inflammation. Diagnosis can be proved by sampling the infected areas and microscopic examination. Some infections require a culture to be requested.[3]

If the patient shows no systemic signs, a topical antimicrobial is preferred.[4] This is due to the fact that topical antimicrobials have fewer systemic side effects and a lesser impact on the normal flora of the body.[5,6] Combinations of corticosteroids such as mometasone furoate with antibacterial and antifungal agents have been shown to be very effective in treating inflammatory cutaneous disorders.[7,8] An example of topical antifungals is miconazole nitrate which is a broad-spectrum antifungal agent.[9] Gentamicin is a topical antibacterial active against both gram-positive and gram-negative bacteria.[10] Thus, using a combination of the three agents may be effective against a wide range of organisms that cause skin infections without the need to use a combination of products. The aim of this study was to evaluate the safety and clinical efficacy of Momenta™ cream (a triple combination of mometasone furoate 1

mg, miconazole nitrate 20 mg, and gentamicin 1 mg) as a topical treatment for mixed skin infections with fungi and bacteria.

MATERIALS AND METHODS

Study Design

This phase IV, prospective, multicenter, observational, cohort study took place between the 6th of March 2019 and the 14th of August 2019. At the sole discretion of the physicians, patients were prescribed Momenta™ cream which is manufactured by Jamjoom pharmaceuticals (Plot No. ME1:3, Phase V, Industrial City, Jeddah, Saudi Arabia) and guided by the summary of product characteristics (SmPC) for 7 to 14 (±3) days after which a study-end visit was conducted. Patients were advised to apply a thin film of the cream to the affected skin areas once or twice daily. The protocol was approved by the Egyptian Ministry of Health and Population (MoHP), and all patients or their legally acceptable representatives provided written informed consent. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and applicable laws and regulations.

Patients

It was planned to include 400 patients of both genders aged 60 years or less, with mixed skin infections (with fungi and bacteria), who were willing and able to complete all study visits and procedures. In addition, patients (or legally acceptable representatives) had to be able to read, understand and sign an informed consent prior to inclusion.

Exclusion criteria included patients who were treated with other topical medications during the 14-day period prior to the study; patients who received systemic corticosteroids or any other immunosuppressants during the 28-day period prior to the study; patients with co-existing active infections (other than skin infections); patients with any clinically significant illnesses, abnormality or prior treatment - which in the opinion of the investigator may interfere with treatment, assessment, or compliance with the protocol; patients with significant cardiovascular, hepatic (hepatitis B or hepatitis C) or renal disease; patients with any chronic condition that was not well controlled or any other serious skin disorder, pigmentation, or extensive scarring in affected areas; patients who need any other type of topical or systemic medication during the study that might affect the course of the disease; patients with a history of congenital or acquired immunodeficiency; patients with a history of hypersensitivity to any of the components of the medication being studied; female patients of childbearing age who were not using contraception; and pregnant or lactating female patients. In addition, patients using any medication that may interfere with the triple combination, within four weeks prior to the study or for five half-lives (whichever was longer) were also excluded.

Outcome Measures

The primary objectives of this study were to evaluate the safety and efficacy of Momenta™ cream in patients with mixed skin infections. We evaluated safety in terms of incidence of study drug related adverse events/ serious adverse events (AEs/SAEs) and number of patients who discontinued the study drug due to AEs. In turn, we evaluated efficacy in terms of mean relative change in the overall score of all signs and symptoms (erythema, crusting, exudation, swelling, pruritus, pain and tenderness) and in terms of the number of patients achieving ≥ 50% relative improvement in the overall total score of all signs and symptoms.

Secondary objectives included 1) evaluating the efficacy of Momenta™ cream in terms of improvement of each presented sign and symptom of mixed skin infections (in terms of the mean relative change in score of each presenting sign and symptom and the number of patients achieving ≥ 50% relative improvement in the score of each presenting sign and symptom), 2) duration till complete resolution, average change in largest lesion's size (considering the longest diameter of the largest lesion), and 3) change in skin culture test results. Additionally, 4) identifying the overall assessment of the clinical outcome of Momenta™ cream by the physician and the patient (Excellent; complete remission, Good; acceptable remission, Fair; slight/incomplete remission, and Poor; unchanged/aggravated). Skin specimens were examined for fungal infections through direct microscopic examination, and culture on suitable culture media [Sabouraud dextrose agar & Dermasel agar]. For bacterial infections, culture was done on enriched and selective media (blood agar medium, MacConkey medium & chocolate agar) and incubated aerobically. Sensitivity was done by the agar disc diffusion method on Mueller-Hinton agar medium.

Statistical Analysis

The sample size of 384 patients was calculated considering the following assumptions: a two-sided significance level of 5%, an expected outcome frequency of 50% (maximum uncertainty), and a precision rate of 5%. This sample size was planned to detect a small effect size of 0.17 for paired efficacy comparisons (before and after treatment) considering an alpha error of 5% and a study power of 90%. With an expected drop-out rate of 4% during the one to two weeks period of the study, a total of 400 patients was considered appropriate. Software used for sample size calculation were "CDC epi-info Version 7-statcalc" and GPower Version 3.1.9.2. Quantitative data were described descriptively using mean and standard deviation for normally distributed variables. When normal distribution was violated, the median and interquartile range were used. For qualitative categorical variables, frequency, percentage and 95% confidence interval were applied.

RESULTS

Baseline Characteristics

A total of 416 patients were enrolled from 4 sites in this study. Eleven patients were excluded due to screening failure and 375 were eligible for primary efficacy analysis. The median (IQR) age was 31.5 (22.72) years and females were 67.7%. We found that 89.1% of the patients never smoked and all of them had normal physical examination. The median (IQR) weight and height were 70 (30) kg and 160 (18) cm, respectively. For vital signs, the median (IQR) heart rate, systolic blood pressure, and diastolic blood pressure were 80 (17) beats/min, 120 (10) mmHg, and 80 (10) mmHg, respectively. Only 4% of the patients had comorbidities. More details are presented in table 1.

Table 1: Baseline Characteristics of Patients.(N = 375)

Characteristic – no. (%)		
Sex		
	Male	121 (32.3)
	Female	254 (67.7)
Age – years		
	Median (IQR)	31.5 (22.72)
Weight – Kg		
	Median (IQR)	70 (30)
Height - cm		
	Median (IQR)	160 (18)
Heart Rate – beats/min		
	Median (IQR)	80 (17)
Systolic Blood Pressure – mmHg		
	Median (IQR)	120 (10)
Diastolic Blood Pressure – mmHg		
	Median (IQR)	80 (10)
Marital Status		
	Single	144 (38.4)
	Married	215 (57.3)
	Divorced	9 (2.4)
	Widow	7 (1.9)
Education		
	Illiterate	88 (23.5)
	Basic/Primary	72 (19.2)
	Secondary	101 (26.9)
	University/Higher	114 (30.4)
Residence		
	Rural	158 (42.1)
	Urban	217 (57.9)
Smoking Status		
	Never	334 (89.1)
	Former	1 (0.3)
	Current	40 (10.7)
Comorbidities Status		
	Absent	389 (95.7)
	Present	16 (4.3)
Concomitant Medications		
	Absent	400 (98.8)
	Present	5 (1.2)
Received Medications (n=5)		
	Beta-blockers	2 (40.0)
	Antidiabetics	3 (60.0)

Primary Objectives

Efficacy

The median (IQR) total score of all signs and symptoms was significantly decreased from 11 (7) at baseline to reach 1 (3) at the end of treatment duration, with a median reduction of 10 points ($p < 0.0001$). In addition, the vast majority (89.9%) achieved ≥ 50% relative improvement in total score of all signs and symptoms at the end of treatment duration. Of the remaining patients who did not achieve ≥ 50% relative improvement (n =

38), 21 patients had an improvement of less than 50%, 9 patients had their score remain constant and 8 patients had their score increased.

Safety

A total of 4 patients experienced 7 adverse events (AEs) during the study period. Pruritus was reported in 4 patients (0.96%) while burning sensation was reported in 3 patients (0.72%). None of these AEs were serious and none led to discontinuation of the study drug. Table 2 shows the primary outcomes of our study. Table 3 provides full description of the reported AEs.

Table 2: Clinical efficacy and safety of Momenta cream in patients with mixed skin infections in terms of the overall total score of all signs and symptoms – Primary objective.

	Baseline Visit 1	At 7-14 Days Visit 2	P-Value
Change in the 4-point Likert scale – Median (IQR)	11 (7)	1 (3)	< 0.0001
Number of patients achieving ≥ 50% relative improvement in the 4-point Likert scale - Count (%)	-	337 (89.9)	-
Number of patients with AEs - Count (%)	-	4 (0.96)	-

Table 3: Adverse events description.

Patient	Date of visit 1	Age (years) at visit 1 (rounded up)	Gender	AE	AE start date	Onset of the AE (days) from starting the treatment	Serious criteria	Intensity	Corrective treatment	Action taken	Outcome by the end of the study	Outcome After AEs'last follow up	Relationship to study medication	Is it an AESI as per the study protocol
02-006	2-April-2019	31	Female	Pruritus	4-Apr-2019	2	Non-serious	Moderate	No corrective treatment was prescribed	No	Recovering	Recovered	Possibly related	Yes
				Burning Sensations	4-Apr-2019	2	Non-serious	Moderate		No				
01-110	2-May-2019	41	Male	Pruritus	16-May-2019	14	Non-serious	Moderate	No corrective treatment was prescribed	No	Recovering	Recovered	Unlikely Related or Probably Not Related	Yes
01-115	22-May-2019	46	Male	Pruritus	28-May-2019	6	Non-serious	Severe	No corrective treatment was prescribed	Dose increased	Not Recovered, the patient had pruritus and burning in the first visit which has increased	No new outcome was reported due to patient's	Probably/Likely Related	Yes

				Burning Sensations	28-May-2019	6	Non-serious	Severe			after prescription of Momenta	unavailability/ unreachability		
03-034	7-july-2019	30	Male	Pruritus	9-Jul-2019	2	Non-serious	Mild	No corrective treatment was prescribed	Dose reduced	Not Recovered, the patient had pruritus and burning in the first visit which has increased after prescription of Momenta	No new outcome was reported due to patient's unavailability/ unreachability	Possibly related	Yes
				Burning Sensations	9-Jul-2019	2	Non-serious	Mild						

Secondary Objectives

The median (IQR) individual score for each sign and symptom was significantly decreased from baseline to end of treatment duration; from 2 (1) to 0 (1) for erythema, crusting, and pruritus; from 1 (1) to 0 (0) for exudation and swelling; from 2 (1) to 0 (0) for pain; and from 1 (1) to 0 (0) for tenderness ($p < 0.0001$ for each sign and symptom). Furthermore, we found that the percentage of patients reporting every moderate and severe sign and symptom was significantly decreased at the end of treatment compared to the baseline (Table 4).

Table 4: Change in percentage of each presenting sign and symptom (N = 375).

Signs and symptoms	Baseline visit			End of treatment			P-Value¥
	Absent	Moderate	Severe	Absent	Moderate	Severe	
Erythema	6 (1.6%)	310 (82.7%)	59 (15.7%)	209 (55.7%)	163 (43.5%)	3 (0.8%)	<0.0001
Crusting	47 (12.5%)	310 (82.7%)	18 (4.8%)	274 (73.1%)	100 (26.7%)	1 (0.3%)	<0.0001
Exudation	40 (10.7%)	310 (82.7%)	25 (6.7%)	302 (80.5%)	67 (17.9%)	6 (1.6%)	<0.0001
Swelling	58 (15.5%)	297 (79.2%)	20 (5.3%)	301 (80.3%)	66 (17.6%)	8 (2.1%)	<0.0001
Pruritus	21 (5.6%)	268 (71.5%)	86 (22.9%)	250 (66.7%)	116 (30.9%)	9 (2.4%)	<0.0001
Pain	61 (16.3%)	282 (75.2%)	32 (8.5%)	300 (80%)	69 (18.4%)	6 (1.6%)	<0.0001
Tenderness	86 (22.9%)	259 (69.1%)	30 (8%)	320 (85.3%)	50 (13.3%)	5 (1.3%)	<0.0001

**4-point Likert scale in which Absent represents score 0, Moderate represents score 1 and 2 and severe represents score 3.*

¥ Wilcoxon signed rank test to compare between Baseline and End of treatment.

Regarding the relative improvement in the individual score of each sign and symptom, we found that erythema and pruritus were relatively improved by ≥ 50% in 87.7% and 83.2% of patients respectively. Similarly, 89.3% and 86.1% of patients achieved at least one-point reduction in the Likert scale of erythema and pruritus respectively. Details on improvement rates of other signs and symptoms are presented in table 5.

Table 5: Rate of achieving ≥ 50% relative improvement or at least one-point reduction in the Likert scale of each presenting sign and symptom (n = 375).

Signs and Symptoms	Patients achieving ≥ 50% relative improvement Count (%)	Patients achieving at least one-point scale reduction in Likert scale Count (%)
Erythema	329 (87.7)	335 (89.3)
Crusting	298 (79.5)	301 (80.3)
Exudation	298 (79.5)	301 (80.3)
Swelling	287 (76.5)	288 (76.8)
Pruritus	312 (83.2)	323 (86.1)
Pain	292 (77.9)	294 (78.4)
Tenderness	273 (72.8)	273 (72.8)

Based on their assessment for patients' clinical outcomes, the physicians reported that 51.2% of the patients achieved excellent outcome, 34.4% achieved good outcome, 10.4% achieved fair outcome, while 4% achieved poor outcome (Table 6). As for patient global assessment of clinical outcome, 52.5% reported excellent outcome, 32.5% reported good outcome, 10.4% reported fair outcome, while 4.5% reported poor outcome at the end of treatment duration. As per the physician assessment, 7 days was the median time for achieving complete or acceptable remission for all patients. Moreover, the median (IQR) diameter for the longest lesion was significantly decreased to 0.5 (1) cm at the end of treatment duration with a median reduction of 2.5 cm ($p < 0.0001$).

Table 6: Global physician assessment of clinical outcome. (N=375)

Clinical outcome	Count	%	95% CI
Excellent	192	52.2	(46.1 – 56.3)
Good	129	34.4	(29.6 – 39.2)
Fair	39	10.4	(7.3 – 13.5)
Poor	15	4	(2 – 5.9)

DISCUSSION

This study aimed to assess the efficacy and safety of a triple combination of mometasone furoate 1 mg, miconazole nitrate 20 mg, and gentamicin 1 mg in suitable cream base in patients ≤ 60 years with mixed skin infections (bacterial and fungal). To our knowledge, the current study is the first to assess the triple combination of mometasone, miconazole, and gentamicin in mixed skin infections. The study took place between the 6th of March 2019 and the 14th of August 2019. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and applicable laws and regulations. A total of 416 patients were enrolled from 4 sites in this study. Patients were prescribed Momenta™ cream and were advised to apply a thin film of the cream to the affected skin areas once or twice daily.

Combining corticosteroids with antibacterials and antifungals was found to be very effective for treating skin infections.[7,8] An example of topical antifungals is miconazole nitrate which is a broad-spectrum antifungal agent.[9] Gentamicin is a topical antibacterial active against both gram-positive and gram-negative bacteria.[10] There are many commercially available combinations of corticosteroids and antibacterials with or without antifungal agents. These exist in the form of otic and ophthalmic drops in addition to topical preparations. However, the combination of mometasone furoate, miconazole nitrate, and gentamicin has not been investigated before.

Mometasone furoate, a moderately-potent steroid, possesses significant anti-inflammatory potency with less inhibitory effects on the hypothalamic-pituitary-adrenal axis (HPA).[11,12] Additionally, the percutaneous absorption of mometasone furoate was found to be low (around 0.4% for the cream and 0.7% for the ointment, making the cream safer) and when it enters the circulation, it undergoes biotransformation in the liver into three different metabolites with very little intrinsic activity.[13]

The British National Formulary emphasizes that children are particularly susceptible to side effects of topical corticosteroids, and that is why they recommend avoiding topical corticosteroids in children or, if necessary, using them with great care and for short periods.[14] The most frequent adverse effects of corticosteroids include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura. Hypertrichosis, pigmentation alterations, delayed wound healing, and exacerbation of skin infections; occur with less frequency. More importantly is the rate of contact sensitization against corticosteroids, which is considerably higher than generally believed. Systemic reactions such as hyperglycemia, glaucoma, and adrenal insufficiency have also been reported.[15] Measures to prevent the side effects include: reduction of frequency of application (for example alternate-day therapy or weekend use), continuing daily application with the weakest effective steroid, tapering treatment on complete healing, and avoidance of occlusion.[16]

Furthermore, in 2019, researchers performed extensive literature search of MEDLINE, Embase and other databases to review the safety and efficacy of multiple formulations of topical mometasone furoate. This has shown that mometasone furoate is a highly effective and potent corticosteroid that has a low risk of local and systemic adverse effects.[17]

Several studies exploring the effectiveness of miconazole nitrate cream showed very promising results. A study by Spraker et al on patients who had diaper dermatitis (DD) complicated by candidiasis revealed that miconazole nitrate 0.25% ointment showed more rapid benefit and a more sustained benefit compared with zinc oxide/petrolatum vehicle control.[18] Concannon et al also found that 0.25% miconazole nitrate ointment was a safe and effective treatment for infantile DD.[19]

Ben Salah et al developed a cream called WR279,396 that contained 15% paromomycin sulfate plus 0.5% gentamicin sulfate in a complex base to aid drug penetration. They provided evidence of the efficacy of paromomycin- gentamicin and paromomycin alone for ulcerative *Leishmania* major disease. They also demonstrated that the efficacy of either cream formulations containing 15% paromomycin with and without 0.5% gentamicin was superior to that of a vehicle-control cream for treating ulcerative cutaneous leishmaniasis caused by *L. major* in Tunisia.[20]

Davenport et al reported that topical gentamicin reduces both effect of exit site infections (ESIs) and peritonitis rates, but this review of routine clinical practice determined that although topical mupirocin reduced overall ESI rates and that combination regimen of topical mupirocin with gentamicin reduced *S. aureus* ESIs, neither regimens reduced overall peritonitis rates.[21]

In a previous study comparing efficacy, safety and tolerability of a combination of clobetasol, neomycin and

miconazole (Group A) versus betamethasone, clotrimazole and neomycin (Group B) versus betamethasone, gentamicin and miconazole (Group C) in subjects with eczematous disorders associated with underlying tinea or yeast infections, the clinical score showed a significant reduction from baseline till the end of day 7 in all groups, i.e. 82.9%, 81.3% and 85.6% in Group A, B and C respectively. However, the difference between the groups were not statistically significant. Mean hyperpigmentation score showed significant decrease of 82.9% in Group A, 81.6% in Group B and 92.2% in Group C from baseline till the end of day 7. The study concluded that the triple combination of antifungal, antibacterial and potent steroid was efficacious, safe and tolerable in reducing signs and symptoms (scaling, inflammation, burning and itching) of eczematous disorder associated with underlying tinea/yeast infection.[22]

Gentamicin sulfate ophthalmic solution is used for topical treatment of ocular bacterial infections (for example: conjunctivitis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis) caused by susceptible strains of microorganisms (Streptococcus pyogenes, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Enterobacteraerogenes, Haemophilusinfluenzae, Escherichia coli, Klebsiellapneumoniae, Neisseria gonorrhoeae, Serratiamarcescens, and Pseudomonas aeruginosa). Gentamicin sulfate cream (USP 0.1%) is indicated for wet, oozing primary infections as well as greasy, secondary infections, such as pustular acne or infected seborrheic dermatitis. If a water-washable preparation is desired, the cream is preferable. Gentamicin sulfate cream (USP 0.1%) was successfully used in infants, adults and children. It was also proven that gentamicin's absorption is faster and better with cream compared to the ointment, but is very poorly absorbed orally.[23]

Our study results have shown that after using a fixed dose combination of mometasone furoate 1 mg + miconazole nitrate 20 mg + gentamycin 1 mg cream for a duration of 7 days (95% CI 6.7-7.3), there was a significant reduction in the measured signs of erythema, crusting, exudation, swelling, pruritus, pain, and tenderness. At the end of the study, proportions of patients who achieved ≥ 50% relative improvement in each presented sign and symptom ranged from 72.8% to 87.7%. Regarding the Physician and Patient Global Assessments of Clinical Outcomes, more than 85% of patients had excellent and good outcomes combined by the end of the study.

Regarding safety, seven adverse events were reported (pruritus and burning sensation). All were non-serious and two of them were severe. No patients discontinued the study drug due to adverse events indicating the high safety feature of the fixed dose combination.

LIMITATIONS

Despite being simple, easy to use, and widely used tool, physician global assessment is a categorical non-validated scale that does not include important information such as body surface area, symptoms, and quality of life. Global assessments are used frequently in studies of skin conditions, but their lack of standardized definitions and implementation preclude any meaningful comparisons between studies.

Similarly, translation and interpretation of patient reported outcomes (PRO) (using patient global assessment); that into measures that are useful, not only for other PRO researchers, but for clinicians, patients and policy makers is challenging.

Other limitations in this study included

- lack of comparative arm(s),
- lack of enough data collected for skin culture (skin cultures were requested by the treating physician for a small proportion of patients), lack of physical examinations details, and lack of data on patients' adherence to treatment.

CONCLUSIONS

We found that the topical application of a cream consisting of a triple combination of mometasone furoate 1 mg, miconazole nitrate 20 mg and gentamicin 1 mg on mixed skin infections for a duration of 1 week leads to a significant reduction in the signs and symptoms of such infections (namely erythema, crusting, exudation, swelling, pruritus, pain and tenderness). The combination has acceptable safety profile with no SAEs being reported.

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DATA AVAILABILITY

The datasets used during the current study are available from the corresponding author upon request.

CONFLICT OF INTEREST

None of the authors have a conflict to declare.

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