

Failure of tacrolimus to prevent aspirin-induced respiratory reactions in patients with aspirin-exacerbated respiratory disease

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Background: In patients with aspirin-exacerbated respiratory disease (AERD), pretreatment with asthma controller medications (leukotriene modifiers, inhaled or systemic corticosteroids, and salmeterol) partially modifies the severity of aspirin-induced asthmatic reactions.

Objective: A recent study showed that pretreatment with tacrolimus completely prevented aspirin-induced respiratory reactions and might allow silent aspirin desensitization.

Methods: Ten patients with rhinosinusitis, nasal polyps, and asthma had a history of asthma attacks after ingesting aspirin and nonsteroidal anti-inflammatory drugs. All underwent baseline oral aspirin challenges and had typical respiratory reactions. They were then randomized to receive tacrolimus (0.1 mg/kg weight; 8 patients) or placebo (2 patients) in a double-blind protocol before rechallenge with aspirin using the previous provoking dose of aspirin. In addition, respiratory reactions sustained by 50 consecutive patients with AERD during 2004 were recorded, analyzed, and compared with the tacrolimus/placebo-treated patients to determine whether there were any differences.

Results: Tacrolimus pretreatment failed to block respiratory reactions to provoking doses of aspirin in 5 of 8 patients with AERD, and in the other 3 patients did not block higher doses of aspirin. The results of oral aspirin challenges in the control population of 50 patients were compared with either the baseline or postchallenge data from the tacrolimus-pretreated or placebo-pretreated patients with AERD, and there were no significant differences.

Conclusions: Use of tacrolimus as add-on pretreatment to prevent reactions to aspirin in patients with AERD or to achieve the goal of silent aspirin desensitization could not be accomplished. (*J Allergy Clin Immunol* 2005;116:755-60.)

Key words: Asthma, aspirin, tacrolimus, aspirin desensitization

Abbreviations used

AERD: Aspirin-exacerbated respiratory disease
GCRC: General Clinical Research Center
LT: Leukotriene
NSAID: Nonsteroidal anti-inflammatory drug

Aspirin desensitization followed by daily treatment with aspirin as add-on therapy has been reported to improve the clinical courses of patients with aspirin-exacerbated respiratory disease (AERD).¹⁻⁴ To achieve aspirin desensitization, oral challenges with aspirin are conducted, and respiratory reactions are induced during the process.⁵ Currently there is no single drug treatment that prevents oral aspirin-induced respiratory reactions. Pretreatment with montelukast, inhaled corticosteroids, and salmeterol is currently the most effective modulator of most oral aspirin-induced lower respiratory tract reactions. However, this regimen does not prevent upper airway reactions or systemic reactions.^{6,7} Therefore, the search for a more effective blocking drug, which would allow us to perform silent, safe outpatient aspirin challenges with resulting aspirin desensitization in all patients with AERD, would be a useful addition. An ideal drug would prevent mast cells from synthesizing or secreting leukotrienes and at the same time block the release of preformed mediators.

Tacrolimus is a macrolide immunosuppressant used to prolong survival of transplanted organs. Its mechanism of action is to bind to an intracellular protein, tacrolimus (FK) binding protein-12 (FKBP-12). This complex prevents dephosphorylation and translocation of nuclear factor-activated T cells (NF-AT), a nuclear component that initiates gene transcription in the formation of cytokines.⁸ Unrelated to its immunosuppressive effects, *in vitro* studies showed that tacrolimus also serves as a substrate for the ATP dependent export pump crucial to the release of synthesized leukotriene (LT) C₄ and histamine from mast cells.⁹ Thus, although leukotrienes were synthesized, they were not exported to the extracellular space. In 2004, Kawano et al,¹⁰ believing that tacrolimus would prevent aspirin-induced bronchospasm, reported their interesting study of 12 patients with AERD. They conducted a double-blind, placebo-controlled crossover oral aspirin

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challenge study, with a week between challenges. Patients received either tacrolimus (0.1 mg/kg body weight) or placebo before the first challenges and then crossed over to the opposite pretreatment intervention during their second challenges. All patients were challenged with the previously established provoking dose of aspirin. In the placebo arm, aspirin induced significant declines in FEV₁ values in all 12 patients, which, as expected, was accompanied by a rise in urinary LTE₄ values. By contrast, pretreatment with tacrolimus prevented established provoking doses of aspirin from inducing bronchospasm or a rise in urinary leukotriene levels in all 12 patients. This study raised the question whether tacrolimus pretreatment would prevent aspirin-induced reactions not only to the aspirin provoking doses but also to advancing doses. The possibility that aspirin desensitization could be achieved without respiratory reactions was also contemplated. Therefore, this pilot study was designed to test the hypothesis that tacrolimus pretreatment, using the same dose of 0.1 mg/kg, would block oral aspirin-induced reactions and allow silent aspirin desensitization.

METHODS

Subjects

Ten Caucasian adults with AERD agreed to participate in this study and signed institutional consent forms approved by the Scripps Human Subjects Committee and the General Clinical Research Center (GCRC) Advisory Committee. All patients gave histories of nasal polyps, recurrent sinusitis, asthma, anosmia, and previous asthma attacks after ingesting aspirin and other COX-1 inhibitor drugs. Two of them had undergone positive oral aspirin challenges in our GCRC in the past. Demographic information, medications consumed, and previous historical reactions to aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs) for these patients are recorded in Table I. As is our policy for standard aspirin challenge/desensitization, usual controller medications were continued throughout the challenges but, as shown in Table I, varied from patient to patient. For patients taking antihistamines or short-acting β -agonists, these drugs were discontinued 48 hours before starting oral aspirin challenges.

Tacrolimus as a blocking drug

Tacrolimus (Prograf; Fujisawa Co, Deerfield, Ill) was purchased from the company and dispensed by the Scripps Pharmacy. Identical capsules of placebo or capsules containing tacrolimus were prepared by the pharmacist and assigned according to a randomized computer program, so that the nurses and physicians in the GCRC were double-blind. We decided to use a 1:4 placebo to tacrolimus ratio to pretreat with tacrolimus as many patients as possible and yet maintain the discipline of objective analysis. The doses of tacrolimus were calculated for each patient based upon body weight (0.1 mg/kg, resulting in doses ranging from 5–10 mg). In the study by Kawano et al,¹⁰ this dosing schedule produced tacrolimus levels, measured by enzyme immunoassay, in peripheral blood at the 4-hour postdosing point of 6.8 ± 0.9 ng/mL. According to the manufacturer, the half-life of tacrolimus, based upon blood concentrations, was 48.4 ± 12.3 hours. In our study, tacrolimus capsules (0.1 mg/kg) or placebos were dispensed at 6:00 AM, and a light breakfast (roll, juice, and decaffeinated coffee) was given between 7:15 and 7:30 AM.

Study design

Phase 1 consisted of admission to the General Clinical Research Center with each patient continuing controller medications, prescribed to prevent bronchial hyperactivity and maintain bronchial airway patency. Patients were admitted the night before. Starting at 7 AM, 2 to 3 placebo challenges at 3-hour intervals were conducted on the first day to prove that airway stability was maintained. FEV₁ values were recorded every hour and as a condition of challenge protocol could not change by more than 10% from AM baseline. Single-blind oral aspirin challenges were then started (30, 45 or 60, 100 mg) every 3 hours, during the afternoon of the first day in 3 patients and starting on the next day in the other 7 patients, until a respiratory reaction occurred (naso-ocular reactions, FEV₁ decline by $\geq 15\%$, or both), thereby establishing the provoking dose of aspirin. The patient's reaction was then treated, and after returning to baseline, the patients were discharged from the GCRC on day 2. While outpatients, they were instructed to avoid aspirin and NSAIDs, take the same controller medications, and return for readmission to the GCRC in 7 days.

Phase 2 consisted of a second admission to the GCRC on the night of the 7th day after their first baseline aspirin-induced respiratory reaction. Again, patients were maintained on the same controller medications (Table I). On the next morning, usual controller medications and tacrolimus or placebo were administered at 6:00 AM. At 7:00 AM, the previously established provoking dose of aspirin was given. The GCRC nurses followed patients with frequent examinations, and FEV₁ determinations were obtained hourly or at the onset of respiratory tract symptoms. If there was no reaction, the doses of aspirin were increased every 3 hours until a dose of 650 mg was achieved (potential silent desensitization). Because such a sequence might involve a second day of aspirin challenges, a second but identical tacrolimus or placebo was administered at 6:00 AM on the second day. If an aspirin-induced reaction occurred on the first day, silent desensitization could not have occurred, and standard aspirin desensitization procedure was then instituted.⁵ Dosing with tacrolimus or placebo on the second day was then abandoned.

Definitions of types of reactions

FEV₁ values that declined by 20% or greater were considered evidence of bronchospasm irrespective of naso-ocular reactions. Declines in FEV₁ values between 15% and 20% were considered evidence of bronchospasm if accompanied by a naso-ocular reaction.

Naso-ocular reactions were defined as a positive response consisted of rhinorrhea plus any of the following: ocular chemosis, injection and periorbital swelling, nasal congestion, and paranasal sinus pain. The scores were recorded as 0, absence of any reactions; 1, nasal congestion and rhinorrhea alone; 2, rhinorrhea, with partial nasal obstruction associated with ocular injection or chemosis; 3, complete nasal obstruction with ocular injection and paranasal headache; and 4, severe reactions with periorbital edema and severe manifestations of all other naso-ocular signs and symptoms.

Laryngeal reactions were defined as crowing sounds over the upper chest and trachea, combined with a flattened and notched inspiratory curve in the flow/volume loop. The threshold or provoking dose of aspirin was recorded as the dose of aspirin given just before the recorded reaction.

The elapse time was the time interval between ingestion of aspirin and onset of the respiratory reaction. Systemic reactions were defined as reactions occurring beyond the respiratory tract, except laryngeal reactions, which were also placed in this category. Thus, urticaria, angioedema other than periorbital edema, flush, hypotension, cramping abdominal pain, nausea, emesis, and diarrhea were assigned to systemic reactions and were listed separately for each patient.

TABLE I. Background information on 8 subjects with AERD participating in the tacrolimus blocking study and 2 patients who received placebo pretreatment via randomization

Patients receiving tacrolimus	Age, y	Sex	Atopy	Number of previous aspirin reactions	Previous NSAID reaction	Inhaled steroids, ug/d	Nasal steroids, ug/d	Montelukast, 10 mg/d	Systemic steroids (prednisone), mg/d
1	54	F	Yes	1	Voltaren, Naproxen	500	200	Yes	0
2	38	M	No	1	Ibuprofen	880	200	Yes	10 mg q.o.d
3	54	F	Yes	5	0	500	128	Yes	0
4	67	F	Yes	2	0	500	0	Yes	0
5	42	F	Yes	2	Ibuprofen	1760	200	Yes	10 mg q.d
6	48	F	Yes	1	0	0	128	Yes	0
7	73	M	Yes	1	0	500	200	Yes	10 mg q.o.d
8	56	M	Yes	1	Ibuprofen	220	100	No	0
Placebo 1	46	F	No	2	0	200	0	Yes	0
Placebo 2	62	F	Yes	2	0	1000	0	Yes	10 mg q.d

Control group of patients with AERD undergoing aspirin oral challenges

To determine whether tacrolimus pretreatment altered the pattern of responses to oral challenges with aspirin, we contrasted our study group of 10 patients with another group of 50 patients with AERD who had most recently been admitted to the GCRC (2004). In this group of 50 consecutive patients who had respiratory reactions during oral aspirin challenges, similar characterizations were made. None of these 50 patients was pretreated with tacrolimus. The purpose of this larger control group was to compare their characteristics, treatment regimens, and aspirin-induced reactions to those of the 10 patients participating in our study.

Statistical analysis

Nonparametric (Wilcoxon signed-rank test) was used to compare changes in reaction responses before and after tacrolimus pretreatment. Parametric statistics (paired *t* test) was used to measure differences between the control group and either the baseline or posttacrolimus challenge results. The Fisher exact test was used to compare percentages of patients from the 50 patients and our study group with respect to characteristics of disease and treatment.

RESULTS

When the study was unblinded after the 10th patient had completed his challenges, as expected, 2 patients received placebos and 8 received tacrolimus. As shown in Table II, silent desensitization was not achieved in any patients. There were no statistically significant differences between aspirin challenge results when comparing the initial or baseline aspirin challenges and the tacrolimus-pretreated aspirin challenges. However, 3 of 8 patients did not react to the same provoking dose of aspirin after pretreatment with tacrolimus. As the doses of aspirin were advanced in these 3 subjects, they had typical respiratory reactions (30-60 mg, 45-150 mg, 60-100 mg). Patient 4 had a nasoo-ocular reaction to 45 mg aspirin at baseline and 150 mg aspirin after tacrolimus. She was the only patient to advance to a second day of pretreatment with tacrolimus, because she did not react to aspirin on day 1 with 45-mg,

60-mg, and 100-mg doses of aspirin. These 3 patients met the criteria for blocking the previously established provoking dose of aspirin. The other 5 patients reacted to the same provoking dose at baseline and after protection with tacrolimus pretreatment. Patients 2, 5, and 8 had nasoo-ocular reactions and bronchospasm, and all 3 required nebulized albuterol. Patient 8 was interesting because he had no asthma symptoms or change in FEV₁ values during the first baseline challenge, but after tacrolimus, he developed chest tightness and wheezing and a 12% drop in FEV₁ values, which required nebulized albuterol. By the random assignment of the computer program, both placebo-pretreated patients had large respiratory and systemic reactions. All patients received treatment with oral antihistamines in response to their reactions, and those with gastrointestinal or cutaneous systemic reactions received intravenous diphenhydramine and ranitidine. Epinephrine was given to the placebo patient who developed severe hives. All 10 patients were desensitized to aspirin and are currently taking daily aspirin for treatment of their AERD.

Systemic reactions were about the same both before and after pretreatment with tacrolimus. Of the 3 of 8 patients experiencing systemic reactions at baseline, all 3 had systemic reactions after pretreatment with tacrolimus. One patient did not have systemic symptoms at baseline but had nausea during the second challenge. Whether this was caused by tacrolimus or was part of her aspirin-induced reaction is unknown. The first placebo-treated patient had nausea during both of her aspirin-induced reactions.

The response to aspirin challenges were examined in the last 50 patients who had positive oral aspirin challenges. Their clinical characteristics and use of medications were similar to those of our study group of 10 patients (Table III). The results of their oral aspirin challenges were the same as those of our 8 study patients both without pretreatment during the first aspirin challenges and after pretreatment with tacrolimus in the second challenges (Table IV). In these 50 patients with proven AERD, the mean aspirin-provoking dose was

TABLE II. Comparison of challenge results with tacrolimus or placebo pretreatment

	Challenges without pretreatment					Tacrolimus/placebo pretreatment				
	Aspirin dose	Naso-ocular	% FEV ₁	Systemic reactions	Elapsed time	Aspirin dose	Naso-ocular	% FEV ₁	Systemic reactions	Elapsed time
1	30	3+	9	0	1.0	60	4+	4	0	1.0
2	45	4+	6	Throat pain	2.0	45	4+	17	Sore throat, GI pain	1.0
3	60	4+	0	0	1.25	60	4+	4	Nausea and emesis	2.0
4	45	2+	3	0	3.0	150	3+	0	0	2.0
5	45	4+	34	Flush, GI pain	2.5	45	4+	3	Flush, GI pain and emesis	2.5
						60	3+	24		3.0
6	100	4+	15	Pruritus	1.5	100	3+	1	Pruritus	2
7	100	4+	4	0	1.5	100	4+	0	0	2
8	60	3+	9	0	3.0	100	3+	12	0	2
Mean	60.6	3.5	10.0	3/8	1.96	84.3	3.7	7.8	4/8	1.87
SD	26.1	0.75	10.2		0.78	34.8	0.5	9.9		0.64
SEM	09.2	0.26	03.8		0.27	12.2	0.2	3.2		0.22
Placebo*	60	4+	24	Nausea	3.0	100	2+	20	Nausea	2.75
Placebo*	30	4+	12	GI pain, urticaria	2.0	60	4+	34	GI pain, emesis, urticaria	2.0

*Placebo, placebo pretreatment, randomly assigned by computer program as per text and not included in these statistical calculations.
GI, Gastrointestinal.

TABLE III. Comparison of the evaluation of the 10 patients enrolled in this study and the last 50 patients admitted to GCRC in 2004

Characteristics	10 study patients, %	50 AERD patients, %	P values*
Age, y	46	54	NS
Sex, female	70	56	NS
Atopy	70	66	NS
Inhaled steroids	90	82	NS
Nasal steroids	70	70	NS
Systemic steroids	40	38	NS
Cysteinyl leukotriene receptor 1 treatment	90	80	NS
Naso-ocular reactions	100	96	NS
>15% decline in FEV ₁	40	44	NS
Systemic reactions	50	38	NS

*Paired *t* test for age differences and Fisher exact test for % differences.

65.5 mg, compared with 60.6 mg at baseline and 84.3 mg after pretreatment with tacrolimus. However, despite this 20-mg increase in provoking dose (largely because of 1 patient advancing from 45 to 150 mg aspirin), differences were not significant ($P = .126$). The other mean values were even closer, and the differences again did not reach statistical significance (Table IV). In a review of the data in Tables II and IV, no differences were found in the challenge results in the study patients either at baseline or after treatment with tacrolimus compared with the last 50 patients undergoing oral aspirin challenges. Therefore, we can conclude that our study group of 10 patients with AERD is reasonably representative of patients who are likely to be referred for aspirin desensitization.

There were no obvious adverse effects from tacrolimus. Only 1 of 8 patients had gastrointestinal symptoms

of pain and/or nausea during aspirin-induced reaction at baseline, but 3 of 8 had gastrointestinal reactions after tacrolimus. However, both placebo-treated patients had gastrointestinal reactions to aspirin at baseline and after placebo. Gastrointestinal side effects from aspirin are relatively common, and because these patients responded to intravenous diphenhydramine and ranitidine, with resolutions of reactions, and all reactions disappeared as aspirin desensitization was completed, it is likely that histamine release from gastrointestinal mast cells was the responsible mediator. In the 50 control patients, 19 (38%) had systemic reactions as extensions of their aspirin-induced respiratory reactions: 10 had gastrointestinal symptoms, 4 flush, 5 laryngeal spasms, and 2 urticarial reactions (2 patients had both gastrointestinal symptoms and flushing). In view of the small size of our pilot study, whether tacrolimus caused or augmented gastrointestinal symptoms is suggested but cannot be stated with certainty.

DISCUSSION

Given the data in the study by Kawano et al,¹⁰ the results of our study were somewhat surprising. Blockade of the aspirin provoking dose occurred in only 3 of our 8 patients. Unfortunately, each of these 3 subjects then reacted to higher doses of aspirin, showing that silent aspirin desensitization could not be achieved. This was true even though tacrolimus was added to our standard pretreatment program of montelukast, salmeterol, inhaled corticosteroids, and in 4 patients, systemic corticosteroids. In fact, the low rate of bronchospasm in this population is characteristic of pretreatment with montelukast in 9 of 10 patients who entered this study.⁶

TABLE IV. Mean values between 50 patients with AERD undergoing oral aspirin challenges and 8 patients undergoing oral aspirin challenges after pretreatment with tacrolimus†

Measure	50 Patients with AERD	8 Patients at baseline	P values 50 patients to baseline*	8 Patients post-tacrolimus	P values 50 patients to tacrolimus*
Aspirin dose, mg	65.5 (3.65)	60.6 (9.23)	NS	84.3 (12.27)	NS
Nasal score	3.20 (0.13)	3.5 (0.26)	NS	3.65 (0.18)	NS
FEV ₁ decline by %	13.08 (1.60)	10.0 (3.78)	NS	7.75 (.3.16)	NS
Elapsed time in hours	1.68 (0.09)	1.96 (0.27)	NS	1.85 (0.22)	NS

*Paired *t* test.
†(SEM).

In reviewing the dosing sequences of tacrolimus and aspirin, a difference between our study and that of Kawano et al¹⁰ might be that they gave tacrolimus 0.1 mg/kg 2 hours before dosing with aspirin in their challenges. Because of our schedules in the GCRC, we gave tacrolimus 1 hour before the provoking dose of aspirin was ingested, and theoretically, this may account for the differences. However, tacrolimus is rapidly absorbed on an empty stomach, and our patients had a light breakfast at 1.25 to 1.50 hours after ingesting tacrolimus. In addition, for 6 of 8 patients, the elapsed time from ingestion of aspirin capsules to onset of reaction was >2 hours (3 hours after tacrolimus ingestion). In fact, 3 of 8 patients did not react to the provoking dose, and 3 hours later, 2 of them reacted to the next highest dose of aspirin. In view of the prolonged half-life of tacrolimus, some 48 hours after oral absorption, one would expect tacrolimus to be available during both the first and subsequent aspirin challenge doses.

Another potential difference is that the patient populations were not the same, both genetically (Japanese vs white) and, probably more importantly, in severity of AERD. In the study by Kawano et al,¹⁰ patients with AERD had asthma mild enough that they did not need systemic corticosteroids and could discontinue inhaled corticosteroids and adrenergic agents for 48 hours before challenges. None of their patients was taking aminophylline, antihistamines, or leukotriene-modifier drugs. As shown in Table I, all of our patients were typical of the patients with AERD whose disease is severe enough to stimulate referral for aspirin desensitization treatment. Therefore, not unexpectedly, our patients could not discontinue their controller medications without airway instability (Table I). Montelukast was used by 9 of 10 subjects, with 4 of 10 taking prednisone at the time of challenges. The need for all of their controller medications, shown in Table I, supports the fact that our population had moderate or severe asthma. By contrast, the patients in the study by Kawano et al¹⁰ could discontinue medications 48 hours before challenges without deterioration in lung function and had mild or intermittent asthma. This may be an important difference why tacrolimus was unsuccessful in preventing positive oral aspirin challenges in our patients.

A third difference in our study is that Kawano et al¹⁰ challenged patients with 1 previously established provok-

ing dose of aspirin. If the investigators had advanced doses of aspirin after the provoking dose was tolerated, they may also have observed respiratory reactions in their patients after pretreatment with tacrolimus. Because escalating doses of aspirin induce larger and larger reactions, it becomes increasingly difficult to block these reactions with any program currently available. This principle seems to be the same for tacrolimus as for any other potential blocking agent. A few years ago, Israel et al¹¹ reported that zileuton pretreatment prevented previously established provoking doses of aspirin from inducing respiratory reactions. However, a second study by Pauls et al¹² showed that as the doses of aspirin were escalated beyond the threshold or previously established provoking doses, blocking effects of zileuton disappeared. Finally, Kawano et al¹⁰ performed concomitant blood levels of tacrolimus and urinary LTE₄ measurements. We did not perform these measurements in our study.

Current evidence supports a central role for leukotrienes as causative mediators of aspirin-induced bronchospasm.¹³⁻¹⁶ Unfortunately, cysteinyl leukotriene receptor 1 antagonists reduce or modulate but do not universally prevent aspirin-induced bronchospasm.^{6,17} Antihistamines, on the other hand, do not provide any protective effects on the lower respiratory tract but prevent part of the aspirin-induced naso-ocular reactions as well as some systemic effects such as flush and urticaria.¹⁸ Systemic and topical corticosteroids are important in stabilizing bronchial airways in preparation for oral or inhalation aspirin challenges but do not prevent aspirin-induced upper or lower airway reactions or systemic reactions.^{6,19} Pretreatment with salmeterol has been reported to prevent aspirin-induced bronchospasm,⁷ but the authors have found that salmeterol and fluticasone combination did not prevent bronchospasm in patients with AERD referred to our institution. Pretreatment with cromolyn sodium has not been universally successful in altering the degree of aspirin-induced bronchospasm, particularly as the doses of aspirin are increased.²⁰⁻²² The best we can do at this point is prepare the bronchi for maximum stability and pretreat with montelukast, inhaled corticosteroids, and a long-acting bronchodilator.

We are not encouraged that tacrolimus can provide additional protection of the lower or upper airways during oral aspirin challenges. This study is disappointing with respect to the practical problems of conducting oral aspirin

challenges in outpatient offices. One would ideally use a blocking program that prevented asthma attacks in all patients and even allowed silent aspirin desensitization to proceed unencumbered by any respiratory or systemic reactions. Tacrolimus, at this dose and by the oral route, failed to provide this specification. Whether higher doses of tacrolimus given orally, or perhaps intravenously, will be effective cannot be stated at this time. However, further studies are warranted, because the goal of pretreatment with medications to conduct silent aspirin desensitization has not been achieved.

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