

REVIEW ARTICLE

Clinical efficacy and safety of benzoyl peroxide for acne vulgaris: Comparison between Japanese and Western patients

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ABSTRACT

Benzoyl peroxide (BPO) has been well established as a common medication for acne vulgaris in many countries (e.g. in Europe and the USA), where clinical data have been accumulated over a long time. In Japan, the use of BPO for acne treatment was approved in 2014, and the results of clinical trials in Japanese patients have recently been reported. This review compares clinical study results between Japanese and Western patients. Clinical studies that had been performed in Western countries were searched on the basis of the criteria, double-blind studies of BPO monotherapy and comparison with a vehicle group. Two reports of Japanese studies were also selected by using the same criteria. Efficacy was assessed by comparing the mean difference between the BPO and the vehicle groups for reduction rate in the number of lesions from baseline, and there were no differences between Japanese and Western patients. Safety assessment also showed that the incidence of adverse events was higher in Japanese patients than in Western patients, but the characteristics of the adverse events were not different. Therefore, we conclude that there are no significant differences in the efficacy and safety of BPO between these patient populations. The efficacy and safety of long-term use in Japanese patients are also expected to be applicable to those in Western patients.

Key words: acne vulgaris, benzoyl peroxide, clinical efficacy, ethnicity, safety.

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease that often affects the hair follicle sebaceous glands on the face, chest and back. It is commonly observed in adolescent males and females, and more than 90% of Japanese develop acne vulgaris during their life.¹ As increased value is put on appearance, adolescents with acne may have a low quality of life with regard to their emotional state.² Therefore, there is a high demand for an efficacious treatment for acne patients. The pathogenesis of acne vulgaris is a complex process involving abnormal lipid metabolism, dyskeratosis and bacterial growth. Antimicrobials form one of the main treatment options, but there are concerns that their long-term use may cause the development and spread of antibiotic-resistant bacteria. In fact, it has been reported that isolation of drug-resistant *Propionibacterium acnes* from acne patients has increased in Japan.³ Topical benzoyl peroxide (BPO) has been used as a treatment for acne vulgaris in many countries, including those in Europe and the USA, where the

corresponding medical guidelines recommend it as the standard treatment for acne vulgaris.^{4,5} The mechanism of action of BPO is considered to be its antiseptic activity and keratolytic effects,^{6,7} and there is not a concern for the development of drug-resistant bacteria to BPO. The Japanese medical guideline for acne vulgaris was revised in 2016, and BPO is recommended as a drug for the treatment of inflammatory and non-inflammatory acne vulgaris lesions and to maintain remission after inflammation has resolved.¹ Western countries have been using BPO as acne treatment since the 1960s, and have accumulated much clinical data. Recently, in fact, Lamel *et al.*⁸ reviewed and investigated the data from clinical studies conducted in Western countries in patients with acne vulgaris using BPO. In the meantime, in Japan, BPO was approved in 2014 for the treatment of acne vulgaris and has been on the market since 2015, and therefore clinical data of Japanese patients has only recently become available.^{9–11} This article reviews the efficacy and safety profiles of BPO, and compares the results of clinical studies between Japanese and Western patients.

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SELECTION OF STUDIES

We selected randomized, double-blind studies that compared a monotherapy with a BPO gel with its vehicle as a placebo control to evaluate the efficacy and safety of BPO for acne vulgaris. Reports were searched in PubMed and Embase (cut-off date of 14 July 2016) using “benzoyl peroxide”, “acne vulgaris”, “placebo” or “vehicle”, and “controlled” or “randomized” as key words. Reports hit by the search were further screened on the basis of their titles and abstracts. As a result, 10 studies including one Japanese study by Kawashima *et al.*,⁹ were selected for our review. A more recently reported study by Kawashima *et al.*,¹⁰ was also used as another clinical study in Japanese patients (Table 1). These two Japanese studies were independent and separate clinical studies and the results were generated from different subject groups. Clinical studies outside Japan were performed in North America and Europe, which means as a result that this review compared Japanese studies in Japanese patients with Western studies in Western patients (mainly Caucasians). In the following comparison, references were limited to studies with gel formulations of BPO as the Japanese studies used. For comparison of efficacy, references that reported the mean reduction rate in number of lesions from baseline were selected, and four studies in Western patients and two studies in Japanese patients were used for the comparison. To investigate the safety profile, we focused on the reports that included incidences of adverse events (AE), and eight studies in Western patients and two studies in Japanese patients were selected. Table 1 shows the outlines and subject backgrounds of the selected studies.

COMPARISON OF EFFICACY BETWEEN WESTERN AND JAPANESE STUDIES

Efficacy of BPO for acne was assessed on the basis of the percentage reduction in numbers of lesions (inflammatory, non-inflammatory and total) at the end of the treatment period from baseline. The mean or median percentage reduction of each study is summarized by lesion type (Fig. 1 for inflammatory lesions, Fig. 2 for non-inflammatory lesions and Fig. 3 for total lesions) and the differences between the BPO and the vehicle groups are also indicated in the figures when the mean values of both groups were available. For the study by Kawashima *et al.*,⁹ additional data that were not available in their publication were obtained from the GSK Clinical Study Register,¹² because the detailed individual data of this study have been presented on the website, not published in print. Likewise, concerning the study of Kawashima *et al.*,¹⁰ the mean percentage reduction and standard deviation were obtained from the original study report. The BPO concentration of the study drugs ranged 2.5–5% in the Western studies and 2.5–3% in the Japanese studies. It has been reported that there is no difference in the efficacy of BPO within the range of a concentration of 2.5–10%,¹³ and thus, we did not take the difference in the BPO concentration into account to compare efficacy. In addition, duration of treatment was 8–12 weeks in the Western studies and 12 weeks in the Japanese studies.

We consider that there is no significant difference in percentage reduction in inflammatory lesion count between the Western and the Japanese studies for both of the BPO and the vehicle groups. The mean difference in percentage reduction in inflammatory lesion count was 13–34% in the Western studies and 28–29% in the Japanese studies, indicating that the differences between the BPO and the vehicle groups for both Western and Japanese studies were clinically meaningful (Fig. 1). In addition, the mean differences in percentage reduction in inflammatory lesion count in the Japanese studies were within the range observed in the Western studies. Therefore, we conclude that the efficacy profiles of BPO for the inflammatory lesions are similar between the Western and the Japanese studies.

We consider that there is no significant difference in percentage reduction in non-inflammatory lesion count between the Western and the Japanese studies for both the BPO and vehicle groups. The mean differences in percentage reduction in non-inflammatory lesion count were 13–41% in the Western studies and 28–30% in the Japanese studies, indicating that the differences between the BPO and the vehicle groups for both Western and Japanese studies (Fig. 2) were clinically meaningful. In addition, the mean differences in percentage reduction in non-inflammatory lesion count in the Japanese studies were within the range observed in the Western studies. Therefore, we conclude that the efficacy profiles of BPO for the non-inflammatory lesions are similar between the Western and the Japanese studies.

We consider that there is no significant difference in percentage reduction in total lesion count between the Western and the Japanese studies for both the BPO and vehicle groups. The mean differences in percentage reduction in total lesion count were 15% in the Western studies and 29–30% in the Japanese studies, indicating that the differences between the BPO and the vehicle groups for both Western and Japanese studies (Fig. 3) were clinically meaningful. However, the mean differences in percentage reduction in total lesion count in the Japanese studies were not within the range observed in the Western studies. This was because only two studies in the Western studies calculated the mean percentage reduction in total lesion count. As the efficacy of BPO for the inflammatory lesions and non-inflammatory lesions is similar between the Western and the Japanese studies, we conclude that the efficacy of BPO for the total lesions is also similar between the Western and the Japanese studies.

COMPARISON OF SAFETY BETWEEN WESTERN AND JAPANESE STUDIES

The incidences of AE were compared between the selected studies (Table 2). In both Western and Japanese studies, the following safety characteristics were commonly reported: most AE were mild in severity and consisted mainly of skin irritation at the application site, no serious treatment-related AE were observed, and the occurrence of AE was higher during the early than later treatment period. Therefore, we conclude that there are no qualitative differences in the safety profile of BPO

Table 1. Selected references

Reference	Study region	Regimen	Treatment group	Subject number	Sex, male %	Age, mean	Ethnicity/race	Baseline lesion counts, mean	
								Total	IL
Eichenfield <i>et al.</i> (2011) ^{17†‡}	USA, Canada, Belize	q.d. × 12 w	BPO 3% Vehicle	328	38	20.6	White, 77%	71.6	44.6
Gold <i>et al.</i> (2009) ^{15‡}	USA, Puerto Rico, Canada	q.d. × 12 w	BPO 2.5% Vehicle	415	50.1	18.4	White, 78%	70.5	44.2
Gollnick <i>et al.</i> (2009) ^{16‡}	USA, Canada, Europe	q.d. × 12 w	BPO 2.5% Vehicle	418	46.9	18.0	White, 62.2%	(76)	(46)
Thiboutot <i>et al.</i> (2009) ^{18†‡}	USA	q.d. × 12 w	BPO 2.5% Vehicle	415	44.6	18.9	White, 64.6%	(76)	(46)
Thiboutot <i>et al.</i> (2007) ^{19‡}	USA	q.d. × 12 w	BPO 2.5% Vehicle	418	41.6	19.2	Caucasian, 79.3%	(74)	(45)
Leyden <i>et al.</i> (2001) ^{20‡}	USA	q.d. × 12 w	BPO 2.5% Vehicle	809	43.8	19.1	Caucasian, 79.2%	(76)	(46)
Tsichen <i>et al.</i> (2001) ^{21‡}	USA	q.d. × 12 w	BPO 2.5% Vehicle	395	51.4	19.4	White, 73.9%	72.6	46.8
Lookingbill <i>et al.</i> (1997) ^{22†‡}	USA	q.d. × 11 w	BPO 5% Vehicle	92	49	18.5	White, 77.2%	70.2	44.0
Mills Jr <i>et al.</i> (1986) ^{13†}	USA	b.i.d. × 10 w	BPO 5% Vehicle	149	64.4	16.5	Caucasian, 76.5%	(74)	(43)
Kawashima <i>et al.</i> (2014) ^{9†‡}	USA	b.i.d. × 10 w	BPO 5% Vehicle	71	56.3	16.6	Caucasian, 73.2%	(78)	(46)
Kawashima <i>et al.</i> (2017) ^{10†‡}	USA	b.i.d. × 10 w	BPO 5% Vehicle	120	48	19	NA	49	NA
	USA	b.i.d. × 10 w	BPO 5% Vehicle	120	40	19	NA	47	NA
	USA	b.i.d. × 10 w	BPO 5% Vehicle	95	46-54	19	NA	NA	NA
	USA	q.d. × 11 w	BPO 5% Vehicle	48	49	18.5	NA	NA	NA
	USA	q.d. × 8 w	BPO 2.5% Vehicle	58	48.4	20	NA	89.9	59.2
	USA	b.i.d. × 8 w	BPO 2.5% Vehicle	25	25	20	NA	101.6	70.1
	USA	b.i.d. × 8 w	BPO 2.5% Vehicle	25	25	20	NA	NA	NA
	Japan	q.d. × 12 w	BPO 3% Vehicle	178	34	21.3	Japanese	72.1	44.2
	Japan	q.d. × 12 w	BPO 2.5% Vehicle	182	36	22.4	Japanese	70.3	42.7
	Japan	q.d. × 12 w	BPO 2.5% Vehicle	203	41.4	19.5	Japanese	54.9 (50)	34.7 (29)
	Japan	q.d. × 12 w	BPO 5% Vehicle	203	38.9	20.0	Japanese	55.9 (51)	35.8 (30)
	Japan	q.d. × 12 w	BPO 5% Vehicle	201	45.3	19.2	Japanese	56.5 (51)	36.4 (30)

†Included in comparison of safety. ‡Included in comparison of efficacy. BPO, benzoyl peroxide; IL, inflammatory lesion; NA, not-available; NIL, non-inflammatory lesion; w, weeks.

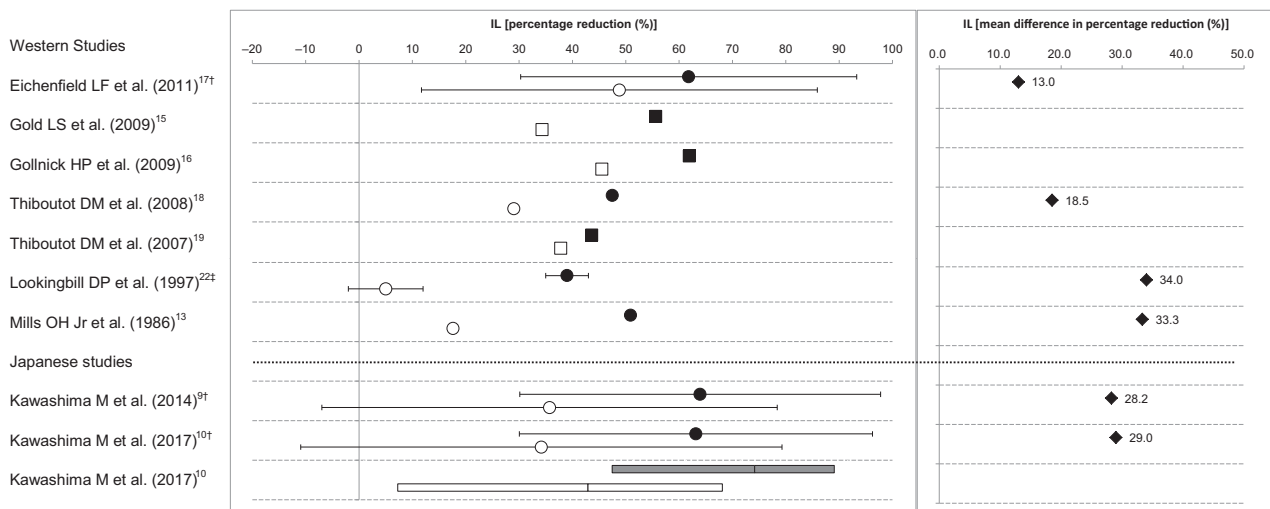


Figure 1. Percentage reduction and mean difference in percentage reduction of inflammatory lesion (IL) counts from baseline between the benzoyl peroxide (BPO) and the vehicle groups. Data indicate the mean (●, BPO; ○, vehicle), the standard deviation (†), the standard error (‡), the median (■, BPO; □, vehicle), the median and interquartile range (gray box, BPO; white box, vehicle), or the mean difference (♦, BPO minus vehicle).

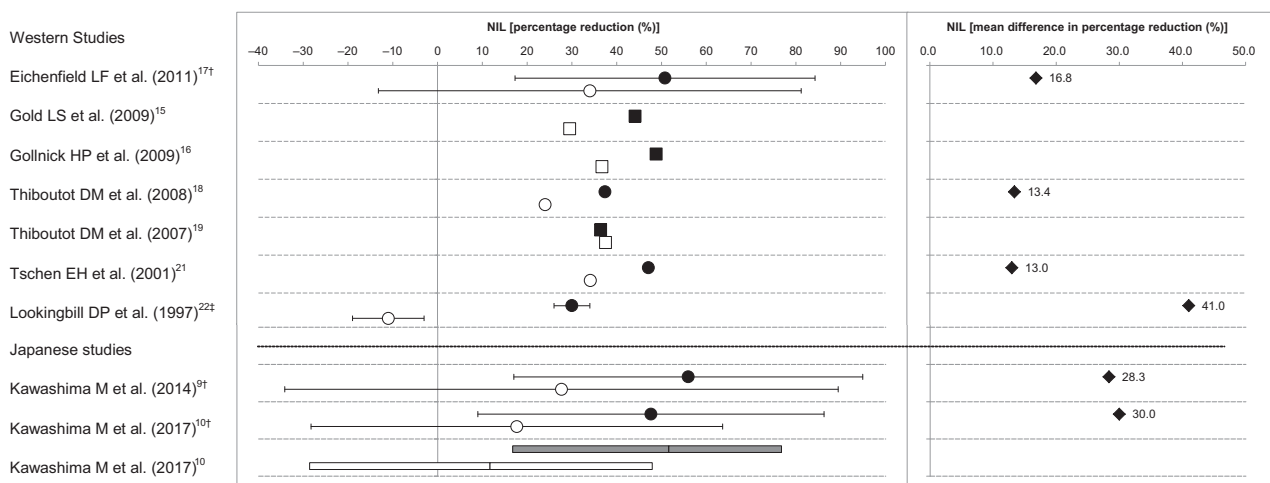


Figure 2. Percentage reduction and mean difference in percentage reduction of non-inflammatory lesion (NIL) counts from baseline between the benzoyl peroxide (BPO) and the vehicle groups. Data indicate the mean (●, BPO; ○, vehicle), the standard deviation (†), the standard error (‡), the median (■, BPO; □, vehicle), the median and interquartile range (gray box, BPO; white box, vehicle), or the mean difference (♦, BPO minus vehicle).

between the Western and Japanese patient populations. However, the incidence of AE was higher in Japanese studies than Western studies (Table 2). Most treatment-related AE in the Japanese studies consisted of skin irritation at the application site, suggesting higher sensitivity to local irritation of BPO in Japanese patients. It has been reported that the skin barrier structure of Asians, including Japanese, is weaker than that of Caucasians,¹⁴ which may be a reason for the higher incidence of AE in Japanese studies.

For patients enrolled in the Western studies, there was a possibility of developing tolerability to BPO because it was very common for these patients to be using BPO, including over-the-counter products, when these studies were conducted. However, it was assumed that most Japanese patients were BPO naive, because no BPO drugs had been approved in Japan at the time. Another possible factor for a higher incidence of AE in Japanese studies was the use of moisturizers. The two Western studies required the concomitant treatment

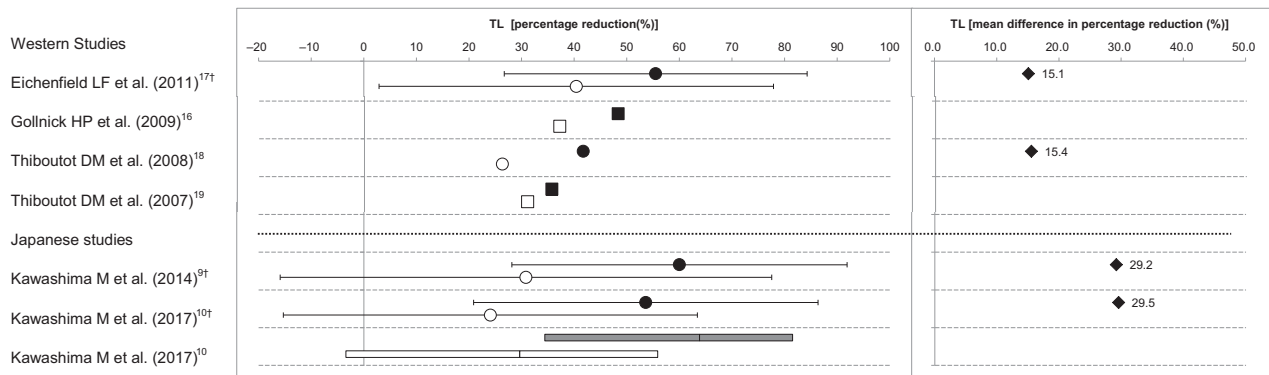


Figure 3. Percentage reduction and mean difference in percentage reduction of total lesion (TL) counts from baseline between the benzoyl peroxide (BPO) and the vehicle groups. Data indicate the mean (●, BPO; ○, vehicle), the standard deviation (†), the median (■, BPO; □, vehicle), the median and interquartile range (gray box, BPO; white box, vehicle), or the mean difference (◆, BPO minus vehicle).

Table 2. Incidences of adverse events

Reference	Regimen	Treatment group	Subject number	Subjects with any AE, %	Subjects with AE related to treatment, %
Eichenfield <i>et al.</i> (2011) ¹⁷	q.d. × 12 w	BPO 3%	328	31	2
		Vehicle	332	26	2
Gold <i>et al.</i> (2009) ¹⁵	q.d. × 12 w	BPO 2.5%	415	NA	NA
		Vehicle	418	NA	NA
Gollnick <i>et al.</i> (2009) ¹⁶	q.d. × 12 w	BPO 2.5%	415	33	13
		Vehicle	418	28	8
Thiboutot <i>et al.</i> (2008) ¹⁸	q.d. × 12 w	BPO 2.5%	809	NA	5.9
		Vehicle	395	NA	6.1
Thiboutot <i>et al.</i> (2007) ¹⁹	q.d. × 12 w	BPO 2.5%	149	29.5	6.7
		Vehicle	71	26.8	5.6
Leyden <i>et al.</i> (2001) ²⁰	b.i.d. × 10 w	BPO 5%	120	29.2	NA
		Vehicle	120	20.8	NA
Tschen <i>et al.</i> (2001) ²¹	b.i.d. × 10 w	BPO 5%	95	52	27
		Vehicle	48	50	19
Lookingbill <i>et al.</i> (1997) ²²	q.d. × 11 w	BPO 5%	92	NA	2.2
		Vehicle	58	NA	1.7
Kawashima <i>et al.</i> (2014) ⁹	q.d. × 12 w	BPO 3%	178	58	30
		Vehicle	182	47	5
Kawashima <i>et al.</i> (2017) ¹⁰	q.d. × 12 w	BPO 2.5%	204	56.4	37.3
		BPO 5%	204	58.8	38.7
		Vehicle	201	47.3	12.9

AE, adverse events; BPO; benzoyl peroxide; NA, not available; w, weeks.

with a moisturizer for subjects who were assessed to have dry skin by the investigator.^{15,16} Because the use of moisturizers had to be decided by the investigator and/or the subjects, the effect of moisturizers was unclear.

BPO FOR LONG-TERM TREATMENT

Kawashima *et al.*,¹¹ was the only study that reported the safety and efficacy of a long-term treatment with BPO monotherapy. Acne vulgaris frequently relapses when treatment is discontinued

after symptoms have improved; thus, remission has to be maintained, even after inflammation has resolved. Because there are no reports of BPO-resistant bacteria, it is commonly believed that the long-term maintenance use of BPO would be reasonable. The efficacy and safety for long-term treatment (up to 52 weeks) with both 2.5% and 5% BPO gel in Japanese patients were reported.¹¹ This report showed that the number of lesions decreased over time from the start of treatment to 12 weeks, and that this status was maintained thereafter. Regarding safety, most treatment-related AE occurred within the first 12 weeks of

treatment, and the incidence rate was low thereafter. Furthermore, the AE that were observed only after the first 12 weeks, and not before that, were dermal symptoms at the application site, and most cases were mild. On the basis of these results, we concluded that no new safety concerns due to prolonged treatment would arise after the early treatment phase.

As previously described, there were no differences in efficacy between Japanese and Western studies up to 12 weeks of treatment. The main mechanism of action of BPO is believed to be oxidative activity at the application site, for which little ethnic difference is expected. Therefore, the efficacy of long-term use reported in Japanese patients would be similar in Western patients. Safety profiles up to 12 weeks did not indicate any clinically meaningful differences between Japanese and Western patients, and no serious problems occurred after 12 weeks in the Japanese study, suggesting that long-term use of BPO in Western patients would be as safe as 12-week treatment.

LIMITATIONS

In this article, we compared the results of clinical studies performed in Japan with those performed in the USA and Europe. However, the comparison was based on historical data, and we should account for its limitations. Baseline severity of acne symptoms of participants, variability in the evaluation when counting lesions and recognition of AE may be different between studies and therefore affect the evaluation of safety and efficacy. In the study of Kawashima *et al.*,¹⁰ the ratio of participants with relatively mild symptoms was higher than in the other studies, which limits the comparison of efficacy. Furthermore, this study included a change for the worse in local skin tolerability score as an AE, and this could also increase the incidence rate of AE in that study. With regard to the long-term safety in Western patients, it was an extrapolation from the comparison of the short-term (12-week) treatment results between Western and Japanese safety data. No concrete data were available to predict the long-term safety in Western patients.

CONCLUSION

This review summarizes clinical trials performed in Japan and those performed in the USA and Europe and compares them for efficacy and safety of BPO. Regarding the efficacy, the results of the Japanese studies are within the range of fluctuations of the studies performed in the USA and Europe, suggesting that there are no differences between these patient populations. Although the safety assessment of the Japanese studies suggested that AE at the application site occurred more often in Japanese patients than Western patients, most of the AE were mild. Except for the difference in the frequency of AE, there were no differences in their respective safety profiles. It is also suggested that the preferable efficacy and safety profiles of the long-term use of BPO shown in Japanese patients would be applicable to Western patients.

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