

Bone Resorption and Inflammatory Inhibition Efficacy of Intermittent Cyclical Etidronate Therapy in Rheumatoid Arthritis

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ABSTRACT. Objective. Osteoclast activation or cartilage and bone destruction are developed in patients with rheumatoid arthritis (RA). The efficacy of etidronate with respect to osteoporosis, inhibition of bone resorption and destruction, and antiinflammation in RA was examined for 72 weeks.

Methods. Sixty-three patients with RA (56 women, 7 men) were divided into a group that received intermittent cyclical etidronate therapy (ICET) (31 patients) and a non-ICET group (32 patients). Over a 72 week followup period, the urinary deoxypyridinoline (DPD), serum bone alkaline phosphatase (BAP), bone mineral density (BMD), Larsen damage score, Lansbury activity index, and concentrations of serum C-reactive protein (CRP) and serum interleukin 6 (IL-6) of the 2 groups were compared.

Results. In the non-ICET group, a significant decrease in BMD and a significant increase in the Larsen damage score were observed. In the ICET group, the level of DPD started to decrease 12 weeks after etidronate administration and progression of the Larsen damage score was significantly inhibited. IL-6 concentration was significantly decreased 72 weeks after etidronate administration. Concentrations of BAP and CRP and the Lansbury activity index were not significantly different between the ICET and the non-ICET groups. A significant correlation between the IL-6 and DPD concentrations was observed.

Conclusion. Etidronate was effective at inhibiting bone resorption and destruction in study patients with RA, while not increasing BAP concentrations; and a correlation was observed between the concentration of DPD and IL-6, indicating the antiinflammatory effect of etidronate. (*J Rheumatol* 2003;30:474-9)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
DEOXYPYRIDINOLINE

OSTEOPOROSIS
LARSEN DAMAGE SCORE

ETIDRONATE DISODIUM
INTERLEUKIN 6

Bone formation is maintained by continuous remodeling such that bone resorption by osteoclasts and osteogenesis by osteoblasts are well balanced. When this balance is disturbed and bone resorption becomes predominant relative to osteogenesis, osteoporosis occurs. In addition, a loss of bone mass is often observed in patients with rheumatoid arthritis (RA), of which administration of corticosteroid, hormonal imbalance due to menopause, and bone disuse atrophy with multiple-joint disorders are considered as causes.

It has been reported that intermittent cyclical etidronate therapy (ICET) is effective at inhibiting osteoporosis caused by administration of corticosteroid¹⁻³ and postmenopausal osteoporosis⁴. One study indicated that administration of

etidronate disodium is effective at maintaining bone mass based on studies of ovariectomized rats⁵.

Many studies suggest that bone mass and bone mineral density (BMD) increased following the administration of etidronate disodium⁶⁻⁹. Further, one study suggested that administration of etidronate disodium was effective at reducing pain in a rat adjuvant arthritis model¹⁰. In this study, the clinical efficacy of etidronate therapy for RA, particularly in maintaining the balance between osteogenesis and bone resorption, and an antiinflammatory effect, were examined.

MATERIALS AND METHODS

Sixty-three patients with RA (56 women, 7 men) who fulfilled the diagnostic criteria of the American College of Rheumatology (ACR) were enrolled as subjects. The patients, selected from the outpatient section of our department, were randomly divided into 2 groups using the closed envelope method; 31 patients (28 women and 3 men) in the ICET group were administered 400 mg of etidronate disodium, and 32 patients (28 women and 4 men) formed the non-ICET group.

Patients' average ages were 63.7 ± 4.5 years in the ICET group and 64.1 ± 8.3 years in the non-ICET group. The average disease duration was 235.2 ± 137.7 months in the ICET group and 196.6 ± 144.12 months in the non-

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ICET group. No significant difference between the 2 groups was found by Mann-Whitney U test.

With respect to the amount of adrenal corticosteroid, 5 mg per day prednisolone was administered to 25 patients in the ICET group, and to 26 patients in the non-ICET group. The total amounts of prednisolone received by the ICET group and the non-ICET group were 5222.3 ± 2956.2 and 4742.4 ± 2906.4 mg, respectively. No significant difference between these 2 groups was found by Mann-Whitney U test.

The types of disease modifying antirheumatic drugs (DMARD) administered to those in the ICET group were as follows: 100 mg per day bucillamine (BUC), 5–7.5 mg per week methotrexate (MTX), 1000 mg per day salazosulfapyridine (SASP), a combination of BUC and MTX, and a combination of MTX and mizoribine; DMARD was not administered to 5 patients in the ICET group. In the non-ICET group, BUC, MTX, and SASP were administered at the same dose as in the ICET group; combinations were between BUC and MTX and between BUC and SASP. DMARD was not administered to the remaining 6 subjects. Vitamin D3 1.0 µg per day was administered to 13 patients in the ICET group and 15 in the non-ICET group. However, calcium was not administered in either group. No significant difference in background features was observed between the 2 groups (Table 1).

In the ICET group, 400 mg etidronate was administered orally between meals once a day for 2 weeks, and it was withheld for the next 10 weeks. This 12 week period was defined as one cycle. Etidronate was administered at the designated periods for 6 cycles (72 weeks, 18 mo). Patients continued taking medications prescribed before the study was initiated. The dosage of medication including vitamin D3 was not increased, and no other medications were administered. All patients gave informed consent.

BMD was measured using the microdensitometry method developed by Inoue, *et al*¹¹. With this method, radiographs taken simultaneously of metacarpal bone density and an aluminum step-wedge are analyzed with a microdensitometer. Urine deoxypyridinoline (DPD) as a marker for bone resorption was measured using an ELISA kit (Pyrilinks™ D, Quidel Corp., San Diego, CA, USA)¹², and serum bone alkaline phosphatase (BAP) as a marker for bone formation was measured using an EIA kit (Alkphase-B, Quidel Corp.)¹³. The Larsen damage score for fingers based on radi-

ographic images, Lansbury's activity index for inflammation and RA activity, and concentrations of serum C-reactive protein (CRP) and IL-6 by ELISA were evaluated for 72 weeks in both groups.

Based on radiographic findings, damage to fingers was graded from 0 to 5 according to the Larsen method¹⁴. Twenty joints, including 10 metacarpophalangeal joints, 8 proximal interphalangeal joints, and 2 interphalangeals of both thumbs of both hands, were evaluated by this method. Two rheumatologists who did not participate in the allocation of patients evaluated the 20 joints for Larsen score; their evaluations were different, and the lower scores were adopted. The Lansbury index we used was the total score for 4 items, namely, morning stiffness, grip strength, number of swollen and painful joints, and erythrocyte sedimentation rate (ESR), among Lansbury's 6 items¹⁵.

Statistical analysis. Percentage changes in DPD, the Larsen damage score¹⁴, and IL-6 at 24, 48, and 72 weeks after administration of etidronate relative to baseline measurements were evaluated using the Wilcoxon signed-rank test. Differences between concentrations of BMD, DPD, BAP, CRP, and IL-6 and the Larsen score and Lansbury index between the ICET group and the non-ICET group before etidronate administration were evaluated using the Mann-Whitney U test. The correlations between concentrations of IL-6 and urine DPD were evaluated using Pearson's correlation coefficient. In each case, $p < 0.05$ was considered significant.

RESULTS

Table 2 shows BMD, DPD, BAP, the Larsen score for fingers, the Lansbury index, serum CRP level, and serum IL-6 level before administration of etidronate. None of these items were significantly different between the 2 study groups before administration. The DPD levels were 9.78 ± 4.21 nM/mM Cr in the ICET group and 9.26 ± 5.28 nM/mM Cr in the non-ICET group. BAP levels were 12.4 ± 13.0 U/l in the ICET group and 16.4 ± 20.2 U/l in the non-ICET group. No significant differences were observed between the 2 groups.

The percentage changes in BMD in the ICET group were -3.1% ($n = 23$), -0.9% ($n = 29$), and -0.5% ($n = 25$) at 24, 48, and 72 weeks after etidronate administration, respectively. Meanwhile, in the non-ICET group, the percentage changes were -2.3% ($n = 21$), -4.2% ($n = 31$), and -2.7% ($n = 27$) at 24, 48 and 72 weeks, respectively. A statistically significant decrease in BMD ($p = 0.0007$) was observed at 48 weeks in the non-ICET group. With respect to the ICET group combined with vitamin D3, the percentage of BMD decreased slightly, -3.07% , at 24 weeks, but increased 5.43% and 4.5% at 48 and 72 weeks, respectively. In the

Table 1. Background data in patients with RA.

| | ICET Group | Non-ICET Group | p |
|----------------------------|----------------|----------------|----|
| N | 31 | 32 | NS |
| Sex, male/female | 3/28 | 4/28 | |
| Age, yrs | 63.7 ± 4.5 | 64.1 ± 8.3 | NS |
| Steinbrocker stage | | | NS |
| I | 1 | 2 | |
| II | 2 | 2 | |
| III | 12 | 11 | |
| IV | 16 | 17 | |
| Taking Steroid, 5 mg/day | | | NS |
| Yes | 25 | 26 | |
| No | 6 | 6 | |
| Taking DMARD | | | NS |
| Bucillamine (BUC) | 10 | 13 | |
| Methotrexate (MTX) | 10 | 8 | |
| Salazosulfapyridine (SASP) | 3 | 2 | |
| D-penicillamine | 0 | 1 | |
| BUC + MTX | 2 | 1 | |
| MTX + mizoribine | 1 | 0 | |
| BUC + SASP | 0 | 1 | |
| None | 5 | 6 | |
| Taking Vitamin D3 | | | NS |
| Yes | 13 | 15 | |
| No | 18 | 17 | |

Table 2. Clinical results in the ICET and non-ICET groups before administration of etidronate disodium. Statistical analysis by Mann-Whitney U test.

| | ICET, n = 31 | Non-ICET, n = 32 | p |
|----------------------------|-------------------|-------------------|----|
| BMD (mm Al) | 1.510 ± 0.492 | 1.751 ± 0.576 | NS |
| DPD, nM/mM Cr | 9.78 ± 4.21 | 9.26 ± 5.28 | NS |
| BAP, (U/l) | 21.0 ± 8.8 | 23.6 ± 9.6 | NS |
| Larsen damage score | 38.3 ± 19.8 | 30.3 ± 12.9 | NS |
| Lansbury activity index, % | 30.4 ± 12.0 | 36.5 ± 18.2 | NS |
| CRP, mg/dl | 1.30 ± 1.51 | 1.65 ± 1.63 | NS |
| IL-6, pg/ml | 13.5 ± 13.1 | 16.2 ± 20.3 | NS |

other groups combined with vitamin D3, the percentage of BMD showed no increase.

The concentration of urinary DPD in all patients with RA before administration of etidronate was 9.55 ± 4.87 nM/mM Cr (Figure 1); in comparison, the level reported in osteoporotic Japanese patients was 5.3 ± 2.0 nM/mM Cr¹⁶. The DPD concentration in patients with RA was higher than that reported for osteoporotic patients. On the other hand, the level of BAP in RA patients was reported to be 22.9 ± 8.9 U/l — within the normal range (9.6 – 35.4 nM/mM Cr)¹⁷. This result suggests that bone resorption in our patients with RA was more accelerated compared with postmenopausal osteoporotic patients in Japan.

The percentage changes in urinary DPD (Figure 2) in the ICET group were -15.65% ($n = 31$), -15.05% ($n = 29$), -18.65% ($n = 25$), and -12.95% ($n = 27$) at 12, 24, 48, and 72 weeks after etidronate administration, respectively. In the non-ICET group the values were 6.4% ($n = 32$), 7.49% ($n =$

32), 13.42% ($n = 29$), and 11.51% ($n = 25$) at 12, 24, 48, and 72 weeks, respectively. A significant decrease was observed at 12 ($p = 0.0002$), 24 ($p = 0.0013$), 48 ($p = 0.0003$), and 72 weeks ($p = 0.0028$) in the ICET group, and the DPD concentrations decreased early after administration of etidronate.

The percentage changes in the Larsen damage score (Figure 3) based on radiographs from the ICET group were 0.2% ($n = 23$), 1.7% ($n = 29$), and 2.2% ($n = 25$) at 24, 48, and 72 weeks after etidronate administration, respectively. In the non-ICET group, the percentage changes in damage score were 4.0% ($n = 21$), 8.5% ($n = 31$), and 13.0% ($n = 27$) at 24, 48, and 72 weeks. Significant increases in the Larsen damage score were observed at 24 ($p = 0.0148$), 48 ($p = 0.0001$), and 72 weeks ($p < 0.0001$) in the non-ICET group.

As shown in Figure 4, in the ICET group, IL-6 concentrations were 13.5 ± 13.1 pg/ml ($n = 31$) before, and 11.8 ± 12.7 ($n = 29$), 11.2 ± 11.4 ($n = 25$), and 4.5 ± 6.1 pg/ml ($n = 27$) at 24, 48, and 72 weeks after etidronate administration,

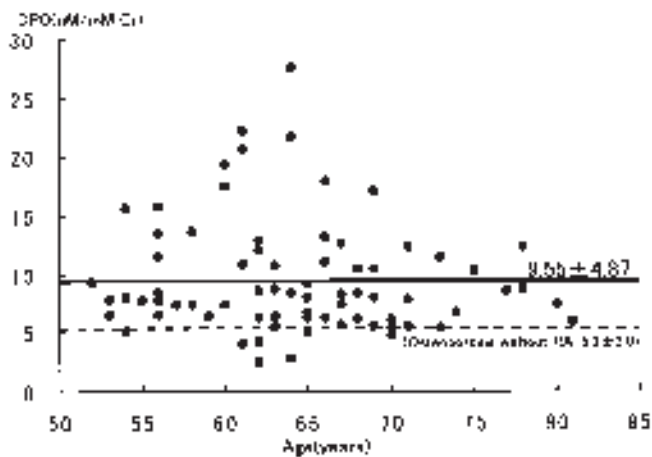


Figure 1. The concentration of urinary DPD in all patients with RA before administration of etidronate was 9.55 ± 4.87 nM/mM Cr; in comparison, the level reported in osteoporotic Japanese patients was 5.3 ± 2.0 nM/mM Cr¹⁶.

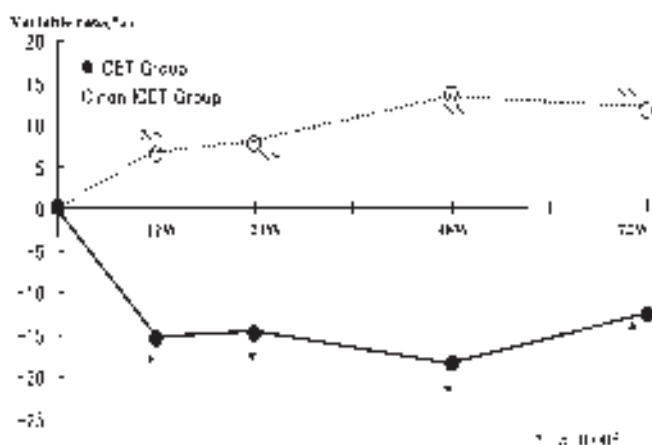


Figure 2. Concentrations of urinary DPD in the ICET group at 24, 48, and 72 weeks after etidronate administration and the non-ICET group. In the ICET group, there was a significant decrease in the level of IL-6 ($p = 0.0187$) at 72 weeks compared with baseline.

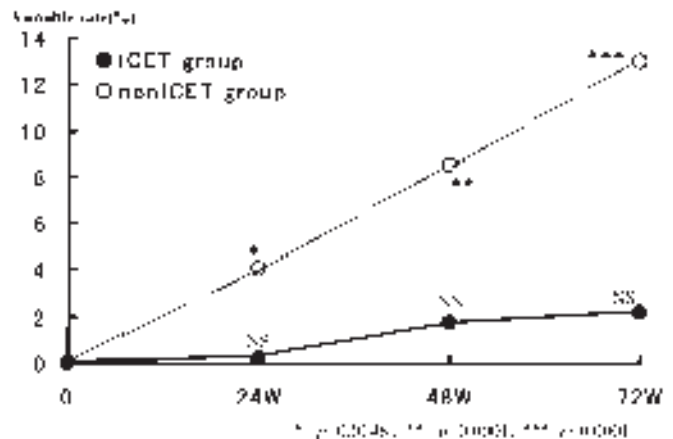


Figure 3. Percentage changes in Larsen damage score based on radiographs in the ICET group at 24, 48, and 72 weeks after administration of etidronate and the non-ICET group. Significant increases in the Larsen damage score were observed in the non-ICET group.

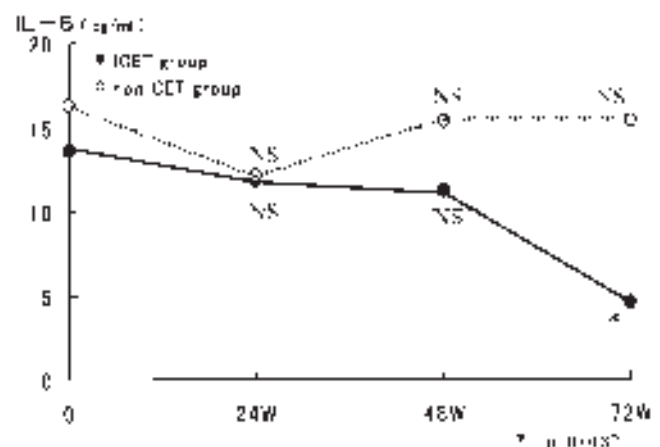


Figure 4. Changes in IL-6 concentration in the ICET group at 24, 48, and 72 weeks after administration of etidronate and the non-ICET group. In the ICET group, there was a significant decrease in IL-6 at 72 weeks.

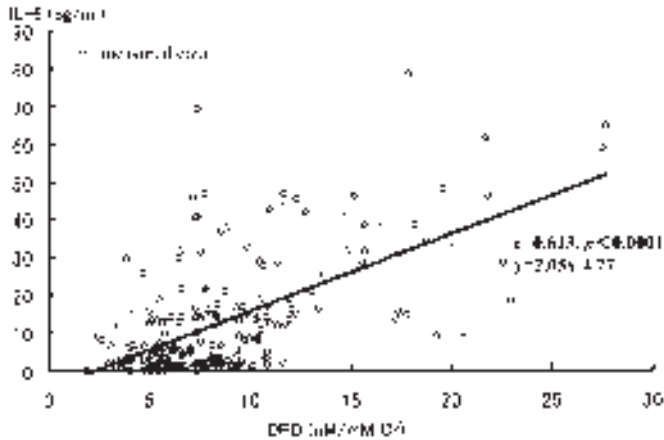


Figure 5. There was a significant correlation between IL-6 and DPD concentrations in patients with RA ($r = 0.613$, $p < 0.0001$).

respectively. A statistically significant decrease in the IL-6 level ($p = 0.0187$) was observed when the level at 72 weeks after etidronate administration was compared with that before administration. In the non-ICET group, IL-6 levels were 16.2 ± 20.3 pg/ml ($n = 32$) before, and 12.2 ± 15.3 ($n = 32$), 15.4 ± 16.6 ($n = 29$), and 15.4 ± 16.3 pg/ml ($n = 25$) at 24, 48, and 72 weeks, suggesting that the level tended to increase with time.

The percentage changes in Lansbury index in the ICET group were 1.68% ($n = 28$), 1.36% ($n = 28$), and 2.04% ($n = 27$) at 24, 48, and 72 weeks. In the non-ICET group, the percentage changes in Lansbury index were -4.29% ($n = 32$), -4.47% ($n = 32$), and 0.81% ($n = 31$) at 24, 48, and 72 weeks. No significant change in Lansbury index was observed in either group at any time point.

In the ICET group, CRP concentrations were 1.88 ± 2.49 , 1.64 ± 1.89 , and 1.44 ± 2.13 mg/dl at 24, 48, and 72 weeks after etidronate administration, respectively. In the non-ICET group, CRP levels were 1.92 ± 2.90 , 2.10 ± 2.64 , and 2.08 ± 2.46 mg/dl at 24, 48, and 72 weeks. No significant differences were observed when each level was compared with that before etidronate administration. Concentrations of BAP did not change significantly for either group throughout the study.

A significant correlation between the IL-6 and DPD concentrations was observed in patients with RA ($r = 0.613$, $p < 0.0001$) (Figure 5).

DISCUSSION

Based on BMD measurement by the microdensitometry method, a significant decrease in the percentage of BMD ($p = 0.0007$) was observed at 48 weeks in the non-ICET group. In the ICET group, a decrease in the bone mass was observed transiently 24 weeks after administration; however, the bone mass increased between 48 and 72 weeks after administration. Masud, *et al*¹⁸ have reported that ICET

combined with vitamin D3 increased BMD in postmenopausal osteoporotic women; in our study patients, ICET combined with vitamin D3 prevented a further decrease in BMD from 48 to 72 weeks after etidronate administration. It has been reported that ICET maintains or increases BMD in patients with osteoporosis induced by adrenal corticosteroid^{1,2,6-9}, which is also true for postmenopausal osteoporosis⁴. BMD can be easily measured by the microdensitometry method; however, this method cannot always indicate bone mass, since the metacarpal bone density is also measured.

In the group that received etidronate in combination with vitamin D3, urinary DPD, a bone resorption marker, decreased compared with the group that received only vitamin D3¹⁹. Urinary DPD started to decrease significantly 12 weeks after etidronate administration in the ICET group, whereas no significant decrease was seen in the non-ICET group.

BAP aids bone formation; Hall, *et al*²⁰ administered hormone replacement therapy to postmenopausal RA patients with osteoporosis; they measured concentrations of BAP, and reported that they observed no significant changes in their study group. Our results are in agreement with those of Hall, *et al*²⁰, suggesting that ICET inhibits bone resorption, with only minimal influence on bone formation.

In the non-ICET group, significant increases in the Larsen damage scores were observed at 24, 48, and 72 weeks, based on the radiographs of fingers. On the other hand, in the ICET group, no significant increase in the Larsen score was observed between the score at each time point and that before administration of etidronate. Eggelmeijer, *et al*²¹ administered a single dose of pamidronate to patients with RA, and reported that clinical scores improved and the number of swollen joints decreased. In addition, etidronate inhibited bone destruction that was observed in the vicinity of swollen joints using experimentally developed arthritis models²². The Ritchie articular index of these patients with RA improved 24 weeks after administration of etidronate disodium²³. Nagaoka, *et al*²⁴ evaluated RA patients before and 24 weeks after etidronate administration, and reported that scores for joints were significantly improved. Our results suggest that the Larsen damage score for fingers did not increase in the ICET group. This finding supports the aforementioned observations^{23,24}, suggesting that administration of etidronate disodium inhibits destruction of joints in arthritis models by inhibiting bone resorption by osteoclasts, and the same results were observed in patients with RA as well as in arthritis models.

Concentrations of ESR and CRP were not improved in RA patients who took etidronate disodium^{23,25}. Bird, *et al*²³ reported that a trend of modest improvement in some biochemical measures including CRP in some patients during 16–24 weeks may suggest improvement after 6

months. Ralston, *et al*²⁵ reported there was no significant effect of aminobisphosphonate on disease activity and clinical and biochemical measures in 2 groups of RA patients except for improvement of the articular index. The joint score as well as the articular index/damage score of joints improved on radiographs. However, other clinical or biochemical variables as well as CRP or IL-6 level may gradually decrease at 48 weeks after etidronate administration. Nagaoka, *et al*²⁴ compared the ACR score and Lansbury index before and 24 weeks after etidronate administration and observed no significant improvements in these levels between the 2 periods.

It has been reported that production of IL-6, an inflammatory cytokine, was inhibited by etidronate *in vitro*^{26,27}. Our observations with RA patients revealed that production of IL-6 was significantly inhibited *in vivo* at 72 weeks after etidronate administration. With respect to the positive correlation between IL-6 and CRP levels²⁸, our result is explainable.

Al-Awadhi, *et al*²⁹ was the only group that studied concentrations of both serum IL-6 and urinary DPD. In this study, we observed that the levels of IL-6 and DPD in the active RA group were significantly higher than those in the suppressed RA and controlled groups. On the other hand, Furumitsu, *et al*³⁰ reported a positive correlation between the levels of IL-6 in synovial fluid and urinary DPD.

Perhaps most importantly, we observed a significant correlation between levels of IL-6 and urinary DPD, suggesting that both are inhibited by intermittent cyclical etidronate therapy. These results suggest the possibility that ICET inhibited the inflammatory activity of RA, thereby preventing destruction of joints that is concomitant with RA. This hypothesis is supported by our finding of reduced Larsen damage scores in the ICET group.

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