Comparison of two formulations of botulinum toxin type A for the treatment of glabellar lines: A double-blind, randomized study

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Background: Different formulations of botulinum toxin type A can behave differently. There has been little clinical research directly comparing formulations.

Objective: We sought to compare the efficacy and tolerability of two botulinum toxin type A formulations—BoNTA[1] and BoNTA[2]—in the treatment of moderate and severe glabellar lines.

Methods: Sixty-two patients with moderate or severe glabellar lines at maximum contraction were randomly assigned to receive 20 U of BoNTA[1] or 50 U of BoNTA[2] (20% in the procerus muscle, 80% in the corrugator muscles).

Results: The incidence of 1-grade improvement or greater in glabellar line severity at maximum contraction was as follows: 77% (BoNTA[1]) versus 59% (BoNTA[2]) at week 12, 53% versus 28% at week 16. The estimated incidence of relapse was 23% (BoNTA[1]) versus 40% (BoNTA[2]) at week 16. Both formulations were similarly well tolerated.

Limitations: Few male and non-Caucasian subjects were studied.

Conclusion: BoNTA[1] offered more prolonged efficacy than BoNTA[2] in the treatment of glabellar lines at the dose ratio of 2.5:1 (BoNTA[2]:BoNTA[1]) used in this study. (J Am Acad Dermatol 2006;55:975-80.)

Hyperkinesis of the muscles in the glabellar region of the forehead contributes to the development of glabellar frown lines, and temporary paralysis of these muscles can reduce the appearance of such lines. Botulinum toxin type A is effective in inducing such paralysis through its ability to block the presynaptic release of acetylcholine.

The efficacy of botulinum toxin type A in the treatment of glabellar lines is now well documented in the literature.[1-5] There are two formulations available—botulinum toxin type A (BoNTA[1]) (Botox, Allergan, Inc, Irvine, Calif) and BoNTA[2] (Dysport, Ipsen Ltd, Slough, UK). BoNTA[1] is currently available in both the United States and Europe and BoNTA[2] is currently available in Europe but not in the United States. These formulations behave in distinctly different ways electrophysiologically and clinically,[6] and results obtained with one formulation cannot be extrapolated to the other.[7,8] There has been little clinical research directly comparing the two formulations in the treatment of glabellar lines, although a recent pilot study compared 20 U of BoNTA[1] with 50 U of BoNTA[2].[9] A trend toward greater efficacy was observed in favor of 20 U of BoNTA[1].

We present the results from a larger comparison of the efficacy and tolerability of BoNTA[1] and BoNTA[2] in the treatment of moderate and severe glabellar lines. These results extend the findings from the earlier pilot study.

From Cranley Clinic, London,[a] and Clinical Research Specialists, Santa Monica.[b]

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METHODS

Patients were eligible to enroll in this double-blind, randomized, parallel-group study if they had moderate or severe glabellar lines at maximum contraction (graded by the investigator using a scale of none, mild, moderate, or severe) and were 18 to 55 years of age. Female patients of childbearing potential were required to have a negative urine pregnancy test result.

Patients were excluded from the study for any of the following reasons: facial cosmetic procedure planned during the study; visible scars or prior cosmetic procedures that could interfere with the evaluation of response; marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or an inability to substantially lessen glabellar lines even by physically spreading them apart; myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuromuscular function; use of an aminoglycoside antibiotic, curare-like agent, or other agent that might interfere with neuromuscular function; profound atrophy or excessive weakness of the muscles in the target injection areas; history of facial nerve palsy; systemic infection or an infection at the injection site; recent evidence of alcohol or drug abuse; participation in an investigational drug study in the preceding 30 days; and treatment with any botulinum toxin serotype in the preceding 12 months.

Patients were enrolled by Drs N. and P. Lowe, and the study was performed in a private practice experienced in conducting dermatologic research (Cranley Clinic). The study was approved by the relevant institutional review boards and conducted according to the principles of the Declaration of Helsinki. All patients signed informed consent.

Treatment regimen

Patients were randomly assigned to receive one of the following: BoNTA[1], 20 U (the dose of this formulation that has been approved by the Food and Drug Administration for the treatment of glabellar lines)[10] or BoNTA[2], 50 U (reported to be the optimal dose of this formulation).[4]

Each dose was divided between 5 injections—one in the procerus muscle and two in each corrugator muscle. All were placed within the mid-pupillary lines and the lateral-most injections in the corrugator muscle were at least 2 cm above the brow line. Each injection was 0.1 mL (total of 0.5 mL per product).

Patients were allowed to continue use of their usual facial products providing they had already been using them for 6 months before starting the study. They were required to refrain from applying facial cosmetics in the 4 hours preceding study visits.

Efficacy outcome measures

At each visit (baseline and weeks 2, 8, 12, and 16), patients' glabellar lines were photographed (using a modified Canfield system) during maximum attempted muscle contraction. The severity of the lines was then graded as none, mild, moderate, or severe. The primary outcome measure was the incidence of at least 1-grade improvement in the severity of the glabellar lines evaluated by the investigator from photographs taken at week 16. Other outcome measures included the incidence of patients whose glabellar line severity was graded as none or mild at maximum contraction, and the incidence of relapse (return of glabellar line severity to baseline levels for two consecutive visits).

Patient satisfaction outcome measures

Patients rated their feelings of attractiveness, and their feelings of satisfaction with their appearance, on a 7-point scale where 0 = not at all and 7 = extremely.

Randomization and masking

An independent clinical research organization provided a computer-generated randomization code, in block sizes of 6, that determined treatment assignments for each individual. "Randomization cards" were prepared, each of which was labeled with the randomization number and contained the treatment assignment. These were kept in a secure location and neither the investigator nor the patients had access to them or their contents. The treatment assigned to each patient was determined at the baseline visit by a pharmacist who opened the card with the lowest available randomization number in order to discover the treatment assignment and then prepared the appropriate syringe. The investigator and the patients were masked as to which product was being used—the syringes were identical in appearance and the volume to be injected was the same regardless of the product.

Statistical analyses

It was calculated that a sample size of 62 subjects was required to be enrolled in this study to detect a 35% difference between groups in the percentage of patients who had relapsed by week 12. This assumed a two-sided test, an alpha of 0.05, 80% power, and a 5% dropout rate.

Data were analyzed on an intent-to-treat basis. A chi-square or Fisher exact test was used to evaluate between-group differences in the incidence of patients with at least a 1-grade improvement from baseline in glabellar line severity, the incidence of patients with glabellar line severity of none or mild, and the incidence of treatment-related adverse

effects. The estimated incidence of relapsers (ie, patients whose glabellar line severity had returned to baseline levels for two consecutive visits) was calculated by adjusting the actual incidence of relapse in completing patients for censored observations (from patients lost to follow-up). The Wilcoxon rank sum test was used to evaluate between-group differences in mean scores for feelings of attractiveness and feeling of satisfaction with appearance.

RESULTS

Patients

A total of 62 patients were enrolled, of whom 59 (95%) completed the study (Fig 1). No patient discontinued because of lack of efficacy or adverse effects and one each discontinued for personal reasons, withdrawal of consent, and need for surgery. The first patient was enrolled in May 2003 and the last patient exited the study in March 2005.

The patients' mean age was 41 years (range, 27-60 years) and they were predominantly Caucasian (97%) and female (90%). The BoNTA[1] group was significantly older than the BoNTA[2] group (44 ± 7.3 [standard deviation] vs 39 ± 6.6 years), but there were no other significant between-group differences in demographic details. The baseline photography showed that the BoNTA[1] group comprised 15 of 31 patients (48%) with moderate glabellar lines and 16 patients (52%) with severe glabellar lines. In the BoNTA[2] group, 17 of 31 patients (55%) had moderate glabellar lines and 14 (45%) had severe glabellar lines at baseline.

Efficacy

The incidence of patients with at least a 1-grade improvement in the severity of their glabellar lines at maximum contraction peaked at week 8 in both groups (Fig 2). However, the duration of this improvement was generally more prolonged with BoNTA[1] than with BoNTA[2]—the overall incidence of such improvement was 77% versus 59% at week 12 and 53% versus 28% at week 16 (Figs 2 and 3). In addition, at week 16, the incidence of patients whose glabellar line severity was none or mild was 23% versus 10% for all patients (not statistically significant) and 50% versus 13% ($P = .05$) for patients with moderate glabellar lines at baseline (Fig 4).

At week 16, the estimated incidence of relapsers was 23% (95% confidence interval [CI], 11.5%-41.6%) with BoNTA[1] and 40% (95% CI, 25.2%-60.1%) with BoNTA[2] (Fig 5).

Patient satisfaction

Throughout the 16-week follow-up, patients' mean scores for how attractive they felt and how satisfied they felt with their appearance were consistently higher with BoNTA[1] than BoNTA[2], with statistical significance achieved for both at week 12 (Figs 6 and 7).

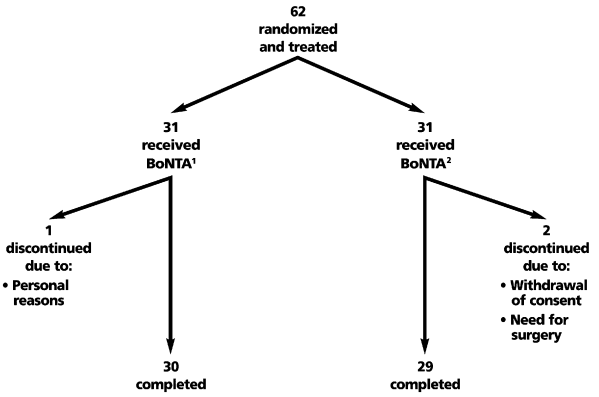

Fig 1. Flow of patients through the study.

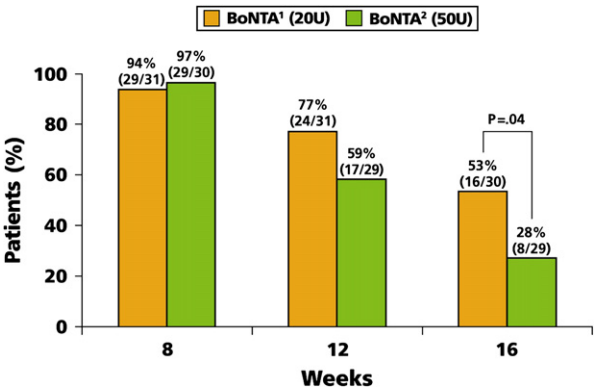

Fig 2. Incidence of at least 1-grade improvement from baseline in glabellar line severity at maximum contraction.

Tolerability

Both products were well tolerated. The only adverse events probably or definitely related to treatment were bruising (3 with BoNTA[1], 2 with BoNTA[2]) and a temporary lump on the forehead (1 with BoNTA[1]). There was no significant between-group difference in the incidence of treatment-related adverse effects.

DISCUSSION

Using masked assessment of standardized photographs—one of the most objective means of evaluating glabellar line severity—it was shown that BoNTA[1] offers more prolonged efficacy than BoNTA[2] when the two products were compared in a 2.5:1 dose ratio (BoNTA[2]:BoNTA[1]). A similar study protocol has also shown more prolonged efficacy with 20-U BoNTA[1] relative to 1000 U or 2000 U of a type B botulinum toxin.[5]

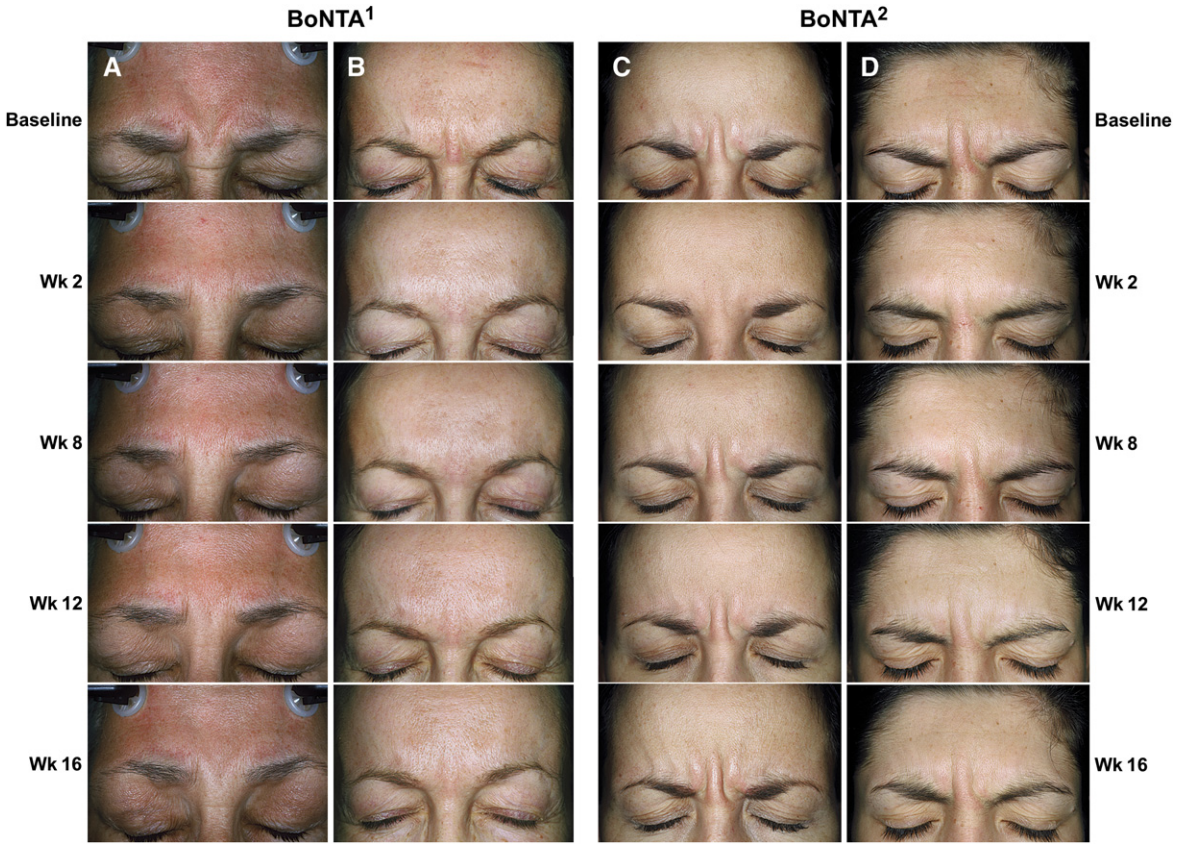

Fig 3. More prolonged duration of improvement with BoNTA[1] (patients **A** and **B**) than BoNTA[2] (patients **C** and **D**).

Consensus guidelines suggest that an appropriate dose of BoNTA[1] for treating glabellar lines in female patients is 20 to 30 U.[11] Within this range, the 20-U dose may be more appropriate for moderate glabellar lines and the 30-U dose may be more appropriate for severe glabellar lines. If the patients in this study with severe glabellar lines had been treated with relatively higher doses of botulinum toxin type A (to promote optimal efficacy), it is possible that statistical significance would have been obtained at the study end point in the "all patients" comparison of the incidence of patients with glabellar line severity of "none" or "mild" (Fig 4, *A*)—just as it was in the subgroup comparison involving only patients with moderate glabellar lines at baseline (Fig 4, *B*). Further research is warranted to explore how the optimal dose of botulinum toxin type A may vary depending on the severity of glabellar lines.

The results of this study also showed that mean patient ratings of feelings of attractiveness, as well as feelings of satisfaction with appearance, were significantly higher with BoNTA[1] than BoNTA[2] at week 12. This is noteworthy because, although a subjective measure, patient judgment is of utmost importance in the evaluation of cosmetic treatments.[4]

A previous pilot study showed a similar result comparing the same doses of these two botulinum toxin type A preparations.[9] In addition, another study has compared a higher dose ratio of these formulations in the treatment of glabellar and other facial wrinkles.[12] A 4:1 ratio of BoNTA[2]:BoNTA[1] resulted in comparable efficacy between the two products, but BoNTA[2] was associated with a significantly higher incidence of complications (lagophthalmos, tingling sensation, and temporary lid swelling) than BoNTA[1] (100% vs 36%; $P < .05$).[12]

The inherent differences between the two formulations in migration and electrophysiologic characteristics means that it is not possible to propose a single dose conversion ratio.[6,8] However, BoNTA[1] appears to offer clinical superiority with a dose ratio of both 2.5:1 and 4:1. At the 2.5:1 dose ratio, the results of the study presented herein suggest that BoNTA[1] offers more prolonged efficacy (and comparable tolerability) relative to BoNTA[2]. The data suggest that the dose of BoNTA[2] may need to be higher than the 50-U dose suggested for the treatment of glabellar lines to achieve a duration of effect and level of patient satisfaction that is comparable with BoNTA[1].[4] However, as mentioned above, a 4:1

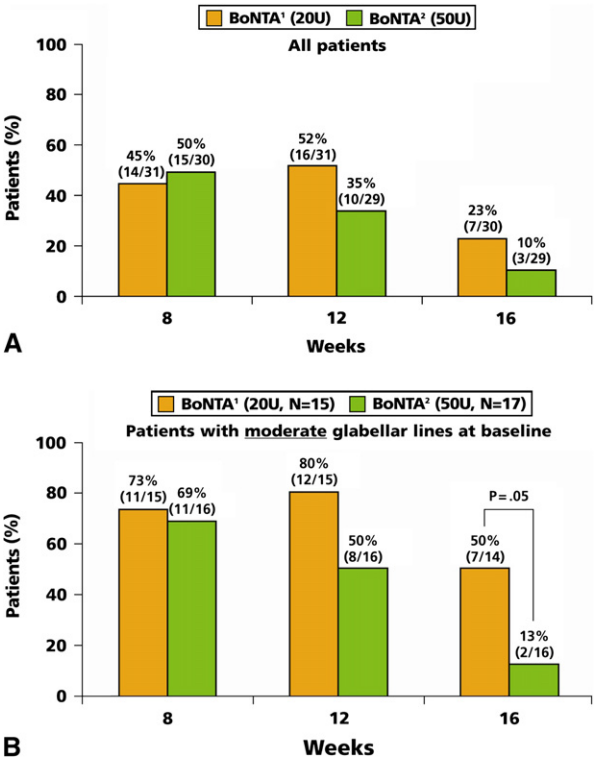

Fig 4. Incidence of patients with glabellar line severity of none or mild at maximum contraction in all patients (**A**) and in patients with moderate glabellar lines at baseline (**B**).

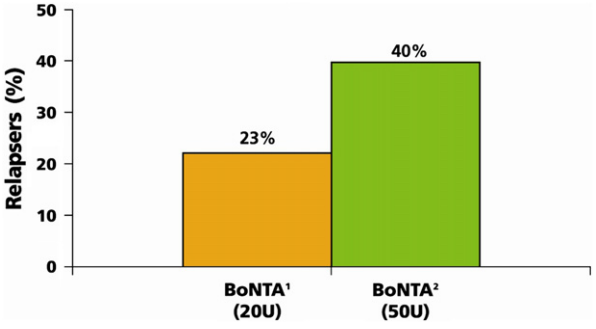

Fig 5. Estimated incidence of relapsers at week 16 (ie, patients whose glabellar line severity had returned to baseline levels for two consecutive visits).

dose ratio has been associated with a significantly higher incidence of adverse effects with BoNTA[2] than with BoNTA[1].[12] Further dose escalation studies are needed to determine the optimal dose ratio.

As a consequence of the greater degree of migration with BoNTA[2] relative to BoNTA[1], it has been suggested that the lateral-most injections of BoNTA[2] should be higher than the other sites and than the sites used for BoNTA[1] injections, so that the potential for ptosis is minimized. However, the potential benefit of this has not been determined in controlled trials. Nevertheless, because of this, the injection

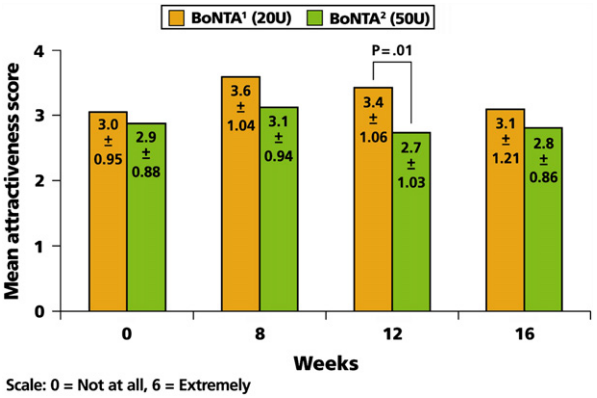

Fig 6. Mean scores for feelings of attractiveness.

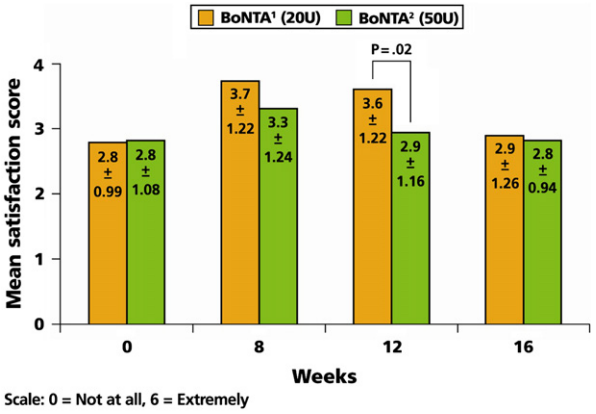

Fig 7. Mean scores for feelings of satisfaction with appearance.

sites used in some BoNTA[2] studies are not identical to those used in BoNTA[1] studies. To ensure that our study was rigorously controlled and double-blind, it was essential that we use identical sites for both agents; our injection sites were therefore selected to be clinically acceptable for both agents. The fact that there was no significant between-group difference in the incidence of treatment-related adverse effects suggests that the sites selected were in fact clinically appropriate.

As well as the differences in migration and electrophysiologic characteristics previously mentioned, the two formulations also differ in neurotoxin protein content—with BoNTA[1] resulting in relatively lower exposure to neurotoxin protein than BoNTA[2] (~5 ng neurotoxin protein/100-U vial of BoNTA[1] and 12.5 ng neurotoxin protein/500-U vial of BoNTA[2]). Theoretically, this results in a lower potential for the development of antibodies against botulinum toxin (which can result in loss of efficacy) with BoNTA[1] than with BoTNA[2]. No obvious differences in the antigenicity of botulinum toxin type A preparations have been detected to date,[13] and this

study was not designed to observe any such difference. A longer term and repeat treatment study incorporating an assay for botulinum toxin antibodies would be required to demonstrate whether or not any difference exists because antibodies develop in very few patients. In addition, antibodies are even less likely to occur in patients receiving the relatively low doses used in aesthetic therapy than in those receiving the higher doses that are required for treating some medical conditions, such as cervical dystonia.

Pain has been reported to be greater with botulinum toxin type B than with botulinum toxin type A,[14] and this has been attributed to the lower pH of the type B formulation (5.6 compared with ~7 with BoNTA[1] and BoNTA[2]). In the study presented herein, no patient reported pain as an adverse event and the pain of injection was not specifically evaluated. However, we have no reason to anticipate any differences between BoNTA[1] and BoNTA[2] in the perception of pain as both formulations have the same pH.

It is difficult to compare the costs of the two formulations as BoNTA[2] is not available in the United States. Furthermore, the price of both formulations varies from country to country. Based on current prices in the United Kingdom, the cost of one 100-U vial of BoNTA[1] is £128.93 and the cost of one 500-U vial of BoNTA[2] is £153.20 (although the latter is supplied only in pairs of vials at twice this cost). At the time of the study, BoNTA[1] was not approved for the treatment of glabellar lines in the United Kingdom; however, subsequently the formulation has been approved and is available from the same company under a different brand name for this indication. The cost quoted above for BoNTA[1] is for the formulation used in this study (which is approved for the treatment of certain therapeutic uses but not glabellar lines.) The cost of the formulation now available for the treatment of glabellar lines is £85 for a 50-U vial. Cost comparisons relative to the units of product actually used in this or other studies cannot be made as the vials are designated for single use only. As a result, the cost of treating glabellar lines specifically may also depend on whether or not the patient receives injections of botulinum toxin type A in other facial lines at the same treatment session.

In conclusion, the results of this study confirm those from a previous pilot study and show that, at the dosages studied, BoNTA[1] offers more prolonged efficacy and higher levels of patient satisfaction than BoNTA[2] in the treatment of glabellar lines.

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