TRANSLATION

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Percutaneous Rheumatic Monotherapy: An Alternative to Oral Therapy?

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Summary:

A multicentre Phase IV study was carried out to investigate whether in patients suffering from soft tissue rheumatism and moderately activated arthrosis the local therapy alone with an ibuprofen 5 % cream is sufficient to alleviate or even completely relieve the complaints without any oral co-medication.
It was shown that in 14,107 patients with severe pain and restricted movement the 3 times daily topical application of the cream for 14 days was sufficient to achieve a highly significant improvement of pain at rest, tenderness on pressure, pain on movement, active and passive movement restriction. The effect on joint swelling was also good.
In more than 50 % of the cases assessed the onset of action was observed within ½ h; same applies to pain relief. Improved movement was achieved within 1 h in 50 % of the patients in whom this parameter was evaluated.
Both the local and systemic tolerability were good. The incidence of side effects was 1.6 %.

Keywords: Percutaneous rheumatic therapy

Ibuprofen, an NSAID of the propionic acid derivatives group, is being worldwide used as an oral analgesic and antiphlogistic agent. Moreover, multiple controlled clinical trials furnished the evidence of the relevant therapeutic efficacy of a topical 5 % pharmaceutical form, documenting the excellent percutaneous penetrability. In the last years two phase IV studies on about 7000 patients were carried out with the ibuprofen 5 % cream (Dolgit Cream)*. The main purpose of these studies was to monitor the tolerability over a 14-day application period. With an incidence of side effects of about 2 %, previously assessed findings of controlled trials carried out on smaller numbers of patients could be entirely confirmed. No systemic side effects were observed (4, 11).

A third multicentre field study which was carried out in 1988 in the North of the Federal Republic of Germany had therefore the aim of ascertaining the onset of action of the cream on a limited group of patients in two indications: sports and accident-related injuries and soft tissue rheumatism.

In more than half of the cases the onset of action could be assessed 30 - 60 minutes after application of standardized doses of 3 x 8 g = 3 x 400 mg ibuprofen per day in cream form (9).

* *Manufacturer: DOLORGIET Pharmaceuticals*
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In 1989 a fourth study was carried out according to the Medicines` Act `76, Art. 67, para. 6, as post-marketing surveillance.

1338 case reports from 232 orthopaedists in private practice were submitted for evaluation. The purpose of this study was to assess whether patients suffering from soft tissue rheumatism, such as lumbo-ischialgia and cervical syndrome, or moderately activated arthrosis, could be treated with Dolgit Cream *alone*.

In two thirds of the cases oral NSAIDs were no more necessary (1).

Formulated Question: Whether Percutaneous Rheumatic Therapy Alone is Sufficient

Purpose of this study was to investigate whether the percutaneous therapy alone with an ibuprofen 5 % cream is sufficient in the above-mentioned indications to rapidly alleviate pain and improve mobility in such a way as to render oral treatment dispensible.
A 14-day duration of treatment was scheduled and only standardized cream doses were to be applied.

The study protocol was approved by an ethical committee. All patients were briefed on the aim and significance of the study, taking into consideration the benefit/risk ratio, and gave their written consent to participate.

MATERIAL AND METHOD

Design of the Study

For this post-marketing research a case record form was drawn up according to the above-mentioned requirements. Only patients suffering from non-acute soft tissue rheumatism, e.g. lumbo-ischialgia or cervical syndrome, and moderately activated arthrosis, were to be treated with the test preparation ibuprofen 5 % cream.

Contraindications were: patients under 18 and over 65 years, pregnancy, lactation, allergic diathesis, fractures, open wounds, hypersensitivity to ibuprofen or other NSAIDs and hypersensitivity to propylene glycol and 4-hydroxy benzoic acid methylester.

The standardized dosage should amount to 200 mg ibuprofen 3 times per day, each corresponding to a 10 cm strip of cream, to be applied to the affected part of the body and broadly rubbed in. The standard duration of treatment should be of 14 days.

Concomitant medication with oral, parenteral, topical analgesic, antiphlogistic agents was to be excluded.

The symptoms were rated according to a scale ranged from 0 - 4. Pain at rest, tenderness on pressure, pain on movement, active and passive movement restriction, joint swelling, hematoma and morning stiffness were to be rated according to this evaluation scale before therapy as well as after 3, 7 and 14 days of percutaneous treatment.

Under proper application according to instructions, side effects were to be reported also stating the day of treatment on which same occurred. Subsequently, general and skin tolerability were to be evaluated.

In the first place, however, the onset of action, pain relief, regression of movement restriction were to be evaluated in the course of time; for this purpose recordings after 1/4, 1/2, 1, 2 h and later were possible. Finally, the overall efficacy from "good" to "poor" was to be rated according to a 4-score scale.

Statistical Method

All case record forms received were examined and the cases which did not comply with the scheduled implementation of the trial were discarded. From the actual evaluation those cases were eliminated, in which the admission and/or exclusion criteria were not complied with, or concomitant medication with analgesic and antirheumatic agents was ascertained as well as cases of premature discontinuation of therapy and those where the data on the indication for admission were missing.

Code lists were set for the open symptomatology ranges. The evaluation was carried out by means of electronic data processing separately for each indication, i.e. patients suffering from soft tissue rheumatism and patients suffering from moderately activated arthrosis.

With regard to the quantitative personal data, such as age, height, body weight, the following parameters were additionally calculated: arithmetic mean value, standard deviation and median. The course of each individual complaint was tested for significance for each of the two indications separately. As statistical method the Wilcoxon Matched-Pairs Signed-Ranks Test was applied, whereby the values measured before treatment were compared with those measured after 3, 7 and 14 days. Further, the values of the 3rd day were compared with those of the 7th and 14th day and the values of the 7th day with those of the 14th day.

In total 16,313 case record forms were at hand for the overall evaluation. 2206 case reports = 13.5 % could not be included in the overall evaluation, as same did not comply with the aforementioned criteria of the scheduled implementation of the trial. Consequently, the results of 14,107 male and female patients could be included in the overall evaluation.

More than 2700 physicians in private practice, mainly general practitioners, internists and also orthopaedists, participated in the present post-marketing research.

Diagnoses

In the 14,107 cases covered by the overall evaluation, the indications for admission to the study were soft tissue rheumatism in 10,135 patients = 71.8 % and moderately activated arthrosis in 3,975 patients = 28.2 %.

The diagnosis "soft tissue rheumatism" was represented as follows: lumbo-ischialgia 36.7 %, cervical syndrome 30.8 %, tendopathy and tendovaginitis 9.2 % and shoulder/ arm syndrome 8.4 %.

In the patients suffering from moderately activated arthrosis the diagnoses given were mainly gonarthrosis 53.3 % and arthrosis 23.2 %, which means that in 76.5 % mainly gonarthrosis, uni and bilateral, was assessed (2).

Results

As shown from the statistical tests over the time, all eight symptoms to be judged according to the evaluation scale ranged from 0 - 4 scores, improved significantly by the topical therapy alone with the ibuprofen 5 % cream for 14 days.

The symptoms pain at rest and active movement restriction, which are particularly difficult to influence therapeutically, are to be judged in their course as follows: It is shown that 87 % of the patients suffering from soft tissue rheumatism and 79 % of those suffering from moderately activated arthrosis had pain at rest before therapy.

This pain at rest was "severe" to "very severe" in 33 % of the patients with soft tissue rheumatism and in about 27 % of those with moderately activated arthrosis.

Already after 3 days about 15 % of the patients with soft

tissue rheumatism and 12 % of those with moderately activated arthrosis were symptom-free. The percentage of the "very severe" to "severe" complaints had decreased to about 8 % in both groups. On the 7th day it was evident that 43 % of the patients of the soft tissue rheumatism group and 35 % of the patients of the moderately activated arthrosis group were symptom-free. At this time "very severe" to "severe" complaints were present only in about 2 - 2.5 % of the cases in both diagnosis groups.

On the 14th day 69 % of all the patients of the soft tissue rheumatism group and 58 % of the patients of the arthrosis group were symptom-free, the "very severe" to "severe" complaints had almost disappeared.

Before therapy 89 % of the patients of both treatment groups suffered from active movement restriction. The intensity prior to the treatment was "very severe" to "severe" in about 53 % of the soft tissue rheumatism group and in about 42 % of the arthrosis group. After 3 days about 5 % of the patients in both groups were symptom-free. The "very severe" to "severe" complaints had decreased already to about 18 % in both treatment groups. Already on the 7th day, 28 % of the soft tissue rheumatism group and 17 % of the arthrosis group were symptom-free. The severe pain had decreased to 4 % in both treatment groups. On the 14th treatment day over half of the patients in the soft tissue rheumatism group were symptom-free and, diagnosis-dependent, only 37 % in the arthrosis group.

The Wilcoxon test applied for the examination of the statistical significance led to the following results:

Both pain at rest and active movement restriction showed already on the 3rd day an obvious improvement compared to the degree of severity before the therapy ($p < 0.001$). Further, on the 7th and 14th day an obvious improvement could be proved in both patient groups in comparison with the intensity on the 3rd day ($p < 0.001$).

A highly significant improvement was also assessed in the 14-day treatment period as to all other symptoms, such as tenderness on pressure, pain on movement, passive movement restriction, joint swelling, hematoma and morning stiffness. A significant improvement could be assessed already on the 3rd day.

Figures 1, 2 and 3 illustrate onset of action, pain relief and regression of movement restriction in the course of time. It is shown that within half an hour more than 50 % of the total of 11,093 patients of both treatment groups felt the onset of action. Same applies to pain relief, whereby for this parameter data of a total of 10,887 patients were at hand. Also here in the cases of soft tissue rheumatism more than 53 % assessed pain relief within half an hour and in the arthrosis group about 47 %. Regression of movement restriction, with reference to 8362 cases, was assessed within half an hour by 34 % of the patients in the soft tissue rheumatism group and 31 % of those in the arthrosis group, i.e. over 50 % of the patients assessed

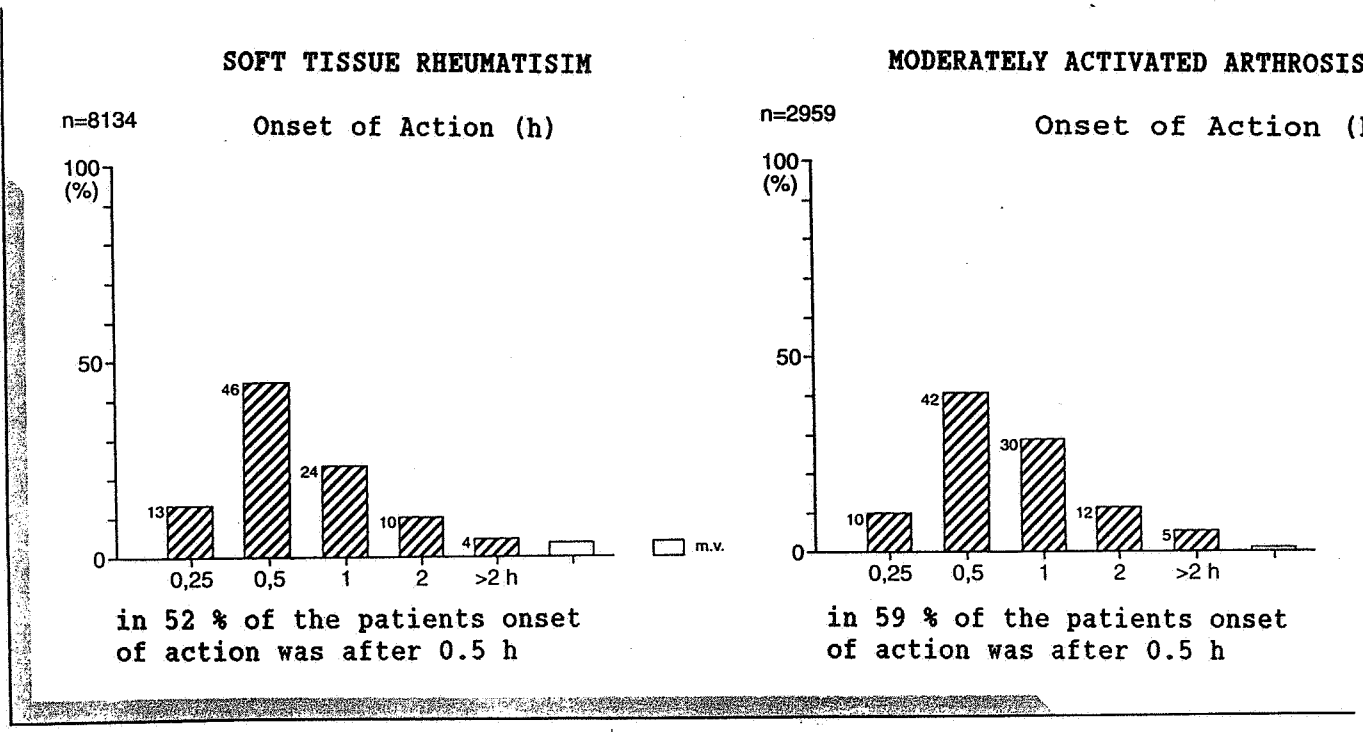

Figure 1 Onset of Action

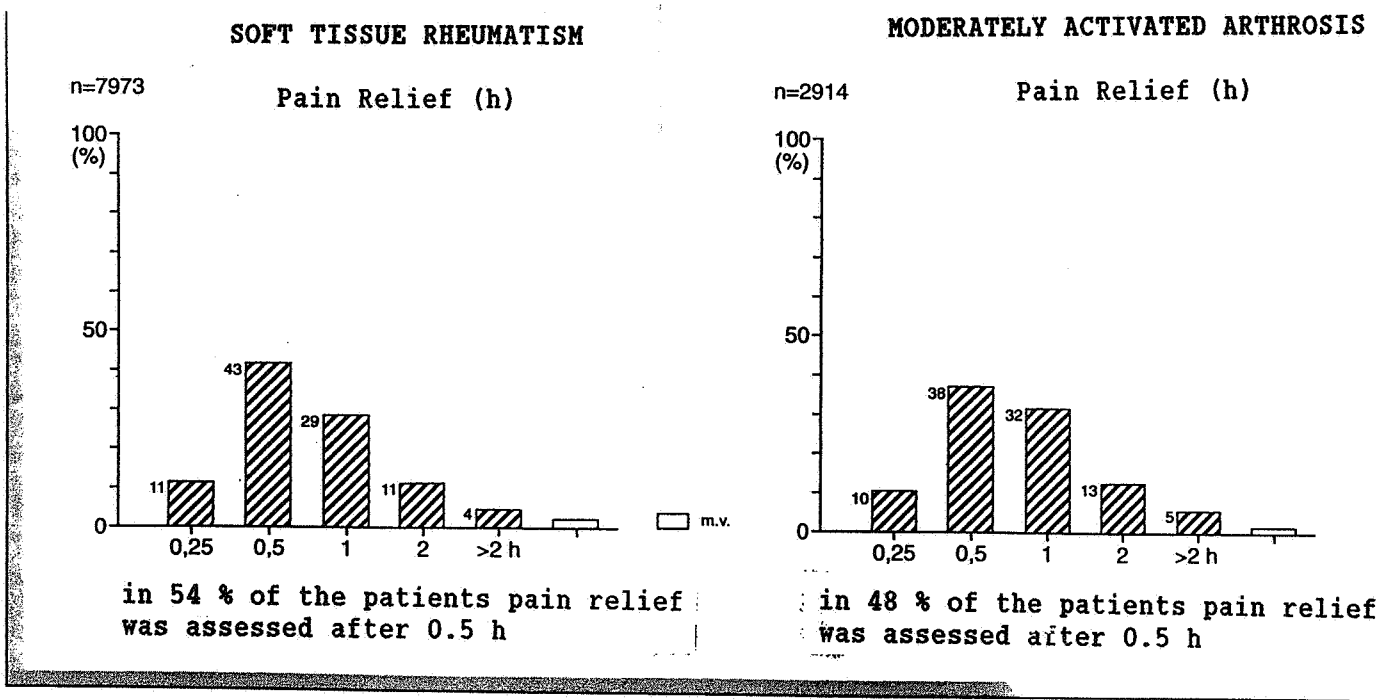

Figure 2 Pain Relief

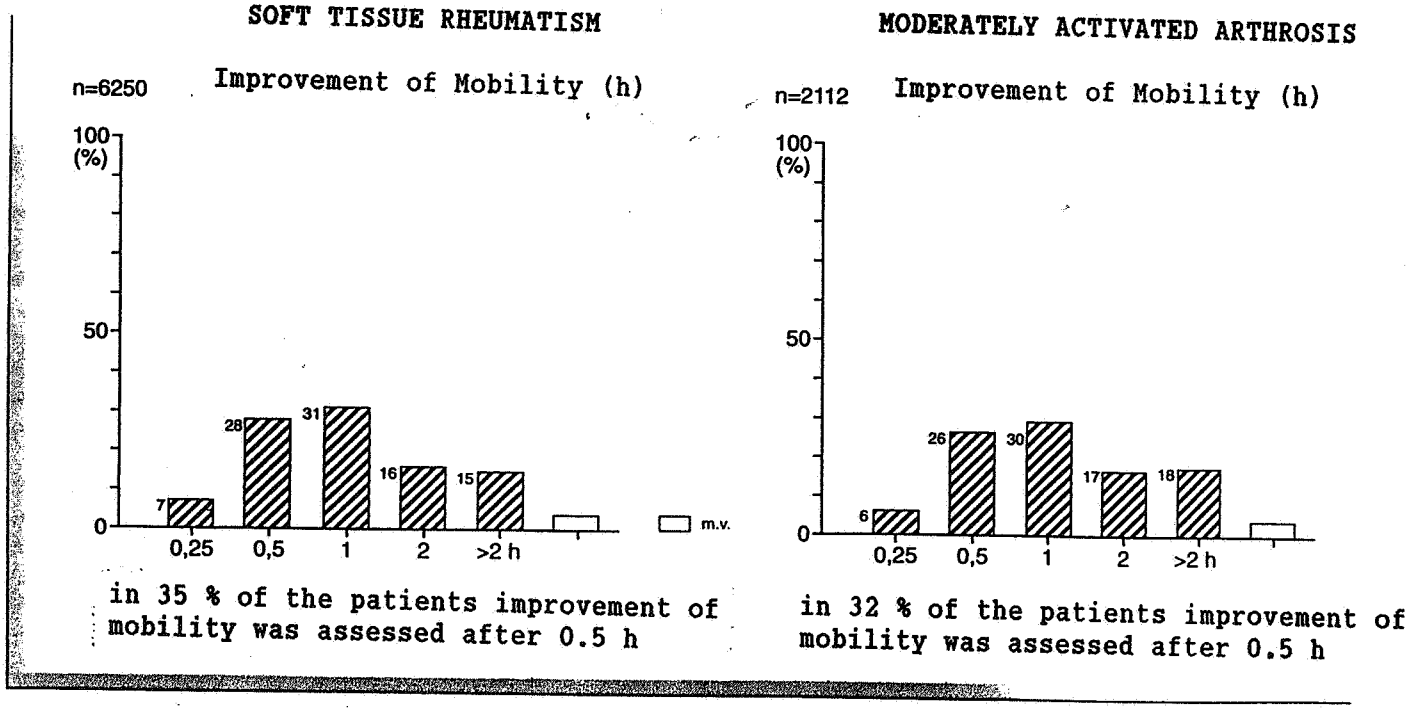

Figure 3 Improvement of Mobility

an obvious improvement of mobility within one hour.

The efficacy was also rated in general as "good" to "satisfactory" in about 90 % of the cases in the soft tissue rheumatism group and in about 85 % of the cases in the arthrosis group. About 12 % of the patients rated the efficacy as "moderate" to "poor"; these have to be classified as so-called non-responders.

With regard to tolerability it can be stated that the general tolerability was rated as "good" by 97.1 % of all the patients of both indication groups. Side effects occurred in 1.6 % of the patients with soft tissue rheumatism and in 1.7 % of those with moderately activated arthrosis, mainly in the form of local irritation such as erythema, pruritus, allergy, dryness of the skin.

Systemic complaints in the form of gastric disorders occurred in 2 patients of the arthrosis group.

Side effects appeared, if at all, within the first three days of treatment, later on almost never. However, in none of the patients of both treatment groups the therapy had to be discontinued due to side effects. Cutaneous and systemic side effects were completely reversible in all cases.

Discussion

The post-marketing research study, which was carried out during the period from December 1989 to May 1990 furnished

the evidence that there is an alternative to the oral (= systemic) rheumatic therapy with NSAIDs for certain indications; namely the percutaneous therapy with an ibuprofen 5 % cream.

Successful Treatment
of Non-Activated Processes is Possible

A successful topical treatment can be achieved in cases of preferential indications; namely soft tissue rheumatism, such as lumbo-ischialgia or cervical syndrome, tendovaginitis, however, not in their acute painful form, but in recurrences. Same applies to moderately activated arthrosis, which flames up ever and again, however, not the acute arthrosis which may be accompanied by conditions of intense pain and also severe exudative processes and movement restriction. The knee joints are particularly suitable for a broad application of ibuprofen cream. A 10 cm strip of cream corresponds to about 200 mg ibuprofen, thus also in the percutaneous rheumatic therapy, doses equivalent to oral administration can be applied.

Striking assessment in this study was that the 14-day treatment had a beneficial effect on all parameters examined, not only pain, but also movement restriction, joint complaints, hydrarthrosis or haemathrosis and morning stiffness. The regression of active and passive movement restriction was a bit slower in the cases of moderately activated arthrosis than in those of soft tissue rheumatism, where the release of tension led

already to freedom from pain and thus to the improvement of mobility. This means:

At first, within half an hour, pain subsides and thereafter, with a delay of one further hour, improved mobility is also achieved.

Such precise data on the point of time of the onset of action and/or pain relief and regression of movement restriction have not hitherto been described for any topical drug or confirmed on such a great number of patients - meanwhile 25,000 - as is shown in the 5 post-marketing surveillance studies.

Symptom-Freedom Already on the Third Treatment Day

From placebo-controlled studies with ibuprofen cream it is known that the 3rd day is particularly important for a judgement on efficacy. On this day a highly significant improvement of the entire symptomatology is assessed and the so-called self-healing or massage effect can be clearly separated from the verum effect (5, 8, 12). For the patient this means that the percutaneous rheumatic therapy does not only lead right, on the first day, to a rapid pain relief, but also that, already on the 3rd day, diagnosis-dependent symptom-freedom, i.e. varying according to the individual complaints, is achieved in a great number of patients. This means that:

The efficacy is judged by 88 % of the patients as good and is considered as sufficient; this is additionally

proved by the numerous handwritten notes of the physicians in the test protocols.

Merely a so-called non-responder incidence of 12 % indicates on the one hand that certain patients do not indeed respond to topical treatment, a phenomenon known about drugs, whether of an oral, rectal or percutanous pharmaceutical form. On the other hand, this group includes also cases of false diagnosis or highly acute cases in which the topical therapy alone is not sufficient. Another reason for the failure of therapy could be that a too low dose was chosen or that the prescribed doses were not applied.

Significantly Lower Side Effects than by Oral Therapy

The tolerability of the cream, both systemic and local, is rated as very good. A 14-day duration of treatment led only to local reversible reactive symptoms, such as erythema, paraesthesia, allergy. This was already assessed in the other four phase IV studies too. Only in two patients out of a total of more than 14,000, slight gastric disorders occurred. The overall incidence of side effects is of about 1.6 % and is thus significantly lower than after a corresponding oral antirheumatic therapy, where it is to be set between 20 and 40 % (6, 7).

The patients enrolled in this study were on average 45 years old. From the concomitant diseases it can be seen that a high percentage of these patients suffer-

ed already from high blood pressure, coronary heart diseases and also hyperlipoproteinaemia, diabetes mellitus, etc., and had to be treated accordingly. At the same time there are also rheumatic complaints; therefore, with the topical treatment alone the patients do not have to take more other oral medicaments, which may possibly lead to further interactions or intolerability reactions.

As it has been proved in numerous kinetical studies that the ibuprofen 5 % cream does not reach the site of action through a systemic distribution, i.e. in cases of soft tissue rheumatism the affected tendines and the perimysium, and in cases of arthrosis into the joint capsule and the synovial fluid, it constitutes, due to its rapid direct penetration, a real alternative for the indications of soft tissue rheumatism and moderately activated arthrosis (3, 10, 13, 14, 15). An additional oral medication is not necessary in these cases, as pain and movement restriction in half of the cases improved within half to one hour to the extent that the patients were able to resume their normal life.

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