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COMBINATION THERAPY WITH CYCLOSPORINE AND METHOTREXATE IN SEVERE RHEUMATOID ARTHRITIS

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Abstract *Background.* *Patients with severe rheumatoid arthritis who are treated with methotrexate frequently have only partial improvement.*

Methods. *In a six-month randomized, double-blind trial, we compared combination therapy with cyclosporine (2.5 to 5 mg per kilogram of body weight per day) and methotrexate (at the maximal tolerated dose) with methotrexate and placebo in 148 patients with rheumatoid arthritis who had residual inflammation and disability despite partial but substantial responses to prior methotrexate treatment. The primary outcome measure was the change in the number of tender joints.*

Results. *As compared with the placebo group, the patients in the treatment group had a net improvement in the tender-joint count of 25 percent, or 4.8 joints (95 percent confidence interval, 0.7 to 8.9; $P=0.02$), and in the swollen-joint count of 25 percent, or 3.8 joints (95 percent confidence interval, 1.3 to 6.3; $P=0.005$); improvement in overall disease activity as assessed by the physician (19 percent, $P<0.001$) and the patient (21 percent, $P<0.001$); and improvement in joint pain (23 percent, $P=0.04$) and in the degree of disability (26 percent, $P<0.001$). Thirty-six patients (48 percent) in the cyclosporine group and 12 patients (16 percent) in the placebo group ($P<0.001$) met the 1993 criteria for improvement of the American College of Rheumatology (more than 20 percent improvement in the numbers of both swollen and tender joints and improvement in three of five other variables). Serum creatinine concentrations increased by a mean of 0.14 ± 0.27 mg per deciliter (12 ± 24 mmol per liter) in the cyclosporine group and by 0.05 ± 0.19 mg per deciliter (4 ± 17 mmol per liter) in the placebo group ($P=0.02$).*

Conclusions. *Patients with severe rheumatoid arthritis and only partial responses to methotrexate had clinically important improvement after combination therapy with cyclosporine and methotrexate. Side effects were not substantially increased. Long-term follow-up of patients treated with this combination is needed. (N Engl J Med 1995; 333:137-41.)*

RHEUMATOID arthritis is a chronic, recurrent inflammatory disease that leads to substantial disability, loss of productivity, and increased mortality.[1-3] The traditional[4] approach to drug treatment emphasizes the stepped use of one medication at a time. When first-line agents such as aspirin and other nonsteroidal antiinflammatory drugs fail, slow-acting antirheumatic drugs such as methotrexate, antimalarial agents, gold salts, penicillamine, or sulfasalazine are considered. Patients treated with cyclosporine, a recent addition to this list, have improvement of similar magnitude to that of patients given other slow-acting agents.[5]

Monotherapy for rheumatoid arthritis is being reconsidered because of dissatisfaction with its effects,[6-8] and combination therapy has attracted increasing attention.[9-11] In an open study, patients who had partial improvement while receiving gold or methotrexate had additional improvement when they also received low-dose cyclosporine.[12] In a multicenter, placebo-controlled, randomized trial, we assessed combination therapy with cyclosporine and methotrexate for patients with severe rheumatoid arthritis.

METHODS

Eligibility

To be eligible for the study, patients had to meet the revised criteria of the American Rheumatism Association for rheumatoid arthritis[13]; had to have had a partial response in symptoms since the start of methotrexate treatment that they considered important and improvement in the number of tender joints, as determined by their physicians; had to have been receiving their maximal tolerated dose of methotrexate (≤15 mg per week) at a stable dosage for a least

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*Additional members of the Methotrexate–Cyclosporine Study Group are listed in the Appendix.

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three months; had to have had the same number of tender joints on two assessments one month apart; had to have active synovitis, defined as six or more actively inflamed tender or swollen joints; and had to be receiving no more than 10 mg of prednisone per day, a stable dose of nonsteroidal antiinflammatory drugs given for at least four weeks, or both.

Patients were excluded from the study if they had abnormal hepatic or renal function, a platelet count below 100,000 per cubic millimeter, leukopenia (total white-cell count, <3000 per cubic millimeter), cancer or a history of cancer, or concomitant therapy with any other experimental drug during the month before entry. Women of reproductive age were required to take appropriate contraceptive measures.

Treatment Groups and Monitoring

After providing written informed consent, patients were randomly assigned to receive cyclosporine or placebo in addition to their maximal tolerated dose of methotrexate. The first patient was enrolled in March 1992, and the last in May 1993. A separate randomization schedule was generated at each center. Gelatin capsules of cyclosporine (Sandimmune, 25 mg and 100 mg) and placebo were prepared by Sandoz (Basel, Switzerland); they were identical in taste and appearance.

The initial dose of cyclosporine or placebo was 2.5 mg per kilogram of body weight per day, given in two divided doses at 12-hour intervals. Serum creatinine concentrations and other laboratory values were monitored, and cyclosporine doses adjusted, by a clinician who was aware of the patient's study group but not involved in assessing outcomes. The dose of cyclosporine (or placebo in identical capsules) was increased by 0.5 mg per kilogram per day to a maximum of 5 mg per kilogram at weeks 2, 4, 8, 12, and 16 if actively inflamed joints remained. The dosage of cyclosporine was reduced by 0.5 mg per kilogram per day if the serum creatinine level increased by 30 percent or more from the base-line level. If after seven days the creatinine level was more than 30 percent above base line, the dosage was decreased by an additional 0.5 mg per kilogram per day each week until the creatinine level decreased to no more than 30 percent above base line. If serum aminotransferase concentrations exceeded twice the upper limit of normal, the white-cell count fell below 3000 per cubic millimeter, or the platelet count fell below 100,000 per cubic millimeter, methotrexate therapy was discontinued until the values became normal. After the base-line assessment, patients were seen twice in the first month and then monthly until the end of the six-month study period.

Clinical Assessments

The patients, primary care physicians, and study investigators were unaware of the study-group assignments. Assessments were performed by rheumatologists, nurses, or clinical metrologists trained in making standardized assessments in clinical trials (to minimize intraobserver variation); each patient's condition was assessed by the same person throughout the study. Benefits were evaluated with a standard classification system for assessing clinical outcomes.[14] Seven clinical variables were evaluated: the tender-joint count (the number of joints with clinically active disease, as determined by pain on passive movement and tenderness on pressure)[15]; the swollen-joint count[15]; pain as recorded on a 100-mm visual-analogue scale[15]; the physician's overall assessment of disease activity[15]; the patient's overall assessment of disease activity[15]; the degree of disability, as measured on the Health Assessment Questionnaire[16]; and the erythrocyte sedimentation rate. The primary outcome measure was the tender-joint count, as defined by the American College of Rheumatology.[15] Blood pressure and the concurrent use of other medications were recorded at base line and at each follow-up visit.

Laboratory Assessments and Side Effects

The following tests were performed at base line, every two weeks for the first month, and monthly thereafter: complete blood count; serum determinations of total bilirubin, aspartate aminotransferase, alkaline phosphatase, creatinine, blood urea nitrogen, electrolytes, and uric acid; and urinalysis. The erythrocyte sedimentation rate was obtained by the Westergren method at base line and at the end of months 2 and 6. Rheumatoid factor was measured at base line and six months. Side effects were monitored at each clinic visit by asking the patient open-ended questions to identify any problems that had occurred since the previous visit.

Statistical Analysis

With the tender-joint count used as the primary outcome, a sample of 75 patients per group was needed in order to have a 5 percent probability of a Type I error and a power of 80 percent to detect a difference of 5 tender joints between groups, with a standard deviation of 9.5,[7] and to allow for a 25 percent dropout rate.

All the study patients were included in the primary analysis, with the data on those who did not complete the study extrapolated from the time of their permanent discontinuation of the study treatment. Changes in continuous variables were compared by the t-test, and changes in categorical data by the chi-square statistic.[17] The scores for changes were expressed as a percentage of each group's mean base line score, and relative improvement was computed by subtracting the percentage of improvement in the placebo group from that in the cyclosporine group.

Results

Among the consecutive patients who were potentially eligible for the study, 148 patients were randomized. Another 36 patients were screened but not randomized for the following reasons: refusal to participate because of the inconvenience of study requirements, an unwillingness to risk potential toxic effects, or the risk of being assigned to placebo (17 patients); abnormal results on laboratory tests (9); the lack of a stable joint count at the base-line assessments (8); and a history of cancer (2).

The base-line characteristics of the 148 patients are summarized in Table 1. There were no substantive differences between the two groups with regard to these characteristics. Although the majority of patients had advanced rheumatoid arthritis, 41 (28 percent) had had their disease for less than five years. Among those enrolled, 117 patients (56 of the 75 in the cyclosporine group and 61 of the 73 in the placebo group) completed the six-month regimen of study medication. Seventeen patients in the cyclosporine group and 12 in the placebo group were withdrawn from the study treatment before six months. The timing and reasons are shown in Table 2. Two patients died, both in the cyclosporine group. Interstitial pneumonitis developed in a 76-year-old woman after 15 weeks of therapy, and she died 5 weeks later. The cause of death was thought to be viral pneumonia; methotrexate could not be ruled out as a contributing factor. An autopsy showed mild pulmonary fibrosis but no hypersensitivity changes characteristic of pneumonia caused by methotrexate. When cyclosporine therapy was discontinued, the dose was 4.0 mg per kilogram and the creatinine concentration was 1.39 mg per deciliter (122 μmol per liter), an increase of 16 percent over the base-line value of 1.19 mg per deciliter (105 μmol per liter). The other patient died in a motor vehicle accident during the fourth week of the study.

The mean (±SD) dose of cyclosporine at the time of the final treatment was 2.97±1.02 mg per kilogram per day. The mean serum creatinine concentration increased from base line to six months by 0.14±0.27 mg per deciliter (12±24 μmol per liter) in the cyclosporine group and 0.05±0.19 mg per deciliter (4±17 μmol per liter) in the placebo group (P=0.02). The mean dia-

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*Table 1. Base-Line Characteristics of the 148 Patients, According to Study Group.**

CHARACTERISTIC	CYCLOSPORINE (N = 75)	PLACEBO (N = 73)
Mean age (yr)	55.4±12.9	54.3±14.5
Female sex	54 (72)	53 (73)
Race		
White	68 (91)	69 (95)
Asian	7 (9)	4 (5)
Functional class†		
I	1 (1)	2 (3)
II	68 (91)	60 (82)
III	6 (8)	11 (15)
Mean duration of disease (yr)	11.2±8.3	9.4±7.8
Second-line drugs used previously		
Hydroxychloroquine	28 (37)	29 (40)
Oral gold	38 (51)	33 (45)
Injectable gold	10 (13)	8 (11)
Penicillamine	18 (24)	9 (12)
Azathioprine	10 (13)	6 (8)
Sulfasalazine	6 (8)	7 (10)
Prednisone	60 (80)	62 (85)
No. of second-line drugs used previously		
≥4	14 (19)	11 (15)
≥3	30 (40)	25 (34)
≥2	53 (71)	48 (66)

*Plus–minus values are means ±SD. All other values are numbers of patients followed in parentheses by the percentage of the group.

†Functional class I denotes complete functional capacity, with the ability to carry on all usual duties without handicaps; functional class II, capacity to conduct normal activities despite discomfort or limited mobility of one or more joints; and functional class III, capacity to perform only a few, or none, of the usual duties of occupation or self-care.[18]

stolic blood pressure in the cyclosporine group rose from 77.6 mm Hg to 78.2 mm Hg at six months, as compared with a decrease from 77.0 to 76.8 mm Hg in the placebo group (P = 0.219). Eight patients in the cyclosporine group and 10 in the placebo group had readings of diastolic pressure above 95 mm Hg and of systolic pressure above 165 mm Hg on at least two occasions. Other adverse events reported included hypertrichosis (in 10 patients in the cyclosporine group, as compared with none in the placebo group), tremors (in 4 and 1, respectively), paresthesia (in 8 and 3), nausea (in 21 and 12), diarrhea (in 13 and 12), dyspepsia (in 3 and 3), gum hyperplasia (in 1 and 2), and mouth ulcers (in 14 and 11). Many of the reported gastrointestinal and neurologic symptoms were not severe enough for the patients to be withdrawn prematurely from the study, and many symptoms improved over time.

The main study outcomes are summarized in Figure 1 and Table 3. There were statistically significant differences between the treatment groups on all clinical measures. As compared with those in the placebo group, the patients in the treatment group had a mean improvement in the tender-joint count of 25 percent, or 4.8 joints (95 percent confidence interval, 0.7 to 8.9; P = 0.02), and in the swollen-joint count of 25 percent, or 3.8 joints (95 percent confidence interval, 1.3 to 6.3, P = 0.005); improvement in overall disease activity as assessed by the physician (19 percent, P<0.001) and the patient (21 percent, P<0.001); and improvement in joint pain (23 percent, P = 0.04) and in the degree of disability, as measured on the Health Assessment Questionnaire (26 percent, P<0.001). The mean erythrocyte sedimentation rate increased by 4.2 mm per hour in the cyclosporine group and decreased by 4.8 mm per hour in the placebo group (P = 0.006). Forty-eight patients (64 percent) in the cyclosporine group improved by at least 25 percent, and 34 (45 percent) by at least 50 percent, in the number of tender joints, as compared with 34 patients (47 percent, P = 0.033) and 20 patients (27 percent, P = 0.023), respectively, in the placebo group.

The proportions of patients in each group who met the preliminary criteria of the American College of Rheumatology for improvement in rheumatoid arthritis[19] are shown in Figure 1. These criteria require that patients improve by 20 percent in the numbers of both swollen and tender joints and in three of the five remaining end points (pain, the patient's global assessment, the physician's global assessment, the degree of disability, and the erythrocyte sedimentation rate).[14] Thirty-six patients (48 percent) in the cyclosporine group met these criteria, as compared with 12 (16 percent) in the placebo group (P<0.001).

DISCUSSION

Patients with rheumatoid arthritis who had only partial responses to methotrexate had clinically important improvement when cyclosporine was added to their treatment. As shown in Figure 1 and Table 3, the benefits were consistent for all clinical end points, including both measurable and detectable physical signs of inflammation, such as joint swelling and tenderness, and information reported by patients, such as pain and disability. The lack of a beneficial effect of the combination of methotrexate and cyclosporine on the erythrocyte sedimentation rate was consistent with the findings in studies of cyclosporine therapy alone.[5]

In rheumatoid arthritis, treatment with a single slow-acting agent rarely results in true remission. Clinical studies of other combinations (such as that of antimalarial agents with gold or penicillamine, or that of meth-

Table 2. Reasons for Early Withdrawal of Patients from the Study, According to Study Group.

REASON	CYCLOSPORINE		PLACEBO	
	NO. OF PATIENTS	MEAN NO. OF WEEKS*	NO. OF PATIENTS	MEAN NO. OF WEEKS*
Lack of efficacy	1	3.7	3	5.9
Adverse reaction†	9	13.4	5	4.8
Intercurrent illness‡	3	15.3	1	8.7
Refusal to continue	2	2.0	2	19.5
Protocol violation	1	2.0	0	—
Death§	2	9.5	0	—
Other	1	6.0	1	7.9
All	19	—	12	—

*After the start of the study treatment.

†The adverse reactions in the cyclosporine group were as follows: gastrointestinal toxic effects (in five patients: nausea and vomiting in three, nausea in one, and diarrhea in one), leg swelling (one), breast tenderness (one), an elevated serum creatinine concentration (one), and possible pneumonia (one); in the placebo group: cough, hemorrhoids, elevated liver enzymes, pruritus, and gastrointestinal discomfort (one each).

‡Denotes one case each of influenza, urinary tract infection, and anxiety in the cyclosporine group; and one case of headache and gastrointestinal cramps in the placebo group.

§In the cyclosporine group, one patient died in a motor vehicle accident, and the other was thought to have died of viral pneumonia.

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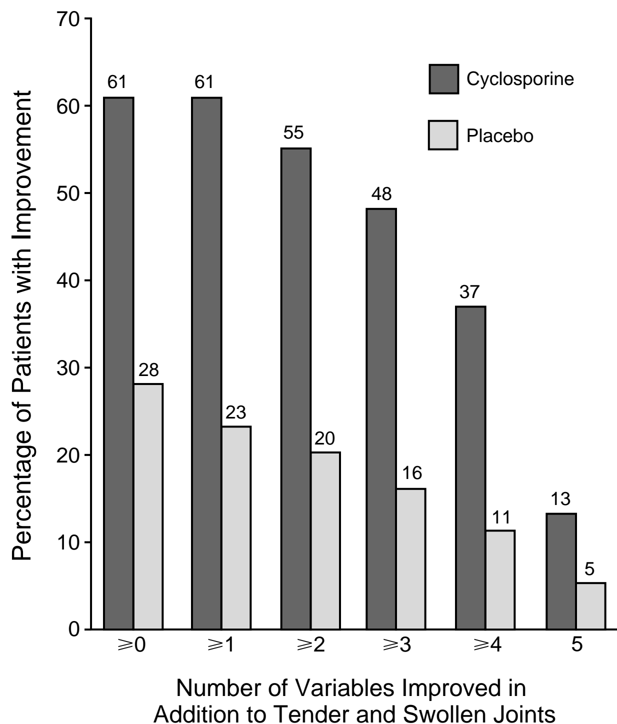

Figure 1. Percentage of Patients with Rheumatoid Arthritis Who Had 20 Percent Improvement in the Number of Tender and Swollen Joints and Improvement in Other Variables.

The American College of Rheumatology defines improvement as improvement in at least three of five variables (degree of disability, pain, patient's global assessment, physician's global assessment, and erythrocyte sedimentation rate) in addition to 20 percent improvement in the number of tender and swollen joints.

otrexate with azathioprine or auranofin) have shown equivocal benefits.[9,11] Favorable experience with combination therapy in transplantation and oncology encouraged us to study two relatively potent agents, methotrexate and cyclosporine. Methotrexate is effective in controlling clinical signs of inflammation in patients with rheumatoid arthritis, has an effect that continues substantially longer than those of other slow-acting drugs,[20,21] and is considered by many rheumatologists to be the second-line drug of first choice.[22] Cyclosporine is effective as a single agent in patients with rheumatoid arthritis.[5] The two drugs together have been shown to be more effective than either used alone.[23] An open study[12] suggested that the combination of cyclosporine and methotrexate was more effective than methotrexate alone in patients with partial responses to methotrexate. Methotrexate and cyclosporine may work through different mechanisms: methotrexate through interleukin-1, macrophages, and monocytes,[24] and cyclosporine through interleukin-2 and T lymphocytes.[25-27]

A randomized, controlled trial design is particularly important to ensure that patients' improvement is not due to the natural history of the disease or to treatment with methotrexate alone. Other trials of combination therapy in patients with rheumatologic diseases require that the drugs be studied alone as well as together. However, when two therapeutic agents are compared in rheumatoid arthritis, there is often a high rate of spontaneous improvement in the placebo group (due to regression to the mean).[10] It is difficult to discern differences between groups without enrolling large numbers of patients and evaluating long periods of therapy. This problem may explain the equivocal results of previous studies of drug combinations in rheumatoid arthritis, such as that of methotrexate with auranofin or azathioprine.[28,29] Our protocol, in which a combination of two drugs was compared with a single drug plus placebo, provided a statistically efficient way of evaluating the efficacy and safety of the combination. Such protocols are commonly used in oncology to evaluate the early efficacy of combination chemotherapy.

The frequency and causes of adverse events were similar to those in prior trials of methotrexate[30] and cyclosporine[5] used alone. Unacceptable toxic effects (e.g., gastrointestinal intolerance and bone marrow suppression) found with other drug combinations[11] did not occur in this trial. Although both drugs affect the kidneys, deterioration of renal function was not a clinical problem. Because the threshold for dose reduction was a 30 percent increase in the serum creatinine concentration, the mean dose of cyclosporine in this study (2.97±1.02 mg per kilogram) was lower than that in our previous placebo-controlled trial of cyclosporine alone[31] (3.8 mg per kilogram), in which the threshold for dose reduction was a 50 percent increase in the creatinine level. The finding of efficacy with lower doses is

*Table 3. Outcomes of Treatment during Six Months of Study in Patients with Rheumatoid Arthritis.**

Outcome Measure	Base Line		Change at 6 Mo		Effect of Treatment	P Value
	Cyclosporine	Placebo	Cyclosporine	Placebo		
	mean ±SD				*mean (95% CI)*	
No. of tender joints	18.9±12.1	20.4±13.7	−7.5±11.3	−2.7±13.7	−4.8 (−8.9 to −0.7)	0.02
No. of swollen joints	15.2±9.5	17.3±12.0	−5.7±6.9	−1.9±8.5	−3.8 (−6.3 to −1.3)	0.005
Global assessment						
By physician	3.0±0.7	3.1±0.8	−0.76±0.78	−0.19±0.85	−0.57 (−0.84 to −0.30)	<0.001
By patient	2.9±0.8	2.9±0.8	−0.64±0.95	−0.04±1.03	−0.60 (−0.92 to −0.28)	<0.001
Pain	40.8±23.1	45.1±23.1	−12.1±27.3	−2.6±28.2	−9.5 (−18.6 to −0.4)	0.04
Degree of disability	1.4±0.6	1.4±0.7	−0.25±0.42	0.03±0.50	−0.28 (0.43 to −0.13)	<0.001
Erythrocyte sedimentation rate (mm/hr)	31.4±22.5	36.2±25.1	4.2±19.1	−4.8±20.1	9.0 (2.6 to 15.4)	0.006

*Negative values indicate improvement, and positive values worsening, in the patients' disease activity. Possible scores ranged from 0 to 68 for the number of tender joints; from 0 to 66 for the number of swollen joints; from 1 (very good) to 5 (very poor) for the global assessments; from 0 (no pain) to 100 (maximal pain imaginable) for pain, measured on a 100-mm visual-analogue scale; and from 0 (no disability) to 3 (high disability) for degree of disability, on the Health Assessment Questionnaire.[16] Measures are based on Outcome Measures in Rheumatoid Arthritis Clinical Trials.[14] CI denotes confidence interval.

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reassuring, since the risk of structural damage to the kidneys from cyclosporine is dose-dependent.[32]

The long-term risk of cancer with the combination of methotrexate and cyclosporine requires further study. Patients with rheumatoid arthritis have a risk of cancer 20 to 30 times higher than people in general, whether or not they have taken second-line agents. Those who take such agents have a risk 10 times higher than those who do not. Although these relative risks are high, they may be acceptable to many patients and physicians, since the absolute risk of cancer is less than 0.1 percent per year.[33] Reversible lymphomas have occurred in patients with rheumatoid arthritis who have received either methotrexate or cyclosporine alone.[34,35] The Sandoz Corporation maintains a registry of lymphomas reported in patients who have ever received cyclosporine; as of June 1994, four lymphomas and one lung cancer had been reported in 2327 patients with rheumatoid arthritis who were so treated.

The usefulness of the type of combination therapy we studied can be evaluated from several perspectives. Symptoms and signs of inflammation lessened to a clinically important degree.[36] Rheumatoid arthritis severe enough to warrant second-line therapy, as assessed by the number of tender joints and the degree of disability, carries a substantially increased risk of long-term disability and a reduced life expectancy.[37,38] Further studies should assess whether this combination therapy decreases disability and reduces mortality in such patients.[36] Many believe that these goals are more likely to be achieved by treating the patient aggressively early in the course of disease — that is, beginning less than two years after diagnosis.[9] Long-term follow-up of patients treated with this combination should also assess whether the benefit is maintained, whether the use of the drugs might be discontinued temporarily or permanently, and whether long-term toxicity is increased.

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Appendix

The following members of the Methotrexate–Cyclosporine Combination Study Group participated in this trial: R. Goldstein, M.D., P. Morassut, M.D., C. Shamess, M.D., and J. Thomson, M.D. (Ottawa center), coinvestigators; R. Brooks, B.S. (Nashville center), M. Cornett, B.Sc.N. (Tucson center), and P. Dale and J. Groh (Ottawa center), research coordinators; L. Yetisir, M.Sc. (Ottawa center), biostatistician; and T. Croft (Ottawa center), data-entry manager.

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