Assessment of Cyclosporine Oral Solution in Patients with Severe Rheumatoid Arthritis

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Abstract

Background: patients with severe rheumatoid arthritis treated with cyclosporine A, frequently showed variability in important improvement.

Objectivs: This study aimed to assess the effectiveness of oral cyclosporine solution in management of severe rheumatoid arthritis.

Methods: In this prospective study, the efficacy and safety of 5 mg per kilogram body weight per day, oral solution of microemulsion pharmaceutical formulation of cyclosporine (Neoral) was assessed in thirty three patients with severe refractory rheumatoid arthritis in Consultant clinic at Al-Yarmook teaching hospital during 2004. None of patient population showed any previous important improvement to methotrexate, sulfasalazine and/or hydroxychloroquine as monotherapy or in different combinations.

Results: 21 out of 33 (63.6%) patients with severe rheumatoid arthritis showed marked improvement i.e. fulfill at least 50% improvement in American College of Rheumatology (ACR) criteria. The remaining number of twelve patients (36.4%) were discontinued the treatment because of adverse reactions and/or ineffective therapy. Patients who continued the therapy and showed improvement were; females rather than males, older, with longer duration of disease, the more period of morning stiffness, the higher leucocytes count, the lower hemoglobin level, and the higher frequency of positive latex test and higher serum C-reactive protein level**.**

Conclusion: Microemulsion oral pharmaceutical formulation of, stable 5 mg per kilogram body weight per day cyclosporine A, is effective and safe remedy for severe rheumatoid arthritis.

Key words: Cyclosporine, Severe Rheumatoid arthritis.

Introduction

Rheumatoid arthritis affects about 1% of the population. It is associated with pain, deformity, decreased quality of life and disability that in turn affect patients' ability to work. In February 4, 1997 Food and Drug administration (FDA) approved Novartis application (filed by Sandoz Pharmaceuticals) to have Neoral® cyclosporine for microemulsion indicated for treatment of severe arthritis. The patient population eligible for cyclosporine therapy would be patients with severe active rheumatoid arthritis that showed at least two slow acting second line therapeutic agents or methotrexate ineffective or not tolerated.

Cyclosporine is immunosuppressant agent belongs to family of cyclic polypeptide, derived from the fungus Tolypocladium Inflatum Gams[1]. It has a very selective inhibitory effect on T lymphocyte and interleukin II [2]. Its efficacy in rheumatoid arthritis is related to suppression of interleukin 15(a potent inflammatory cytokine) and enhancing the production of interleukin 10 (a potent anti-inflammatory cytokine) [3]

Several reviews discussed the guidelines of the therapeutic implications in rheumatoid arthritis and warned from the potential serious adverse reactions [4-8]. The guidelines for the use of cyclosporine in rheumatoid arthritis that introduced by two international consensus meeting in 1994 and 1995 are practiced [5,6].

Most of studies conducted on 1980s, advised to use high doses of cyclosporine via different therapeutic regimens of different duration of time. Such regimens showed a considerable percent of clinical improvement but they weren't free from serious adverse reactions [9-11].

Some authors believe that it is possible to minimize the adverse reactions and to improve the percent of clinical remission by utilizing two phases regimen, an initial dose of 2.5 mg/kg for few weeks followed by a maintenance high doses for long period of time[12]

This study is aimed: firstly, to introduce a new therapeutic regimen utilizing stable dose of 5 mg/kg cyclosporine in an open-ended randomized prospective clinical trial in a small sample size of patients with severe refractory classical rheumatoid arthritis. Secondly, to identify the characteristics of patients who are more likely to respond and/or tolerate cyclosporine.

Methods

This study was conducted in consultant clinic at Al-Yarmook Teaching hospital in Baghdad during 2004.

To be eligible for the study, patients had to meet the revised criteria of American College of Rheumatology(previously known as The American Rheumatism Association)[13]: had to have severe rheumatoid arthritis, had to have no response in symptoms to slow-acting antirheumatic drugs (chloroquine, methotrexate, or salazopyrine), had to be receiving not more than 10 mg prednisolone per day, had to have the same number of tender joints on two assessments, one month apart, and had to

have active synovitis (defined as six or more actively inflamed tender or swollen joints).

Patients were excluded from the study if they had leucopenia (total white cells count < $3000mm^3$), cancer or history of cancer. Women of reproductive age were required to take appropriate contraceptive measures.

After providing written informed consent, patients were required to stop all antirheumatic agents and allowed small doses of prednisolone (5-7.5 mg/day). Patients were randomly assigned to receive cyclosporine after 4 weeks, washing period, from discontinuation of other antirheumatic agents. The first patient was enrolled in 10^{th} of January 2004 and the last in 13^{th} of July 2004.

Oral solution of cyclosporine (Sandimmune ,Neoral 100mg/mL, Novartis). The dose of cyclosporine was 5 mg /kg body weight per day, given in two divided doses at 12 hour intervals. Serum creatinine concentrations and other laboratory values were monitored including complete blood picture, erythrocyte sedimentation rate and C-reactive protein.

After the baseline assessment, patients were seen twice in the first month and then monthly until the end of the study.

Clinical assessments were performed by the author, a consultant of rheumatology. The following clinical variables were evaluated: The patient's global assessment and physician's global assessment, the number of diseased joints, extent of inflammation (swollen and tenderness), secondary osteoarthritis, joints range of movement, grip power in kilogram (by dynamometer), morning stiffness and rheumatoid nodules.

The following laboratory tests were performed at base line, every two weeks for the first month and monthly thereafter: complete blood count and serum creatinine, the erythrocyte sedimentation rate was determined by the Westergren method and C-reactive protein at base line and every couple of months. 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

The results are presented as number, percentage, median and mean ± SD.

Results

Table 1 shows the basic characteristics of patients enrolled in this study. Female: male ratio was 4.5:1, and the median age was 48 years. All patients were presented with clinical symptoms and signs of rheumatoid arthritis in more than twenty joints and the median duration of their illness seven years (table 2). Physical examination revealed that the median morning stiffness was 3 hours and the median grip power was 3 kilograms for right hand and 2 kilograms for left hand (table 2).

Table 1. Base characteristics of study.

Number	33
Sex (No.)	
Male	06
Female	27
Age (year)	
Mean ± SD	44.66 ±11.15
Median	48

Table 2. Characteristics of disease.

Type:	Classical, severe, erosive
No. of diseased joints	> 20
Duration (year):	
Mean ± SD	9.59 ± 5.59
Median	7
Morning stiffness (hour)	
Mean ± SD	3.25 ± 1.75
Median	3
Hand grip (right)[Kg]:	
Mean ± SD	3.60 ± 3.99
Median	3
Hand grip (left)[Kg]:	
Mean ± SD	3.07 ± 3.32
Median	2

Laboratory investigations showed high level of erythrocyte sedimentation rate (ESR: 88 mm/h), low hemoglobin level (10 g/dl) and within normal leucocytes count (7000/mm^3) (table 3). Most of cases had positive latex test (30 out of 33) and abnormal C-reactive protein (32 out of 33) (table3). The mean serum creatinine level was 0.91 mg/dl before the initiation of treatment.

Regarding the effectiveness of cyclosporine monotherapy, 21 out of 33 patients continued the treatment with marked improvement in their signs and symptoms, of 50% improvement in 7 patients and more than 70% improvement in 14 patients i.e. 63.6% of patients were improved. The remaining number of twelve patients (36.4%) were discontinued the treatment because of adverse reactions and/or ineffective therapy (table 4).

Further analysis revealed that the characteristics of patients who continued the therapy and showed improvement were; female rather than male, older, with longer duration of disease, the more period of morning stiffness, the higher leucocytes count, the lower hemoglobin level, and the higher frequency of positive latex test and higher serum C-reactive protein level (table 5).

Table 3. Indices of disease activity

ESR (mm/h) Mean ± SD	84.21 ± 15.54
Median	88
WBC (per cu.mm)	
Mean ± SD	7018 ± 1732
Median	7000
Hb (g/dl)	
Mean ± SD	10.13 ± 1.10
Median	10
Latex test (No. of cases)	
Positive	30
Negative	03
CRP (No. of cases)	
Within normal range	01
Above normal level	32
(> 200 mg/L)	
Serum creatinine (mg/dl):	
Mean ± SD	0.914 ± 0.090
Median	0.9

Table 4. Reported adverse reaction

Severe nausea and vomiting	12
Hirsutism	2
Elevated serum creatininine	4

Table 5. Comparative data between the criteria of patients who continued cyclsporine therapy, and those failed to continue the study.

	Continued treatment	Stop treatment
Male	3	3
Female	18	9
Age (year)	48	42.5
Duration of disease (year)	10	6.75
Morning stiffness (hour)	3	2.75
Grip (Kg) (Right)	2	3.0
(Left)	2	2.5
ESR (mm/h)	88	89
WBC (cell/mm^3)	7000	6400
Hemoglobin (g/dL)	9.9	10.1
Latex test (negative): No. of cases	1	2
Normal C-reactive protein level): No. of cases	0	1
Serum creatinine (mg/dL)	0.9	1
Duration of therapy (month)	14	4

The results represent as median value or number (No.) of cases.

Discussion

Patients with severe refractory rheumatoid arthritis failed to response to numbers of disease modifying antirheumatic drugs (DMARDs) had clinically important improvement after stable dose of cyclosporine oral solution (5 mg/kg body weight per day). This study provides the following clinically important effects of Neoral solution:

First:

Neoral oral solution showed important improvement in 63.3% of cases in this study that is higher than other studies used conventional cyclosporine [14]. This variation may be related to the pharmaceutical formulation of cyclosporine. The intra-patient variability in pharmacokinetic of cyclosporine microemulsion formulation is reduced in comparison with other formula [15]. The mean bioavailabilty of cyclosporine from the microemulsion formulation was 23% higher than from conventional cyclosporine [16]. Also, Shah *et al* 1999 observed that Neoral is the superior cyclosporine formulation and is associated with lower rejection incidence of organ transplantation in comparison with sandimmune [17]. It is expected to observe that not all patients were responded to cyclosporine because there are more than one interleukin involved in pathogenesis of rheumatoid arthritis[18]. This study is added another observation that oral solution of cyclosporine is highly effective in comparison with other oral solid dosage form.

Second:

Cyclosporine is administered with stable dose of 5 mg per kilogram body weight per day in initial and maintenance phases. This therapeutic regimen is differed from that reported with others. Johns and Littlejohn 1999 reported 65% of 46 patients with refractory rheumatoid arthritis showed important improvement at a mean dose of cyclosporine 2.94 mg per kilogram body weight per day in combination with methotrexate and higher doses of prednisolone for a mean duration of 10.5 months [19]. Also it is important to mention here that the combined therapeutic regimen used by Johns and Littlejohn is effective in patients who had short duration of illness unlike what is reported in this study. Also Altman *et al* 1999 found that cyclosporine is ineffective, in none-refractory rheumatoid arthritis, in a dose of 1.5 mg per kilogram body weight per day while the dose of 2.5 mg fared better and a further improvement is observed when the mean dose escalated to 2.85 mg [20] .Moreover, in this study, cyclosporine mono-

therapeutic regimen for long duration of time showed that the tolerability and the adverse reactions weren't more than those reported with smaller doses.

Third:

In this study, cyclosporine is administered as third line *de novo* disease modifying antirheumatic agent i.e. this product is neither used by patients before the commence of the study nor it is added or combined with other disease modifying antirheumatic drugs. This observation impressed the effectiveness of cyclosporine as monotherapy in refractory rheumatoid arthritis.

Fourth:

Although there are few articles recommend the use of cyclosporine in early rheumatoid arthritis but the FDA approval recommended its indication for severe cases. The results reported *herein* clearly demonstrated that the efficacy and the tolerability of cyclosporine are observed in worst cases. Therefore, I recommend this remedy for severe cases. Such indication improved the percent of recover and reduced the number of withdrawal cases. Also such therapeutic regimen can be extended for long duration of time without any serious side effects.

It was concluded that stable dose of 5 mg per kilogram body weight per day of Neoral solution is a suitable and safe remedy for severe rheumatoid arthritis. It can be prescribed for long period of time without carrying very important or serious side effects.

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