Clinical and Experimental Rheumatology 2005; 23: 681-684.

Inclusion criteria as widely used for rheumatoid arthritis clinical trials: Patient eligibility in a Turkish cohort

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Received on October 5, 2004; accepted in revised form on April 18, 2005.

Key words: Rheumatoid arthritis, anti-TNF agents, clinical trial criteria, total joint count.

ABSTRACT

Objective. *To identify the proportion of patients fulfilling the inclusion criteria widely used in most clinical trials for rheumatoid arthritis (RA) – including the recent clinical trials of anti-Tumor Necrosis Factor α (TNFα) agents – in a Turkish cohort.*

Methods. *186 consecutive RA patients attending a routine tertiary rheumatology clinic were evaluated in 2 groups: Early RA group (group E): 31 patients with a disease duration of ≤ 3 years (mean: 1.9 ± 0.9 years); late RA group (group L): 155 patients with a disease duration of >3 years (mean: 13.3 ± 8.6 years). Patients were evaluated according to 2 different sets of inclusion criteria: (i) The widely used common inclusion criteria for RA clinical studies, as outlined by Sokka and Pincus; (ii) the criteria of two major anti-TNF clinical studies, ERA and ATTRACT.*

Results. *No patients in group E, and 9 (6%) patients in group L fulfilled the common criteria used in clinical studies for RA. In group E, 28 patients had already been started on methotrexate; 2 patients were on sulphasalazine and one patient was on leflunomide. Nevertheless, even if the criterion for previous use of methotrexate was not applied patients did not fulfill the rest of the criteria of ERA study. In group L, 9 out of 155 patients (6%) met the criteria for the ATTRACTstudy.*

Conclusion. *Only few patients met the widely used inclusion criteria for most RA clinical trials and the recent clinical trials of TNFα agents in this Turkish cohort. This may be explained by the milder disease activity in this geographical region, which further emphasizes the need to consider development of new criteria for inclusion in clinical trials.*

Introduction

Recent studies have shown that patients taking part in drug trials may not represent patients seen in actual clinical practice (1, 2). It has in fact been reported that only 15.3% of patients with rheumatoid arthritis (RA) seen in clinical practice fulfill the inclusion criteria to major reported clinical trials (2).

This incongruity between characteristics of the patients seen in daily practice and that enrolled in clinical trials would assume more importance when one applies the information obtained from results of formal drug trials in one geography to the patients in another when there is reason to believe that are differences in disease severity between regions. There is some evidence that RA might run a less severe course in Mediterranean countries (3-5) as compared to Western Europe or the United States of America, regions where most clinical trials are conducted. Therefore, we attempted to assess the proportion of patients fulfilling the widely used inclusion criteria in clinical trials for RA, including the recent clinical trials of anti-TNFα agents, among a cohort of RApatients from Turkey.

Patients and methods

Patients

186 consecutive RA patients attending a routine tertiary rheumatology clinic in Istanbul, Turkey, were evaluated in two groups: Group E (early) and Group L (late). All patients met the American College of Rheumatology criteria for RA. Group E was made up of 31 patients with a disease duration of ≤ 3 years (mean 1.9 ± 0.9SD years) while group L consisted of 155 patients with RAwith a disease duration of > 3 years (mean 13.3 ± 8.6SD years). Patients were evaluated according to 2 different sets of inclusion criteria:

1. The widely used common inclusion criteria for RA clinical studies, which as outlined by Sokka *et al.* are (2): 1) ≥ 6 tender joints 2) ≥ 6 swollen joints 3) ESR of ≥28 mm/h and 4) morning stiffness of ≥45 minutes. Patients were also analyzed according to whether they met ACR criteria for remission: 1) no joint swelling or soft tissue swelling of tendon sheaths; 2) no joint tenderness or pain on motion; 3) normal ESR of < 30 in women and < 20 in men; 4) morning stiffness ≤ 15 minutes; 5) absence of joint pain; 6) absence of fatigue. Present status of DMARD use was tabulated for all patients.

2. Based on the criteria of two major anti-TNF clinical studies: ERA and ATTRACT (6, 7). The inclusion criteria for the ERA clinical trial required

the following: (i) no previous use of methotrexate; (ii) ≥ 12 tender joints and ≥ 10 swollen joints; (iii) rheumatoid factor positivity of presence of radiographic erosions; and (iv) morning stiffness of ≥45 minutes, erythrocyte sedimentation rate (ESR) ≥28 mm/ hour or CRP level of ≥2mg/dl. The inclusion criteria for the ATTRACT study were: (i) ≥ 6 tender joints and ≥6 swollen joints; (ii) 2 of the following (iii) morning stiffness of ≥ 45 minutes, ESR of ≥ 28 mm/h or CRP level of ≥ 2 mg/dl; (iv) methotrexate dose of ≥12.5mg/ week. CRP and radiographic erosions were not included in these criteria for it was not available in all patients

Measures of clinical status

All patients were examined by the same clinician (FG). Swollen and tender joint counts were done during a single visit at 42 joints: 10 hand proximal interphalangial, 10 metacarpal, 2 wrist, 2 elbow, 2 shoulder, 2 knee, 2 hip, 2 ankle, 10 metatarsophalangial joints. ESR, duration of morning stiffness and the current DMARD status was noted.

Statistical analysis

Mean values of painful and swollen joint counts, morning stiffness, ESR were analyzed by descriptive statistics performed by SPSS 11.0.

Results

The patient characteristics are shown in Table I.

Eligibility for common inclusion criteria used in clinical studies of RA

No patients in group E and 9 (6%) patients in group L fulfilled all the 4 common criteria used in clinical studies for RA. The number of patients providing for each and combination of some of the common criteria used in clinical studies for RA are shown in Tables II and III.

Eligibility for the ERA trial

Two patients were on sulphasalazine and one patient was on leflunomide. CRP and radiographic erosions were not included in the criteria for it was not available in all patients. However, had these criteria were available for all the patients, the percentage of subjects who met the inclusion criteria for ERA would not differ markedly as out of 31 patients, 28 had already been prescribed methotrexate. The number of patients providing for each and combination of some of ERA criteria are shown in Table II.

Eligibility for the ATTRACT trial

9/151 (%6) patients in group L met the criteria for the ATTRACT study. The numbers of patients meeting each or combinations of some of the ATTRACT criteria are shown in Table III.

Remission criteria for RA

No patients in group E and 2 patients in group L fulfilled the remission criteria.

DMARD status

Methotrexate appears to be the most preferred DMARD therapy (90% in group E, 71% in group L) in both groups.

Among the 31 patients in Group E, 26 patients were on only methotrexate. One patient was on a combination of methotrexate and sulphasalazine; one patient was on a combination of methotrexate and chloroquine. Two patients were on sulphasalazine and one patient was on leflunomide.

In Group L, 2 patients were not taking any DMARDs as they were considered to be in remission. Ninety-four patients were on methotrexate, 16 patients were on sulphasalazine, 14 patients were on a combination of these. Eight patients

Table I. Demographic and clinical characteristics of patients in group E and group L.

	Group E	Group L	p
No. of patients	31	155	
Age, mean ± SD years	42.8 ±14.2	52 ±12.4	
Disease duration, mean ± SD years	1.9 ± 0.9	13.3 ± 8.6	
RF positive,%	72.7	72.9	0.87
ESR, mean ± SE	26.3 ± 3.2	34.3 ± 1.9	0.76
Swollen joint count, mean ± SE	3.4 ± 1.6	4 ± 1.2	0.69
Tender joint count, mean ± SE	5.5 ± 1.3	5.9 ± 0.7	0.76
Morning stiffness, mean ± SE minutes	48.7 ±13.3	53.1 ± 5.5	0.89

Table II. For group E, the number of patients meeting each and combination of some of the ERAand common clinical criteria used for RAclinical studies.

	No. of patients (%)
≥ 12 painful joints	4 (13)
≥ 10 swollen joints	1 (0.3)
≥ 12 painful joints + ≥ 10 swollen joints	2 (0.6)
≥ 6 painful joints	9 (29)
≥ 6 swollen joints	2 (6.5)
≥ 6 painful joints + ≥ 6 swollen joints	2 (6.5)
Morning stiffness ≥ 45 minutes	12 (39)
ESR 28 mm/h	10 (32)
Morning stiffness ≥ 45 minutes + ESR ≥ 28 mm/h	2 (0.6)

Table III. For group L, the number of patients meeting each and combination of some of the ATTRACTand common clinical criteria used for RAclinical studies.

	No. of patients (%)
≥ 6 painful joints	46 (30.4)
≥ 6 swollen joints	15 (9.9)
≥ 6 painful joints + ≥ 6 swollen joints	12 (7.9)
Morning stiffness ≥ 45 minutes	62 (41)
ESR ≥ 28 mm/h	74 (48)
Morning stiffness ≥ 45 minutes + ESR ≥ 28 mm/h	31 (20.5)

were on chloroquine, 8 were on a combination of methotrexate and chloroquine, and 9 were on leflunomide. The less preferred combinations were sulfasalazine + leflunomide, methrotrexate + leflunomide, methotrexate + sulfasalazine + chloroquine with one patient in each combination. One patient was on azathioprine. Six of the 9 patients who fulfilled the ATTRACT criteria were on methotrexate; 2 of these were on combination therapy with chloroquine. The remaining 3 patients were on monotherapy with sulphasalazine, leflunomide and chloroquine.

Discussion

Data presented here show that none of the patients in group E and only 6% of patients in groups L fulfilled the common criteria for RA trials, and similarly, only 6% of patients in group Lhave fulfilled the criteria for the ATTRACT study and none of the group E patients for those of ERA. The criteria of morning stiffness and ESR ≥28mm/h allowed inclusion of more patients from both groups L and E. Morning stiffness was met by 41% of patients in cohort L and 39% of patients in group E whereas ESR ≥ 28mm/h was met by 32% and 48% of patients in groups L and E respectively (Table III).

Tender and swollen joint counts, duration of morning stiffness and rheumatoid factor positivity percentage did not differ between groups L and E. A longitidunal study by the GIARA registry group (Gruppo Italiano Artrite Rheumatoide Aggressiva) also did not reveal any difference in the tender and swollen joint counts between the early and late RA groups. However the RF positivity percentage was lower in the early RAgroup; this might be due to the cut-off period for early RA in the GIARA registry, which was 4 months (8).

One obvious explanation why so few of our patients met the study criteria was the fact that they had already been on a DMARD therapy. There has been major improvement in the treatment of RA in the last two decades. Until the 1990s DMARD therapy was deferred until the disease was present for well over a few years. One reason for deferring DMARD therapy was the potential toxicity of the then available drugs like gold salts and penicillamine. In 1980's it has become apparent that RAwas not as benign as once was thought. Parallel to this the introduction of methotrexate – much safer and more potent than the other DMARDS – changed the pyramide approach for the treatment of RA. Since then methotrexate has become widely used for the treatment of RA(9, 10). In fact methotrexate both as a monotherapy and in combination with other agents had already been prescribed for majority of our patients in both group L and E.

Another possible explanation for our findings may be the geographical factor. It has been shown in a number of studies that RA follows a milder clinical course in south-east Europe (3-5). In the study of Sokka *et al*. on a 28 joint count, in their group L, 42.5% of patients had ≥ 6 swollen joints, 25.3% had ≥ 6 painful joints, 19.9% had both ≥ 6 swollen and ≥ 6 painful joints (2). In our study on the other hand, in group L our findings were 9.9%, 30.4% and 7.9% respectively. Moreover, all joint counts in our study were made on a 42 joint count.

An additional interesting point about our findings is that all the patients were being followed up at a dedicated tertiary referral centre where one would accept the presence of more severe cases with aggressive therapy regimes. On the other hand the majority of patients in both group L and E were on a single DMARD. It could as also be said that the reason for not fulfilling the study criteria could be that rest of the patients would be in remission. In fact that was not the case for only 2 patients in group L and none in group E met the ACR criteria for remission. Thus in both groups L and E patients could fulfill neither the study nor the remission criteria. Similar to our findings, in the study by Sokka *et al*. 6 out of 146 consecutive patients in group L and none in group E met the ACR criteria for remission (2). For this reason Sokka *et al.* have suggested that the present inclusion criteria for drug trials may no longer be optimal in view of current rheumatological practice and there is need for the further development of optimal therapeutic goals for clinical trials. They have stated that although therapies for RAhave changed considerably over the 2 decades, criteria for inclusion in clinical trials – which belong to a time when drug therapy was not as effective as today – have not (1, 2).

Considering that our data come from a tertiary referral centre in Turkey, our findings may be interpreted as supporting the notion of a milder disease course in Mediterranean countries. Current literature for rheumatology is based on clinical studies performed in the West where the course of rheumatoid arthritis is considered to be more severe than that of Mediterranean countries. Sokka *et al*. have reported a discrepancy between characteristics of the patients seen in daily practice and that enrolled in clinical trials. Similarities of the data between two different settings like United States and Turkey might suggest that these findings are more generalizable rather than being due to geographical differences. However, our findings imply that this discrepancy would be more pronounced in a Mediterranean country.

We, like Sokka and Pincus, emphasize the need for development of new criteria for inclusion in clinical trials which, in addition, should be tailored to possible geographical clinical differences in disease presentation. In geographical places where RA is known to have a milder disease course, a milder set of clinical activity criteria – such as the presence of fewer painful and swollen joint counts – could be sought.

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