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Most rheumatoid arthritis patients seen in the "real world" do not qualify for clinical trials for the treatment of rheumatoid arthritis

Klinikte görülen romatoid artrit hastalarının çoğu romatoid artrit tedavisi için yapılan klinik çalışmaların ölçütlerine uymuyor

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Objectives: We analyzed rheumatoid arthritis (RA) patients seen in a cohort from Brooklyn, NY over the last three years to determine what percentage of patients would fulfill common inclusion criteria for RA clinical trials at any time during their care.

Patients and Methods: One hundred and twenty-three consecutive patients with RA, seen between April 2001 and December 2003 by a single rheumatologist, were included. Patients were analyzed according to whether they met four common inclusion criteria in most recent RA trials, and according to the inclusion criteria for the recent anti-tumor necrosis factor alpha (anti-TNFα) trial involving etanercept and methotrexate in early RA (ERA trial) and the STAR (Safety Trial of Adalimumab in Rheumatoid arthritis) trial. All visits were analyzed to identify any visit where patients fulfilled the inclusion criteria.

Results: When the most common inclusion criteria for RA clinical trials were applied, 3/146 (2.1%) visits and two of 72 (2.8%) patients fulfilled these criteria. The inclusion criteria for the ERA and STAR trials were met in 4/123 (3.3%) and 17/123 (13.8%) patients, respectively.

Conclusion: A large majority of RA patients seen in this cohort would not have qualified for the most common RA clinical trials and the recent anti-TNFα trials. It is timely to consider new inclusion criteria for RA clinical trials to reflect the current characteristics of most RA patients. This would increase the applicability of the results of these important and usually very expensive studies and therapies.

Key words: Arthritis, rheumatoid; patient selection; randomized controlled trials/standards.

Amaç: Brooklyn New York'ta üç yıl boyunca takip edilen romatoid artritli (RA) hasta grubunda, tedavinin belirli bir anında ne kadar hastanın, RA ile ilgili klinik çalışmalarda kullanılan katılım ölçütlerine uygun olduğu araştırıldı.

Hastalar ve yöntemler: Çalışmaya, Nisan 2001 ile Aralık 2003 tarihleri arasında aynı romatolog tarafından izlenen ardışık 123 RA'lı hasta alındı. Hastaların çalışmalara katılma için en sık kullanılan dört ölçüte ve erken RA'da etanersept ve metotreksat kullanımıyla ilgili anti-TNFα çalışmalarına (ERA çalışması) katılma ölçütlerine ve STAR çalışmasının (Safety Trial of Adalimumab in Rheumatoid arthritis) katılma ölçütlerine uygun olup olmadıkları değerlendirildi. Hastaların bütün vizitleri incelenerek, herhangi bir vizitte bu ölçütlerin bulunup bulunmadığı araştırıldı.

Bulgular: En sık kullanılan ölçütlere bakıldığında, 3/146 (%2.1) vizitin ve 2/72 (%2.8) hastanın bu ölçütlere uygun olduğu görüldü. ERA çalışması ölçütleri için 4/123 (%3.3), STAR çalışması ölçütleri için 17/123 (%13.8) hastanın uygunluk gösterdiği görüldü.

Sonuç: Bu çalışmada değerlendirilen RA hastalarının büyük çoğunluğu yapılmış olan RA çalışmalarının ve anti-TNFα çalışmalarının katılım ölçütlerine uymamaktadır. Romatoid artritle ilgili çalışmalarda çoğu hastanın güncel özelliklerini yansıtacak şekilde yeni katılım ölçütlerinin belirlenmesi gerekmektedir. Bu şekilde bu önemli ve masraflı çalışma ve tedavilerin uygulanabilirliği de artabilecektir.

Anahtar sözcükler: Artrit, romatoid; hasta seçimi; randomize kontrollü çalışma/standartlar.

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Randomized controlled trials are the most commonly used method in determining if a drug, singly or in combination, is better than placebo or another drug or combination of drugs. Data from these are used to develop "evidence-based medicine" guidelines, and, deservedly or not, for the most part to determine how medicine is to be practiced. One of the strengths of these studies is that pre-defined criteria are applied to patients in different settings, ascertaining that similar patients are enrolled at various sites.[1]

Sokka and Pincus[1] reported in 2003 that most of the rheumatoid arthritis (RA) patients under their care did not meet most commonly used inclusion criteria for most of the RA clinical trials conducted in the 1990s. In addition, very few of their RA patients were eligible for recent anti-tumor necrosis factor alpha (anti-TNFα) trials.[2] Göğüş et al.[3] conducted a similar investigation among Turkish RA patients in Istanbul, Turkey, and found that an even lower percentage of patients were eligible for recent anti-TNFα trials.

The importance of these data is twofold. First, if only a small number of RA patients seen in routine care are eligible for clinical trials, the results of these trials cannot be extrapolated to most RA patients, thus, limiting the applicability of these studies. Secondly, these data may be pointing to a change in the character and severity of clinical symptoms of RA patients, imposing implications for both treatment and prognosis.[4]

In this study, we analyzed RA patients seen at our center in Brooklyn, NY, over the last three years, to determine what percentage of these patients would fulfill common inclusion criteria for RA clinical trials at any time during their care. We also analyzed this cohort to see if they would be eligible for the recent anti-TNFα trial involving etanercept and methotrexate in early RA patients (ERA)[5] and for the STAR (Safety Trial of Adalimumab in Rheumatoid arthritis) trial, both of which stated that their methods were designed to approximate clinical practice.[6]

PATIENTS AND METHODS

The Brooklyn Outcomes Arthritis Registry Database (BOARD) was started in 2001, to collect outcomes data for all rheumatology patients seen in our facility. All patients fill out a multidimensional health assessment questionnaire (MDHAQ) to assess functional disability on a modified HAQ (MHAQ) (range 0-3); pain, global status, and fatigue on a 10 cm visual analog scale (VAS) (0-10); duration of morning stiffness in minutes, and a checklist of 60 symptoms (0-60). Data regarding physician assessment of disease activity on a 10 cm VAS (0-10) are also recorded. Laboratory blood work, medications, and demographic information are collected and added to the database. Data are entered into an Access database designed for a standard protocol to evaluate RA.[7] To assess tenderness and swelling, all RA patients also get a 42-joint count for the following joints: hand proximal interphalangeal (n=10), metacarpophalangeal (n=10), wrist (n=2), elbow (n=2), shoulder (n=2), knee (n=2), hip (n=2), ankle (n=2), and metatarsophalangeal (n=10). Among these, the hip and shoulder joints are not examined for swelling. Radiographs of the hands and feet are obtained at baseline and yearly thereafter. However, not all data are collected at all visits. Some patients visit our office to have their methotrexate, etanercept, or adalimumab injections administered by a nurse. They fill out an MDHAQ form but no joint count is recorded because they do not present to a rheumatologist at these visits. Also, laboratory blood work is not carried out at every visit.

One hundred and twenty-three consecutive RA patients in the BOARD were included in our study. All patients met the American Rheumatism Association (ARA) criteria for RA.[8] All patients were seen between April 2001 and December 2003 by a single rheumatologist (YY).

Patients were analyzed according to whether they met four common inclusion criteria in most recent RA trials:[1] *(i)* ≥6 swollen joints; *(ii)* ≥6 tender joints; *(iii)* erythrocyte sedimentation rate (ESR) ≥28 mm/hr; *(iv)* morning stiffness ≥45 minutes.

In addition, they were analyzed according to the inclusion criteria for the ERA[5] and STAR[6] trials. Criteria for ERA included *(i)* no previous use of methotrexate (MTX); *(ii)* ≥12 tender joints and ≥10 swollen joints; *(iii)* rheumatoid factor positivity or radiographic erosions; *(iv)* morning stiffness ≥45 minutes, or ESR ≥28 mm/hr. (C-reactive protein was not included in these criteria because it was not available for all the patients and the normal cutoff level was different for different laboratories). Criteria for the STAR trial included *(i)* ≥9 tender joints and ≥6 swollen joints; *(ii)* no history of biologic agent use.

TABLE I

Characteristics of 123 patients

	No.	Percentage	Mean±SD	Median	Range
Age (years)			55.6±14.9		
Sex					
Female	98	79.7			
Male	25	20.3			
Race					
Black	45	36.6			
Caucasian	35	28.5			
Hispanic	34	27.6			
Asian	9	7.3			
Education (years)			12.5±3.5		
Disease duration (years)			1.9±2.1	1.3	0.1-16
Rheumatoid factor positivity	101	82.1			
Swollen joint count			1.5±3.3	0	0-26
Tender joint count			3.8±4.6	2	0-26
Erythrocyte sedimentation rate (mm/hr)			32.9±30.4	21	1-140
Morning stiffness (min)			48.9±70.9	20	0-301
Pain score			5.2±2.9	5.5	0-10
Fatigue score			4.7±3.0	4.8	0-10

Since remission is one reason for not meeting inclusion criteria,[1] patients were analyzed according to whether they met the American College of Rheumatology (ACR) criteria for remission, which are *(i)* no joint swelling or soft tissue swelling of tendon sheaths; *(ii)* no joint tenderness or pain on motion; *(iii)* normal ESR; *(iv)* morning stiffness ≤15 minutes; *(v)* absence of joint pain on a VAS pain scale (VAS=0); *(vi)* absence of fatigue on a VAS fatigue scale (VAS=0).

We analyzed all the visits that these patients had, to control for the natural course of RA consisting of active and quiet periods and to make sure we would not miss any visit where patients might fulfill inclusion criteria.

All data were entered into an Access database which was converted to Excel and analyzed using descriptive statistics.

RESULTS

Of the cohort, the mean age was 55.6±14.9 years, disease duration was 1.9±2.1 years, and 79.7% were females. Forty-five (36.6%) were black, 35 were Caucasian, 34 were Hispanic, and nine were Asian. The median level of formal education was 12 years (Table I).

The mean number of swollen joints was 1.5 and the mean number of tender joints was 3.8. The mean ESR was 32.9 mm/hr and the mean duration of morning stiffness was 48.9 minutes. The mean VAS scores for pain and fatigue were 5.2 and 4.7, respectively (Table I). One hundred and one patients (82.1%) were rheumatoid factor positive.

Half of the patients were on MTX (49.6%) at their last visit, and the most common combination

TABLE II

Disease modifying antirheumatic drugs at last visit

Drugs	No. of patients	%
Methotrexate (MTX)	61	49.6
Hydroxycholoroquine	50	40.7
Prednisone	46	37.4
Sulfasalazine (SLZ)	30	24.4
Leflunomide	18	14.6
Etanercept	12	9.8
Combination therapies		
MTX + Prednisone	45	36.6
SLZ + Prednisone	24	19.5
MTX + Hydroxycholoroquine	19	15.5
SLZ + Hydroxycholoroquine	13	10.6
MTX + SLZ	10	8.1

TABLE III

Number of patient visits meeting common inclusion criteria for RA clinical trials

Criteria	Total		ESR ≥28 mm/hr		Morning stiffness ≥45 min	
	No.	%	No.	%	No.	%
≥6 swollen joints	43/461	9.3	5/11	45.5	23/38	60.5
≥6 tender joints	127/460	27.6	19/41	46.3	50/113	44.3
Erythrocyte sedimentation rate (ESR) ≥28 mm/hr	107/233	45.9	NA	–	64/214	29.9
Morning stiffness ≥45 min	233/682	34.2	95/214	44.4	NA	–
≥6 swollen joints+≥6 tender joints	42/460	9.1	5/11	45.5	23/37	62.2
+ ESR ≥28 mm/hr or morning stiffness ≥45 min	25/146	17.1	NA	–	NA	–
+ ESR ≥28 mm/hr and morning stiffness ≥45 min	3/146	2.1	NA	–	NA	–

NA: Not applicable.

treatment was MTX and low-dose (≤5 mg) oral prednisone (36.6%) (Table II).

Patients had a total of 729 visits over 32 months. Joint counts were recorded in 461 of these visits. Patients had ≥6 swollen joints in 43 visits (9.3%), ≥6 tender joints in 127 (27.6%) visits, and both in 42 (9.1%) visits (Table III).

Seventy-two patients had 146 visits where all the data were recorded. Among these, a combination of three (≥6 swollen and ≥6 tender joints, and ESR ≥28 mm/hr or morning stiffness ≥45 minutes) were seen in 25 visits (17.1%).

ESR ≥28 mm/hr was seen in 107 (45.9%) of 233 visits. Morning stiffness ≥45 minutes was reported in 233 visits (34.2%).

Only three visits (2.1%) of two patients fulfilled the common inclusion criteria for recent RA trials (Table III).

According to the ERA inclusion criteria, only four patients (3.3%) were found to be eligible for the study based on clinical/laboratory findings. However, only one patient remained eligible when the criterion of previous use of MTX was applied.

Concerning the STAR trial inclusion criteria, 28 (6.1%) of 460 visits and 20 patients (16.3%) were eligible. When the "no history of biologic agents" criterion was applied, three patients no longer fit the inclusion criteria, making 17 patients (13.8%) eligible.

We also analyzed if any of these patients met the ACR remission criteria for RA (Table IV). In 290/461 (62.9%) visits patients had no swollen joints, in 127/460 (27.6%) visits had no tender joints, in 126/233 (54.1%) visits had normal ESR values, in 320/682 (46.9%) visits had morning stiffness of less than 15 minutes, in 93/729 (12.8%) visits had a VAS pain score of 0, and in 126/718 (17.6%) visits had a VAS fatigue score of 0. Only one patient (1.4%) met the remission criteria at four (2.7%) out of 146 visits.

TABLE IV

Number of patient visits meeting the ACR remission criteria

Measure	No. of visits	Percentage
No swollen joints (0-28)	290/461	62.9
No tender joints (0-28)	127/460	27.6
Normal erythrocyte sedimentation rate	126/233	54.1
Morning stiffness ≤15 minutes	320/682	46.9
No pain (<1 on 0-10 VAS)	93/729	12.8
No fatigue (<1 on 0-10 VAS)	126/718	17.6
No. of visits meeting remission criteria	4/146	2.7
No. of patients meeting remission criteria	1/72	1.4

DISCUSSION

Based on their data, Sokka and Pincus[1,2] concluded that most of the RA patients seen in routine care did not meet common inclusion criteria for RA clinical trials and also did not meet inclusion criteria for the recent anti-TNFα trials. They used the last[1] and the first visits[2] of their patients in two studies, respectively.

We examined all visits of 123 patients over 32 months. Our results showed that less than 3% of all visits and patients would qualify for the most common RA clinical trials and the ERA trial. The inclusion criteria of the STAR trial, however, fared better, covering 16.3% of patients for eligibility. By setting the inclusion criteria to involve smaller numbers of swollen and tender joints, more patients are encompassed by the STAR criteria. When ESR and morning stiffness cutoff levels were not incorporating into the inclusion criteria, the STAR trial became more inclusive than the common clinical trial criteria even though the numerical requirements for swollen and tender joints were similar. Only one patient met the ACR remission criteria in our study. Sokka and Pincus[1] found that none of the patients fulfilled the remission criteria.

There are some shortcomings of our study. This is a cohort from one rheumatology practice of one rheumatologist. As a treatment policy, all patients are treated early and aggressively, and this may influence the number of patients having a higher number of swollen and tender joints. However, this also points to the fact that possibly most of these patients do not require anti-TNF agents and are adequately treated with MTX and small doses of steroids. Also, as stated in the Methods section, not all data are collected at all visits, limiting the number of visits to be eligible for all inclusion criteria.

Randomized controlled trials are important in providing data about new therapies against placebo or other disease modifying antirheumatic drugs (DMARDs). They usually select patients with high degrees of disease activity to be able to show a greater reduction in disease severity with therapy. However, this approach seems to exclude a large portion of RA patients seen everyday in the real world. Randomized controlled trials are considered superior to observational data; however, they do not measure actual patient responses seen in routine care, and it is these responses that determine how we treat RA patients and how we choose which DMARDs to use.[9] In a previous study, we showed that most rheumatologists in the current era see patients who present with less swollen and tender joints than previously.[10] If these patients (i.e. <6 swollen and <6 tender joints) were included in clinical trials, this would reflect a more valid picture of the clinical characteristics of current RA patients. It might also help in assessing the utility of the drugs being studied, in that higher ACR 20, 50, and 70 responses can be achieved when the "disease burden" to control is set to six swollen and six tender joints instead of a higher number of swollen and tender joints, allowing us to gather data applicable to the majority of our RA patients and treat them more effectively.

Observational studies and long-term cohorts that use a standard data collection protocol not only provide necessary long-term outcomes data in rheumatology, but also identify the true characteristics of RA patients seen in routine care.[9] These data suggest that the results of the recent anti-TNF trials and most of the RA trials over the last 10 years have limited applicability for the current RA patients seen in routine care.

These data may also implicate that RA, as suggested before,[4,10] may be getting less severe, making the need for redefining inclusion criteria even more urgent and important.

It has been suggested that the ACR remission criteria are very rigorous and few patients achieve them.[11] A less restrictive definition of remission has also been proposed.[12] The fact that only one patient fulfilled the ACR remission criteria in our cohort justifies the efforts to establish new remission criteria.

In summary, we believe that it is timely to consider new inclusion criteria for RA clinical trials to reflect the characteristics of the usual patient profile seen in the clinical practice. This would surely increase the real life applicability of the results of these important and usually very expensive drug studies and, consequently, allow for new drug therapies.

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