Aggressive rheumatoid arthritis registry in Italy. Characteristics of the early rheumatoid arthritis subtype among patients classified according to the ACR criteria

GIARA* Registry Study Group

*GIARA: Gruppo Italiano Artrite Reumatoide Aggressiva.

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ABSTRACT

The Italian Society of Rheumatology in the year 2000 decided to sponsor the creation of a data base (Registry) of consecutive patients who fulfilled the diagnosis of rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) criteria. The registry is designed to collect data on the "aggressive" type of RA all over the country in order to determine the percentage of patients who satisfy the established criteria among incident cases of RA and to define the therapeutic approach according to the characteristics of the enrolled patients. Predefined criteria set up by eight recognized opinion leaders on the disease were used by all the centers to create the database.

The GIARA registry (Gruppo Italiano Artrite Reumatoide Aggressiva) has now enrolled 706 patients who will be followed up for 24 months. They have been divided into two major subsets – patients with early (<4 months' disease duration) and late (>4 months) RA – with the aim of establishing whether differences in clinical, serological, radiographic and therapeutic (DMARDs: disease modifying antirheumatic drugs) parameters may distinguish the two subsets. The major conclusion of this preliminary analysis is that an overall tendency to undertreatment is discernable.

Introduction

In 1999 the Italian Society of Rheumatology (SIR) decided to analyse in a multicenter study the following previously unaddressed points:

1. the clinical and epidemiological features of rheumatoid arthritis (RA) newly admitted to rheumatology units;
2. the incidence of the most active and severe cases;
3. the initial therapeutic approach of Italian rheumatologists to RA patients, especially those with an aggressive phenotype (1).

A scientific committee composed of 8 recognized opinion leaders in Italian rheumatology met and defined the simplest items that could allow the rheumatologists operating at the community level, as well as tertiary referral centers, to establish diagnostic subtypes. All patients were required to fulfill the ACR criteria for the classification of RA. Once the classification was made, the patients were divided into two sub-cohorts, one with a disease duration of less than 2 years, and the other with a disease duration of between 2 and 5 years. Twenty tertiary and 74 secondary or primary referral centers, equally distributed between the southern (33 centers), central (22 centers) and northern regions (39 centers) of Italy were asked to recruit the first 1,000 RA patients attending their outpatient clinics over the next 12 months and to classify the RA patients into two major subsets, those with: (a) aggressive RA (ARA); or (b) non-aggressive ARA (NARA).

Using the Delphi technique the following characteristics were determined to be necessary to classify a patient as having an aggressive phenotype ARA:

1. within the first 2 years of the disease (since the onset of symptoms) a patient was defined as a carrier of the aggressive phenotype once he or she exhibited the following characteristics: (a) 10 or more swollen joints for at least 6 weeks (1); (b) positive rheumatoid factor (RF > 20 IU/ml using the nephelometric technique); and (c) the presence of at least one definite erosion on X-ray.
2. between 2 and 5 years, ARA was

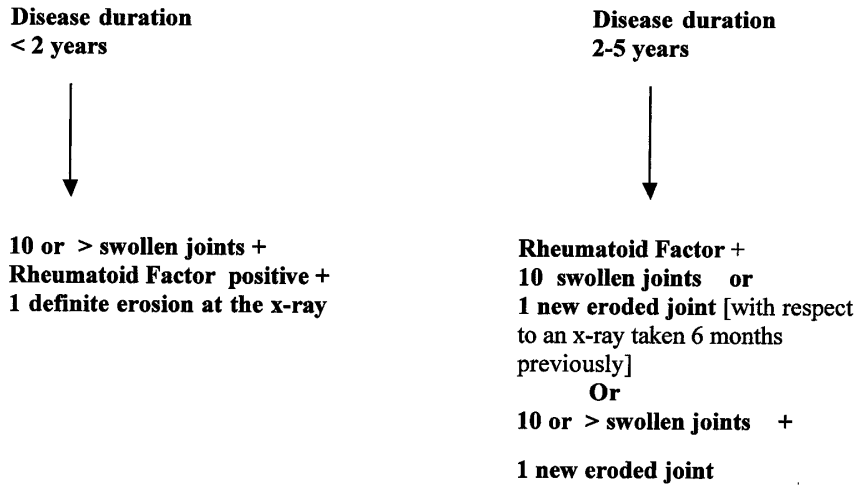

Fig. 1. Algorithm for the definition of aggressive rheumatoid arthritis in consecutive patients enrolled in the registry.

Table I. Items recorded for the whole cohort of patients entered into the registry and values (means ± SD) for the two subsets of early (< 4 months disease duration) and late (< 4 months up to 5 years) RA patients.

		Early RA (n = 341)	Late RA (n = 365)	p
Age		55.3 ± 15.3	54.1 ± 13.6	
Sex (F %)		76	79.2	
RF (> 20 IU/ml) % pos.		62.5	75.1	< 0.001
ESR mm/hr (mv)		39.7	39.4	
CRP mg/L (mv)		9.8	10.5	
Tender joint count		18.3	19.2	
Swollen joint count		11.50	12.1	
Physician's assessment of global activity (VAS) mv		52.1	60.5	< 0.001
Patient's assessment of global activity (VAS) mv		57.7	62.2	
Pain (VAS) mv		58.7	57.7	
Number of eroded joints (hands, feet) mv		1.4	2.6	< 0.001
Analgesics- NSAIDs	%	68.9	57.3	0.03
Steroids on Rx	%	47.0	66.4	< 0.001
No DMARDs	%	51.1	83.3	(0.001
DMARDs monotherapy	%	15.2	16.4	
Methotrexate (MTX)	%	18.9	42.0	< 0.001
Cyclosporine A (CsA)	%	2.4	10.3	< 0.001
Sulphasalazine (SSZ)	%	1.2	5.7	0.002
Antimalarials (AM)	%	18.3	29.0	< 0.001
Combination of 2 DMARDs	%	17.1	40.5	< 0.001
Combination of 3 DMARDs	%	3.7	10.3	< 0.001
SF-36 PF mv		48.1	43.2	0.02
SF-36 RP mv		21.6	25.0	
SF-36 PI mv		33.1	36.6	0.02
SF-36 GH mv		44.0	36.7	< 0.001
SF-36 VT mv		41.7	41.1	
SF-36 SF mv		54.1	51.8	
SF-36 RE mv		38.7	37.5	
SF-36 MH mv		51.0	52.0	
SF-36 MCS mv		40.3	39.8	
SF-36 PCS mv		33.0	32.2	
HAQ mv		1.4	1.4	

ERA:early rheumatoid arthritis; LARA: late rheumatoid arthritis; PF:physical functioning ; RP: role-physical; PI: pain index; GH: general health perception; VT: vitality; SF: social functioning; RE:role - emotional; MH:mental health; MCS:mental component scale; PCS:physical component scale; HAQ: health assessment questionnaire.

defined by the presence of: (a) positive RF plus 10 swollen joints or at least one new eroded joint with respect to an x-ray taken 6 months previously; or (b) 10 swollen joints plus one new eroded joint, in the absence of RF-positive RA (Fig. 1).

A follow-up period of 24 months was established in order to accumulate longitudinal data for each patient in the registry, and to obtain clues as to the possible influence of each variable on the radiographic and disability outcomes.

Items in the Registry

For each patient the following were recorded: demographic data (age, sex, initials); disease-related parameters: date of the first visit, date of diagnosis since the beginning of the intial symptoms, weight, height, arterial pressure, number of swollen joints in a 66-swollen joint count, number of tender joints in a 68-tender joint count, global assessment by the patient and by the physician (using a visual analogue scale), pain (visual analogue scale), Health Assessment Questionnaire (HAQ, validated Italian version) (2) for functional status, Medical Outcome study 36-item Short Form (SF-36, validated Italian version) (3), x- rays of the hands (postero-anterior) and feet (antero-posterior), biochemistry assays (liver function tests - ALT, g-GT, alkaline phosphatase), haematology (RBC, WBC, platelet counts), urine sediment, acute phase reactants [erythrocyte sedimentation rate (Westergren), C-reactive Protein (nephelometric assay)], uricemia, creatinine and creatinine clearance, blood urea, RF positivity; co-morbidities; drug treatments: previous therapies administered for symptoms, therapies administered after the first diagnosis (NSAIDs, DMARDs in monotherapy or in combination, steroids considered as DMARDs when used at the daily dose of 10 mg prednisone equivalent, route of administration of each medication, duration of the therapeutic schedule), therapies administered for the co-morbidities; and surgery already performed or to be performed during the follow-up.

Each patient was informed of the aim

of the study and the nature of the registry and the follow-up, and their consent obtained before they were enrolled.

Each center was allowed to recruit no more than 2% of the whole cohort in order to have an equal distribution of patients from all over the country.

Some of the x-rays (randomly selected) were evaluated by an independent reader (radiologist) at one of the centers during the follow-up in order to have an independent evaluation of disease progression during the follow-up.

Registry

The first patient was registered in January 2001, and the last patient in February 2002. At the end of the recruitment period over 1,000 patients were registered.

Preliminary analysis of the data set (complete data was available for 706 patients) at this interim point allows us to make certain observations regarding early RA. Inclusion required in particular certain clinical and laboratory assessments thought to be necessary for the correct classification of the patients (rheumatoid factor-RF, number of swollen joints, assessment of eroded joints) and for the further analysis of the relationship between "aggressiveness" and impaired health (HAQ and SF-36 scores). Table I lists all the data recorded in the Registry, as well as data regarding the cohort, divided into two groups based on the disease duration, early RA (disease duration < 4 months), and late RA (disease duration > 4 months and up to 5 years). It can be seen that early RA differs mainly in the physician's global assessment. None of the clinical or laboratory variables allow us to distinguish between early and late RA.

The strongest and best distinction between early and late RA, as expected, was made based on the number of eroded joints on x-ray, which clearly should allow the clinician to distinguish between those with a poor and those with a better prognosis. The data on therapy shows that rheumatologists treat patients with early and late RA quite differently. From the analysis it appears that the common praxis of Italian rheumatologists is to treat early RA mainly with NSAIDs; in a lower number of cases steroids are used and in less than a quarter of the cases DMARDs, the two most common being methotrexate (MTX) and antimalarials (AM). Interestingly 17% of the early RA patients receive combination therapy within 4 months from the disease onset. By contrast, in late RA more than 40% of the patients receive MTX,AM or a combination of the two, and 10% receive cyclosporine A (CsA) in combination with the previous 2 DMARDs.

Conclusion

The major aim of the GIARA Registry (Gruppo Italiano Artrite Reumatoide Aggressiva) is to study the therapies adopted by rheumatologists to treat two subtypes of RA, the aggressive and the less aggressive phenotypes. In this paper, we focused on characteristics of the patients, the basis of disease duration, and describe the common therapeutic approach in the two cohorts.

The first comment to be made on the data presented here is that, despite a substantial similarity in the majority of the variables between the two subsets, the therapeutic approach is definitely less aggressive in early than in late RA. There appears to be a sort of "wait and see" attitude for early RA, with NSAIDs and steroids used in this phase to see what their effect will be. The therapeutic program for late RA appears to be much more appropriate, as about 40% of the patients are treated with an aggressive pharmacologic approach. In fact, about the same percentage of patients is treated with combination therapies and 10% with a triple DMARD schedule.

Considering that RA represents a "medical emergency" (4,5), the findings from this Registry indicate that the situation in Italy in terms of treatment strategies is far from ideal (6). The first need is to implement DMARD monotherapy in the great majority of patients in the early phases of the disease, and after identifying severe cases based on prognostic factors, with combination therapies in the more advanced phases. However, this study of the situation was necessary before a campaign of education and implementation can be begun.

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