The Italian Registry of Aggressive Rheumatoid Arthritis — the GIARA Project

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ABSTRACT. ***Objective.*** In 1999, the Italian Society of Rheumatology started a project to determine the prevalence and clinical characteristics of aggressive rheumatoid arthritis (ARA).

Methods. For 1 year, all patients with RA for < 5 years and referred to participating centers were entered in a registry and classified as having ARA if they fulfilled the following criteria: 10 swollen joints for at least 6 weeks, positive rheumatoid factor (RF), and at least one bone erosion (if disease duration of 2 years); (a) RF-positive and having 10 swollen joints or at least one newly eroded joint, or (b) if RF-negative, having 10 swollen joints and at least one newly eroded joint (if disease duration > 2 to < 5 years).

Results. The 94 participating centers enrolled 1218 patients with RA, 1130 of whom had enough data to be classified as ARA (29.0%) or non-ARA (71.0%). The frequency of ARA was 15% in the 2-year group and 63% in the > 2 to < 5-year group, but 35% of the patients in the 2-year group had erosions. Bone erosions were associated with disease duration, a Health Assessment Questionnaire value > 1.5, female sex, and RF positivity. Conditions other than RA were recorded in about 50% of the patients, and only 30%–40% were taking disease modifying antirheumatic drugs.

Conclusion. In an Italian RA population, the GIARA (Gruppo Italiano Artrite Reumatoide Aggressiva) criteria for ARA were met by 15% of the patients with disease duration of 2 years, but erosions were seen in 35%. Upon referral, most of the RA patients were inadequately treated and had other conditions. (First Release Nov 15 2007; J Rheumatol 2007;34:2374–81)

Key Indexing Terms:
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EARLY ARTHRITIS
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Rheumatoid arthritis (RA) is a relatively frequent autoimmune chronic inflammatory disease that, according to a recent report, affects 0.46% of the Italian population[1] and, as a result of persistent synovitis, leads to joint damage and functional disability in a substantial number of patients. It has now been established that early intervention, aggressive treatment, and combination therapy with disease modifying antirheumatic drugs (DMARD) as small molecules or biological agents are needed to prevent a poor outcome in severe RA[2-11]. However, as aggressive RA treatment is expensive and may be toxic, and only some patients develop structural joint damage and the related disability, early identification of the patients with aggressive disease is of paramount importance.

The recent introduction of potent biological drugs that have greatly increased the chances of achieving thorough disease control but are costly and potentially harmful has reinforced the concept of tailoring the treatment to disease severity. Unfortunately, the literature is not uniform in identifying prognostic factors, and there are differences in opinion concerning the identification of clinical, radiological, and laboratory indicators predicting poor outcome[12,19]. As there are no data about the frequency and characteristics of aggressive RA in the Italian population, the Italian Society of Rheumatology supported the creation of the Italian Group for the study of Aggressive Rheumatoid Arthritis (GIARA: Gruppo Italiano Artrite Reumatoide Aggressiva) in 1999. The objective of the GIARA project was to create an Italian Registry of aggressive

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RA with the aims of (1) establishing the prevalence of aggressive RA in an Italian rheumatoid population; (2) defining the clinical characteristics of RA patients newly admitted to rheumatology centers; and (3) evaluating the therapeutic approach of Italian rheumatologists to aggressive RA.

This report describes only the baseline characteristics of the study population, except for the therapy data, of which the 12-month results are shown. We used the acronyms ARA and NARA for aggressive RA and non aggressive RA, respectively. The members of the GIARA are listed in the Appendix.

MATERIALS AND METHODS

Definition of ARA. A steering committee of 8 rheumatologists expert in RA was appointed to draw up the protocol, and started by establishing the criteria for defining ARA, which had to be easy and quick to measure, minimally invasive, inexpensive, reliable and reproducible between study centers, as specific and sensitive as possible, and capable of predicting disease severity.

The Registry was created by entering prospectively all patients with an established diagnosis of RA according to the American College of Rheumatology (ACR) criteria[20] and a disease duration of < 5 years from diagnosis at their first referral to a participating center. They were first divided into 2 groups on the basis of disease duration (≤ 2 years and between 2 and 5 years) and then classified as having ARA or NARA on the basis of the arbitrary case definitions established by the steering committee:

1. In the case of patients with a disease duration ≤ 2 years: (a) the presence of 10 or more swollen joints for at least 6 weeks; (b) rheumatoid factor (RF) positivity (> 20 IU/ml by nephelometry); (c) the presence of at least one erosion on traditional hand and foot radiographs.
2. In the case of patients with a disease duration of 2–5 years: (a) RF positivity (as above) and the presence of 10 or more swollen joints or at least one joint with a new erosion during the previous 6 months; or (b) in RF-negative patients, 10 or more swollen joints and at least one newly eroded joint within the previous 6 months.

The patients were classified ARA or NARA only once at study entry, and so the classifications were based on the patients' clinical and radiological features at that time only.

Characteristics of the registry. The patients giving their written informed consent were entered in the GIARA registry with their age, sex, height, weight, systolic and diastolic blood pressure, disease duration, number of swollen joints on a 66-joint count, number of tender joints on a 68-joint count, patient assessment of pain using a 100-mm visual analog scale (VAS), patient and physician overall assessment of disease activity on a 100-mm VAS, disability index according to the Italian version of the Health Assessment Questionnaire (HAQ)[21], general health status according to the Italian version of the SF-36 questionnaire, the presence of erosions on antero-posterior foot and postero-anterior hand radiographs, concomitant diseases and associated treatments, current and previous DMARD therapies, current intake of corticosteroids (expressed as prednisone equivalents) and nonsteroidal antiinflammatory drugs (NSAID), and hemato-biochemical measures [hemoglobin, hematocrit, red and white blood cells, platelets, 1-hour erythrocyte sedimentation rate (ESR) by the Westergren method, C-reactive protein (CRP), serum creatinine and creatinine clearance, serum nitrates, uric acid, potassium, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, RF]. For the purposes of the registry, these variables had to be recorded every 6 months, except for radiography in the NARA group, which was scheduled every 12 months.

Given the well known interobserver variability in making joint counts and reading radiographs, investigator training sessions were held before the start of the study. However, it was decided that a number of radiographs randomly selected from all sites had to be independently read by an expert reader. An exploratory analysis of the associations between disease severity (defined on the basis of erosions and HAQ values > 1.5) and the baseline characteristics of the patients with centralized radiograph reading was also performed.

The registry enrolment period was 12 months and each patient was followed up for 24 months. In order to ensure balanced patient distribution throughout the country, no center was allowed to include more than 2% of the entire study population.

Registry centers and patients. Ninety-four study centers throughout Italy (20 tertiary and 74 primary or secondary care centers) enrolled 1218 patients: the first patient was entered in January 2001 and the last in February 2002. Given the high frequency of missing data, the steering committee identified a core set of data considered essential for the analysis, which included basic demographic data, the ACR criteria for the evaluation of RA (number of swollen and tender joints, patient pain assessment, patient and physician overall assessment of disease activity, HAQ score, ESR, and CRP), RF (a well known risk factor of disease severity), and hand and foot radiographs (bone erosions are the most important indicators of disease severity).

Statistical analysis. As the aim of the study was to provide an overview of the frequency and characteristics of aggressive RA in an Italian population, the statistical analysis was purely descriptive. The significances of the differences due to the selection criteria (e.g., joint erosions in the ARA and NARA groups) were not statistically weighed. As the analysis was based on categorizations of ARA/NARA and disease duration (≤ 2 or > 2 < 5 yrs), all comparisons were made using a 2 × 2 factorial design and analysis of variance (ANOVA). Significant interactions between 2 factors were further compared between times within the ARA and NARA groups. As the data for some parameters could have a non-normal distribution, ANOVA of ranked data was also used; the significance of the results of the analyses of original data are reported only if the original and ranked data analyses were consistent. As there was no protection against the multiplicity of tested parameters, the results should be interpreted cautiously.

Fisher's exact test was used to evaluate the association between RF and the presence of erosions, and to compare the percentages of NARA and ARA subjects treated with each antirheumatic drug. McNemar's test was used to evaluate changes in therapy from baseline to Month 12. P values < 0.05 were considered significant. The associations between clinical factors and the markers of disease severity (erosions and the HAQ index) were evaluated by means of logistic regression; the final model was obtained using a backward elimination method with a threshold of 0.10, and Wald confidence intervals (95%) were calculated for the independent variables remaining in it. When sufficient HAQ data were available, the sample was split and the model obtained from the first subsample was checked against the second. As the model obtained from the subsample was fully consistent with that obtained on the whole sample, only the data of this sample are presented.

RESULTS

Figure 1 shows the process of patient enrolment. The minimum dataset for patient classification was available for 1130 of the 1218 enrolled patients: 327 patients (29.0%) met the ARA criteria and 803 (71.0%) were classified as NARA. At the time of analysis, a complete set of core data was available for 706 patients, who were therefore analyzed in detail; there were no significant differences in the demographic and clinical data relating to these patients and those of the registered population as a whole.

The population of 706 patients analyzed had a mean age of 54.7 ± 14.4 years, and included 548 women (77.6%) with a mean age of 53.8 ± 14.8 years, and 158 men (22.4%) with a mean age of 57.7 ± 12.7 years: 199 (28.2%) were classified as ARA and 507 (71.8%) as NARA. Mean disease duration was 5.24 ± 6.79 months in the ARA/≤ 2-year subgroup and 4.13 ± 5.88 months in the NARA/≤ 2-year subgroup; the corresponding figures in the ARA/2–5-year and NARA/2–5-year subgroups were 41.33 ± 10.96 and 40.53 ± 11.34 months, respectively.

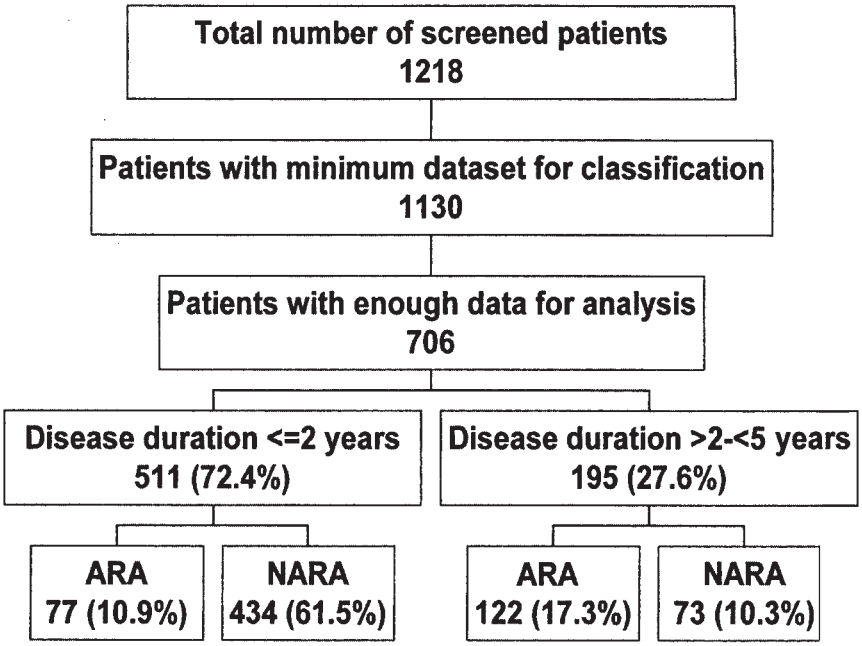

Figure 1. Patient groups by disease duration (≤ 2 years and > 2 but < 5 years) and ARA/NARA criteria. ARA: aggressive RA; NARA: not aggressive RA.

Radiological, laboratory, and clinical features. As expected, the percentage of patients with erosions was much greater in the ARA group (164/199, 82.4%) than in the NARA group (137/507, 27.0%). The data concerning erosions and RF positivity are shown in Table 1. The majority of patients with erosions in both groups had between one and 4 erosions. Only about 12% of the 511 patients in the ≤ 2-year group and about 28% of the 195 patients in the 2–5-year group had more than 4 erosions. The mean number of eroded joints in the ARA group was obviously higher than in the NARA group (4.7 ± 6.0 and 1.0 ± 2.4, respectively). All of the 77 ARA/≤ 2-year patients were RF-positive (by definition), as were 117 (95.59%) of the 122 ARA/2–5-year patients; thus, only 5 of the 2–5-year patients were classified as ARA on the basis of the criterion of "at least one newly eroded joint within the previous 6 months if RF was negative." Given the inclusion criteria, the combined presence of erosions and RF was very high in the ARA group (about 76%) and low in the NARA group (about 12.8%). The association between RF positivity and the presence of erosions in the sample as a whole was significant ($p < 0.001$): 44% of the patients had erosions and were RF-positive, and 31% were both RF- and erosion-negative.

The mean values of the patients' main clinical and laboratory characteristics are shown in Table 2: all were significantly higher in the ARA group than in the NARA group, and slightly higher in the ≤ 2-year group than in the 2–5-year subgroups. Mean values of all the other laboratory data (not shown) were comparable in the ARA and NARA groups.

Quality of life was evaluated by means of the SF-36 questionnaire (8 items), the results of which are shown in Table 3. With the exception of Role-physical, the mean values of all the items were significantly lower in the ARA group, and were

Table 1. Erosions and RF positivity.

Feature	NARA			ARA		
	≤ 2 yrs, n = 434 (%)	> 2 < 5 yrs, n = 73 (%)	Subtotal, n = 507 (%)	≤ 2 yrs, n = 77 (%)	> 2 < 5 yrs, n = 122 (%)	Subtotal, n = 199 (%)
No. of patients with 1–4 erosions	72 (16.6)	19 (26.0)	91 (17.9)	47 (61.0)	46 (37.7)	93 (46.7)
No. of patients with > 4 erosions	32 (7.4)	14 (19.2)	56 (11.0)	30 (39.0)	41 (33.6)	71 (35.7)
Mean no. of eroded joints	0.8 ± 2.3	1.9 ± 3.1	1.0 ± 2.4	4.9 ± 5.6	4.7 ± 6.3	4.7 ± 6.0
No. of RF-positive patients	255 (58.8)	38 (52.1)	293 (57.8)	77 (100)	117 (95.9)	194 (97.5)
No. of RF- and erosion-positive patients	54 (12.4)	11 (15.1)	65 (12.8)	77 (100)	74 (60.6)	151 (75.9)

NARA: not aggressive rheumatoid arthritis; ARA: aggressive rheumatoid arthritis; RF: rheumatoid factor.

Table 2. Main clinical and laboratory features. Values are given as mean (SD).

Clinical and Laboratory Features	NARA ≤ 2 yrs, n = 434	NARA > 2 < 5 yrs, n = 73	NARA Subtotal, n = 507	ARA ≤ 2 yrs, n = 77	ARA > 2 < 5 yrs, n = 122	ARA Subtotal, n = 199	p*
No. of tender joints	17.9 (11.4)	13.0 (8.9)	17.2 (11.2)	24.3 (12.5)	21.8 (11.5)	22.7 (11.9)	< 0.0001
No. of swollen joints	10.5 (7.4)	6.3 (4.6)	9.9 (7.3)	18.6 (7.7)	15.2 (7.7)	16.5 (7.9)	< 0.0001
Physician-assessed disease activity (100 mm VAS)	51.5 (20.5)	46.7 (20.8)	50.8 (20.6)	67.8 (17.8)	64.2 (18.8)	65.6 (18.5)	< 0.0001
Patient-assessed disease activity (100 mm VAS)	58.3 (24.6)	46.5 (23.6)	56.6 (24.8)	64.7 (24.1)	60.6 (24.3)	62.2 (24.3)	< 0.0001
Pain (100 mm VAS)	57.1 (24.0)	49.2 (22.2)	55.9 (23.9)	63.9 (22.1)	60.6 (23.3)	61.9 (22.8)	< 0.0001
ESR, mm/h	37.5 (23.7)	36.2 (22.3)	37.3 (23.5)	48.2 (28.0)	43.1 (23.9)	45.1 (25.6)	< 0.0001
CRP, mg/dl	9.3 (25.3)	6.4 (12.4)	8.9 (23.9)	16.2 (31.3)	11.7 (22.2)	13.4 (26.1)	0.00746

* Difference between mean subtotals in the ARA and NAA groups.

Table 3. Mean values (SD) of the 8 items in the SF-36 quality of life questionnaire. Values are mean (SD).

Item (0–100 scale)	NARA ≤ 2 yrs, (434 pts)	NARA > 2 < 5 yrs, (73 pts)	NARA Subtotal, (507 pts)	ARA ≤ 2 yrs, (77 pts)	ARA > 2 < 5 yrs, (122 pts)	ARA Subtotal, (199 pts)	p*
Physical functioning	48.4 (26.8)	46.6 (28.3)	48.1 (27.0)	38.9 (24.8)	39.4 (21.5)	39.2 (22.8)	< 0.001
Role-Physical	23.6 (35.5)	30.8 (39.0)	24.7 (36.1)	19.8 (32.8)	20.3 (33.1)	20.1 (32.9)	NS
Pain index	34.9 (21.1)	42.7 (22.0)	36.1 (21.3)	31.4 (22.5)	32.3 (17.2)	31.9 (19.4)	< 0.005
General health perceptions	42.9 (17.3)	37.7 (21.1)	42.2 (18.0)	37.8 (17.3)	33.7 (16.4)	35.3 (16.8)	< 0.01
Vitality	42.2 (20.6)	46.5 (19.0)	42.8 (20.4)	38.7 (22.2)	37.0 (17.9)	37.7 (19.6)	< 0.005
Social functioning	54.6 (25.9)	58.9 (27.0)	55.2 (26.1)	45.8 (25.9)	47.8 (23.7)	47.0 (24.5)	< 0.0001
Role-Emotional	39.2 (41.9)	46.1 (39.5)	40.2 (41.6)	35.1 (39.3)	31.1 (37.8)	32.7 (38.3)	< 0.05
Mental health index	52.0 (20.8)	55.4 (21.3)	52.5 (20.9)	47.7 (22.0)	49.5 (19.8)	48.8 (20.7)	< 0.05
SF-36, physical component	33.3 (8.6)	33.4 (10.7)	33.3 (8.9)	30.8 (8.4)	30.5 (6.9)	30.6 (7.5)	< 0.005
SF-36, mental	40.4 (11.0)	42.8 (11.1)	40.7 (11.0)	38.4 (12.1)	38.4 (10.2)	38.4 (10.9)	< 0.01

* Difference between the total values in the ARA and NARA groups.

generally lower in the ≤ 2-year than in the 2–5-year subgroups (with the exception of General Health Perceptions, Vitality, and Role-emotional, which were lower in the ARA/2–5-year subgroup; and Physical Functioning, which was lower in the NARA/2–5-year subgroup). The mean value (SD) of the HAQ disability index was 1.3 (0.8) in the NARA group and 1.6 (0.7) in the ARA group ($p < 0.0001$). In the NARA ≤ 2-year and 2–5-year subgroups, it was 1.3 (0.7) and 1.2 (0.8), respectively; in the ARA ≤ 2-year and 2–5-year subgroups, it was 1.6 (0.8) and 1.6 (0.6), respectively.

Comorbidities and therapy. The comorbidities recorded upon entry in the GIARA registry are shown in Table 4. Cardiovascular disorders were the most frequent concomitant diseases in both groups, followed by metabolic/endocrine conditions.

In terms of therapy, only 409 (57.9%) of the 706 patients analyzed were receiving corticosteroids and/or DMARD for their rheumatic condition at baseline. To determine the influence on treatment of referral to a rheumatology center, the baseline and 12-month data of the patients with a complete dataset at study end were evaluated independently (Tables 5A, 5B).

Analysis of the data for patients with centralized radiograph readings. Centralized radiograph readings were made in 122/706 patients with a complete set of core data. A logistic regression model with the presence of erosions as the dependent variable showed that the only independent variables of the set considered (VAS scores, number of swollen joints and tender joints, RF, age, sex, disease duration, ESR, CRP, and HAQ dichotomized into < 1.5 and ≥ 1.5) retained at the 0.10 probability level were sex (male vs female: point estimate 0.367, 95% CI 0.126–1.072), disease duration (point estimate 2.277, 95% CI 1.636–3.170), and HAQ score > 1.5 (point estimate 0.472, 95% CI 0.197–1.130). A logistic regression model using HAQ as the dependent variable showed that pain (point estimate 1.032, 95% CI 1.024–1.041), the number of tender joints (point estimate 1.029, 95% CI 1.012–1.047), age (point estimate 1.025, 95% CI 1.012–1.038), sex (male vs female: point estimate 0.655, 95% CI 0.472–1.004), CRP (normal vs abnormal: point estimate 0.418, 95% CI 0.275–0.635), and the SF-36 mental component (point estimate 0.956, 95% CI 0.939–0.972) all correlated significantly with HAQ ≥ 1.5.

DISCUSSION

The 94 Italian rheumatology centers participating in the GIARA study enrolled 1130 patients, but only 706 fulfilled

Table 4. Comorbidities at study entry. Data are number (%).

Disease Type	NARA > 2 < 5 yrs, n = 73	NARA ≤ 2 yrs, n = 434	NARA Total, n = 507	ARA 2–5 yrs, n = 122	ARA ≤ 2 yrs, n = 77	ARA Total, n = 199
Cardiovascular	22 (30.1)	100 (23.0)	122 (24.1)	18 (14.8)	23 (29.9)	41 (20.6)
Liver	4 (5.5)	16 (3.7)	20 (3.9)	6 (4.9)	5 (6.5)	11 (5.5)
Gastrointestinal	7 (9.6)	42 (9.7)	49 (9.7)	13 (10.7)	8 (10.4)	21 (10.6)
Metabolic/endocrine	11 (15.1)	81 (18.7)	92 (18.1)	18 (14.8)	23 (29.9)	41 (20.6)
Neurological/psychiatric	6 (8.2)	24 (5.5)	30 (5.9)	2 (1.6)	4 (5.2)	6 (3.0)
Respiratory	2 (2.7)	31 (7.1)	33 (6.5)	4 (3.3)	5 (6.5)	9 (4.5)
Renal	2 (2.7)	8 (1.8)	10 (2.0)	3 (2.5)	0 (0.0)	3 (1.5)
Urogenital	0 (0.0)	24 (5.5)	24 (4.7)	3 (2.5)	6 (7.8)	9 (4.5)
Neoplastic	1 (1.4)	5 (1.2)	6 (1.2)	1 (0.8)	1 (1.3)	2 (1.0)
Other	6 (8.2)	27 (6.2)	33 (6.5)	4 (3.3)	5 (6.5)	9 (4.5)
Totals	40 (54.8)	237 (54.6)	277 (54.6)	47 (38.5)	51 (66.2)	98 (49.2)

Table 5A. Distribution of antirheumatic treatments (corticosteroids and DMARD) at study entry in the 409/706 patients undergoing therapy and the 138/218 with 12-month data. Data are percentages of treated subjects in the subgroups.

Treatment	NARA, n = 507	ARA, n = 199	p	NARA, n = 154	ARA, n = 64	p
Treated	n = 275 (54.2%)	n = 134 (67.3%)	< 0.005	n = 95 (61.7%)	n = 43 (67.2%)	NS
Corticosteroids, %	53.5	65.7	< 0.05	52.6	62.8	NS
DMARD monotherapy, %	43.6	47.0	NS	41.1	58.1	NS
Methotrexate	19.6	23.1	NS	18.9	30.2	NS
Antimalarials	16.4	13.4	NS	12.6	11.6	NS
Cyclosporine	3.3	1.5	NS	3.2	0.0	NS
Sulfasalazine	1.8	4.5	NS	4.2	7.0	NS
Other*	2.5	4.5	NS	2.1	9.3	NS
DMARD combination therapy	9.8	17.9	< 0.05	12.6	18.6	NS

* Gold salts, thiols, cyclophosphamide, azathioprine, leflunomide. DMARD: disease modifying antirheumatic drugs; NS: nonsignificant.

Table 5B. Distribution of antirheumatic treatments (corticosteroids and DMARD) in the 218 patients with 12-month data. Data are percentages of treated subjects in the subgroups.

Treatment	NARA, n = 154 Baseline	NARA, n = 154 Month 12	p	ARA, n = 64 Baseline	ARA, n = 64 Month 12	p
Treated	n = 95 (61.7%)	n = 154 (100%)	NC	n = 43 (67.2%)	n = 64 (100%)	NC
Corticosteroids, %	32.5	66.2	< 0.0001	42.2	75.0	< 0.0001
DMARD monotherapy, %	25.3	51.9	< 0.0001	39.1	42.2	NS
Methotrexate	11.7	27.3	< 0.0001	20.3	23.4	NS
Antimalarials	7.8	11.0	NS	7.8	4.7	NS
Cyclosporine	1.9	8.4	< 0.005	0.0	6.3	NC
Sulfasalazine	2.6	0.6	NS	4.7	1.6	NS
Other*	1.3	4.5	NS	6.3	6.3	NS
DMARD combination therapy	7.8	46.8	< 0.0001	12.5	56.3	< 0.0001

* Gold salts, thiols, cyclophosphamide, azathioprine, leflunomide. NC: not computable; NS: nonsignificant.

the set of core criteria necessary to be included in the data analysis. However, as these patients were comparable with the registered population in demographic and clinical terms, and the percentage of ARA-NARA cases, it is likely that the data were not influenced by a selection bias. The number of patients and their even distribution throughout the country were such as to provide reliable results concerning the characteristics of early RA (disease duration < 5 yrs) in Italy; this cutoff point was chosen because at the time the study was planned (1999), 5 years was considered appropriate to define early RA. Further, it was believed to be long enough to include patients with mild (oligoarticular or palindromic) disease at onset, to obtain more complete data concerning therapies during the first years of disease, and to identify the arthritis subset that benefits most from aggressive treatment.

As the first objective of the registry was to establish the frequency of ARA in patients with early disease in Italy, it was necessary to define it. The severity of RA can be defined in many ways, but the development of irreversible structural joint damage and the related disability are indisputable signs of aggressive disease, and it has been demonstrated that radiographically revealed erosions and RF positivity are the strongest predictors of further anatomic joint damage[15]. Other factors commonly associated with a poor outcome are the number of swollen joints, high values of the HAQ disability index, disease duration, and, more recently, the presence of anti-cyclic citrullinated peptide (CCP) antibody[22]. All these factors contribute to establishing the risk of a potentially poor outcome in individual patients at a very early stage of disease. For the purposes of our registry, the GIARA Steering Committee decided to use the strongest clinical predictors of RA severity: the presence of at least one erosion, RF positivity, and at least 10 swollen joints. These were also chosen because they can be easily recorded in standard clinical practice; unfortunately, although they are powerful predictors of disease severity, anti-CCP antibody measurements could not be used because they were not widely available when the study was started.

As the characteristics of RA vary over time (patients with the disease for a few months can be very different from those who have had it for 4 years), the enrolled patients were divided into 2 subgroups on the basis of disease duration (≤ 2 or 2–5 yrs). In order to be classified as having ARA, patients with disease duration ≤ 2 years had to show all 3 risk factors (RF, bone erosions, at least 10 swollen joints), whereas those with a longer disease duration could also be RF-negative or erosion-free provided they had developed at least one new erosion (in addition to at least 10 swollen joints) over the previous 6 months or had at least 10 swollen joints (in addition to a positive RF). On the basis of the GIARA definition, the frequency of ARA was 15.1% in the ≤ 2-year subgroup and 62.6% in the 2–5-year subgroup. The low percentage of patients with ARA in the ≤ 2-year subgroup suggests that the criteria were too strict: if erosions are indicative of ARA, their presence alone may be enough to define a patient with early disease as having ARA (but this was not the case in the GIARA registry). As 104 (20.4%) of the NARA patients in the ≤ 2-year subgroup showed radiographic erosions, a total of 35% of the subjects in this subgroup developed early erosions, which is consistent with the findings of other registries of early arthritis[23]. However, as more than 60% of the patients in the 2–5-year subgroup had ARA, even 35% in the ≤ 2 year subgroup seems to be too low. This discrepancy was possibly due to the fact that the ARA criteria for patients in the 2–5-year subgroup were less strict (even erosion-free or RF-negative patients could be classified as ARA) and that RF positivity increases over time. The criteria used in our study to classify the ≤ 2-year patients as ARA proved to be poorly sensitive and therefore inadequate to establish the prevalence of ARA in early RA. However, they were easy and quick to use, minimally invasive, inexpensive, reliable, and reproducible between study centers. As the mean values of all the clinical variables of disease activity were significantly worse in the ARA population, they also proved to have construct validity for disease activity. In conclusion, patients with ARA according to the GIARA criteria were likely to have very severe RA but, as most of the patients with erosions in the ≤ 2-year subgroup did not fulfil these criteria, prevalence of ARA in early RA was underestimated. The 2-year followup of the registry patients should provide further data concerning the validity of the criteria as outcome predictors and the factors associated with a poor disease outcome.

The second objective of the GIARA project was to evaluate the clinical characteristics of Italian patients with ARA and NARA. Erosions were much more frequent in the ARA group, but not only did 20% of the NARA patients in the ≤ 2-year subgroup have erosions (see above), 62 of them (12.1%) had more than 4 erosions. In addition to confirming the relative insensitivity of the GIARA criteria in identifying ARA, this finding is even more interesting if we consider that the mean disease duration in this group was only about 5 months. A previous subanalysis of GIARA patients with very-recent-onset disease (< 4 mo) found that the median number of eroded joints in these patients was 1.4[24]. All of this also suggests that there may be a subset of RA patients with particularly aggressive disease requiring correspondingly aggressive treatment. Among the NARA patients, the mean number of joints with erosions was higher in the 2–5-year subgroup than in the ≤ 2-year subgroup (1.9 vs 0.8), probably because of the natural disease trend to develop structural damage over time. Surprisingly, the mean number of joints with erosions among the ARA patients was comparable in the 2 subgroups (4.9 vs 4.7), which suggests that erosions may tend to develop mainly in the joints in which they first occurred. However, further followup data are essential before any hypothesis can be postulated in this regard.

As the bone erosions revealed by standard radiographs represented a key element in the definition of ARA, a multivari-

ate analysis was carried out in the patients with centralized radiograph readings to identify which factors were associated with them. In the model based on all of the demographic and clinical variables, time since diagnosis was the only factor that correlated closely with the presence of erosion, although there was a weak association with female sex and a HAQ score > 1.5. This finding confirms that structural joint damage is a time-related process, but also emphasizes the difficulty in understanding which clinical factors could help identify the patients at greater risk of a poor outcome; once again, the followup data could provide useful information.

There was a significant association between RF positivity and the presence of erosions in the GIARA population as a whole (44% of the RF-positive patients had erosions, in contrast to only 31% of the RF-negative patients), which suggests that RF is associated with structural damage in Italian patients with RA as well as in other populations[25]. However, it is worth noting that this association was not confirmed in the multivariate analysis. Of the other laboratory variables, only the mean ESR and CRP values were significantly higher in both ARA subgroups (≤ 2 and 2–5 yrs), which suggests greater disease activity in the patients with more aggressive disease.

The mean values of the patient assessments of pain and disease activity and the physician assessment of disease activity were higher in both ARA subgroups, and therefore consistent with considerable disease activity in these subgroups. Analysis of the quality of life expressed by the SF-36 showed generally lower mean scores among the ARA patients, which is consistent with greater disease activity and severity. The mean scores of the HAQ disability index were high in both ARA subgroups (1.6 vs 1.3 in the NARA ≤ 2-yr subgroup and 1.2 in the NARA 2–5-yr subgroup). As a HAQ score of 1.5 seemed to discriminate patients with and without functional impairment in the GIARA population, we used a multivariate analysis to evaluate which factors were associated with a HAQ score > 1.5. In the model based on all the demographic and clinical variables, pain, number of tender joints, age, female sex, CRP, and SF-36 mental component all showed a significant correlation.

Comorbidity was quite frequent, occurring in about 50% of the population. Among the ARA patients, it was more frequent in the ≤ 2-year subgroup, whereas there was no difference between the 2 NARA subgroups. Cardiovascular diseases were the most frequent causes of comorbidity, and affected more than 20% of the patients: among the ARA patients, they were more frequent in the ≤ 2-year subgroup (29.9%), but among the NARA patients, they were more frequent in the 2–5-year subgroup (30.1%). As age was comparable in all the subgroups, there is no straightforward explanation for this difference, which suggests the need for careful monitoring of cardiovascular diseases in patients with RA. Metabolic/endocrine disorders were the second most frequent concomitant conditions (affecting nearly 20% of the population), presumably due to diabetes and hypercholesterolemia. Gastrointestinal conditions, which are usually very common in patients with rheumatic disorders because of the toxicity of a number of antirheumatic drugs, were recorded in only about 10% of the patients.

Finally, the therapy data showed that more than 40% of the patients were not receiving any antirheumatic therapy at the time of their first referral to a rheumatology center and, of those receiving therapy, only about 64% of the ARA and 53% of the NARA patients were taking DMARD. The only significant difference between the ARA and NARA groups was in the use of corticosteroids and DMARD combinations, both of which were used more frequently in the ARA group. The subanalysis of the 218 patients with a complete 12-month dataset showed that all of them were receiving DMARD therapy by Month 12. It is also worth noting that a significantly larger number of patients were using corticosteroids, and that the percentage of patients using DMARD combination therapy had risen from 7.8% to 46.8% in the NARA group, and from 12.5% to 56.3% in the ARA group. It is clear that referral to a rheumatology center had a considerable influence on antirheumatic therapy. As anti-tumor necrosis factor agents were not commercially available at the time the study started, they were not recorded in the GIARA registry, and only a few patients were taking leflunomide because in Europe it was first marketed in 1999.

In conclusion, analysis of the GIARA project baseline data yielded some interesting results. The GIARA criteria for the definition of ARA were valid and capable of identifying patients with severe and very active RA, but they were also insensitive. The prevalence of ARA in the studied population varied significantly depending on disease duration (from 15% to 60%) but, as erosions were seen in more than 35% of the patients with disease duration ≤ 2 years, the absolute number of ≤ 2-year patients with ARA was underestimated. The results showed that the GIARA criteria used to classify the registry patients as ARA or NARA were unable to identify most ARA cases in the ≤ 2-year subgroup, and therefore caution is required when using them to assess patients with early RA. Joint damage correlated mainly with disease duration (by multivariate analysis), but also with RF positivity (by univariate analysis). A HAQ disability index score of 1.5 seemed to be the cutoff value discriminating patients with ARA from those with NARA, and pain was the main determinant of disability (by multivariate analysis). Quality of life was greatly affected by disease severity and activity. Comorbidities (especially cardiovascular conditions) were very frequent and were apparently unrelated to disease duration, activity, and severity. Finally, a large number of patients were not receiving appropriate antirheumatic treatment when referred to our rheumatology centers, but the 12-month data showed that referral led to much more aggressive therapy.

APPENDIX

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