Evaluation of diagnostic and therapeutic delay in patients with rheumatoid arthritis and psoriatic arthritis

M. Iacovantuono[1], S. Ferrigno[1], P. Conigliaro[1], P. Triggianese[1], A. D'Antonio[1], F.R. Spinelli[2], A. Bergamini[1], M.S. Chimenti[1]

[1]Rheumatology, Allergology and Clinical Immunology, Department of Systems Medicine, Tor Vergata University, Rome, Italy; [2]Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University, Rome, Italy

SUMMARY

Objective. A monocentric cross-sectional study recruiting rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients residing in the Lazio region, Italy, to assess factors related to diagnostic delay and treatment accessibility.

Methods. Clinical/serological data, including the time between symptom onset, diagnosis, and the beginning of treatment, were collected. Residence, referral to a rheumatologic center, physician who made the diagnosis, and previous misdiagnosis were also evaluated.

Results. A higher diagnostic delay (p=0.003), and time between symptom onset and the start of I-line therapy (p=0.006) were observed in PsA compared to RA. A delayed start of II-line therapy was observed in RA compared to PsA (p=0.0007). Higher diagnostic delay (p=0.02), and time between symptom onset and the start of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (p=0.02) were observed among residents of small-medium cities for both groups. Patients who have been diagnosed by another physician rather than a rheumatologist had a longer diagnostic delay (p=0.034) and a delayed start of I-line therapy (p=0.019). Patients who received a different previous diagnosis experienced greater diagnostic delay (p=0.03 and p=0.003) and time of start of csDMARDs (p=0.05 and p=0.01) compared with those receiving RA or PsA as the first diagnosis. PsA had a delay in starting targeted synthetic disease-modifying anti-rheumatic drugs (p=0.0004) compared to RA. Seronegative RA had delayed diagnosis (p=0.02) and beginning of therapies (p=0.03; p=0.04) compared to seropositive ones.

Conclusions. According to our results, greater diagnostic delay was found in PsA compared to RA, in patients living in small-medium cities, in those who did not receive the diagnosis from a rheumatologist, in those who were previously misdiagnosed, and in seronegative RA.

Key words: Rheumatoid arthritis, psoriatic arthritis, diagnostic delay, rheumatologic referral.

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■ INTRODUCTION

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are inflammatory diseases characterized by a chronic-relapsing course with the possibility of erosive damage that can cause permanent disability. RA affects women more frequently, with a female-to-male ratio of 3:1 (1). Its prevalence is estimated at 0.5-1% in the Caucasian population, although it is variable according to the geographical area (2). PsA affects men and women in a 1:1 ratio, and its prev- alence is estimated to be 0.05-0.25% in the general population and 6-41% in psoriatic patients (3). In both cases, joint involvement leads to erosive damage, with consequent deformity and functional impairment. RA and PsA are associated with a reduced quality of life and different comorbidities, including cardiovascular, metabolic, and psychiatric diseases, leading to their being considered systemic diseases (4). Benefits deriving from setting up therapies aimed at achieving a specific target (treat-to-target) (5-7) and from tight and periodic monitor-

Corresponding author:
Sara Ferrigno
Rheumatology, Allergology
and Clinical Immunology,
Department of Systems Medicine,
Tor Vergata University,
Via Montpellier 1, Rome, Italy
E-mail: sara.ferrigno16@gmail.com

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ing of disease activity (tight control) (8) are well known to reach better long-term outcomes and achieve ambitious results such as early remission or low disease activity. Therefore, early diagnosis is essential. It has been observed that in RA patients treated within the first 15 days after diagnosis, radiographic progression at 6 months is lower than in those treated within 4 months (9). It has also been shown that starting treatment with disease-modifying antirheumatic drugs (DMARDs) more than 16 weeks after diagnosis reduces the probability of obtaining remission, increasing the risk of damage progression (10). Moreover, longer disease duration is a risk factor for multidrug failure (11). Similarly, a population of PsA patients with a median disease duration of 7 months reported at least one joint erosion in 47% despite treatment in a 2-year follow-up (12). A subsequent study revealed a higher prevalence of bone erosions and greater disability assessed by the health assessment questionnaire in patients with a diagnostic delay of at least 6 months (13). "Window of opportunity" was defined as the period for starting treatment and drawing effects in terms of long-term remission and prevention of erosions (14). In RA, this period was defined as 3 months from symptom onset (15). In PsA, a clear time frame has not yet been identified, but it is known that an earlier start of treatment with DMARDs prevents bone damage, especially in patients with risk factors associated with a worse outcome at disease onset (16), such as polyarticular involvement and high medication level (17). Although the importance of an early diagnosis is well known, a diagnostic delay of 16-36 weeks in RA and 1-4 years in PsA has been estimated in Europe (16). There are also situations in which the correct diagnosis is not immediately reached, as emerges from the study of Meer *et al.*, where the most frequent misdiagnoses are joint trauma and gouty arthritis (18).

The present study aimed to investigate the factors associated with diagnostic delay and delayed rheumatological referral, leading to the late setting of therapies. The residence area of the study population was also evaluated as a possible variable influencing the diagnostic delay.

■ MATERIALS AND METHODS

A cross-sectional study was conducted in a single-center cohort of patients referring to the rheumatology clinic at the Tor Vergata University of Rome. Patients aged ≥18 years with a diagnosis of RA classified according to the American College of Rheumatology/European League Against Rheumatism 2010 criteria (19) and of PsA according to the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria (20) were enrolled from June to September 2022. Exclusion criteria were the absence of clinical information and patients already under treatment with conventional synthetic (cs)DMARDs and targeted synthetic or biologic (ts/b)DMARDs. Data collection was conducted through a questionnaire directed to the patients. The information obtained was collected in a database. Clinical data (sex, age, presence of personal or family psoriasis), serological data such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) positivity (19), and the time (years) elapsed between symptoms onset, diagnosis, and starting of treatment with csDMARDs and ts/bDMARDs were collected. We also evaluated the city of residence, defined as a large city (population greater than 200.000 citizens) or a small-medium city (population less than 200.000 citizens), the physician who made the diagnosis (rheumatologist or other doctor), the person responsible for the rheumatological referral at the center where the first treatment was prescribed (none/family doctor/ other specialist) and data regarding previous different diagnoses. Written informed consent was obtained from patients according to the Declaration of Helsinki (updated 2008), and the study was approved by the Scientific Ethics Committee of the Policlinic of Rome Tor Vergata, Italy.

Statistical analysis was conducted using the GraphPad Prism version 8.0.2 platform (GraphPad Software, San Diego, CA, USA). Continuous variables are presented

as mean ± standard deviation and were compared using the statistical Student's T test, Mann-Whitney U test, and one-way analysis of variance when appropriate. Categorical variables were presented in absolute numbers and percentages and compared using the $\chi 2$ test. The significance of each correlation was determined by Pearson's or Spearman's correlation test, when appropriate. P values <0.05 were considered significant.

■ RESULTS

A total of 100 patients with RA (23 males and 77 females) and 100 patients with PsA (35 males and 65 females) were enrolled. The patient's mean age was 61.3±12 years (range 23-85) in RA and 55±13.9 years (range 21-85) in PsA. Among PsA patients, 68 (68%) were affected by psoriasis. Among RA patients, 66 (66%) had RF positivity, 63 (63%) had ACPA positivity, and 56 (56%) had double positivity. 47 (47%) RA patients and 46 (46%) PsA patients lived in big cities, while 53 (53%) RA patients and 54 (54%) PsA patients lived in small cities. Figure 1 shows the demographic distribution of the study population according to Lazio region districts.

The diagnosis of RA and PsA was made by a rheumatologist in 81 (81%) and 85 (85%) patients, respectively, while in 19 (19%) and 15 (15%) patients, the diagnosis was made by another physician. In RA patients, the referral to the center that started the I-line treatment was carried out by spontaneous decision, from the family doctor or by another specialist, in 36 (36%), 36 (36%), and 28 (28%) patients, respectively. In PsA patients, the referral was made by their own decision in 43 patients (43%), by their family doctor in 17 (17%) patients, and by another specialist in 40 patients (40%). Finally, the presence of previous misdiagnoses was investigated. Misdiagnoses were present in 32 (32%) RA patients and in 44 (44%) PsA patients. In RA, the most frequent misdiagnoses were osteoarthritis (11 patients, 35.5%) and undifferentiated connective tissue disease (5 patients, 16.1%), while in PsA, they were osteoarthritis (14
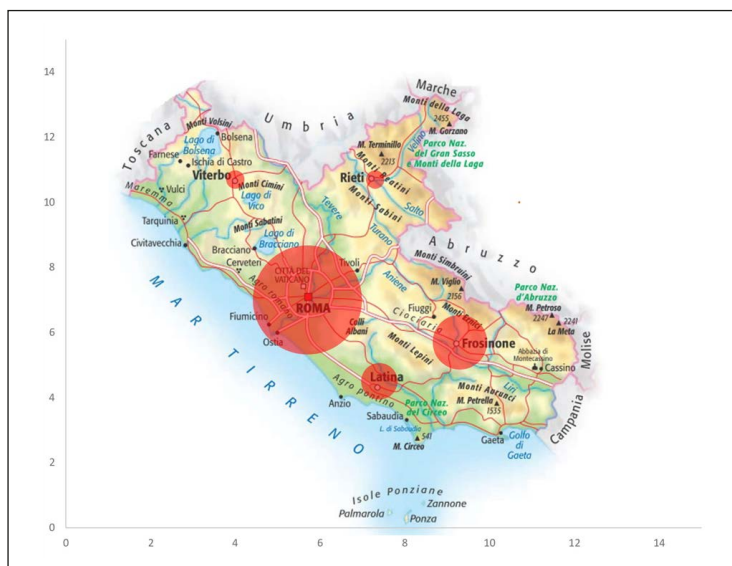

Figure 1 - Demographic distribution of rheumatoid arthritis and psoriatic arthritis patients according to Lazio region districts.

patients, 34.15%) and fibromyalgia (8 patients, 19.1%). Table 1 details the demographic, clinical, and serological data of the cohort.

Significant differences were observed between PsA and RA patients, particularly in diagnostic delay (PsA 5.2±7.6 years *versus* RA 2.5±4.6 years; p=0.003), time elapsed between symptom onset and the start of cs-DMARDs (PsA 5.3±7.6 years *versus* RA 2.7±5.1 years; p=0.006), and time between diagnosis and the start of ts/bDMARDs (PsA 3.5±5.5 years *versus* RA 7.1±8.6 years; p=0.0007). In the two groups, statistically significant differences emerged between the patients living in small and medium-sized cities compared to the inhabitants of large cities, both in the diagnostic delay (6.1±10.2 years *versus* 2±1.8 years; p=0.02) and in the time between symptom onset and the start of I-line therapy with cs-DMARDs (6.4±10.7 years *versus* 2.3±1.9 years; p=0.02). Furthermore, comparing patients who were diagnosed by another specialist with those whose diagnosis was made by a rheumatologist, a significantly higher diagnostic delay (4.7±11.1 years *versus* 3.9±6.2 years; p=0.034) and a longer time between symptom onset and the start of I-line therapy (4.7±11 *versus*

Table I - Demographic, clinical, and serological characteristics of the study cohort.

	AR (n=100)	PsA (n=100)	Total
Sex (n/%) Males Females	 23 (23) 77 (77)	 35 (35) 65 (65)	 58 (29) 142 (71)
Age (mean±SD)	61,3±12	55±13,9	58,1±13,3
PsO (n%)	NA	68 (68)	/
RF (n/%)	66 (66)	NA	/
ACPA (n%)	63 (63)	NA	/
Small city (n%) Big city (n%)	47 (47) 53 (53)	46 (46) 54 (54)	93 (46,5) 107 (53,5)
Diagnosed by rheumatologist (n/%)	81 (81)	85 (85)	166 (83)
Rheumatologic referral (n/%) Own decision Family doctor Another specialist	 36 (36) 36 (36) 28 (28)	 43 (43) 17 (17) 40 (40)	 79 (39,5) 53 (26,5) 68 (34)
Previous diagnoses (n/%)	32 (32)	44 (44)	76 (38)

SD, standard deviation; RA, rheumatoid arthritis; PsA, psoriatic arthritis; PsO, psoriasis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibodies.

4.2±6.7 years; p=0.019) were observed in the first group.

Considering RA patients, those with a previous misdiagnosis had a greater diagnostic delay (3.7±6.7 years *versus* 1.9±3.1 years; p=0.03) and consequently a delay in starting csDMARDs (4±6.8 years *versus* 2.1±4 years; p=0.05) compared to patients receiving RA as their first diagnosis. In seronegative RA, diagnostic delay (4.2±4.7 years *versus* 1.8±4.6 years; p=0.02) and time between symptom onset and the start of cs-DMARDs and ts/b-DMARDs were greater compared to those with positive serology (4.5±5.3 years *versus* 2±5.1 years, p=0.03 and 11.6±9.6 years *versus* 7.9±7.8 years, p=0.04, respectively). Similarly, in PsA patients with a previous misdiagnosis, there was a greater diagnostic delay (8.1±10 years *versus* 3±4.1 years; p=0.003) and a prolonged period between symptoms onset and the start of csDMARDs (8.1±10 years *versus* 3.1±4.2 years; p=0.001) and ts/b-DMARDs (12±11.1 years *versus* 6±6.5 years; p=0.0004). In both forms of arthritis, gender, age, and type of referral have not shown a significant influence on diagnostic delay or the start of treatment (data not shown). No significant correlations were found between diagnostic delay and the presence of psoriasis in PsA patients (data not shown).

■ **DISCUSSION**

In inflammatory arthritis, early diagnosis and prompt treatment are crucial for early control of the inflammatory process and a better disease outcome. The present study aimed to investigate factors associated with delayed diagnosis and rheumatological referral, resulting in treatment start delays. According to our results, PsA patients achieved the diagnosis in twice the time of RA patients, leading to a delayed start of I-line therapy. In a study by Sørensen et al. conducted in 2000, it was observed that PsA patients were diagnosed 53 months after symptoms onset, compared to 29 months for RA patients; in the last decade, time was reduced by 3-4 months in both diseases (21). Awareness of early diagnosis has grown over the years, although a significant diagnostic delay is still recorded in PsA patients. This could be explained by the absence of specific disease biomarkers, such as inflammatory markers, often appearing normal, the absence of disease-characterizing autoantibodies, the insidiousness of symptoms, and their pre-

sentation similar to that of other rheumatic diseases (22). Joint symptoms may precede the onset of psoriasis in 10-15% of cases, making it more difficult to suspect PsA (23). Furthermore, early manifestations of PsA may be subclinical, as for isolated enthesis involvement, and may escape clinical evaluation. It has been demonstrated that diagnostic delay occurs more likely in patients with a younger age at symptoms' onset and with a lower educational level, which could be related to low income (13). Obesity can cover clinical signs of joint involvement on physical examination and the first symptoms, often attributed to mechanical overload (16). Several limitations also concern the use of CASPAR criteria, since they were developed on a population with long-lasting disease (12.5 years) and have low sensitivity for its early stages. On the other hand, factors determining the diagnostic delay in RA are large joint involvement as an atypical presentation, advanced age at onset, and a low socio-economic level (24). Even extra-articular manifestations that precede the musculoskeletal involvement can delay diagnosis, as for the RA-related interstitial pulmonary disease, often diagnosed as idiopathic (25). Finally, according to the literature, patients affected by seronegative arthritis have greater diagnostic and therapeutic delay (26) and this is confirmed in our study population. This underlines the importance of ACPA monitoring, which is more specific than RF and can help to achieve diagnosis, especially in the early stages (27).

In our study, we observed that bDMARDs or tsDMARDs treatment was started earlier in PsA than in RA patients. This is likely a consequence of different disease clinical domains, such as axial involvement, which require a I-line treatment directly based on the use of ts/bDMARDs, according to the latest Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations (28).

Sex had no significant impact on diagnostic delay in both groups. This finding is in accordance with the literature on RA patients, in which recent studies have reported that no differences exist between the two sexes in early diagnosis and treatment start (29). On the other hand, data regarding PsA patients are different; despite the similar prevalence of the disease, there is a greater diagnostic delay in women than in men (30). The female population had more often polyarticular involvement than males, who more often experienced axial involvement. When axial involvement occurs in women, there is a reduced radiographic progression due to the greater lumbar flexibility and a diagnostic delay due to the underestimation of real joint involvement. Since evaluation scales of disease activity are based on subjective pain, the physician could have an underestimation attitude towards the pain reported by women, given their greater sensitivity towards painful stimuli (30), documented by a greater value of patient global assessment (PtGA) (31). Furthermore, enthesitic involvement is often attributed to fibromyalgia, a condition more prevalent in females (32). Furthermore, in our study, there were no significant differences in terms of age-related diagnostic delay between the two groups, a point on which the literature is very heterogeneous. In several studies, age was not linked to diagnostic delay, while other studies proved that rheumatologic consultation is accelerated in older patients (29).

In our population, we demonstrated that the residence area of patients and the professional figures who made the diagnosis can influence the diagnostic delay. The inhabitants of small cities had a greater diagnostic delay and a consequent delay in starting treatment, probably due to the greater difficulty of consulting a rheumatologist when living far from health facilities, such as the inhabitants of rural areas (33). Similar results emerged for patients in whom the diagnosis was made by another non-rheumatologist specialist. Finally, the presence of a previous misdiagnosis was a factor conditioning the diagnostic delay in both RA and PsA. Regarding the type of referral to the rheumatology center, no significant difference in diagnostic delay was demonstrated, although PsA patients who were referred to the rheumatologist

by the general practitioner represent only 17% of the total population. This data underlines the limited knowledge of inflammatory joint diseases. In fact, it is essential to consider the role of the family doctor for patients with early arthritis, although current data indicate that the rheumatologist is consulted after four visits to primary care centers (34). This is especially evident in PsA, where 67% of patients presenting to a rheumatologist for the first time showed at least one erosion (35).

Another factor contributing to treatment start delays with DMARDs is that patients themselves do not ask for help from the doctor. Many patients do not perceive the early inflammatory symptoms as a reason to ask for a medical consult and attempt to self-manage pain with non-specific therapies. Therefore, educating the general population about inflammatory arthritis may optimize diagnostic accuracy (36). In a review conducted by Villenueve et al., causes of a diagnostic delay before reaching the rheumatological consultation were analyzed and resolution strategies were proposed, such as television or web information campaigns for the awareness of patients with autoimmune arthritis, the creation of technological tools that can help to suspect the diagnosis by the patient himself, the education of family doctors, and the standardization of triage methods to overcome system delays, using referral letters between primary and secondary care centers (34). An American survey showed that patients often ask pharmacies before turning to their family doctor, so the community of pharmacists should also be the subject of an information campaign to direct the right referral (37).

In our study population, the presence of psoriasis did not influence the time of treatment start. This is a significant issue if we consider that the cutaneous onset often precedes the articular one. In fact, patients with PsA often come to the rheumatological consultation after having consulted other professional figures, such as the dermatologist. Therefore, information addressed to specialists who are more likely to come into contact with PsA patients is also important, including dermatologists, ophthalmologists, orthopedists, podiatrists, gastroenterologists, and physiotherapists (38, 39). Given that the most severe forms of psoriasis, such as those characterized by scalp, intergluteal, and perianal region involvement and the presence of nail dystrophy, are associated with a greater probability of developing PsA (40), the presence of multidisciplinary teams, including dermatologists and rheumatologists, could increase the chances of early detection of PsA and direct the right referral (41).

The main limitations of our study are the presence of a small study population and retrospective data collection. Therefore, further analysis will be necessary to increase the accuracy of the results.

■ CONCLUSIONS

Our data showed a greater diagnostic delay in PsA than in RA, resulting in delayed initiation of I-line therapy, although in PsA treatment with ts/b-DMARDs, it occurs earlier than in RA patients. Living in a small city, receiving the diagnosis from a non-rheumatologist, and having previous misdiagnoses are risk factors associated with diagnostic delay for both diseases. The absence of RF or ACPA positivity in RA patients increased the risk of diagnostic delay, while in PsA patients, the presence of psoriasis did not influence the time to diagnosis. In conclusion, this study analyzed the main factors related to diagnostic delay in RA and PsA, which still appeared to be significant. This confirmed the need to improve physicians' information and the collaboration between different specialists to guarantee an appropriate and prompt referral for early diagnosis and related therapeutic management.

Contributions
MSC, FRS, PC, PT, AB, made substantial contributions to the conception or design of the work; MSC, MI, SF, AD, FRS, contributed to the acquisition, analysis and interpretation of data for the work; MSC, MI, SF, PC, FRS, drafted the work and revised it critically for important intellectual con-

tent; MSC, FRS, PC, PT, AB, gave final approval of the version to be published. MI, SF, contributed equally to the study. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest
The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate
The study was approved by the Scientific Ethics Committee of the Policlinic of Rome Tor Vergata, Italy.

Patient consent for publication
Written informed consent was obtained from patients according to the Declaration of Helsinki (updated 2008).

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Availability of data and materials
Data are available upon reasonable request.

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