Does Delay Matter in Early Rheumatoid Arthritis?

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Abstract

Aims: The aims of this study were to explore the effect of delayed presentation to a rheumatologist on the clinical outcomes in patients with early rheumatoid arthritis (RA) after 2 years of follow-up and to determine the predictors of failure to achieve therapeutic targets in those patients. Methods: It is a retrospective study; patients were recruited from Dubai Arthritis Registry (DAR). All patients with symptoms of RA <6 months, who attended early arthritis clinic and subsequently completed a follow-up of 2 years in the general rheumatology clinic, were included in the study. We extracted clinical and demographic data from DAR. Results: We have enrolled 78 patients with ERA. Their median age was 49 years (interquartile range [IQR]: 34–52) years, 88.5% were female and 5.2% were current or past smokers. The median delay between symptom onset and seeing a rheumatologist was 34 (IQR: 13–71) days. About 75.4% achieved clinical targets at 24 months of follow-up. Seventy per cent had a good response, 14% had a moderate response and 16% had no response. The proportion of non-responder was higher in the delayed group than those who presented early after the onset of symptoms (odds ratio = 2.6, 95% confidence interval: 1.2–5.9 and P = 0.02). Female gender, Anti-Citrullinated Protein Antibodies (ACPA) positive and Disease Activity Score 28 (DAS28) at baseline are independent predictors of achieving clinical targets after 2-year follow-up. Conclusion: Delayed presentation to rheumatologist adversely affects the clinical outcomes in patients with early RA. Indeed, female gender, DAS28 at baseline and ACPA positivity remain independent predictors of achieving clinical outcomes in patients with ERA.

Keywords: Disease Activity Score 28, early rheumatoid arthritis, gender, referral

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Introduction

The treatment goals of rheumatoid arthritis (RA) have evolved in the past two decades from controlling inflammation, symptoms and disease activity to achieve remission and preventing joint damage. The greatest damage occurs in what is so-called ‘window of opportunity’ early in the disease.[1,2] Delayed treatment was frequently associated with radiographic damage in RA patients.[3] Hence, the EULAR recommendations for the management of early arthritis in 2007, and 2016, strongly advocate that ‘patients presenting with arthritis should be referred to, and seen by, a rheumatologist, within 6 weeks after the onset of symptoms’.[4,5]

The main aim of starting disease-modifying antirheumatic drug (DMARD) therapy in early RA is to achieve clinical remission. Studies have shown that patients with early RA respond better to treatment than patients with established RA.[6] In fact, disease duration was shown to be an independent predictor of response to DMARD treatment in a meta-analysis of 14 different randomised clinical trials.[7] Given this difference in response, the American College of Rheumatology (ACR) has distinguished the treatment of early RA from established RA based on the available data in the past ACR update on the management of RA.[8]

Few studies in the literature have explored the effect of the delay on patients’ outcome in early RA.[9,10] As the definition of early RA has changed over the years from symptom or disease duration of <2 years to a recent consensus that early RA is patient with symptoms or disease duration of a <6 months. There is a great need to study the effect of delayed presentation on the clinical outcomes, in those who have the symptoms/disease <6 months. Furthermore, there are limited data in the literature published from the Middle East on the predictors of clinical outcomes in patients with early RA.

Objectives

The objectives were to study the effect of delayed...
presentation to a rheumatologist, as defined by EULAR recommendations,[4,5] on clinical outcomes after 2 years of follow-up in patients with early RA,[8] and to explore the predictors of failure to achieve therapeutic targets in those patients after 2 years of follow-up.

**Methods**

**Study design**

It is a retrospective study. Patients were recruited from Dubai Arthritis Registry (DAR), in Public Hospital that looks after early arthritis in Dubai Health Authority.

**Patients**

We recruited all patients who have attended the early arthritis clinic after the launch of DAR in December 2014. Those patients who fulfilled the inclusion criteria and completed 2 years of regular follow-up in general rheumatology clinic were included in the study.

The inclusion criteria were as follows: age between 18 years and 80 years, meeting ACR/EULAR 2010 RA classification criteria for RA and symptom/disease onset <6 months from the initial presentation (early RA). We have excluded patients with established RA, patients with undifferentiated or other rheumatological disorders and those who lost follow-up for ≥6 months.

**Demographic and referral data and clinical assessments**

Patients who attended early arthritis clinic were assessed at baseline and enrolled in DAR. Their regular visits to the rheumatology clinic, which is usually once every 3 months over a period of 2 years, were also entered in the registry. To answer our research question, we extracted the following information from DAR including demographic data, date of symptom onset, date of referral, date of initial rheumatologist consultation, rheumatoid factor, ACPA positive, baseline Disease Activity Score 28 (DAS28) within 2 weeks from the first presentation, number of conventional DMARDs and biologics used over the 2 years, the number of hospitalisation day and sick days, the Health Assessment Questionnaire after 2 years of follow-up and DAS28 after 2 years of follow-up.

**Grouping**

Eligible participants were grouped into one of the two groups: the early group: those who seen within 6 weeks of their symptom onset to a rheumatologist and the delayed group: those who presented after 6 weeks after their symptom onset. We compared the demographic, clinical and immunological features of the groups at baseline and after 2 years of regular follow-up with rheumatologist.

**Clinical targets**

At the end of the 2 years, patients were assessed for achieving clinical targets, namely DAS28 of <2.6, i.e., remission, or DAS28 <3.2, i.e., low disease activity (LDA).[11] Furthermore, we compared the fraction of patients in the early and delayed groups for achieving EULAR response criteria.[12,13]

**Statistical analysis**

Descriptive statistics, Student’s t-test and Fisher’s exact test were used as appropriate. Demographic data and disease and treatment characteristics are described as median and 25th–75th interquartile range (IQR). 2 × 2 tables were used to calculate the odds ratio and 95% confidence interval on comparing the fractions in the early and delayed groups.

Multivariate regression analysis was used to investigate the effect of delay of presentation to rheumatologist on achieving clinical targets after two years of follow up defined by DAS28 <3.2, taking in to account; patient demographic and clinical characteristics at baseline and during follow-up. Variables included in the different models tested were selected based on their statistical significance in the univariate analysis and also on their clinical relevance. Significant variables were finally isolated using stepwise forward selection. In all statistical tests used; Student’s t-test, Fisher’s exact test, and multivariate regression, we considered the results are statistically significant if the P-value < 0.05. Statistical analysis was performed using Minitab software version 18.1, Minitab, LLC, State College, Pennsylvania, USA.

**Results**

We identified 78 RA patients who presented with symptoms <6-month duration and completed 2-year follow-up in general rheumatology clinic. The median age was 49 years (IQR: 34–52 years), 88.5% were female and 5.2% were current or past smokers. The median delay between symptom onset and seeing a rheumatologist was 34 days (IQR: 13–71 days). The baseline characteristics of enrolled patients enrolled in the study and subgroups are outlined in Table 1. About 75.9% achieved clinical targets at 24 months of follow-up, 49.4% had a DAS28 <2.6 and 26% had DAS28 ≥2.6 but <3.2. The median reduction of DAS28 since the initial presentation to a rheumatologist was 1.65 (IQR: 1–2.3). Applying EULAR response criteria, we found that 70% had a good response, 14% had a moderate response and 16% had no response.[12]

**Early presentation versus delayed presentation**

The median time lag between symptom onset and the first presentation to a rheumatologist in the early group was 19 days (IQR: 10–32 days) and the delayed group was 90 days (68–116) (P < 0.0001). On comparing the early group with the delayed group, there was no significant difference between the groups at baseline or after 2 years for follow-up. The median reduction of DAS28 after 24 months was 1.7 (IQR: 1.1–2.4) in the early group and 1.5 (IQR: 0.6–2.3) in the delayed group (P = 0.13).

However, on exploring the clinical targets, the delayed group had a higher proportion of patients in remission (DAS28 <2.6) than the early group (60.0% vs. 41.7%, respectively, P = 0.02), whereas the early group had a higher proportion of patients in LDA (DAS28 ≥2.6 but <3.2) than the delayed group (31.3% vs. 16.7%, respectively, P = 0.03) [Table 2].
Similarly, there was no difference between the groups in the frequency of EULAR good response. Nevertheless, patients in the early group had a statistically significantly higher proportion in moderate response and a lower proportion in no response categories than patients in the delayed group [Table 3].

**Predictors of clinical in patients with early rheumatoid arthritis**

Univariate analysis showed that achieving clinical targets after 2 years of follow-up was dependent on the age at presentation, female gender, ACPA positive, rheumatoid factor positive, DAS28 at baseline and number of DMARDs used over 2 years.

Multiple regression analysis showed that female gender, ACPA positive and DAS28 at baseline were independent predictors of achieving clinical targets after 2-year follow-up [Table 4].

**Discussion**

Our study showed that delayed presentation to a rheumatologist of 6 weeks or more in patients with early RA, symptoms <6 months, can influence the response to treatment after 2 years. Overall, almost three-quarters of the patients achieved clinical targets defined as LDA or remission after 2 years in both the groups. This can be attributed to the tight control strategy used in our centre in daily practice, and physicians are keenness to treat patients with RA to reach the recommended clinical targets. This is in line with what is reported by others.[14]

There was no significant difference in the use of conventional DMARDS, biologics and the percentage of patients achieving good clinical response at the end of 2-year follow-up between those who presented in the early and delayed groups. However, a higher proportion of patients in the delayed group were classified as non-responder, as per EULAR criteria for response, than those who presented early. This is comparable to what is described in the literature. In a study including 487 patients with early RA, symptom duration of 1 year, all were treated with methotrexate monotherapy. The investigator found that long symptom duration decreases the likelihood of EULAR response in methotrexate-naive ERA patients.[15]

Similarly, in another multicenter study, included 1,795 patients with arthritis for <12 months of different etiology, of which 711 patients were diagnosed to have early RA. A shorter

| Table 1: Baseline characteristics of all patients enrolled in the study and the subgroups |
|---------------------------------------------|----------------|----------------|--------|---|
| Variables                              | All patients | Early | Delayed | P  |
| Total Number of Patients              | 78           | 30    | 48     |    |
| Median Age at presentation (Yrs)       | 49           | 48    | 51     | NS* |
| Interquartile (25%-75%)                | (37.3-56.8)  | (36.3-55.3) | (40.5-57.8) |    |
| Female %                              | 88.5%        | 89.6% | 86.70% | NS* |
| Current or past smoker                 | 5.10%        | 4.20% | 6.60%  | NS* |
| RF positive %                          | 59.0%        | 60.4% | 56.7%  | NS* |
| DAS 28 at baseline (Median)            | 4.2          | 4.2   | 4.17   | NS* |
| Interquartile (25%-75%)                | (3.82-4.8)   | (4.1-5) | (3.6-4.35) |    |

*Statistically Non-significant

| Table 2: Summary of treatment and clinical outcomes after two years of follow up |
|---------------------------------------------|----------------|----------------|--------|---|
| Variables                              | All patients | Early | Delayed | P  |
| Median DAS 28 after 2 years              | 2.58         | 2.58  | 2.15    | NS* |
| Interquartile (25%-75%)                  | (2.0-3.0)    | (2.1-3.1) | (1.9-2.8) |     |
| DAS 28 remission %                       | 49.4%        | 41.7% | 60.0%   | 0.02*|
| DAS 28 LDA %                            | 26.0%        | 31.3% | 16.7%   | 0.03*|
| % Achieving clinical targets             | 75.4%        | 73.0% | 76.7%   | NS* |
| Average number of DMARDs used per patient| 1.4          | 1.3   | 1.5     | NS* |
| Average number of biologics used per patient | 0.3         | 0.4   | 0.2     | NS* |

*Statistically Non-significant, *P*<0.05 is statistically significant, *Disease-modifying antirheumatic drugs

| Table 3: The proportion of EULAR response after 24 months of follow up in the early & delayed group |
|---------------------------------------------|----------------|----------------|---------|---|
| EULAR criteria for response                | Early | Delayed | Odds Ratio | 95% Confidence interval | P  |
| No response                               | 10.4% | 23.3%  | 2.6      | 1.2-5.9   | 0.02*|
| Moderate response                         | 20.8% | 10.0%  | 0.41     | 0.19-0.94 | 0.05*|
| Good response                             | 68.8% | 66.7%  | 0.9      | 0.5-1.6   | 0.88 |

*P*<0.05 is statistically significant
The delayed presentation to rheumatologist adversely affects the clinical outcomes in patients with early RA. Indeed, female gender, DAS28 at baseline and ACPA positivity remain independent predictors of achieving clinical outcomes in patients with ERA.

**Ethical approval**

The study was approved by Dubai Scientific Research Ethics Committee (Ref: DSREC-08/2018_11).

**Consent**

All participants have orally consented to use their clinical information anonymously for the purpose of this study as per the regulation of Dubai Scientific Research Ethics Committee.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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**Table 4: Results of Multiple regression analysis**

| Variables                        | Coefa | SE Coefa | Estimated Odds Ratio | P    |
|----------------------------------|-------|----------|----------------------|------|
| DAS28 Baseline                   | 0.2595| 0.0919   | 1.3                  | 0.006b |
| Female                           | 1.124 | 0.28     | 3.0                  | 0.0001c |
| ACPA Positive                    | 0.367 | 0.18     | 1.4                  | 0.045d |
| Current or past Smoker           | -0.835| 0.53     | 0.45                 | NSd  |
| Number of DMARDs                 | 0.163 | 0.31     | 1.18                 | NSd  |
| Time lag before seeing a rheumatologist | 0.101 | 0.24     | 1.1                 | NSd  |

*Coef: Coefficient Estimate, aSE Coef: Standard Error of Coefficient Estimate, bP<0.05 is statistically significant, cStatistically Non-significant*
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