RHEUMATOLOGY

Rheumatology 2016;55:1843–1848
doi:10.1093/rheumatology/kew261
Advance Access publication 3 July 2016

Concise report

Components of treatment delay in rheumatoid arthritis differ according to autoantibody status: validation of a single-centre observation using national audit data

Arthur G. Pratt[1], Dennis Lendrem[1], Ben Hargreaves[1], Osman Aslam[1], James B. Galloway[2] and John D. Isaacs[1]

Abstract

Objective. To determine whether time to treatment following symptom onset differs between RA patients according to autoantibody status.

Methods. A single-centre retrospective analysis of a UK early RA inception cohort was first undertaken to identify those components of the patient journey that differed by serological subtype. Data from a UK national audit of early inflammatory arthritis patients was accessed to replicate the key finding.

Results. A total of 173 RA patients were diagnosed over a 31-month period, of whom 80 (46%) were ACPA/RF double-seropositive ($ACPA^+/RF^+$), 53 (31%) $ACPA^-/RF^-$, 17 (10%) $ACPA^+/RF^-$ and 23 (13%) $RF^+/ACPA^-$. Overall, $ACPA^+/RF^+$ patients experienced significantly longer symptom duration before DMARD initiation. This was accounted for by delays in their presentation to primary care following symptom onset—a finding that was robustly confirmed in an independent dataset of 2192 UK early RA patients. In contrast, $ACPA^-/RF^-$ patients were significantly more likely to experience delays in DMARD initiation after presenting to secondary care.

Conclusion. Causes of treatment delays in early RA differ according to patients' autoantibody status. More insidious symptom onset and/or distinct health-seeking behaviours among $ACPA^+/RF^+$ patients may contribute to late presentations in primary care, whereas $ACPA^-/RF^-$ patients experience delayed diagnosis and treatment in secondary care. These observations inform the research agenda, potentially influencing the design of service delivery for early arthritis patients.

Key words: rheumatoid arthritis, auto-antibodies, anti-citrullinated peptide, rheumatoid factor

CLINICAL SCIENCE

Rheumatology key messages

- Following RA symptom onset, ACPA/RF double seropositivity is associated with delayed presentation to primary care.
- Diagnostic uncertainty amongst seronegative RA patients contributes to treatment delays in secondary care.

Introduction

An established body of evidence now underlines the importance of promptly treating RA with DMARDs [1]. Increasing evidence for a window of opportunity after symptom onset, during which therapeutic intervention meaningfully interrupts the disease's natural history [2, 3], supports this approach [4, 5]. However, despite a proliferation of early arthritis clinics intended to expedite diagnosis, patients continue to

[1]National Institute for Health Research Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle upon Tyne and [2]Academic Department of Rheumatology, King's College London, King's College London School of Medicine, Weston Education Centre, London, UK

Submitted 10 September 2015; revised version accepted 24 May 2016

Correspondence to: Arthur G. Pratt, Institute of Cellular Medicine (Musculoskeletal Research Group), Newcastle University, NE2 4HH, Newcastle upon Tyne, UK. E-mail: arthur.pratt@ncl.ac.uk

experience substantial and multifactorial delays between symptom onset and treatment initiation [6–8].

When considering interventions to address this problem, it has proved informative to account for those components of the patient journey that contribute to delay. These include the time from symptom onset to assessment in primary care, primary care assessment to secondary care rheumatology referral, rheumatology referral to rheumatology assessment and rheumatology assessment to DMARD initiation [8]. Individual components of this journey have been shown to vary markedly across healthcare infrastructures in Europe [7], with the lag between symptom development and primary care consultation being particularly important in the UK [6, 9]. Intriguingly, Kumar *et al.* [6] provided preliminary evidence that RF-positive patients tended to endure a longer delay before primary care presentation than their seronegative counterparts. Conversely the publication of updated classification criteria for RA [10] might have accelerated the diagnosis of seropositive patients due to the significance attached to autoantibodies [11].

A better understanding of how serological status may impact on treatment delay in RA could influence management guidelines in this heterogeneous disease. We have conducted a retrospective analysis of a well-characterized early RA cohort, to address whether treatment delay varies according to serological status and, if so, which components of the patient journey are most affected.

Methods

Newcastle patients

Consecutive patients referred to the Newcastle early arthritis clinic (EAC) with an ultimate diagnosis of RA [12] were eligible for inclusion in this observational study, provided they were naïve to immunomodulatory therapy (including corticosteroids) at the time of enrolment. Primary care physicians are encouraged to refer patients to this rapid-access service, without performing blood tests, in all cases where a new-onset inflammatory arthritis is suspected on clinical grounds alone, and autoantibody results do not form part of the referral criteria. Recruitment took place between November 2011 and November 2014, and the median duration of follow-up from first rheumatology assessment was 17 months.

A detailed baseline clinical assessment was completed for all patients. When available, timing of symptom onset (as recollected by the patient) was recorded, alongside the dates of primary care referral, EAC assessment and subsequent DMARD initiation. The date of first presentation to primary care, as recollected by the patient, was recorded for a subgroup of the cohort. All patients provided written, informed consent for inclusion in the study, which was approved Newcastle and North Tyneside 2 Research Ethics Committee (reference 12/NE/0251).

Healthcare Quality Improvement Partnership Replication dataset

The National Clinical Audit for rheumatoid and early inflammatory arthritis (EIA Audit) represents one of a number of government-funded UK audits against evidence-based standards overseen by the Healthcare Quality Improvement Partnership (HQIP). Anonymized data collected between February 2014 and June 2015 inclusive were made available, following an application to the British Society for Rheumatology Research Committee, for the attempt to validate a key finding of the current study. Analysis of newly referred EIA patients was restricted to those with baseline diagnoses of RA or undifferentiated arthritis (UA) that evolved into RA over a 3-month follow-up period, and for whom recollected symptom duration prior to primary care presentation was recorded. Sufficient data was also required to permit classification according to whether or not individuals were ACPA/RF double seropositive ($ACPA^+/RF^+$). All EIA Audit data derived from The Freeman Hospital, Newcastle, were excluded from the analysis.

Statistical analysis

Differences in continuous and categorical variables between comparator groups were determined using the Kruskal–Wallis/Mann–Whitney U and chi-squared tests, respectively, with significance set at $\alpha = 5\%$. To determine and visualize differences in time components between symptom onset and DMARD initiation according to serotype, time-to-event data were analysed using Kaplan–Meier survival plots; differences between serotypes were tested using the Mantel–Cox log-rank method or Cox regression modelling when adjusting for covariates (likelihood ratio test). A total of 173 consecutively diagnosed RA patients contributed to the final Newcastle dataset, although component time points were missing for some individuals (as stipulated in Table 1). A sensitivity analysis of a subcohort of 144 patients, in whom $\geqslant 3$ time components were available, gave similar results to the complete cohort (compare Table 1 with supplementary Table S1, available at *Rheumatology* Online). The same analysis approach was applied to the HQIP replication cohort.

Results

Newcastle patient characteristics

The clinical characteristics of the complete Newcastle cohort are described in Table 1, stratified by autoantibody serotype. Of this cohort, 80 (46%) were ACPA and RF double-seropositive ($ACPA^+/RF^+$), 53 (31%) were ACPA and RF double-seronegative ($ACPA^-/RF^-$), 17 (10%) were $ACPA^+/RF^-$ and 23 (13%) were $ACPA^-/RF^+$. A tendency for $ACPA^+/RF^+$ RA patients to be younger achieved marginal significance ($P = 0.05$). A trend towards lower disease activity at baseline was also observed in this group and, conversely, $ACPA^-/RF^-$ individuals appeared enriched for males (both non-significant). No significant differences in NSAID use were observed between the four groups, with 60% of patients reporting usage at enrolment. The durations of the various components of the patient journey are also listed in Table 1. Out of the overall cohort of 173 patients, 24 evolved diagnoses of RA during

TABLE 1 Characteristics of RA patients, stratified by serotype

Characteristics	RA patients n = 173				
	Double seropositive (n = 80)	ACPA+/RF − (n = 17)	RF+/ACPA − (n = 23)	Double seronegative (n = 53)	P-valuea
Age, years[b]	58 (49–71)	63 (48–71)	65 (50–74)	68 (57–75)	**0.050**
Female sex, %[b]	67	82	73	58	0.244
CRP, g/dl[b]	9 (5–22)	10 (7–16)	17 (11–38)	14 (6–27)	0.090
ESR, mm/min[b]	23 (11–35)	27 (17–32)	35 (14–49)	23 (9–34)	0.387
SJC/68[b]	2 (1–5)	2 (1–4)	4 (0–7)	3 (1–7)	0.081
TJC/68[b]	4 (1–8)	3 (1–5)	5 (2–11)	5 (2–11)	0.103
DAS28[b]	4.26 (2.79–5.33)	4.28 (3.19–4.88)	5.03 (4.18–5.70)	4.41 (3.78–5.35)	0.161
Symptoms-DMARD, weeks, n = 167[c]	24 (10 to > 52)	13 (6 to >52)	9 (6–15)	17 (10–30)	**0.006**
Symptoms-PC Referral, weeks, n = 144[c]	15 (6–44)	7 (4–19)	6 (2–11)	9 (5–19)	**0.012**
Symptoms—first PC visit, weeks, n = 43[c]	14 (4–37)	4 (2–25)	2 (0.5–13)	4 (0–27)	**0.036**
First GP visit—PC Referral, weeks, n = 43 [c]	1 (0–10)	2 (0–6)	3 (0–4)	4 (0–12)	0.989
PC Referral-EAC, weeks, n = 154[c]	3 (2–4)	3 (1–4)	3 (2–3)	2 (2–4)	0.924
EAC-DMARD, weeks, n = 173[c]	0 (0–2)	0 (0–3)	0 (0–1)	1 (0–8)	**0.005**

All values given as median (interquartile range) unless otherwise indicated. P <0.05 are highlighted in boldface. [a]Kruskall–Wallis (non-parametric analysis of variance) for continuous variables; Chi-squared test for sex. [b]Clinical characteristics are shown for all patients at the time of presentation to the Early Arthritis Clinic (EAC). [c]Indicated time periods are shown for subgroups of patients for which data is available (number indicated by n). SJC/68: swollen joint count out of 68 joints and TJC/68: tender joint count out of 68 joints; DAS28 (28 joints, ESR); PC: primary care.

the course of follow-up in secondary care, having initially presented with UA.

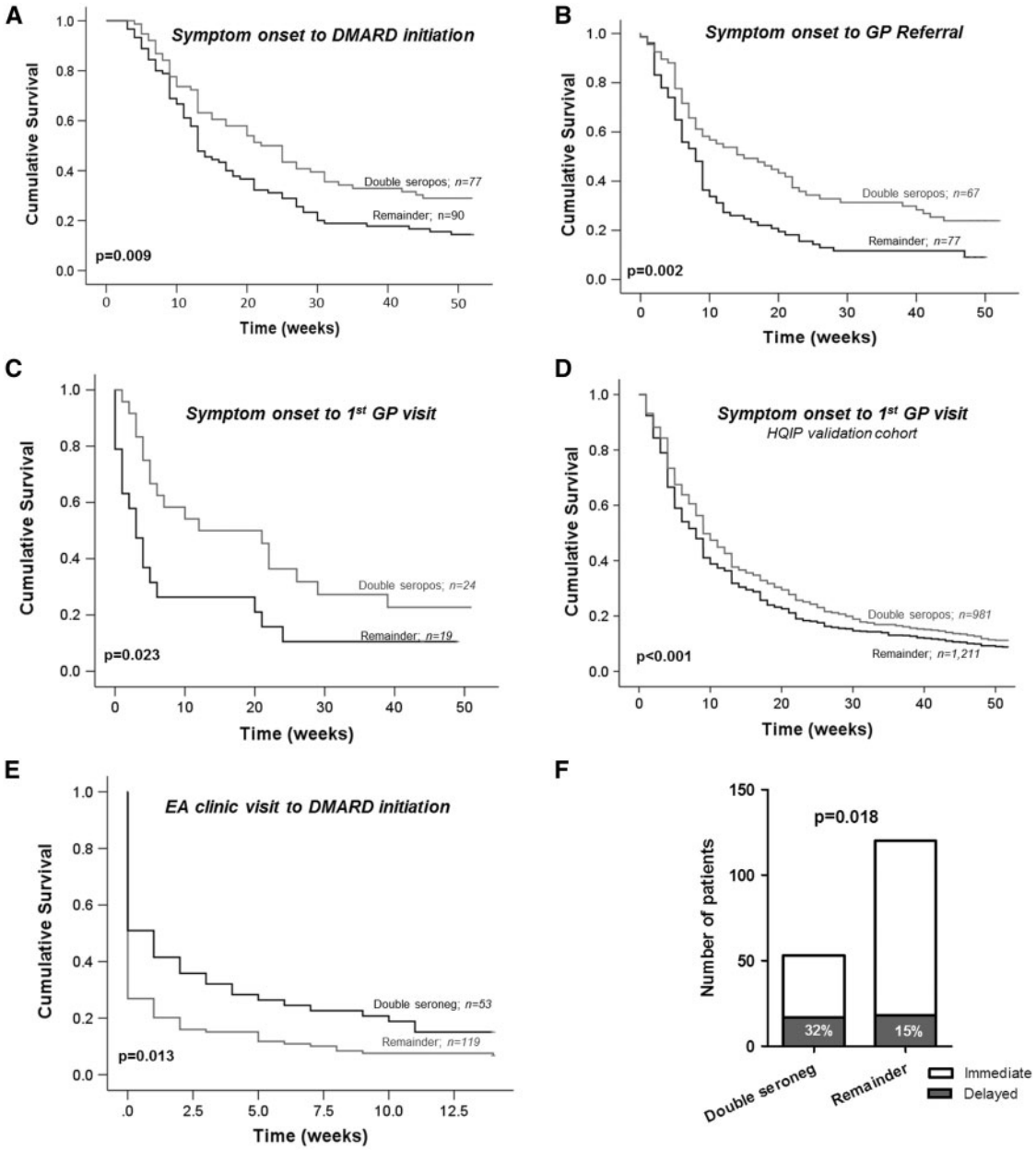
ACPA/RF seropositivity predicts prolonged symptom duration before primary care referral

The median time between symptom onset and DMARD initiation was 17 weeks for the complete cohort (data available for 167 patients). However, clear differences were seen in time-to-treatment when patients were stratified by autoantibody serotype, with ACPA$^+$/RF$^+$ individuals experiencing the longest delays (P = 0.006) (Table 1 and Fig. 1A). Given the trend towards lower acute phase response and DAS28 in the ACPA$^+$/RF$^+$ group, and to exclude a confounding effect of these variables in our primary analysis, Cox regression confirmed that serotype remained associated with treatment delay independently of these two parameters (P = 0.028). As depicted in Fig. 1B, the relative delay in treatment initiation among ACPA$^+$/RF$^+$ patients was fully accounted for by the time between symptom-onset and primary care referral date; neither time between primary care referral and EAC consultation in secondary care, nor time between EAC consultation and DMARD initiation, contributed to the difference (Table 1). Interestingly, analysis of a subcohort of 43 patients for whom the date of first primary care consultation was available demonstrated that treatment delays for ACPA$^+$/RF$^+$ RA patients resulted from patient rather than primary care factors—specifically a delay in the patient's presentation to primary care following symptom onset (Fig. 1C)—and not in the primary care physician's decision to refer (Table 1).

Validation of single-centre observation using national audit data

Although not without precedent [6], the finding that ACPA$^+$/RF$^+$ RA patients present to primary care with protracted symptom duration appeared counterintuitive, considering established evidence for this being the more aggressive disease subset. We therefore sought to validate our observation using appropriate national audit data. The independent EIA dataset comprised 4334 individuals diagnosed at baseline with RA or UA evolving into RA, from a total of 169 secondary care UK rheumatology units. Among these, sufficient data were available for only 2192 individuals (51%). ACPA$^+$/RF$^+$ patients were significantly younger than comparator RA patients in this cohort, whose characteristics are summarized in supplementary Table S2, available at *Rheumatology* Online. As in the Newcastle cohort, ACPA$^+$/RF$^+$ patients were symptomatic for longer than patients seronegative for one or more autoantibodies prior to their first primary care consultation, providing a robust validation of our single-centre observation (P < 0.001; Fig. 1D)—a finding that was robust to incorporation of age as a covariate. Interestingly, in contrast, analysis of the HQIP replication cohort revealed that RA patients were subsequently referred by their primary care physician significantly more quickly if they were ACPA$^+$/RF$^+$—and this largely reversed any overall delay between symptom onset and primary care referral

FIG. 1 Components of treatment delay in early RA patients differ according to serological status



(**A**) Kaplan–Meier plot depicting patient survival, symptom onset to DMARD initiation, stratified by autoantibody double-seropositivity. (**B**) Analogous plot to A, symptom onset to general practitioner (GP) referral. (**C**) Kaplan–Meier plot for subcohort of patients with available data, depicting survival, symptom onset to first GP visit. (**D**) Kaplan–Meier plot analogous to C, pertaining to Healthcare Quality Improvement Partnership replication cohort. (**E**) Survival from first EA clinic consultation to DMARD initiation, stratified by autoantibody double-seronegativity. (**F**) Bar chart contrasting proportions of double seronegative RA patients according to whether they encountered treatment delays in secondary care.

observed between groups (supplementary Table S2, available at *Rheumatology* Online).

Seronegative RA patients are subject to delayed DMARD initiation once in secondary care

After assessment by a consultant rheumatologist, most RA patients were commenced on one or more DMARDs immediately, but significant delays of a month or more occurred in 35 (20%) cases, ranging up to 56 weeks in duration. $ACPA^{-}/RF^{-}$ patients experienced a consistently prolonged time-to-treatment following secondary care assessment, compared with counterparts who were seropositive (Fig. 1E), and they were more likely to experience delays of $\geqslant$1 month before DMARD initiation

($P = 0.018$, chi-squared test; Fig. 1F). Diagnostic delay appeared to be an important contributor, with a significantly higher proportion of $ACPA^-/RF^-$ patients initially presenting with UA (19 of 53; 36%), compared with patients seropositive for either antibody (5 of 120, 4%; $P < 0.001$, Chi-squared test).

Discussion

Some important observations arise from our work. First and foremost, ACPA/RF double seropositivity appears to be a risk factor for delayed presentation of early RA patients to primary care following symptom onset. We have replicated our single-centre observation using a large national clinical audit dataset, providing an early example of the HQIP EIA resource's value as a research tool. In Newcastle, delayed presentation to primary care accounted for overall delays in DMARD initiation in $ACPA^+/RF^+$ RA patients compared with those of other serotypes. Given the importance of prompt therapeutic intervention in the condition, which is arguably even more urgent in seropositive disease, this observation may have important prognostic implications. A more insidious symptom course among double-seropositive RA patients is suggested by our data, and continued efforts to define symptom and health-seeking behaviour patterns in this apparently younger group are prescient [13]. Further studies, employing qualitative approaches and/or prospective designs, are now needed to properly understand the phenomenon, and the extent to which it is replicated across healthcare systems remains to be determined. Taken together, however, our validated observation adds credence to the notion that autoantibody status defines pathophysiologically distinct, if overlapping, disease phenotypes [14]. The finding may also have implications for clinical service provision, potentially supporting readier access to ACPA screening in the community.

However, such an approach needs to be balanced against the risk that autoantibody seronegativity may provide false reassurance to primary care physicians when considering referral of patients with possible RA to secondary care. Although not altogether conclusive, contrasting data from the Newcastle and HQIP replication cohorts seem to illustrate this point: while delays between primary care presentation and referral were equivalent between $ACPA^+/RF^+$ patients and those of other serotypes in Newcastle (where pre-referral blood tests are discouraged), delays were significantly longer for RA patients with one or more negative autoantibodies in the national cohort, in which specific referral pathways and practices vary greatly. It is therefore conceivable that channelling by autoantibody serotype prior to referral occurred preferentially in the replication cohort. Mapping optimal practice in the light of such observations presents an important challenge for future studies.

Finally, our study has highlighted the ongoing clinical challenge that rheumatologists face in diagnosing seronegative RA, despite the advent of classification criteria developed specifically for use in early disease. UA was more frequently diagnosed in this group, which was also uniquely subject to delays in DMARD initiation after presentation to consultant rheumatologists in secondary care. Interventions that aid in this process, in the form of diagnostic biomarkers that reflect disease-specific immune dysregulation, are the subject of ongoing investigation [12, 15].

Our single-centre study was large and utilized an unselected, real-life RA patient cohort; no evidence was found for bias as a result of missing data (see Methods; Statistical analysis section). The generalizability of its findings was tested against a UK replication cohort, placing them in a national context. Analysis of the HQIP replication cohort was hampered by substantial missing data, likely reflecting the organizational challenge of collecting complex datasets at the level of individual rheumatology units—and this cannot be excluded as a source of bias.

Acknowledgements

We thank Claire Humphrey, Christine Routledge, Julie Norris, and Lesley Tiffin for their role in collecting clinical data. We thank all participating patient volunteers. We gratefully acknowledge the British Society for Rheumatology Research Committee for their role in facilitating access to the Healthcare Quality Improvement Partnership early inflammatory arthritis audit data, and our colleagues at all units participating in this national clinical audit.

Funding: This work was supported by the National Institute of Health Research Newcastle Biomedical Research Centre at Newcastle Hospitals Foundation Trust and Newcastle University. Views expressed are those of the authors' and not necessarily those of the NHS, the NIHR or Department of Health. Newcastle researchers receive infrastructural support via the Arthritis Research UK Centre of Excellence for the RA pathogenesis.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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