Referring early arthritis patients within 6 weeks versus 12 weeks after symptom onset: an observational cohort study

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Summary

Background The first recommendation of the European League Against Rheumatism for the management of early arthritis states that patients should be referred to, and seen by, a rheumatologist within 6 weeks after symptom onset. However, implementation of this recommendation is a challenge, and evidence supporting this timeframe compared with longer timeframes is absent. Therefore, we aimed to investigate whether visiting a rheumatologist within 6 weeks of symptom onset relates to improved long-term outcomes compared with visiting a rheumatologist between 7 and 12 weeks after symptom onset.

Methods In this observation cohort study, consecutive patients with rheumatoid arthritis from the Leiden Early Arthritis Clinic (EAC) and the French Etude et Suivi des Polyarthrites Indifferenciées Recentes (ESPOIR) were included. In this analysis, we included patients who were diagnosed with rheumatoid arthritis and classified according to 1987 American College of Rheumatology criteria, and with symptom onset and remission data available. Patients were categorised into groups based on time between symptom onset and first encounter with a rheumatologist: within 6 weeks, between 7 weeks and 12 weeks, and after 12 weeks. The main outcomes were sustained disease-modifying antirheumatic drug (DMARD)-free remission and radiographic progression. Multivariable Cox regression, linear mixed models, and meta-analyses were used.

Findings 1025 patients with rheumatoid arthritis included in the EAC between Jan 1, 1996, and Dec 31, 2017, and 514 patients with rheumatoid arthritis included in ESPOIR between Nov 1, 2002, and April 30, 2005, were included in this analysis. Median follow-up was 7·1 years (IQR 3·9–12·2) in the EAC and 10·0 years (9·0–10·0) in ESPOIR. After 7 years of follow-up in the EAC, 30 (24%) of 127 patients with a time to encounter of 6 weeks or less, 45 (20%) of 223 patients with a time of 7–12 weeks, and 100 (15%) of 675 patients with a time of more than 12 weeks achieved sustained DMARD-free remission. After 10 years of follow-up in ESPOIR, three (27%) of 11 patients with a time to encounter of 6 weeks or less, 11 (11%) of 100 patients with a time of 7–12 weeks, and 41 (10%) of 403 patients with a time of more than 12 weeks had sustained DMARD-free remission. In the EAC multivariable analysis, patients who encountered a rheumatologist within 6 weeks obtained sustained DMARD-free remission more often than those seen between 7 and 12 weeks (hazard ratio [HR] 1·59 [95% CI 1·02–2·49], p=0·042), and after 12 weeks (1·54 [1·04–2·29], p=0·032). In the ESPOIR multivariable analysis, similar but non-significant effects were observed (HR 2·81 [95% CI 0·75–10·53], p=0·12, for within 6 weeks *vs* 7–12 weeks and 3·05 [0·89–10·49], p=0·077, for within 6 weeks *vs* more than 12 weeks). The meta-analysis of both cohorts showed that the time to encounter of 6 weeks or less was associated with a higher chance of achieving sustained DMARD-free remission than a time of 7–12 weeks (HR 1·69 [95% CI 1·10–2·57], p=0·016) and a time of more than 12 weeks (1·67 [1·08–2·58], p=0·020). The multivariable analysis showed that patients who encountered a rheumatologist within 6 weeks had similar radiographic progression to those seen between 7 and 12 weeks in both cohorts (β=1·00 [95% CI 0·95–1·05], p=0·96, in the EAC and 0·93 [0·80–1·07], p=0·30, in ESPOIR) and to those seen after 12 weeks (β=0·96 [95% CI 0·92–1·00], p=0·064, in the EAC and 0·89 [0·77–1·02], p=0·10, in ESPOIR). In the meta-analysis, a time to encounter of 6 weeks or less was not associated with less radiographic progression than a time of 7–12 weeks (β=0·99 [95% CI 0·95–1·04], p=0·75) but was associated with less radiographic progression than a time of more than 12 weeks (0·95 [0·91–0·99], p=0·028).

Interpretation Visiting a rheumatologist within 6 weeks of symptom onset had benefits for achieving sustained DMARD-free remission, but not for radiographic progression.

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Introduction

The European League Against Rheumatism (EULAR) recommendations for the management of early arthritis state that patients presenting with arthritis should be referred to, and seen by, a rheumatologist within 6 weeks after the onset of symptoms.[1] Abundant evidence points to the usefulness of very early (ie, within 6 weeks) initiation of disease-modifying antirheumatic drugs (DMARDs)

Research in context

Evidence before this study

The first European League Against Rheumatism (EULAR) recommendation for the management of early arthritis states that patients presenting with arthritis should be referred to, and seen by, a rheumatologist within 6 weeks after the onset of symptoms. Implementation of this recommendation provides huge challenges in practice. More importantly, the evidence supporting referral within 6 weeks compared with longer timeframes such as 12 weeks is currently missing. We searched PubMed for studies published in English between Jan 1, 2000, and Dec 31, 2018, investigating a referral time of 6 weeks or less, using the search terms "early referral", "rheumatology criteria", and "early rheumatoid arthritis". We identified no previous studies assessing the contribution of very early referral (≤6 weeks) to a rheumatologist in relation to long-term disease outcomes.

Added value of this study

Two longitudinal cohorts, the Leiden Early Arthritis Clinic and French Etude et Suivi des Polyarthrites Indifferenciées Recentes, were studied to investigate whether time to encounter a rheumatologist within 6 weeks, compared with 12 weeks or less, resulted in better long-term disease outcomes. A beneficial effect was demonstrated for sustained disease-modifying antirheumatic drug (DMARD)-free remission, which is a proxy measure of resolution of disease chronicity. However, to minimise structural damage, a time to encounter within 6 weeks does not seem necessary.

Implications of all the available evidence

These findings add knowledge regarding whether or not to try to implement the EULAR recommendation on time to encounter a rheumatologist within 6 weeks, as this might depend on the long-term treatment aim. Since clinically relevant joint destruction has become infrequent and sustained DMARD-free remission is increasingly achievable, achieving time to encounter within 6 weeks, although challenging, might become of increasing importance.

for early chronic inflammatory arthritis to reduce joint damage and disability.[2,3] However, 6 weeks or less after symptom onset is shorter than the 12 weeks or less which is generally considered as the window of opportunity. The implementation of patients being seen by a rheumatologist within 6 weeks after the onset of symptoms in clinical practice provides huge logistical challenges; the time between symptom onset and encountering a rheumatologist consists of different components, and the sum of these components should not exceed 6 weeks. The first component is patient delay, indicating that it takes time for patients to recognise the importance of early symptoms of rheumatoid arthritis. Secondly, primary care physicians see many patients with musculoskeletal symptoms and might have difficulty recognising those with arthritis of recent onset. This early recognition might be hampered by the fact that general practitioners have limited experience with joint examination and arthritis of small joints is initially mostly subtle. Finally, rheumatologists might have waiting lists.[4,5] Current data about how often patients are visiting a rheumatologist within 6 weeks after symptom onset are scarce. However, one European study showed that 8–42% of patients are seen within 12 weeks,[5] suggesting that the proportion of people with symptoms seen within 6 weeks will be even lower.

Although it is known that visiting a rheumatologist within 12 weeks of symptom onset is associated with less radiographic progression and a higher chance of achieving drug-free remission,[6–11] there is currently no evidence that an initial visit within 6 weeks leads to improved long-term outcomes compared with an initial visit between 7 and 12 weeks. We aimed to investigate whether time to encounter a rheumatologist within 6 weeks of symptom onset, compared with between 7 and 12 weeks, results in improved long-term disease outcome.

Methods

Study design and patients

In this observational cohort study, we included consecutive patients with rheumatoid arthritis from the Leiden Early Arthritis Clinic (EAC) and the French Etude et Suivi des Polyarthrites Indifferenciées Recentes (ESPOIR) cohorts.

The EAC is an inception cohort that began on Feb 24, 1993, and is ongoing. Patients with suspected arthritis are referred by general practitioners to the rheumatology outpatient clinic at Leiden University Medical Center (Leiden, Netherlands), which is the only centre for rheumatic diseases in a region of more than 400 000 inhabitants. The EAC includes patients aged 18 years or older with clinically confirmed inflammatory arthritis at the initial physical examination (ie, at least one swollen joint) and symptom duration of less than 2 years (from first patient-reported symptom, either pain or swelling, which is relevant to the current presentation of arthritis according to the treating rheumatologist).[12] Patients with rheumatoid arthritis included in the EAC between Feb 24, 1993, and Dec 31, 1995, were excluded from this study because their initial therapy comprised non-steroidal anti-inflammatory drugs (NSAIDs) but not DMARDs. Patients were followed up in the first year at months 3, 6, and 12, and then yearly. Data were extracted on Aug 1, 2018, and included all available data at that time from patients included in the EAC between Jan 1, 1996, and Dec 31, 2017.

ESPOIR is a longitudinal multicentre cohort that started recruitment of patients from 14 French rheumatology centres on Nov 1, 2002, and ended recruitment on

April 30, 2005. EPSOIR included patients aged 18–70 years with a diagnosis of rheumatoid arthritis or suspected to develop rheumatoid arthritis based on the clinical expertise of the rheumatologist, and required at least two swollen joints at the initial physical examination.[13] Patients were followed up every 6 months for 2 years and then yearly until a maximum of 10 years. The last follow-up visit was July 31, 2015, after which the database was locked, and data were collected. All patients from ESPOIR were eligible for this study.

Patients with rheumatoid arthritis in both cohorts were classified according to fulfilment of at least four of the seven 1987 American College of Rheumatology (ACR) classification criteria,[14] which were assessed cumulatively based on all available data that were collected in the first year after inclusion. This process was done in a similar manner in both cohorts because we aimed to select comparable patients with rheumatoid arthritis. In addition, only patients with symptom onset and remission data were included in this analysis.

According to the protocols of both studies, at baseline, patients filled out questionnaires (not used in this study), joint counts (swollen joint count using 66 joints [66-SJC] and tender joint count using 68 joints [68-TJC]), laboratory evaluations (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], rheumatoid factor, and anti-citrullinated protein antibodies [ACPA]), and radiographic evaluations were done. The yearly follow-up included clinical (physical examination, including 68-TJC and 66-SJC), laboratory (CRP and ESR), and radiographic evaluations. Patients were DMARD-naive at the time of the first rheumatology visit (and thus at inclusion in the cohorts) and were treated according to routine practice, including DMARD tapering and cessation in case of remission based on the disease activity score.

Written informed consent was obtained from all participants, and both cohorts received approval by their ethical committees.

Definition of time to encounter

Symptom onset was defined as the first musculoskeletal symptom (either pain or swelling) relevant to the current presentation of arthritis according to treating rheumatologists. Time to encounter a rheumatologist was defined as the duration between this first patient-reported symptom onset and the first visit to the rheumatology outpatient clinic, expressed in weeks. This time includes patient delay to visit the general practitioner, delay in referral by the general practitioner, and waiting time to see a rheumatologist. In the EAC, the time to see a rheumatologist is short because patients are referred by their general practitioners to an early arthritis recognition clinic, which has no waiting list, if they are unsure of the presence of arthritis. Additionally, patients referred with suspected inflammatory arthritis to the general outpatient clinic were seen with priority, generally within 1 week.[15] Patients were categorised into groups based on time to encounter a rheumatologist: within 6 weeks, between 7 weeks and 12 weeks, and more than 12 weeks.

	Total (n=1025)	Time to encounter ≤6 weeks (n=127)	Time to encounter 7–12 weeks (n=223)	Time to encounter >12 weeks (n=675)
Age, years	56·7 (15·5)*	57·9 (14·7)	60·3 (15·4)	56·1 (15·6)
Sex				
Female	671 (65%)*†	88 (69%)	126 (57%)	457 (68%)
Male	354 (36%)	39 (31%)	97 (43%)	218 (32%)
Time to encounter a rheumatologist, weeks	18·4 (9·4–35·6)	··	··	··
Swollen joint count using 66 joints	8 (4–12)	9 (3–15)	7 (4–13)	8 (4–12)
Tender joint count using 68 joints	6 (4–10)	6 (4–10)	6 (4–10)	6 (4–10)
CRP, mg/L	14 (5–35)*	15 (6–39)	17 (7–40)	12 (4–30)
ESR, mm/h	29 (16–48)*‡	36 (20–56)	34 (19–46)	27 (14–46)
Rheumatoid factor positive	598/1017 (59%)	68/126 (54%)	120/222 (54%)	410/669 (61%)
ACPA positive	529/994 (53%)*‡	50/126 (40%)	92/217 (42%)	387/651 (59%)

Data are mean (SD), n (%), or median (IQR). Some serology data were missing in the Leiden EAC: CRP (n=23), ESR (n=9), rheumatoid factor (n=8), and ACPA (n=31). ACPA=anti-citrullinated protein antibodies. CRP=C-reactive protein. EAC=Early Arthritis Clinic. ESR=erythrocyte sedimentation rate. *Significant differences between 7–12 weeks and more than 12 weeks groups. †Significant differences between within 6 weeks and 7–12 weeks groups. ‡Significant differences between within 6 weeks and more than 12 weeks groups.

Table 1: **Baseline characteristics of patients with rheumatoid arthritis in the EAC**

	Total (n=514)	Time to encounter ≤6 weeks (n=11)	Time to encounter 7–12 weeks (n=100)	Time to encounter >12 weeks (n=403)
Age, years	48·6 (11·8)	46·6 (14·7)	48·1 (12·4)	48·8 (11·6)
Sex				
Female	398 (77%)	10 (91%)	84 (84%)	304 (75%)
Male	116 (23%)	1 (9%)	16 (16%)	99 (25%)
Time to encounter a rheumatologist, weeks	21·3 (13·1–33·5)	··	··	··
Swollen joint count using 66 joints	7 (4–12)*†‡	5 (3–12)	9 (6–13)	7 (4–11)
Tender joint count using 68 joints	8 (4–14)‡	14 (12–21)	10 (6–16)	7 (3–13)
CRP, mg/L	10 (5–27)	6 (4–67)	10 (4–36)	10 (5–25)
ESR, mm/h	24 (12–42)	33 (15–45)	23 (11–41)	24 (12–42)
Rheumatoid factor positive	290 (56%)‡	6 (55%)	47 (47%)	237 (59%)
ACPA positive	253 (49%)	3 (27%)	41 (41%)	209 (52%)

Data are mean (SD), n (%), or median (IQR). Some serology data were missing in ESPOIR: CRP (n=9) and ESR (n=5). ACPA=anti-citrullinated protein antibodies. CRP=C-reactive protein. ESPOIR=Etude et Suivi des Polyarthrites Indifferenciées Recentes. ESR=erythrocyte sedimentation rate. *Significant differences between within 6 weeks and 7–12 weeks groups. †Significant differences between within 6 weeks and more than 12 weeks groups. ‡Significant differences between 7–12 weeks and more than 12 weeks groups.

Table 2: **Baseline characteristics of patients with rheumatoid arthritis in ESPOIR**

Outcomes

The main outcomes were sustained DMARD-free remission and radiographic progression. Sustained DMARD-free remission was defined as the sustained absence of arthritis

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
≤6 *vs* 7–12 weeks	1·26 (0·82–1·94)	0·30	1·59 (1·02–2·49)	0·042
≤6 *vs* >12 weeks	1·84 (1·25–2·71)	0·0020	1·54 (1·04–2·29)	0·032
7–12 *vs* >12 weeks	1·47 (1·07–2·01)	0·018	0·97 (0·69–1·36)	0·85

All results from multivariable analysis were adjusted for age, sex, erythrocyte sedimentation rate, swollen joint count, and anti-citrullinated protein antibodies. DMARD=disease-modifying antirheumatic drug. EAC=Early Arthritis Clinic.

Table 3: **Association of time to encounter a rheumatologist and the chance of achieving sustained DMARD-free remission in the EAC cohort**

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
≤6 *vs* 7–12 weeks	3·70 (1·02–13·40)	0·046	2·81 (0·75–10·53)	0·12
≤6 *vs* >12 weeks	4·03 (1·24–13·07)	0·020	3·05 (0·89–10·49)	0·077
7–12 *vs* >12 weeks	1·09 (0·56–2·13)	0·80	1·09 (0·55–2·15)	0·82

All results from multivariable analysis were adjusted for age, sex, erythrocyte sedimentation rate, swollen joint count, and anti-citrullinated protein antibodies. DMARD=disease-modifying antirheumatic drug. ESPOIR=Etude et Suivi des Polyarthrites Indifferenciées Recentes.

Table 4: **Association of time to encounter a rheumatologist and the chance of achieving sustained DMARD-free remission in the ESPOIR cohort**

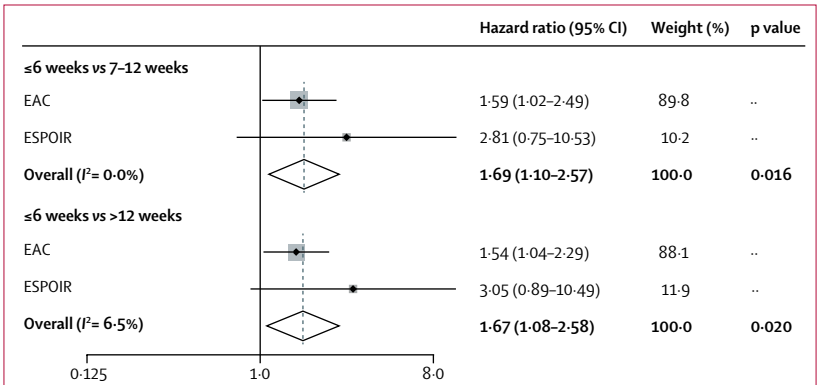

Figure 1: **Association of time to encounter a rheumatologist and the chance of achieving sustained DMARD-free remission**

Meta-analysis of both cohorts. All results from multivariable analyses were adjusted for age, sex, erythrocyte sedimentation rate, swollen joint count, and anti-citrullinated protein antibodies. Weights are from the random-effects model. DMARD=disease-modifying antirheumatic drugs. EAC=Early Arthritis Clinic. ESPOIR=Etude et Suivi des Polyarthrites Indifferenciées Recentes.

See Online for appendix

(absence of swelling by physical examination) after discontinuation of DMARD therapy, including biologics and glucocorticoids (systemic and intra-articular), for the entire period of follow-up (which had to be at least 1 year after DMARD cessation). The time between last swollen joint and time to achieve sustained DMARD-free remission was also determined. In the EAC, all medical files were explored until April 30, 2017. In ESPOIR, all structured visits in the database were reviewed.

Radiographic progression was studied using radiographs of hands and feet that were scored according to the Sharp-van der Heijde scoring method. These serial radiographs were scored blinded to clinical data, as described previously.[12,16] Radiographic evaluations were scored in patients who were included between Jan 1, 1996, and Dec 31, 2006, in EAC and between Nov 1, 2002, and April 30, 2005, in ESPOIR (appendix pp 1–2).

Data analysis

We used Cox proportional hazards regression models to analyse the effect of the time to encounter a rheumatologist on sustained DMARD-free remission. The date of sustained DMARD-free remission was defined as 1 year after the date that DMARDs were withdrawn due to remission of the disease. The date of censoring was the date of reviewing the medical records or an earlier date in case patients were lost to follow-up or had died.

We log transformed radiographic scores to approximate a normal distribution. We used a linear mixed model to estimate yearly radiographic progression, as described previously.[17]

All multivariable analyses were adjusted for age, sex, ESR, SJC, and ACPA. Two comparisons were made: patients with a time to encounter of within 6 weeks were compared with those with a time of more than 12 weeks (used in previous studies[7,9,18]), and patients with a time to encounter of within 6 weeks were compared with those with a time of 7–12 weeks.

Results from cohorts were combined in inverse variance meta-analyses (random effects), for both comparisons. p values of less than 0·05 were considered significant. Statistical analyses were done with SPSS (version 25.0), STATA (version 15.1), and GraphPad Prism (version 8.0.1).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

3585 (90%) of 4005 patients with early arthritis were included in the EAC cohort between Jan 1, 1996, and Dec 31, 2017. 1277 (36%) of 3585 patients were diagnosed with rheumatoid arthritis and classified according to the 1987 ACR criteria. 252 (20%) of 1277 patients were excluded because of missing symptom-onset data or missing remission data, and thus 1025 (80%) patients were included in this analysis (appendix p 1). In the ESPOIR cohort, 813 (100%) of 813 patients were included between Nov 1, 2002, and April 30, 2005, of which 632 (78%) were diagnosed with rheumatoid arthritis and classified according to the 1987 ACR criteria. 118 (19%) of 632 patients were excluded because of missing symptom-onset data or missing remission data, and thus the remaining 514 (81%) patients were included in this analysis (appendix p 2).

Patients from ESPOIR were significantly younger, more frequently female, had longer symptom duration, higher

TJC, and lower ESR and CRP values at baseline than those from the EAC (tables 1, 2). In the EAC, 127 (12%) of 1025 patients had a time to encounter of 6 weeks or less, 223 (22%) had a time to encounter of 7–12 weeks, and 675 (66%) had a time to encounter of 12 weeks or more. In ESPOIR, 11 (2%) of 514 patients had a time to encounter of 6 weeks or less, 100 (19%) had a time to encounter of 7–12 weeks, and 403 (78%) had a time to encounter of 12 weeks or more.

Most baseline characteristics were not different between patients with a time to encounter of 6 weeks or less and those with a time of 7–12 weeks (tables 1, 2). In the EAC, patients with a time to encounter of 6 weeks or less were more frequently female (table 1). In ESPOIR, the only significant difference was related to SJC; patients with a time to encounter of 6 weeks or less had fewer swollen joints than those with a time of 7–12 weeks (table 2). Median follow-up for patients included in this study was 7·1 years (IQR 3·9–12·2) in the EAC and 10·0 years (9·0–10·0) in ESPOIR.

In the EAC, sustained DMARD-free remission was achieved after a median of 4·6 years (IQR 2·6–6·2) of disease. The median time between last swollen joint and achieving sustained DMARD-free remission was 2·3 years (IQR 1·1–4·0), showing that physicians took a median of 1·3 years to taper and stop DMARDs. The median follow-up after achieving sustained DMARD-free remission was 5·6 years (IQR 2·1–9·4). The median period between first visit and first DMARD initiation was 2·4 weeks (IQR 1·3–5·3) in the EAC. The prevalence of sustained DMARD-free remission was assessed after 7 years (the median follow-up time); 30 (24%) of 127 patients with a time to encounter of 6 weeks or less, 45 (20%) of 223 patients with a time of 7–12 weeks, and 100 (15%) of 675 patients with a time of more than 12 weeks achieved sustained DMARD-free remission.

Patients who encountered a rheumatologist within 6 weeks achieved sustained DMARD-free remission more often than those with a time to encounter of 7–12 weeks in the multivariable analysis (hazard ratio [HR] 1·59 [95% CI 1·02–2·49], p=0·042), but not in the univariable analysis (1·26 [0·82–1·94], p=0·30; table 3). Patients who encountered a rheumatologist within 6 weeks also achieved sustained DMARD-free remission more often than those who encountered a rheumatologist after more than 12 weeks (HR 1·84 [95% CI 1·25–2·71], p=0·0020, in the univariable analysis and 1·54 [1·04–2·29], p=0·032, in the multivariable analysis; table 3).

In ESPOIR, sustained DMARD-free remission was achieved after a median of 7·9 years (IQR 4·5–9·3) of disease. The median time between the last swollen joint and achieving sustained DMARD-free remission was 2·0 years (IQR 2·0–4·3). The median follow-up after achieving sustained DMARD-free remission was 1·0 year (IQR 0·0–3·5). The median period between first visit and first DMARD initiation was 2·6 weeks (0·4–7·3) in ESPOIR. After 10 years of follow-up (the median follow-up time), three (27%) of 11 patients with a time to encounter of 6 weeks or less, 11 (11%) of 100 patients with a time of 7–12 weeks, and 41 (10%) of 403 patients with a time of more than 12 weeks had sustained DMARD-free remission. A time to encounter of 6 weeks or less was associated with a higher chance of achieving sustained DMARD-free remission than was a time of 7–12 weeks in the univariable analysis (HR 3·70 [95% CI 1·02–13·40], p=0·046) but not in the multivariable analysis (2·81 [0·75–10·53], p=0·12; table 4). Similarly, patients seen within 6 weeks were more likely to achieve sustained DMARD-free remission than those seen after 12 weeks (HR 4·03 [95% CI

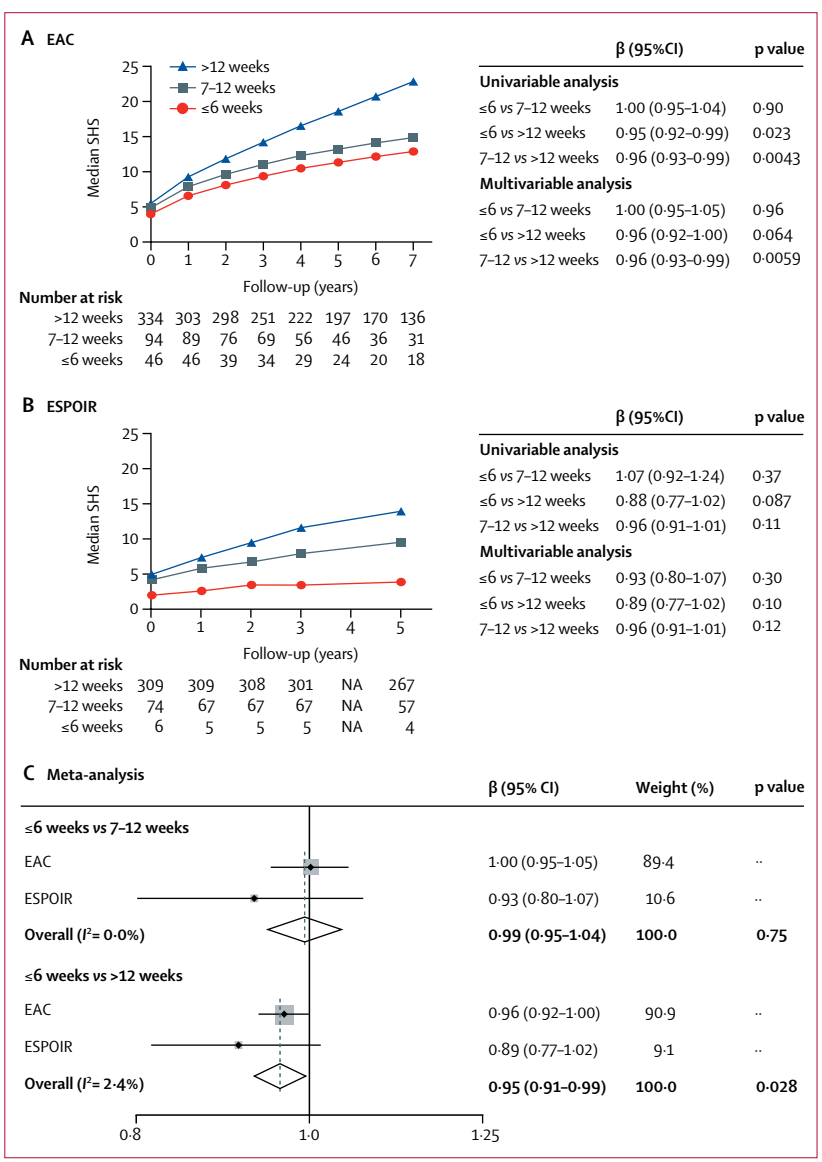

Figure 2: **Association of time to encounter a rheumatologist and radiographic progression**
(A) Univariable and multivariable analyses of the EAC cohort. (B) Univariable and multivariable analyses of the ESPOIR cohort. (C) Meta-analysis of both cohorts. Multivariable models were adjusted for age, sex, erythrocyte sedimentation rate, swollen joint count, and anti-citrullinated protein antibodies. Weights are from the random-effects model. EAC=Early Arthritis Clinic. ESPOIR=Etude et Suivi des Polyarthrites Indifferenciées Recentes. NA=not assessed. SHS=Sharp-van der Heijde score.

1·24–13·07], p=0·020, in the univariable analysis, but significance was again lost in the multivariable analysis: 3·05 [0·89–10·49], p=0·077; table 4).

A meta-analysis testing the associations in both cohorts after adjustments in multivariable analyses, showed that a time to encounter of 6 weeks or less was associated with a higher chance of achieving sustained DMARD-free remission than a time of 7–12 weeks (HR 1·69 [95% CI 1·10–2·57], p=0·016) and a time of more than 12 weeks (1·67 [1·08–2·58], p=0·020; figure 1).

In the EAC, radiographic progression was not different between patients with a time to encounter of 6 weeks or less and those with a time of 7–12 weeks in the univariable analysis (β=1·00 [95% CI 0·95–1·04], p=0·90) or multivariable analysis (1·00 [0·95–1·05], p=0·96). By contrast, in the univariable analysis, a time to encounter of 6 weeks was associated with less radiographic progression than patients with a time of more than 12 weeks (the reference group used in previous studies; β=0·95 [95% CI 0·92–0·99], p=0·023; figure 2A). However, no difference was seen in the multivariable analysis (β=0·96 [95% CI 0·92–1·00], p=0·064).

In ESPOIR, no difference in radiographic progression was seen between patients with a time to encounter of 6 weeks or less and those with a time of 7–12 weeks (β=1·07 [95% CI 0·92–1·24], p=0·37, in the univariable analysis and 0·93 [0·80–1·07], p=0·30, in the multivariable analysis; figure 2B) or a time of more than 12 weeks (0·88 [0·77–1·02], p=0·087, in the univariable analysis and 0·89 [0·77–1·02], p=0·10, in the multivariable analysis).

In the meta-analysis of both cohorts, a time to encounter of 6 weeks or less was not associated with less radiographic progression than a time of 7–12 weeks (β=0·99 [95% CI 0·95–1·04], p=0·75; figure 2C). Compared with a time to encounter of more than 12 weeks, a time of 6 weeks or less was associated with less radiographic progression (β=0·95 [95% CI 0·91–0·99], p=0·028; figure 2C).

Discussion

We found that time to encounter a rheumatologist within 6 weeks of symptom onset was associated with an increased chance of achieving sustained DMARD-free remission, but not with a reduced severity of radiographic progression, when compared with 7–12 weeks.

The reference time to encounter a rheumatologist of 7–12 weeks was included in this study because it allowed us to determine whether reducing the time window for a first rheumatology visit from 12 weeks or less to 6 weeks or less is beneficial. One of EULARs recommendations for the management of early arthritis is that patients should be referred to, and seen by a rheumatologist, within 6 weeks of symptom onset.[1] Implementation of this first recommendation is tremendously challenging in daily practice.[4] A European study showed that the proportion of patients seen by a rheumatologist within 12 weeks was low, suggesting that a first visit within 6 weeks is even more infrequent.[5] Because of these logistical challenges, it is of utmost importance to determine the evidence for such early identification.

This study was based on observational cohort data. Theoretically, a randomised controlled trial would have been the most optimal study design because the time to encounter could not be affected by a combination of both known and unknown patient and environmental characteristics. Randomised controlled trials in which the time to encounter is determined by randomisation do not have a risk that the causality of the associations with symptom duration is susceptible to confounding and reverse causation bias. However, to our knowledge, no randomised controlled trials have randomly assigned patients to see a rheumatologist within 6 weeks, between 7 and 12 weeks, or after 12 weeks, and we anticipate that such a trial would be difficult to accomplish. Even though the used study design is suboptimal, known characteristics were mostly not significantly different between the patients with a time to encounter of 6 weeks or less and those with a time of 7–12 weeks, and significantly different patient characteristics were included in the multivariable models. We assume that the effect of (known) confounding is minimised with this approach. Nonetheless, because of the observational nature of current data, we cannot exclude the presence of residual confounding (caused by unmeasured variables) that explains a late presentation and a prolonged time to encounter a rheumatologist.

In the EAC, a larger proportion of patients encountered a rheumatologist within 6 weeks than in ESPOIR (12% *vs* 2%). This difference is probably due to the fact that the health-care system around Leiden is more optimised to enable a very rapid first visit (eg, by an Early Arthritis Recognition Clinic).[15] Importantly, the patients visiting ESPOIR within 6 weeks were not patients with more severe symptoms, as baseline characteristics of the patients who first saw a rheumatologist within 6 weeks and those who saw a rheumatologist between 7 and 12 weeks were largely similar.

Similarly, although access to a rheumatology outpatient clinic was relatively easy in Leiden, and it could be assumed that patients with a favourable natural disease course will be more frequently included, patients who encountered a rheumatologist within 6 weeks did not have less severe symptoms because (except from a difference in sex) baseline characteristics were not significantly milder in these patients than those in the 7–12-week group. Therefore, the observed higher rate of sustained DMARD-free remission in patients with a time to encounter of 6 weeks or less in the EAC is unlikely to be caused by selection of patients with milder symptoms. Moreover, similar observations for sustained DMARD-free remission were found in ESPOIR.

We noted that the EULAR recommendations for early arthritis endorsed different periods to encounter a rheumatologist (≤6 weeks, recommendation 1) and start DMARD treatment (≤12 weeks, recommendation 4).[1] Our data from both cohorts suggested that rheumatologists

generally start DMARDs considerably faster than after 6 weeks (median period between first visit and first DMARD initiation 2·4 weeks [IQR 1·3–5·3] in the EAC and 2·6 weeks [0·4–7·3] in ESPOIR).

This study has several limitations. In both cohorts, onset of symptoms was defined as self-noticed symptoms by patients, which could have induced some heterogeneity due to inter-individual differences in symptom awareness. Second, we used data of longitudinal cohort studies of patients treated in routine care, and decisions to taper and stop DMARDs were not made according to protocols, and were instead determined by the patients and rheumatologists, possibly resulting in underestimation of sustained DMARD-free remission. Furthermore, ESPOIR data on sustained DMARD-free remission were obtained by structured visits, whereas in the EAC information from medical files was also available; sustained DMARD-free remission in ESPOIR could therefore be underestimated. Finally, the sample size of ESPOIR was smaller than that of the EAC, and further validation is required.

In conclusion, the decision about whether or not to try to implement the EULAR recommendation to see a rheumatologist within 6 weeks of symptom onset might depend on the long-term treatment aim. A beneficial effect was demonstrated for sustained DMARD-free remission, which is a proxy measure of resolution of disease chronicity. However, to minimise structural damage, a time to encounter of 6 weeks or less does not seem necessary. Since clinically relevant joint destruction has become infrequent and sustained DMARD-free remission is increasingly achievable,[19] achieving a time to encounter within 6 weeks, although challenging, might become of increasing importance.

Contributors

EN and AHMvdH-vM performed study planning and design. EN performed data analysis. EN, MD, BC, AHMvdH-vM contributed to data interpretation. EN wrote the manuscript. All authors participated in editing the manuscript and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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