Decreasing time to treatment in rheumatoid arthritis: review of delays in presentation, referral and assessment

Rheumatoid arthritis (RA) is a common inflammatory arthritis with effective treatments. Early active treatment is now accepted as best practice; early treatment is more effective and is more likely to induce remission. Suspected RA is therefore a problem that should be referred to a rheumatologist promptly. Treatment of RA by a rheumatologist leads to a higher quality of care and improved outcomes at no increased cost. Identification of obstacles to timely care and working to overcome them is essential to improvements in RA care. Research has demonstrated a range of expected and unexpected reasons for delays in presentation, referral and assessment of suspected RA. These include knowledge deficit, access, socioeconomic, interpersonal and geographical factors. Better identification of these barriers and work to reduce or eliminate their impact is important to providing good care for RA patients.

KEYWORDS: diagnosis ■ DMARD ■ early arthritis ■ priority ■ rheumatoid arthritis ■ triage ■ undifferentiated arthritis

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the need for early treatment in RA
- Describe obstacles to timely care of RA
- Describe strategies to reduce time to treatment in RA

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Early treatment of rheumatoid arthritis (RA) leads to reduced disease activity, reduced joint damage, decreased functional impairment and increased chance of remission [1–3]. The majority of rheumatologists now specify remission as a major goal of RA treatment [4]. It is possible that there is a period where the natural history of the disease can be altered; this has been termed 'the window of opportunity' [5,6] and the evidence suggests that this is a 3-month period [1,3,5,7]. A challenge is to have patients assessed early by a rheumatologist as this delivers the best outcomes at no increased cost [8–10]. A number of studies, both qualitative and quantitative, have examined the factors that affect presentation, referral and assessment of suspected RA. The research on factors that influence assessment and treatment are summarized in this paper.

Literature for this review was obtained from a comprehensive search of MEDLINE (1996 to September 2010). Terms used were: 'early rheumatoid arthritis', 'undifferentiated arthritis', 'unclassified arthritis', 'triage', 'priority', 'diagnosis' and 'prognosis'. Literature that was known to the authors from previous research in this area was also used and all reference lists were extensively searched for other relevant research. The term primary care physician (PCP) has been used throughout the text for consistency and has been used in place of general practitioner where that was used in the original description.

Definitions

A number of descriptions of different presentations and disease states are used; their definition, background and basis for allocation are discussed in this section.

Early arthritis

This term is generally applied to cases seen in an early arthritis clinic (EAC) or those with arthritis of recent onset. A common cut-off for 'early arthritis' is 2 years, but this varies widely. It is nondefining and makes no claim as to the etiology of the arthritis. RA, psoriatic arthritis, crystal arthritis, spondyloarthritis and sarcoid arthritis, among other diagnoses, are all represented in EACs [11].

Undifferentiated arthritis

Undifferentiated arthritis (UA) has generally been defined as arthritis which does not meet the 1987 American College of Rheumatology classification criteria for RA or have another classifiable cause [12]. It has also been termed undifferentiated peripheral inflammatory arthritis (UPIA) by the 3E group (Evidence, Expertise, Exchange) [13]. This diagnosis is commonly applied after initial assessment in those with inflammatory synovitis of short duration. It has been argued that this is more accurate than classifying the patient as possible RA as it is unknown if they will develop RA or not [14]. Up to half the patients initially classified as UA (based on not fulfilling the 1987 criteria [12]) have self-limiting synovitis [15]. In the 2007 Leiden cohort study, 570 out of 1700 patients were classified as UA after their first clinical assessment, and serology and radiology were known [16]. Of these 570, 31% were diagnosed with RA at 1 year, 16% had alternate rheumatic disease and 26% were in remission (as defined by discharge from clinic with no disease-modifying antirheumatic drug [DMARD] treatment). The remaining patients continued to be defined as UA. The Norfolk Arthritis Register showed that the number of UA patients diagnosed with RA rises with time [17]. There is new evidence emerging on the effect of corticosteroids, methotrexate and biologics in UA, which indicate that intervention may modify the course of UA and progression to RA [18–22].

Early RA

At one extreme this description has been applied to early inflammatory synovitis that has not yet reached classification criteria and on the other it has been applied to RA with a duration of up to 7–8 years [23]. In the setting of early arthritis there is resistance to this term being applied to inflammatory arthritis of the hands without further evidence of RA [14]. This is understandable as the purpose of assigning a diagnosis or classification is to assist with prognostication and treatment decisions. Therefore, to assign this without adequate basis seems to be counter-productive. Standardization of this term would be useful to assist research in this area.

Diagnosis of RA & new 2010 criteria

The diagnosis of RA is a critical issue for treatment and prognosis. We know that early treatment improves outcome, but we also know a significant percentage of UA patients do not develop RA. Accurate diagnosis and/or prediction is therefore critical. The 1987 RA criteria have been criticized as being insensitive [24]. This was due to established RA patients with disease duration of approximately 8 years being used to construct the criteria. The inclusion of rheumatoid factor (RF; due to delayed seroconversion), rheumatoid nodules and erosions on plain radiographs leads to the insensitivity in early disease [25,26]. Almost all research published to date in predicting RA has used the 1987 criteria as the end point and in some ways this is appropriate as patients meeting this criteria arguably have what historically has been called RA. The new 2010 criteria [27] were constructed to address early disease and so the 1987 criteria [12] may still continue to be used to define a type of gold standard for eventual diagnosis/outcome.

The 2010 RA classification criteria were specifically designed to address the deficiencies in the 1987 criteria, primarily a lack of sensitivity [12,27]. The stated aim was to develop an approach to UA to "identify that subset of patients who are at sufficiently high risk of persistent and/or erosive disease – this being the appropriate current paradigm underlying the disease construct 'rheumatoid arthritis' – to be classified as having RA" [27]. Entry criteria requiring one swollen joint have been introduced and then features are numerically scored.

According to the 1987 criteria a patient with inflammatory polyarthritis and negative serology could stay unclassified for a significant period of time pending, for example, typical rheumatoid erosions or seroconversion of RF/anti-cyclic citrullinated peptide (CCP) antibody [12]. The 2010 criteria mean a patient can be classified as RA if they have a polyarthritis involving more than ten joints for 6 weeks or more [27]. This change improves sensitivity, but it must sacrifice specificity. The criteria will reclassify a proportion of UA as RA and therefore the entity which was previously known as UA/UPIA will diminish in frequency. This issue has also been highlighted in the recent 3E UPIA recommendations [13]. The change in criteria will affect historical comparisons about the frequency of UA and RA. The effect of the criteria on clinical care will have to await studies using the new and old criteria simultaneously.

Inception cohort & registry studies

Inception cohorts and registry studies have examined the presentation and evolution of early arthritis (see review elsewhere [28]). They often draw their patients from EACs, which have been set up in an increasing number of centers, such as Leiden in The Netherlands [29]. There have also been multicenter cohorts set up such as the French Evaluation et Suivi de Polarthrites Indifférenciées Récentes (ESPOIR) cohort [30] and the Norfolk early arthritis register in England [31]. The nature of early arthritis presentations means that, among other things, cohorts can be constructed which compare patients that present early with those that present late.

The groups are not randomized and therefore it should be kept in mind that different factors may drive people to present earlier or present later. As clinical factors often guide treatment this is another important point to remember when interpreting data from nonrandom and nonstandardized cohorts. Treatment is not then uniform but tailored to disease severity. Those with mild disease can receive no treatment and may then do well actuarially. To formally answer the question of whether early treatment is better than late treatment, randomized studies would provide the best evidence but these would not now be feasible.

Predictive models for the probability of RA and for persistent and/or erosive arthritis have been constructed with data from these prospective cohorts. The Leiden study, which attempted to model persistent and/or erosive arthritis [11], used a different design and therefore addressed some of the sensitivity issues associated with the 1987 RA criteria that were available at the time [12]. Other models have chosen only clinical and laboratory factors in an attempt to model daily clinical practice [16].

Evidence for early treatment

There are a number of nonrandomized studies that provide evidence for the benefit of early treatment in RA. One example is the study by Nell and colleagues from Austria [3]. They observed 40 patients seen in their EAC over 3 years. The start of the study was preceded by a public awareness campaign called 'Early Arthritis Action', which generated significantly increased referrals [32]. They observed 20 patients who had their DMARD initiated at a median of 3 months after symptom onset (Very Early Rheumatoid Arthritis [VERA] cohort) and 20 patients who had their DMARD initiated at a median of 12 months after symptom onset (Late Early

Rheumatoid Arthritis [LERA] cohort). Some of these patients may have been classified as UA at DMARD initiation as they only had to fulfill the 1987 RA criteria by 1 year. Both groups started with disease activity score for 28 joints (DAS28)-defined high disease activity (DAS28 >5.1) and both groups received routine care, which at the time generally meant changing DMARD after 3 months of nonresponse [3]. They found the VERA cohort had a significantly lower DAS28 3 months after DMARD initiation and achieved DAS28-defined low disease activity (DAS28 <3.2) within 12 months. The LERA group achieved only moderate disease activity (DAS28 3.2–5.1), had more joint damage and progressed faster compared with the VERA group.

One point to note is that the trial was not randomized and so some VERA patients potentially may not have become LERA patients, even with no treatment.

There is some evidence that the course of UA can be altered by early treatment with methotrexate. The Leiden group randomized 55 UA patients to methotrexate at a dose of 15 mg/week or placebo, and the methotrexate was uptitrated if disease activity score for 44 joints (DAS44) was greater than 2.4 [20]. They found that the diagnosis of RA by 1987 criteria [12] was delayed and radiographic joint damage was reduced. As discussed above, there is emerging evidence for the roles of biologics and other agents in UA [18,19,21,22].

Early treatment is likely very beneficial for RA, but cohorts have shown that a significant proportion of those who present with synovitis spontaneously remit [15]. Overtreatment is a risk in the drive to treat potentially developing RA early. Overtreatment exposes the patient to the risk of side effects with no potential benefit if RA does not develop. There is a significant body of work on attempts to accurately predict whether RA will develop and this work is ongoing.

Factors influencing steps in the assessment & treatment process

The determinants of early assessment and treatment have been surveyed in a number of studies. Following is an overview of factors shown to influence progression through the pathway of assessment and treatment. An important factor that can impact greatly on arthritis assessment and treatment is the design and funding of the healthcare system. Differences that are important in some regions are not important in others. Measurement of these differences between healthcare systems is difficult.

Undefined delay/total delay

Research on overall delay provides some insights that are discussed in this section. The evidence is summarized in Table 1.

There may be two different streams of patients that transition through the system at different speeds. Those who present early to their PCP are referred early and start DMARDs early; and those who present late are referred late and have their DMARDs started late. Research from both New Zealand and England has noted this [33,34]. Disease severity may be a factor in this dichotomization [33,35,36].

Multivariate regression analysis of a Leiden EAC cohort showed that gradual onset of symptoms (2.2 times delay of reference [TDR]; 95% CI: 2.02–2.44), older age (1.004 TDR for each year older; 95% CI: 1.002–1.007), involvement of small joints (1.31 TDR; 95% CI: 1.18–1.46), anti-CCP antibody positivity (1.31 TDR; 95% CI: 1.13–1.51), RF positivity (1.20 TDR; 95% CI: 1.04–1.37) and lower C-reactive protein (CRP) level (0.995 per 1 g/l increase TDR; 95% CI: 0.993–0.995) were independently associated with a longer duration of total delay [1]. Crystal arthritis, reactive arthritis and sarcoid arthritis had the shortest delay in the Leiden EAC [1]. This would seem to suggest (in light of the rapid assessment of all referrals to the Leiden EAC) that these problems present differently.

Patient factors undoubtedly play a large role [37]. The Patient Partner Program is a Belgian initiative where trained patients assist in education of medical students and PCPs about RA diagnosis [38]. They compared 21 patient partners to 28 RA controls and found the patient partners had a time from symptom onset to diagnosis of 0.8 years compared with 2.8 years for controls. The patient partners had more social activities, better ability to work, a lower stress level and a more positive mood. More active coping strategies, more reassuring thoughts and less depressive symptoms were also more common. The patient partners were chosen for their ability to teach so this study has to be interpreted with caution, but it does augment results from Sheppard that personality issues impact on the decision to seek medical advice regarding arthritis [35].

Factors that influence patient presentation to primary care

Studies in this area are mostly qualitative but two studies do provide quantitative data on clinical factors that were associated with a

Table 1. Influences on total/overall delay.

Quantitative influence	Direction	Strength of effect (95% CI)	p-value	Level of evidence
Advancing age	Prolonged time	1.004 TDR† (1.002–1.007)	<0.001	Cohort study
Gradual onset of symptoms	Prolonged time	2.22 TDR (2.02–2.44)	<0.001	Cohort study
Involvement of small and large joints vs only large joints	Prolonged time	1.16 TDR (1.02–1.32)	<0.001	Cohort study
Involvement of small joints vs large	Prolonged time	1.31 TDR (1.18–1.46)	<0.001	Cohort study
Positive rheumatoid factor	Prolonged time	1.20 TDR (1.04–1.37)	0.010	Cohort study
CRP level	Reduced time	0.995 TDR‡ (0.993–0.995)	<0.001	Cohort study
Positive anti-CCP antibody	Prolonged time	1.31 TDR (1.13–1.51)	<0.001	Cohort study
Female gender	Prolonged time	1.12 TDR (1.02–1.22)	0.014	Cohort study

†Relative prolongation of 1.004 for every additional year.
‡Relative reduction of 0.995 for every CRP unit increased.
CCP: Cyclic citrullinated peptide; CRP: C-reactive protein; TDR: Times delay of reference.
Data from [1].

prolonged patient delay remission [1,37]. The factors identified by research that influence patient presentation are summarized in Table 2.

Qualitative research by Sheppard and colleagues in Birmingham (UK) found that following the onset of symptoms, patients would often seek advice when the explanations they gave themselves did not seem to explain their symptoms adequately anymore [35]. Participants stated that they did not attend their PCP about their joint symptoms as they did not want to waste a PCP's time or be a drain on health resources. A patient's relationship with their PCP and their patient's experience of interacting with the healthcare system also influenced their decision to seek advice in relation to their symptoms [35]. Exacerbating these issues is the lack of knowledge of the general public about RA, its importance and the necessity of early treatment [35,39]. Low socioeconomic status was cited as a barrier to seeking care in a Canadian qualitative study [39]. Access issues including a lack of PCPs, no available appointments with PCPs and the need to use an alternative such as the emergency room were barriers cited in Canadian research [39]. English qualitative research from patient interviews did not identify this as an issue, which may be consistent with better PCP access in the UK compared with Canada [37,40].

Kumar and colleagues found that age and gender did not influence time to present to a PCP [37]. This was in contrast to themes from qualitative studies which indicated that men often put off seeking help and ignored advice from those around them to seek a medical opinion [35,39].

The Leiden EAC study found gradual onset of disease (2.38 TDR; 95% CI: 2.09–2.70), involvement of joints of lower extremities versus upper extremities (0.73 TDR; 95% CI: 0.63–0.84),

Table 2. Influences on time to presentation to primary care/patient delay.

Quantitative influence	Direction	Strength of effect (95% CI)	p-value	Level of evidence	Ref.
Gradual onset	Prolonged time	2.38 TDR (2.09–2.70)	<0.001	Cohort study	[1]
Involvement of lower limbs vs upper	Reduced time	0.73 TDR (0.63–0.84)	<0.001	Cohort study	[1]
Involvement of both limbs vs upper	Reduced time	0.90 TDR (0.77–1.04)	0.155	Cohort study	[1]
Positive anti-CCP antibody	Prolonged time	1.21 TDR (1.04–1.39)	0.01	Cohort study	[1]
CRP level†	Reduced time	0.995 TDR (0.995–0.998)	<0.001	Cohort study	[1]
Positive rheumatoid factor	Prolonged time	13 vs 4 weeks	0.001	Cohort study	[37]
Qualitative influence	***Direction***	***Study design***			***Ref.***
Access to primary care	Prolonged time	SFGIs			[39]
Knowledge	Both directions	SFGI/individual face-to-face semi-structured patient interviews			[35,39]
Symptom perception	Both directions	Individual face-to-face semi-structured patient interviews			[35]
Socioeconomic status	Both directions	SFGIs			[39]
Prior interaction with the health system	Both directions	Individual face-to-face semi-structured patient interviews			[35]
Male gender	Prolonged time	SFGI/individual face-to-face semi-structured patient interviews			[35,39]

†Reduction of 0.995 for every CRP unit increased.
CCP: Cyclic citrullinated peptide; CRP: C-reactive protein; SFGI: Structured focus group interview; TDR: Times delay of reference.

involvement of joints of both extremities versus upper extremities (0.90 TDR; 95% CI: 0.77–1.04), anti-CCP antibody (1.21 TDR; 95% CI: 1.04–1.39) and CRP level (0.995 per increase of 1 g/l TDR; 95% CI: 0.995–0.998) influenced patient delay [1]. This suggests that the type (as measured by distribution, anti-CCP antibody and pattern of onset) or severity of arthritis (as measured by CRP) had an influence on when patients presented to a doctor. For example, one could hypothesize that an arthritis that limited mobility by effecting lower limb joints may precipitate earlier consultation than one that did not limit mobility. A gradual-onset arthritis with low inflammatory activity may be ignored by people due to the nondisabling symptoms.

In summary, factors that influence a patient's decision to present include the way symptoms are perceived and the importance placed on them. Knowledge of RA and the perceived importance of the diagnosis is also important. The relationship between the patient and their PCP and their prior interactions with the healthcare system strongly influence the decision to seek help. Finally, quantitative studies suggest the pattern and severity of symptoms play a role.

Factors that influence referral to a rheumatologist

A diverse range of factors influence if and when patients are referred to a rheumatologist once they have presented to their PCP. The factors identified to date that influence referral to a rheumatologist are summarized in Table 3.

Suter and colleagues conducted a qualitative study of 19 PCPs in Connecticut, USA. The relationship between both the primary carer and the patient as well as the relationship between the PCP and the rheumatologist influenced the decision to refer a patient [39,41]. PCPs would often immediately refer someone they did not know regardless of clinical or laboratory results. The Connecticut doctors said they would delay referral of those patients who they knew so as to

Table 3. Influences on referral to secondary care/primary care physician delay.

Quantitative influence	Direction	Strength of effect (95% CI)	p-value	Level of evidence	Ref.
CRP level	Reduced time	0.995 TDR† (0.993–0.995)	<0.001	Cohort study	[1]
Female gender	Reduced time	1.01 OER (1.01–1.03)	<0.05	Cohort study	[36]
	Prolonged time	1.14 TDR (1.01–1.29)	0.04	Cohort study	[1]
	Prolonged time	93 vs 58 days	0.008	Cohort study	[44]
	Prolonged time	10 vs 3 weeks	0.039	Cohort study	[43]
Advancing age	Reduced time‡	1.333 HR (1.24–1.43)	<0.05	Observational study	[42]
	Prolonged time	1.004 TDR§ (1.002–1.009)	0.004	Cohort study	[1]
	Prolonged time	0.994 HR (0.991–0.997)	<0.05	Observational study	[42]
Gradual onset	Prolonged time	1.93 TDR (1.69–2.20)	<0.001	Cohort study	[1]
Symmetrical distribution of complaints	Reduced time	0.79 TDR (0.69–0.90)	<0.001	Cohort study	[1]
Positive anti-CCP antibody	Prolonged time	1.33 TDR (1.09–1.63)	0.006	Cohort study	[1]
Positive rheumatoid factor	Prolonged time	1.22 TDR (1.01–1.47)	0.039	Cohort study	[1]
Qualitative influence	***Direction***	***Study design***			***Ref.***
Relationship between PCP and patient	Both directions	Individual face-to-face interview			[41]
Relationship between PCP and rheumatologist	Both directions	Individual face-to-face interview			[39,41]
Comorbidity	Both directions	Individual face-to-face interview			[41]
Atypical symptoms	Both directions	Individual face-to-face interview			[41]
Patient health beliefs/preferences	Both directions	Individual face-to-face interview			[41]
Milder disease	Prolonged time	Individual face-to-face interview			[41]
Slower progression	Prolonged time	Individual face-to-face interview			[41]
Prior alternate diagnoses	Prolonged time	Individual face-to-face interview			[41]
Clinical improvement without treatment	Prolonged time	Individual face-to-face interview			[41]
Access issues	Prolonged time	Individual face-to-face interview			[39,41]

†Relative reduction of 0.995 for every CRP unit increased.
‡Gender difference reduced with advancing age.
§Relative prolongation of 1.004 for every additional year.
CCP: Cyclic citrullinated peptide; CRP: C-reactive protein; HR: Hazard ratio; OER: Odds of early referral; PCP: Primary care physician; TDR: Times delay of reference.

ask a more definite clinical question of the specialist [41]. A good relationship between the PCP and rheumatologist facilitated speedy referral and a poor relationship impeded referral. PCPs also noted a tendency not to refer if they lacked confidence in the rheumatologist [41].

The specialty of the assessing doctor may also influence the decision to refer. The McGill University group found a nonsignificant difference in early referral between PCPs and non-PCPs with a probability of early referral of 1.29 (95% CI: 0.60–2.77) if the patient did not see a PCP [36].

Mild disease, slow progression and clinical improvement with or without treatment were found to deter referral in the qualitative study of Connecticut PCPs [41]. This is supported by the finding from the Leiden EAC that gradual symptom onset was independently associated with a longer duration of total delay [1]. Multivariate analysis of a cohort of early arthritis patients from McGill University showed a raised CRP (possibly indicating a more florid presentation) was associated with earlier referral [36]. We have found that PCPs requested an urgent appointment if there were swollen joints and a raised CRP, supporting the Canadian findings [33].

Coexistent problems such as psychiatric illness and substance abuse have been cited by PCPs as both reasons to refer and reasons to defer referral [39]. Supporting these findings is that more comorbidity was associated with reduced time to a rheumatologist consultation in a Quebec (Canada) administration database study [42].

The patient's attitude to the suspected diagnosis also has a bearing, with some patients seeing the diagnosis of RA as 'not important', so this discouraged referral by PCPs [41]. On the other hand, some demanded immediate referral, sometimes even when the referrer felt it unnecessary [41].

Access issues have an impact with both lack of rheumatologists in the geographical area as well as lack of timely appointments influencing the decision to refer to a rheumatologist [39,41]. A number of PCPs noted that if clinical and administrative leadership prioritized quality care and timeliness then care was improved [41].

In two studies, women were referred to rheumatologists later than men (35–49 days later) [43,44]. This did not affect the overall delay in the Norse study of 44 patients and the overall delay was not stated in the Leiden study of 224 patients. By contrast, women had a shorter time to rheumatology consultation in an administrative database study from Quebec [42], but the difference between men and women reduced as patients aged (hazard ratio of a shorter time to consultation: 1.54 decreasing to 1.21 from age 40 to 74; 95% CIs not stated) [42]. There was no difference in time to assessment between men and women found in a UK cohort study of 169 patients [33].

The Leiden EAC study found age at inclusion (1.004 per increase in age of 1 year TDR; 95% CI: 1.002–1.009), female gender (1.14 TDR; 95% CI: 1.01–1.29), gradual onset (1.93 TDR; 95% CI: 1.69–2.20) and symmetric distribution (0.79 TDR; 95% CI: 0.69–0.90), anti-CCP antibody (1.33 TDR; 95% CI: 1.09–1.63), RF (1.22 TDR; 95% CI: 1.01–1.47) and CRP level (0.995 per increase of 1 g/l TDR; 95% CI: 0.993–0.995) influenced PCP delay [1].

In summary, relationships between patients, PCPs and rheumatologists influence referral behavior. Mild disease deters referral and more florid disease possibly encourages referral. Comorbid health problems, access issues and management priorities have also been cited as influential. Gender possibly plays a role, but the research is contradictory. Finally, quantitative research shows that clinical characteristics influence when a patient is referred.

Factors influencing priority allocation by rheumatology services

This is an area that is not well studied, perhaps since most studies of early arthritis occur in the context of EACs rather than ordinary clinical care [29,45]. EACs usually see patients within a few weeks [29] or can even visit them in their homes after referral [46]. Where an EAC is not present, early arthritis patients have to be seen in a standard rheumatology outpatient clinic. How quickly a patient is seen following referral depends upon how the service is organized and resourced. One element of departmental organization is triage so as to accord higher priority to patients who need to be seen the most urgently [33,47]. Factors identified by research to influence triage allocation are summarized in Table 4.

Referral letters to rheumatology services often lack important information and irrelevant information is often included; this has an impact on the triage category allocated [33,48–52]. Mentioning the suspected diagnosis of RA in the referral letter resulted in a reduced time to assessment compared with the absence of this stated suspicion in an English study [53]. Certain investigations are often included in referral letters,

Table 4. Influences on triage allocation by rheumatology services.

Quantitative influence	Direction	Strength of effect (95% CI)	p-value	Level of evidence	Ref.
Advancing age	Prolonged time	0.97† OR (0.93–0.99)	<0.001	Cohort study	[33]
PCP-requested urgency	Reduced time	13.34 OR (2.20–81.02)	<0.001	Cohort study	[33]
Mentioning the suspected diagnosis	Reduced time	Not stated		Cohort study	[53]
Information in referral letter	Both directions	18% change in priority		Cohort study	[50]
	Both directions	47% change in priority		Cohort study	[54]

†Odds of urgent triage of 0.97 for every additional year.
OR: Odds ratio; PCP: Primary care physician.

likely reflecting their longstanding use in disease assessment. RF was supplied in 92% of cases that were eventually diagnosed with RA in our study [33]. Graydon found RF in 80% of general rheumatology referrals [50], but anti-CCP antibody was only present in 14% of referral letters in our study [33].

A Canadian study of 206 referrals employed a simple triage system and when the patient was seen they reassessed for the accuracy of the original triage [50]. This resulted in a change in triage category in 47% of cases. This demonstrates either an inadequate referral letter, change in clinical status between referral and assessment, or most plausibly a better assessment by the rheumatologist compared with the PCP. The sensitivity of this triage system (probability of assigning urgency to a patient which does indeed turn out to be urgent) was 59%. This could reflect the poor documentation of important clinical details in the referrals. By contrast, priority change occurred in only 18% of referrals in another study of similar design from England [54]. The reason for such a substantial difference is unclear but may be partly related to study design and the different healthcare systems where the studies were conducted.

We found younger age and a referrer request for an urgent appointment in the referral letter as factors that predicted an urgent triage allocation by a triaging rheumatologist [33].

Importantly, 9% of patients in our study had a positive anti-CCP antibody and a positive RF but were not allocated to urgent triage [33]. This demonstrates a lack of knowledge of the prognostic importance of these factors (which seems unlikely), failure to read the referral letter properly or a reluctance to triage to urgent due to the administrative burden of fitting urgent patients into already fully booked clinics. These problems are the sort of system-based issues that create obstacles to timely care.

A Canadian study found that not triaging patients (by allocating appointments on a first referred first appointed basis) resulted in a median wait time of 27 days [47]. RA patients were seen at approximately the same time as conditions that were ultimately assessed as non-urgent. Wait time in this type of setting would be solely dependent on the balance of referral volume to service provision.

Early arthritis clinics are unlikely to be available universally due to differences in funding, research involvement and service provision. Therefore, it will remain crucial for many practitioners to see early arthritis in their normal clinics. Appropriate documentation of important information in referral letters and accurate triaging will remain an issue critical to the timely assessment of early arthritis. Details of the ideal history, examination findings and investigations for arthritis referral letters are documented in Box 1.

Strategies to improve time to treatment in RA

There are a number of approaches to improving time to treatment. A fundamental decision is whether to encourage referrers to stratify suspected RA before referral or to refer everyone who they suspect may have inflammatory arthritis. It is important to remember that although at a population level inflammatory arthritis is common, each individual PCP will only see approximately one new case of RA per year [55]. The chosen strategy has to be simple and easily applicable for the majority of PCPs. There are trade-offs involved with each approach.

In encouraging referrers to stratify patients, a higher proportion of patients attending rheumatology clinics will have RA, but potentially at the cost of time while undergoing stratification procedures in primary care. In this case a referrer may see the patient and request laboratory tests such as CRP, anti-CCP antibody and RF. The patient is then told to return either as required or at some later time point to discuss results and assess the effect of initial treatment. This runs the risk of the patient not returning to consult the PCP and, if laboratory tests are negative or normal, a wait-and-see approach by the assessing doctor. This introduces delays into

the process (especially in view of the potential delays in assessment after referral in some settings), which may mean the difference between timely treatment, in a contemporary sense, and delayed treatment.

Alternatively, referral for suspicion of inflammatory arthritis creates a workload that requires increased secondary care resources. Due to the ease of access it is possible that referrers would use it as a way to have other musculoskeletal problems assessed quickly (research from EACs have found this [56]). The cost–effectiveness of this strategy needs to be properly evaluated.

Emery and colleagues published guidelines in 2002 that advocated the latter approach [57]. They advised rapid referral to a rheumatologist if there was morning stiffness lasting 30 min or more, three or more swollen joints or metatarsophalangeal/metacarpophalangeal squeeze test positive [57]. These recommendations notably did not include laboratory factors such as RF or anti-CCP antibody. Suresh recommended using similar criteria for early referral of suspected RA, but also included a positive RF, raised inflammatory markers and systemic features such as weight loss as reasons for referral [58]. Both Suresh and Emery stated that normal imaging, antibodies or inflammatory markers should not deter referral. Notably, an English study from 2003 found PCPs deferred referral if the RF was negative and a significant proportion felt the result excluded RA [59].

While there are published referral guidelines [57,58], the evidence from both rheumatology and nonrheumatology settings is that simply distributing guidelines will not improve practice [56,60,61]. There is some evidence that disseminating the referral guidelines in conjunction with education sessions from specialists could improve the quality of the referrals [60]. Consistent with this, workshops on musculoskeletal conditions for Canadian family physicians demonstrated a significant increase in knowledge and a high level of satisfaction [62,63].

A study from Northern Ireland took a small number of PCPs and nurses and trained them in four half-day clinics [56]. They then undertook EAC assessments and were compared with rheumatologists and specialist registrars as the gold standard. The trained assessments had a positive predictive value for inflammatory arthritis of 88–93% and had substantial agreement with the rheumatologists with a κ statistic of 0.77 (95% CI: 0.64–0.90) for PCPs and 0.79 (95% CI: 0.67–0.91) for nurses [56]. Undertaking this training and then maintaining these skills in PCPs would be challenging due to the relative scarcity of new RA cases for each PCP [55].

Box 1. Ideal referral letter information.

Investigations for inflammatory arthritis [13,25]
- Rheumatoid factor
- Anticyclic citrullinated antibody
- Erythrocyte sedimentation rate
- C-reactive protein
- Antinuclear antibody

Additional possible investigations depending on clinical setting [13,25,73]
- Uric acid
- HLA-B27
- Full blood count
- Alanine aminotransferase/aspartate aminotransferase
- Synovial fluid analysis
- Urinalysis
- Lyme disease
- Parvovirus
- Hepatitis B and C
- Urethral or cervical swabs
- Radiographs

Documented clinical details [50,73]
- Duration of symptoms
- Presence and duration of morning stiffness
- Pattern of joint involvement
- Number and location of swollen joints
- Number and location of tender joints
- Rash
- Fever
- Connective tissue disease symptoms
- Functional status

It is likely that education of both the public and PCPs plays a major role in either strategy. Kiely and colleagues advocated an education programme for PCPs and community healthcare team members about treating undifferentiated arthritis as 'urgent' [64] since many stakeholders feel that lack of awareness is a barrier to optimal care [35]. Patients have commented that they know much about problems such as heart disease due to advertising campaigns but had never heard of RA [34].

A number of education campaigns have been run including Early Arthritis Action in Austria and Every Day Counts, run by the Asia–Pacific League of Associations for Rheumatology [32,101]. The US National Arthritis Action Plan had as one of its goals to "Increase awareness of arthritis, its impact [and] the importance of early diagnosis" [102]. These campaigns and others are designed to raise awareness of arthritis and the potential benefits of early consultation and treatment.

Bell and colleagues have developed a pre-primary care questionnaire in an attempt to increase early referral but its performance characteristics

are yet to be published [65]. Research into education programs in pharmacies is planned by the Canadian McGill University group [39].

Ultimately it will take time for practitioners to become aware of the need for early referral. Educating medical students is crucial in this regard, as well as utilizing resources such as enthusiastic patients. The Patient Partner Programme in Belgium uses patients with RA to teach PCPs and medical students about RA and the importance of early treatment [38].

Triage is required to identify suspected early arthritis in the absence of EACs to expedite timely assessment. Numerous studies have found a poor quality of referral letters and a deficiency of supplied information [33,48–52]. Evidence suggests that form letters are better than nonform letters and contain more information with no increase in length [66].

Changing appointment management and clinic organization has the potential to reduce time to treatment in RA. Changing the way clinics are managed through 'advanced access' schemes which utilize short-notice slots, change in appointment length and an increased patient focus can reduce wait times [67]. Pre-appointment screening of referred patients using medical records can reduce the need to see some patients and so improve access for those with early arthritis [68]. Flexibility on the part of the physician and managers to implement site-specific solutions is required as not all strategies will be appropriate for each setting. EACs probably provide the best solution but they are not always possible.

The different health insurance/social security systems can have a large impact on presentation of early arthritis. For example, patients have to pay to see PCPs in New Zealand, but not in the UK. Geographical availability of specialists either covered by the patient's insurance or supplied by the national health service impacts greatly on access for early arthritis patients. Insurance copayments or patient out-of-pocket payments can deter patients seeing specialists or returning for medication titration. Patients are often seen frequently around the time of diagnosis and this can deter attendance if they have large copayments. Coverage of pharmaceutical costs by third-party payers can impact early RA treatment. Methotrexate is relatively inexpensive, but if biologics become indicated earlier in the course of RA this will pose a significant issue due to their large differential in cost compared with methotrexate.

Modifiable factors include time for patients to present to their PCP, time for patients to be seen by their PCP, time until referred onto a rheumatologist and time for the patient to see a rheumatologist. Kiely pointed out that there is little evidence to support changes in outcome following education campaigns [64]. The absence of evidence does not necessarily mean the absence of effect though. It must also be argued that most people believe chest pain is a reason to see a doctor quickly and so with time and appropriate resources why can this attitude not apply to the symptoms of inflammatory arthritis? The other steps in the patient journey are modifiable and EACs are a significant step forward but they are not present everywhere. Regardless of the presence or not of EACs it still requires referral from PCPs on suspicion of RA; this requires education of PCPs.

In conclusion, there are a large number of potential improvements that can be implemented. The strategy chosen for each region or site will depend on resourcing, research involvement and access issues. Education of both the public and PCPs is critical to achieving the goal of early assessment of RA by rheumatologists. Initiatives such as changing practice set-ups, triage of referral letters and advanced access programs have scope to improve access. Future work on pre-primary care questionnaires and education in pharmacies is being developed.

Conclusion

The rapid assessment of suspected RA is now a crucial task for the rheumatologist. Delay leads to the loss of opportunity to control disease and change outcome for the patient. Significant research has focused on the barriers in this process, with both expected and unexpected results. Focusing on the patient journey prior to seeing a rheumatologist is critical to prompt treatment.

Future perspective

The issues are now twofold: reducing time to assessment by rheumatology; and introducing better predictive tools and/or improving currently available tools in order to make the prediction of prognosis more accurate. Making advances in knowledge relevant to the clinician and able to be applied in daily practice is crucial. The field is advancing rapidly and new developments will change it significantly.

An excellent public knowledge of the existence of RA and the importance of early treatment will be crucial to earlier presentation. A strong awareness within the medical community about the importance of early treatment will, over time, drive practice change. When people know that hand stiffness and swelling is something they

should see their doctor about quickly then a large part of the problem will be solved. Future research is being planned by groups into the interaction between demographic variables and influences on presentation [35], to better understand and tackle obstacles to presentation. Other approaches being planned include education in pharmacies [39].

Prognosis prediction and treatment initiation is also a critical area that will influence future RA care. RA lacks a pathognomonic symptom or diagnostic sign and lacks a gold standard in diagnosis and so there remain significant challenges in further advancing the field. It is likely that further significant breakthroughs in this field will come from three major areas. The first is the development of new assessments or the new application of current assessments. The second area of advance is likely to come from continued large cohort and registry studies which have the power to demonstrate the value of new tools and/or the new application of existing tools. Finally, an area that would significantly assist in early RA treatment would be the further definition of specific phenotypes which have different characteristics; for example, genetic signature or the presence/absence of a biomarker. This would likely stem from work in the two previous areas. Currently RA is largely seen as one group with heterogeneous characteristics including antibody presence, erosion potential and joint involvement. In practice we know from clinical experience and studies such as the Probable Rheumatoid Arthritis Methotrexate Versus Placebo Trial (PROMPT) study that seronegative RA behaves differently to seropositive RA [20]. van der Helm-van Mil and Huizinga have preliminarily suggested subclassifications based on anticitrullinated protein/peptide antibodies (of which anti-CCP antibody is one) but acknowledged there is much further work to do in this area [69].

Pre-arthritis is a term that was introduced by Smolen and colleagues [70]. They suggested in the future that we may treat pre-arthritis and there have been a small number of publications related to this. Identified gene signatures predictive of arthritis development with gene expression profiling in patients with arthralgia is one example of work in this area [71]. This is truly the future of RA, identifying patients before they develop RA and treating them to avoid it ever emerging [72].

Executive summary

- Rheumatoid arthritis (RA) requires early effective treatment and this is acknowledged by the rheumatology community. There is evidence of a 'window of opportunity' of 3–4 months where effective therapy can change prognosis.
- Terms used in this area include early arthritis, undifferentiated arthritis (UA) and early rheumatoid arthritis.
- The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for RA have recently been published and their aim is to identify those with UA with a poorer prognosis who will likely progress to RA and/or a persistent/erosive phenotype.
- The new criteria will classify patients with RA earlier and so the prevalence of UA will decrease.

Inception cohort & registry studies

- Prognostic factors have been derived from inception cohorts and early arthritis registers which help to predict progression from UA to RA.

Evidence for early evidence

- There is a growing body of evidence that supports the introduction of early disease-modifying antirheumatic drug treatment. This has been demonstrated in a number of cohort studies, for example the study from Austria which demonstrated a significant difference in disease activity and erosion development between those that receive early treatment compared with those that receive later treatment.

Factors influencing steps in the assessment & treatment process

- A number of factors can influence a patient's decision to seek medical advice about their arthritis including their gender, perception of their symptoms, socioeconomic status and prior experiences of interacting with the healthcare system. The factors that influence a primary care physician to refer to a rheumatologist include the severity of symptoms, access issues and the patient's own wishes. Early arthritis clinics have a large effect on when patients are seen. When early arthritis clinics are not present the information in the referral letter and a request for an urgent appointment has an effect on time to treatment initiation.

Strategies to improve time to treatment in RA

- Strategies to improve RA treatment include pre-primary care-targeted education, education of the general public and primary carers, reorganization of clinics and better triage systems.

Conclusion

- Future improvement in RA diagnosis and care will come from public education and awareness amongst doctors and other healthcare professionals about the need for early RA treatment.
- The ultimate goal will be to identify accurately those who will develop RA prior to them developing it and treating them to prevent it developing.

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Medscape EDUCATION Decreasing time to treatment in rheumatoid arthritis: review of delays in presentation, referral and assessment

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Your patient is a 49-year-old white female with early evidence of arthritis thought possibly to be rheumatoid arthritis (RA). Based on the above review by Drs Robinson and Taylor, which of the following statements regarding need for early recognition and treatment of RA is most likely correct?

- ☐ **A** Because of the lack of effective treatments for RA, there is no need to rush to early diagnosis
- ☐ **B** Early treatment of RA is no more effective than later treatment
- ☐ **C** Treatment of RA by a rheumatologist leads to a higher quality of care and improved outcomes at no increased cost
- ☐ **D** The 'window of opportunity' for RA where effective treatment can change prognosis is 1–2 years

2. Based on the above review, which of the following is most likely to result in more rapid initiation of treatment for the patient described in Question 1?

- ☐ **A** Sudden onset of symptoms
- ☐ **B** Involvement of large joints
- ☐ **C** Higher C-reactive protein (CRP) level
- ☐ **D** Crystal arthritis

3. Based on the above review, which of the following statements about strategies to reduce time to treatment in RA is most likely correct?

- ☐ **A** Use of the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for RA will classify patients with RA later
- ☐ **B** The referral letter from primary care physician to rheumatologist does not affect time to treatment initiation
- ☐ **C** Education should be targeted at specialty clinics
- ☐ **D** Reorganization of clinics, including emphasis on early arthritis clinics, and better triage systems may be helpful