

REVIEW

# Barriers to the Diagnosis of Early Inflammatory Arthritis: A Literature Review

Liliana Saraiva<sup>1</sup>, Catia Duarte 10,12

<sup>1</sup>Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; <sup>2</sup>iCBR, Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal

Correspondence: Catia Duarte, Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Praceta Mota Pinto, Coimbra, 3000-004, Portugal, Tel +351 960330278, Email catiacmduarte@gmail.com

Abstract: The early identification of patients with inflammatory arthritis and their referral to rheumatologists in order to establish a diagnosis and to start treatment plays a crucial role in patient outcomes. However, it is recognized that a large proportion of patients with inflammatory arthritis are diagnosed very late, losing the opportunity to start treatment in the very early stages of disease, resulting in a worse prognosis. This delay depends on several factors related to the patient, the disease, socio-demographic and health system aspects. Over time, several strategies have been developed and implemented at different levels aiming to overcome such barriers and to reduce the time from the onset of the symptoms until the diagnosis and start of adequate treatment. In this non-systematic comprehensive review, we will describe the main barriers in the identification of patients with inflammatory arthritis at different levels. We will also discuss the different strategies that have been implemented with the objective to overcome the recognized barriers and their impact in the reduction of delays.

Keywords: inflammatory arthritis, early diagnosis, barriers

## Introduction

Inflammatory arthritis is a distinctive feature of rheumatic diseases such as rheumatoid arthritis (RA), spondyloarthritis and connective tissue diseases. The early identification of patients with inflammatory arthritis and their referral to rheumatologists plays a crucial role in patient outcomes.

Data from observational studies and clinical trials indicate that early initiation of immunosuppressive therapy promptly after diagnosis results in better outcomes. This period, called the "window of opportunity", is estimated to comprise the first 12 weeks after symptoms onset. Therefore, diagnosing arthritis within this period of time is essential.

A wide range of delay from symptom onset to the diagnosis of inflammatory arthritis is reported and only a small proportion of patients receive treatment in the first 12 weeks.<sup>3</sup> A study conducted in 10 European countries reported a median delay from symptom onset to assessment by a rheumatologist of 24 weeks (ranging from 9–192 weeks) in RA patients, with a small proportion being observed in the first 12 weeks.<sup>4</sup> Similar results were found in studies from Canada, where patients with RA were seen by a rheumatologist for the first time with a median of 5.5 months after symptom onset,<sup>5</sup> with 20.7% of patients observed within 2.5 to 3–5 years.<sup>6</sup> In a study conducted in Catalonia, Spain, the mean delay was 11 months.<sup>7</sup> In non-developed countries this delay could be of several years. The mean lag time between symptom onset and diagnosis of RA in a Venezuelan study was 40.5 months (range 1–424).<sup>8</sup>

Several factors may contribute to this delay. Firstly, musculoskeletal complaints are common within the general population and it is difficult for patients to identify their symptoms as a manifestation of an inflammatory disease. Additionally, the rarity and heterogeneous nature of inflammatory rheumatic diseases contributes to the difficulty of non-rheumatologist health-care providers to recognize them among the large proportion of patients with musculoskeletal complaints. Lastly, the accessibility to a rheumatologist assessment in some geographical areas and the organization of

the healthcare system may contribute to these delays. Recognition of the barriers to referral and early diagnosis of patients with inflammatory arthritis is crucial to implement measures to reduce them.

# Levels of Delay to Early Diagnosis

Between the patient experiencing the initial symptoms and receiving a diagnosis and starting treatment there are several steps that need to be taken and at each of these steps delays are possible. Four main levels of delay can be considered:<sup>10</sup> (Figure 1)

## Individual Level

Defined as the period between the onset of the first related musculoskeletal symptom and the first assessment of the patient, usually in primary care.

## Primary Care Level

Period between the first assessment by primary care until the referral to a rheumatologist.

# Rheumatologist Level

From the rheumatologist referral to the first assessment in a Rheumatology Department.

# Diagnosis and Management Level

From the first assessment by a rheumatologist to the establishment of the diagnosis and start of an effective treatment with Disease Modifying Anti-Rheumatic Drugs (DMARDs).

### **Barriers at Each Level**

#### Level 1: Individual Level

This level of delay corresponds to the period from the symptom onset until the patient seeks medical help and has been identified as the most relevant reason why patients miss the "window of opportunity". <sup>4,11</sup> A recent literature review reported a mean delay of 3.14 months from onset of symptoms to the first contact with a physician, ranging between 0–5.7 months. <sup>12</sup>

For a person with joint symptoms to look for medical attention he/she needs to assume a causal disease for which a specific treatment exists. Socio-demographic factors, psychological aspects, the knowledge and beliefs about the disease play a crucial role in the decision making of those who seek medical advice. Additionally, people usually misinterpret symptoms, interpreting them as natural consequence of age, any physical effort or some kind of injury and commonly try to auto-manage their symptoms or resort to non-pharmacologic therapies. The previous concept that "there is nothing to do" and the lack of knowledge of effective and specific treatments for inflammatory arthritis are possible reasons to explain the delay of looking for help following symptom onset.

The main barriers for the early diagnosis of RA at this level are classified in the following five areas. 16

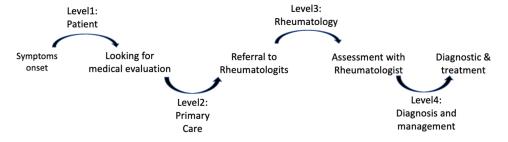


Figure I Levels of delay in early diagnosis of inflammatory arthritis.

#### Perceived Cause of Symptoms

The way in which symptoms are interpreted and evaluated by an individual, strongly influences their behavior in response to them. Usually, patients interpret their joint symptoms as a natural consequence of age, associate them with any physical efforts, with over/too much use, caused by some kind of injury or trauma, heat or cold, consequence of existing or previous medical problems or attribute these symptoms to another form of arthritis, such as osteoarthritis. Little knowledge about a specific condition, regarding its causes and gravity, is associated with longer delay in seeking medical advice. For example, patients with a family history of RA or who know someone with RA, usually seek GP evaluation earlier, in the presence of any joint complaint. 16,23

#### Factors Related to the Clinical Presentation

Characteristics of joint involvement and previous experience of symptoms were reasons given by patients as influencing their need for medical care. <sup>16,24</sup> These findings were found to be relevant in an observational study with 612 patients with arthralgia from two Early Arthritis Recognition Clinics, where more insidious onset was associated with a longer diagnostic delay as well as palindromic (recurrent) pattern. <sup>25</sup> Similar findings have been reported in studies from the UK. <sup>26</sup> A systematic review of qualitative literature also reported that the severity, intensity and duration of symptoms such as pain, stiffness, joint swelling and fatigue and onset influence whether people sought help. An abrupt onset, with very intense symptoms, affecting multiple joints often results in a prompt help-seeking. <sup>18</sup> These findings were also reported in a recent qualitative study from India. <sup>22</sup>

#### Perceived Impact of Symptoms

The impact of the symptoms on patients' lives plays an important role in seeking medical advice. When daily activities are disrupted due to symptoms, patients tend to seek help. 16,19,27

### Self-Management of Symptoms

Patients with musculoskeletal symptoms tend to relieve their symptoms with easily available drugs such as non-steroid anti-inflammatory drugs or paracetamol, or even alternative therapies, particularly when they have mild to moderate and non-disruptive symptoms, leading to a delay in seeking consultation with their GP. 16,17,27 Furthermore, patients usually get advice from friends and family, who may play an important role. Interestingly, knowing someone with inflammatory rheumatic disease leads to a shorter delay, probably because they are encouraged to seek help from their GP. 16

#### Drivers and Barriers Related to General Practitioner (GP) and Health-Care System

Beliefs and attitudes about the health system were also found to be a determinant factor for delay at the individual level, with a direct correlation with lack of confidence in GPs, bad previous experiences with the health system, fear of not being understood, or even being blamed by the GP.<sup>20,24,28</sup> The reduced proximity to primary healthcare centers in certain rural areas<sup>29</sup> and geographic areas with low density of GPs are associated with longer delays.<sup>29,30</sup> Circumstantial factors may cause delays in seeking medical help. For example, during the COVID-19 pandemic period incidence of inflammatory rheumatic diseases decreased,<sup>31,32</sup> which could be partially explained by fewer patients presenting with inflammatory arthritis who sought for medical care. The belief that the health system was only focused on COVID-19 care, without capacity for other conditions, or even being afraid about accessing services may justify these findings.<sup>31</sup>

# Level 2: Primary Care Level

GPs play a key role in identifying patients with inflammatory arthritis, as they typically serve as "gatekeepers" for rheumatologists, being the first contact with the health system for about 90% of patients. A recent systematic review reported a mean delay of 2.3 months (0.5–6.6) at this level. In a study conducted by de Cock et al only 44.1% of the cases of RA were suspected in the first visit with the GP, with nearly 25% requiring 5 or more visits.

Several reasons have been reported to justify this delay at the primary care level. A qualitative study from Belgium identified low confidence in identifying inflammatory arthritis, limited access to specialists and poor professional collaboration between sectors.<sup>34</sup> Similar findings were reported in a study from the UK.<sup>35</sup> More recently, a qualitative study with Danish GPs identified the main reasons related with the delay at the primary care

level to be the atypical presentation of symptoms or no clear evidence of swollen joints, the GP's role as a gatekeeper in several conditions, suboptimal collaboration with rheumatologists and limitations in performing and trusting in laboratory tests. The overarching reason mentioned by GPs for the delay was the difficulty to detect RA, seeming "like finding a needle in a haystack", given its rarity and that symptoms often resembled those of non-inflammatory conditions, such as osteoarthritis. These difficulties increase when patients have a non-classical clinical picture. A study conducted with UK GPs showed that swollen and painful small joints, longer stiffness and symmetrical involvement were associated with a reduced delay in GPs' perspectives.

The difficulty in identifying patients who need to be referred is important and high responsibility in the process is commonly appointed to GPs. This is exacerbated when the relationship with the rheumatologist is poor, or when there is a lack of quick response from rheumatologists, with GPs commonly feeling as reproved by the colleagues.<sup>34</sup> These feelings lead GPs to make a referral only when they are certain about the diagnosis.<sup>39</sup>

The lack of self-confidence of GPs is an important cause of delay, strongly supported by a study conducted in the UK reporting that GPs tend to value laboratory tests more than their clinical view, with 74% of the respondents preferring to wait for blood tests before referring patients.<sup>38</sup> Using laboratory results to support referral decisions will lead to most patients failing to be referred within the recommended period due the several days needed to obtain all the results.<sup>5</sup> Additionally, patients with negative rheumatoid factor are referred less frequently (66% vs 35%)<sup>40</sup> and had a longer period of delay (67 vs 22 days),<sup>41</sup> compared with those with positive rheumatoid factor. The same conclusion was reached by Kumar et al.<sup>11</sup> This scenario is more dramatic when considering X-rays,<sup>42</sup> given the absence of radiographic changes in the early stage of the disease.

Socio-demographic and health-care system characteristics may also play a role in the referral of patients with inflammatory arthritis. In a Canadian study, poor primary care access and continuity, low density and weak proximity to rheumatologists had a negative impact on encounter rates with a rheumatologist.<sup>43</sup>

Some studies also stated previous experiences of referring patients with rheumatoid arthritis, easy access to rheumatology departments and the availability of an Early Arthritis Clinic as having a relevant impact in the referral timelines by GPs. 9,25,34

# Level 3: Rheumatologist Level

The delay from the referral until rheumatology assessment ranges widely across European centers,<sup>4</sup> despite having less relevance than the previous levels of delay.<sup>4,11</sup>

The cultural differences in the health-care system organization and the number of rheumatologists per capita play an important role at this level of delay. Geographic areas with few rheumatologists and rheumatology departments have more difficulties in scheduling urgent appointments for patients with suspected inflammatory arthritis.<sup>24</sup>

Another important reason for the delay at this level is the correct triage of patients that are more likely to have inflammatory arthritis among the total of patients referred to the rheumatology department. The existence of triage clinics, Early Arthritis Clinics and an adequate system of triage of patients referred to a rheumatology assessment are shown to reduce the delay at this level.<sup>10</sup>

However, it is important to recognize that prioritizing patients for urgent assessment by a rheumatologist is challenging and depends on adequate primary care evaluation and referral system.

# Level 4: Diagnosis and Management Level

The period after a patient is first assessed by a rheumatologist until the diagnosis and treatment with DMARDs has an important role in the prognosis of patients with recent onset of inflammatory arthritis. Ideally, the treatment with DMARDs should start in a period that allows the modulation of biologic processes while they are in a more reversible stage, avoiding structural damage. In a European study, this was the less relevant level of delay, with a median of 4 weeks, ranging from 1–8 weeks in the different centers. However, the delay at this level can be longer in non-developed countries as reported in a study from Venezuela, with a mean delay of 13.4 months.

With the more recent ACR/EULAR classification criteria for RA<sup>44</sup> patients are identified in an earlier stage of disease than in the 1987 classification criteria, which included rheumatoid nodes or erosions on the X-ray, both common in long-standing disease.

However, delays at this level have been reported in patients with more atypical presentation, involvement of few joints, proximal joints and negative rheumatoid factor and anti-CCP. 46,47 In older patients, the differential diagnosis with other diseases such as osteoarthritis, microcrystalline arthritis, or rheumatic polymyalgia can be challenging and contribute to the delay at this level.

# Strategies to Reduce the Delay

Several approaches are available and should be implemented to minimize the barriers to the early diagnosis of inflammatory arthritis (Figure 2). These include public awareness about rheumatic diseases, mainly inflammatory diseases, programs of continuous education of GPs about musculoskeletal symptoms and conditions, early referral guidelines, early triage, rheumatologist good response, good communication and quick-referral routes for patients with inflammatory arthritis. These strategies will allow reductions in the delay in the diagnosis of patients with inflammatory arthritis and should include a synergistic and continuous intervention over time.

# Public Awareness Strategies

Strategies promoting public awareness may play an important role in reducing the time between onset symptoms and help being sought by the patients.

With the growing internet access, patients increasingly use the web as a source of information. The widespread information in public websites may increase public awareness of inflammatory arthritis. National scientific societies and patients' associations have trusted information about inflammatory disease and could be used as sources of information, easily accessible in their sites in the internet. However, a previous evaluation of internet information on inflammatory arthritis reported that although the websites had accurate information, their reading levels were too high for the average reader, and were generally poor in terms of giving a differential diagnosis, prioritizing the possibilities and none provided an algorithm for action, thus were likely to be of little help to them and could delay their seeking appropriate attention. 50

Several campaigns have been conducted in various countries to increase awareness regarding rheumatic diseases, in particularly inflammatory conditions. The Austrian Rheumatology Society launched an initiative providing easy, nonformal, free access to counselling by rheumatologists or pain specialists. A mobile unit (an adapted broadcast bus) was parked at easily accessible sites allowing passers-by to step in, talk to a specialist and receive information and further guidance. In this campaign, almost 3% of the clients seemed to have unrecognized inflammatory rheumatic diseases, with 1% each presumed to have RA. Among these patients, 10% of them never sought medical care and in one-third the inflammatory condition was only or the first time considered by the physician in the bus.<sup>51</sup> Similar findings were found in

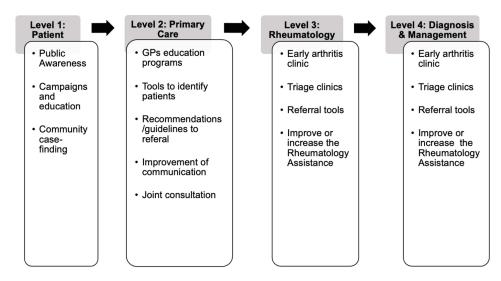


Figure 2 Summary of potential strategies to reduce the delay of diagnosis of inflammatory arthritis at each level.

"The Rheuma-Bus project 2018", a similar campaign conducted in rural areas. <sup>52</sup> In 2017, the EULAR launched the Europe-wide campaign entitled "Don't Delay, Connect Today" aiming to highlight rheumatic and musculoskeletal diseases (RMDs) as major diseases and a public health concern. <sup>53</sup> Similar campaigns were launched by other societies such as the American College of Rheumatology and the UK's National Rheumatoid Arthritis Society. However, to our knowledge, no data were published to assess the efficacy of such strategies to improve the public awareness of inflammatory arthritis and in the reduction of delays.

A television advertising campaign conducted by Arthritis New Zealand in 2011 to raise public awareness of AS was associated with a significant increase in referrals to rheumatology services for suspected AS and an increase in the diagnosis of axial SpA in clinics.<sup>54</sup>

Despite the limited information on interventions to improve public awareness, there is evidence that some mass media interventions may have an important role in influencing the use of health-care interventions.<sup>55</sup> Therefore an important concern raised by primary health-care providers about these campaigns is the rapid increase of help-seeking behavior, leading to an extra workload in primary care, in which many of the additional patient consultations would be inappropriate and result in an overwhelming of rheumatology departments.<sup>56</sup> Therefore, these campaigns should be accompanied by an adequate response of the health system.

The lack of information about inflammatory arthritis for the general public is commonly recognized as an important reason of delay in seeking medical care and different strategies to increase public awareness have been implemented. Such campaigns should be updated over time, and its impact and cost-effectiveness evaluated.

## Community Case-Findings Strategies

Self-questionnaires were developed to identify individuals with risk of inflammatory arthritis, providing low cost, relatively quick and time-limited methods to find patients at risk. Individuals identified as "at high risk" should receive further information to visit a physician for a more detailed evaluation.

A simple self-administered test comprising a handshake, a four-finger grip around a pencil and pincer grip of a sheet of paper to detect inflammatory arthritis was described.<sup>57</sup>

A patient self-reported questionnaire adapted from the ACR criteria for RA was developed and shown to be well understood by individuals and with good accuracy (74%) to detect patients with early RA.<sup>58</sup>

The Early RA Screening Questionnaire was developed to identify patients with high risk of RA among patients with joint pain for less than 3 months. It was based on the van der Helm-van Mill et al prediction rule for RA and disseminated through the Arthritis Foundation's website. Individuals who scored  $\geq$ 3.5 were considered as "likely to have RA" and evaluated by a rheumatologist. <sup>59</sup>

A community active health-fair screening approach using the combination of the Connective Tissue Disease Screening Questionnaire and antibodies testing (Rheumatoid Factor and Anti-CCP) was developed, showing good psychometric properties.<sup>60</sup>

# **GP** Training

Difficulties in recognizing patients with inflammatory arthritis have been one of the most relevant factors recognized by GPs in the referral of these patients.<sup>26,37</sup> Only around one-quarter of patients referred to rheumatologists as possibly having an inflammatory arthritis later receives the diagnosis of RA. Therefore, interventions to increase knowledge and confidence of GPs in the identification of inflammatory arthritis have been recognized as having an important role and should be implemented. Strategies such as continuous medical education through workshops, training in rheumatology (particularly training courses for specialized GPs), joint consultation, tele-clinic and distribution of educational material have been mentioned by GPs as strategies to improve the referral of patients with inflammatory arthritis.<sup>9</sup>

Despite recognizing some risk of reporting bias, there is evidence that continuous training of GPs can improve the referral process. A systematic review of strategies to decrease the delay in the diagnosis showed that education programs, despite the modality, had some success in improving the awareness and aptitude of GPs to identify inflammatory arthritis, leading to improvement of referrals.<sup>10</sup> In the "joint adventures program", workshops coordinated through a national continuing education program, resulted in an improvement of knowledge and skill acquisition and self-assessed change

in practice, that changed their care of musculoskeletal disorders.<sup>61</sup> The efficacy of referral support and training actions was also reported in a prospective, randomized study.<sup>62</sup> More recently, a study evaluated the efficacy of an educational program of GPs in SpA, concluding that after the educational program GPs more frequently recognized SpA and the proportion of referred patients to a rheumatologist increased significantly in the intervention group, when compared with GPs without educational training (with features of axial SpA (71% versus 15%), and with features of peripheral SpA (48% vs 0%)).<sup>63</sup>

# Screening Tools and Guidelines

One of the challenges is ensuring that the patients more likely to have an inflammatory arthritis are seen in rheumatology departments in a short period of time, this being particularly relevant when considering Early Arthritis Clinics. Selecting patients for a rapid assessment with the rheumatologist is challenging and depends on correct primary care evaluation. Several triage tools, simple and easy to perform, have been developed to provide an initial guide for GPs to identify patients with inflammatory arthritis (Table 1).

The Early Inflammatory Arthritis (EIA) detection tool is an 11-question instrument, self-administered, that captures relevant dimensions to having peripheral inflammatory arthritis as articular pain, swelling, and stiffness, distribution of joint involvement, function, and diagnostic and family history. It is scored either using the sum of the number of positive

**Table 1** Screening Tools to Screen Patients with High Probability of Having a Peripheral Inflammatory Arthritis and the Need for an Assessment with a Rheumatologist

Inflammatory Arthritis Detection Tool* 64,65	The Clinical Arthritis Rule <sup>66</sup>		EULAR Defined Characteristics Describing Arthralgia at Risk for RA <sup>69</sup>
I. Do you have pain in your joints?	Male gender	(0.5)	History taking:
<ol> <li>Do you have pain in your wrists and hands?</li> <li>Are your hands or wrists swollen?</li> <li>Do you have trouble making a fist?</li> <li>Are your joints stiff in the morning?</li> <li>From the time you wake in the morning, does it take &gt; 60 min for your joints to move more freely?</li> <li>Are the same joints involved on both sides of your body?</li> <li>Have important activities in your life been affected because bone or joint problems, such as difficulty with personal care or having to make change regarding leisure or work activities?</li> <li>Have you ever been told that you have rheumatoid arthritis (RA)?</li> <li>Does anyone in your family have RA?</li> <li>Have you been diagnosed with a rash called psoriasis?</li> <li>Have you had these symptoms for &gt; 6 weeks and &lt; 1 year?</li> </ol>	Age >60 (0.5)	(0.5)	<ul> <li>Joint symptoms of recent onset (duration <i li="" year)<=""> <li>Symptoms located in MCP joints</li> <li>Duration of morning stiffness ≥60 min</li> <li>Most severe symptoms present in the early morning</li> <li>Presence of a first-degree relative with RA Physical examination:</li> <li>Difficulty with making a fist Positive squeeze test of MCP joint</li> </i></li></ul>
	Symptom duration.		
	<6 weeks	(0.5)	
	6–51.9 weeks	(1.0)	
	Morning stiffness.		
	>60 min	(0.5)	
	Number of patient- reported painful joints		
	I-3	(2.5)	
	≥4	(1.5)	
	Number of patient- reported swollen joints		
	≥1.	(1.5)	
	Difficulty in making a fist.	(0.5)	
AUC: 0.915, Sensitivity: 0.855; Specificity of 0.873	AUC: 0.74 ≥4 Sensitivity=93.6%; Specificity=35.6% ≥6		AUC: 0.92, 95%  ≥3 parameters:  Sensitivity =90.4%; Specificity=72.2%;  ≥4

**Note**: \*(Response options Yes = I, No = -I).

Abbreviations: AUC, Area Under the Curve; MCP, metacarpophalangeal; RA, rheumatoid arthritis.

responses,<sup>64</sup> or using a weighted scoring algorithm.<sup>65</sup> Higher scores mean a higher probability of a patient having a peripheral inflammatory arthritis and the need for an assessment with a rheumatologist in a short time period.

More recently, the Leiden Early Arthritis Clinic developed a new tool for the referral of patients with early inflammatory arthritis, easily applicable in clinical practice. This tool does not focus on the identification of a swelling joint, one of the most difficulties faced by GPs. This simplified rule consisting of seven scored items and a total score ranging from 0–7.5 with corresponding predicted risks. A patient with a score of  $\geq$ 6 has 71% risk of having inflammatory arthritis.<sup>66</sup>

Guidelines for inflammatory rheumatic diseases management have been published, emphasizing early referral. <sup>67,68</sup> The *EULAR* recommendations are based on clinical findings as duration of symptoms less than 12 months, inflammatory pattern and involvement of hands joints. <sup>69</sup> These guidelines have been used and adapted by several Early Arthritis Clinics to improve the referral of patients with inflammatory arthritis.

Regarding spondyloarthritis, two tools to detect patients were developed, with comparable efficacy. These tools are based on clinical manifestations, laboratory and imaging features of SpA. Patients with chronic low back pain lasting >3 months and onset before age of 45 years should be referred to rheumatology if presenting one of the following: inflammatory back pain (IBP), positive HLA-B27 or sacroiliitis on imaging; or two of the following findings: family history of axial SpA, good response to non-steroidal anti-inflammatory drugs, extra-articular manifestations. <sup>70–72</sup>

Another important point is the triage of referred patients, which is particularly relevant in departments without dedicated Early Arthritis Clinics. Definition of strategies of triage help to prioritize appointments for patients with inflammatory arthritis. In the standard care, patients are usually graded into different levels of urgency, with patients with high suspicion of inflammatory arthritis receiving the highest level, to be seen in few weeks. <sup>10</sup> However, the efficacy of such triage is based on the information provided by the GP. Referral forms that help to standardize and provide important information for triage should be developed and made available. The use of referral forms for triage process increased significantly the capacity to detect urgent cases and in reducing the waiting time for the appointment. <sup>73–76</sup>

## Early Arthritis Clinics

During the last decades Early Arthritis Clinics (EACs) were established in rheumatology departments, which have dedicated appointments for patients with suspected persistent synovitis in early stages. EACs have been shown to be effective in the prompt diagnosis and in achievement of good outcomes in patients with inflammatory arthritis. Data from Leiden EACs showed that duration of symptoms at first appointment in the rheumatology clinic were shorter in patients referred to EACs when compared with routine care (14.1 vs 37 weeks, respectively),<sup>77</sup> with an improvement in a similar analysis some years later.<sup>78</sup> More recently, van Nies and collaborators reported a shorter GP-delay in the identification of patients with a higher rate of identification of arthritis among patients referred to EACs.<sup>25</sup> A systematic literature review showed the Early Arthritis Clinics strategy reduced significantly the time to referral when compared with the standard/routine care.<sup>79</sup>

Commonly the EACs include programs of education for GPs, referral guidance and a direct channel of communication with GPs. All these points are relevant to change the relationship and communication between primary and secondary care clinicians for patients with a suspected new-onset inflammatory arthritis, contributing to the relevance of EACs in the early detection and the good outcomes of these patients.

However, we should note the complexity of EACs development which can limit their widespread implementation in a routine clinical setting, particularly in countries with scarcity of rheumatologists and limited access to DMARDs. Moreover, their acceptance by patients and clinicians as well as their cost-effectiveness requires further research.

# **Summary**

The delay in diagnosis of patients with inflammatory arthritis remains a real problem, with wide disparities across the world.

The delay occurs at different levels, with the time since the symptom's onset until referral to a rheumatologist (levels 1 and 2) being the most relevant.

Several reasons, related with the patient, the disease and the health-care system have an important impact, constituting important barriers to the early diagnosis of patients.

Misinterpretation of the symptoms, lack of knowledge about the disease, clinical presentation and impact of symptoms, difficulty in detecting arthritis by GPs, lack of confidence, poor collaboration between health-care providers and scarcity of rheumatologists are the main reasons identified. Circumstantial factors, such as the pandemic era, should also be taken into account.

Several strategies have been developed and implemented at the different levels outlined to overcome the difficulties and the barriers to early diagnosis.

Public awareness campaigns, training of GPs, referral and triage tools, early arthritis clinics and rapid access showed some efficacy in reducing the delay.

Despite the positive impact observed with such strategies, there is still opportunity to develop and implement new ones to reduce such delay.

# Research Agenda

Continuous development of strategies to increase awareness of inflammatory arthritis at different levels is needed.

Studies are required to evaluate how such strategies improve the recognition of relevant symptoms by the patients so that they look for medical assistance sooner.

Research should also focus on the impact of education programs of non-rheumatologists, as it will result in an early recognition of symptoms and increase the self-confidence of GPs to refer patients, one the biggest barriers identified.

The development of referral and triage tools with better diagnostic/screening performance, that help to identify patients with an increased risk of inflammatory arthritis.

#### **Disclosure**

The authors report no conflicts of interest in this work.

## References

- 1. Hazes JM, Luime JJ. The epidemiology of early inflammatory arthritis. Nat Rev Rheumatol. 2011;7(7):381-390. doi:10.1038/nrrheum.2011.78
- Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis definitions and supporting evidence: from old to new perspectives. RMD Open. 2019;5(1):e000870. doi:10.1136/rmdopen-2018-000870
- 3. De Cock D, Meyfroidt S, Joly J, Van der Elst K, Westhovens R, Verschueren P. A detailed analysis of treatment delay from the onset of symptoms in early rheumatoid arthritis patients. *Scand J Rheumatol.* 2014;43(1):1–8. doi:10.3109/03009742.2013.805242
- 4. Raza K, Stack R, Kumar K, et al. Delays in assessment of patients with rheumatoid arthritis: variations across Europe. *Ann Rheum Dis.* 2011;70 (10):1822–1825. doi:10.1136/ard.2011.151902
- 5. Barnabe C, Xiong J, Pope JE, et al. Factors associated with time to diagnosis in early rheumatoid arthritis. *Rheumatol Int.* 2014;34(1):85–92. doi:10.1007/s00296-013-2846-5
- 6. Feldman DE, Bernatsky S, Haggerty J, et al. Delay in consultation with specialists for persons with suspected new-onset rheumatoid arthritis: a population-based study. *Arthritis Rheum*. 2007;57(8):1419–1425. doi:10.1002/art.23086
- Corominas H, Narváez J, Díaz-Torné C, et al. Diagnostic and therapeutic delay of rheumatoid arthritis and its relationship with health care devices in Catalonia. The AUDIT study. Retraso diagnóstico y terapéutico de la artritis reumatoide y su relación con dispositivos asistenciales en Catalunya. Estudio AUDIT. Reumatol Clin. 2016;12(3):146–150. doi:10.1016/j.reuma.2015.08.002
- 8. Rodríguez-Polanco E, Al Snih S, Kuo YF, Millán A, Rodríguez MA. Lag time between onset of symptoms and diagnosis in Venezuelan patients with rheumatoid arthritis. *Rheumatol Int.* 2011;31(5):657–665. doi:10.1007/s00296-009-1358-9
- 9. Baymler Lundberg AS, Esbensen BA, Jensen MB, Hauge EM, Thurah A. Facilitators and barriers in diagnosing rheumatoid arthritis as described by general practitioners: a Danish study based on focus group interviews. *Scand J Prim Health Care*. 2021;39(2):222–229. doi:10.1080/02813432.2021.1913925
- 10. Villeneuve E, Nam JL, Bell MJ, et al. A systematic literature review of strategies promoting early referral and reducing delays in the diagnosis and management of inflammatory arthritis. *Ann Rheum Dis.* 2013;72(1):13–22. doi:10.1136/annrheumdis-2011-201063
- 11. Kumar K, Daley E, Carruthers DM, et al. Delay in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. *Rheumatology*. 2007;46(9):1438–1440. doi:10.1093/rheumatology/kem130
- 12. Barhamain AS, Magliah RF, Shaheen MH, et al. The journey of rheumatoid arthritis patients: a review of reported lag times from the onset of symptoms. *Open Access Rheumatol*. 2017;9:139–150. doi:10.2147/oarrr.s138830
- 13. Simons G, Belcher J, Morton C, et al. Symptom recognition and perceived urgency of help-seeking for rheumatoid arthritis and other diseases in the general public: a mixed method approach. *Arthritis Care Res.* 2017;69(5):633–641. doi:10.1002/acr.22979
- Unger-Saldaña K, Infante-Castañeda CB. Breast cancer delay: a grounded model of help-seeking behaviour. Soc Sci Med. 2011;72(7):1096–1104. doi:10.1016/j.socscimed.2011.01.022
- Pelaez I, Infante C, Quintana R. Help-seeking trajectory in patients with rheumatoid arthritis. Clin Rheumatol. 2015;34(Suppl1):S17–S28. doi:10.1007/s10067-015-3013-z

16. Simons G, Mallen CD, Kumar K, Stack RJ, Raza K. A qualitative investigation of the barriers to help-seeking among members of the public presented with symptoms of new-onset rheumatoid arthritis. *J Rheumatol*. 2015;42(4):585–592. doi:10.3899/jrheum.140913

- 17. Townsend A, Backman CL, Adam P, Li LC. A qualitative interview study: patient accounts of medication use in early rheumatoid arthritis from symptom onset to early postdiagnosis. *BMJ Open*. 2013;3(2):e002164. doi:10.1136/bmjopen-2012-002164
- 18. Stack RJ, Shaw K, Mallen C, Herron-Marx S, Horne R, Raza K. Delays in help seeking at the onset of the symptoms of rheumatoid arthritis: a systematic synthesis of qualitative literature. *Ann Rheum Dis.* 2012;71(4):493–497. doi:10.1136/ard.2011.155416
- 19. Townsend A, Adam P, Cox SM, Li LC. Everyday ethics and help-seeking in early rheumatoid arthritis. *Chronic Illn.* 2010;6(3):171–182. doi:10.1177/1742395309351963
- 20. Sheppard J, Kumar K, Buckley CD, Shaw KL, Raza K. 'I just thought it was normal aches and pains': a qualitative study of decision-making processes in patients with early rheumatoid arthritis. *Rheumatology*, 2008;47(10):1577–1582, doi:10.1093/rheumatology/ken304
- 21. Kumar K, Daley E, Khattak F, Buckley CD, Raza K. The influence of ethnicity on the extent of, and reasons underlying, delay in general practitioner consultation in patients with RA. *Rheumatology*. 2010;49(5):1005–1012. doi:10.1093/rheumatology/keq011
- 22. Jain A, Aggarwal A, Adams J, et al. Delay in seeking medical help in patients with rheumatoid arthritis in India: a qualitative study. *Int J Rheum Dis.* 2020;23(12):1707–1718. doi:10.1111/1756-185x.14001
- 23. Van der Elst K, De Cock D, Vecoven E, et al. Are illness perception and coping style associated with the delay between symptom onset and the first general practitioner consultation in early rheumatoid arthritis management? An exploratory study within the CareRA trial. *Scand J Rheumatol*. 2016;45(3):171–178. doi:10.3109/03009742.2015.1074278
- 24. Mølbaek K, Hørslev-Petersen K, Primdahl J. Diagnostic delay in rheumatoid arthritis: a qualitative study of symptom interpretation before the first visit to the doctor. *Musculoskelet Care*. 2016;14(1):26–36. doi:10.1002/msc.1108
- 25. van Nies JA, Brouwer E, van Gaalen FA, et al. Improved early identification of arthritis: evaluating the efficacy of Early Arthritis Recognition Clinics. *Ann Rheum Dis.* 2013;72(8):1295–1301. doi:10.1136/annrheumdis-2012-202289
- 26. Stack RJ, Nightingale P, Jinks C, et al. Delays between the onset of symptoms and first rheumatology consultation in patients with rheumatoid arthritis in the UK: an observational study. *BMJ Open*. 2019;9(3):e024361. doi:10.1136/bmjopen-2018-024361
- 27. Townsend A, Backman CL, Adam P, Li LC. Women's accounts of help-seeking in early rheumatoid arthritis from symptom onset to diagnosis. *Chronic Illn*. 2014;10(4):259–272. doi:10.1177/1742395314520769
- 28. Rasmussen S, Søndergaard J, Larsen PV, et al. The Danish symptom cohort: questionnaire and feasibility in the nationwide study on symptom experience and healthcare-seeking among 100,000 individuals. *Int J Family Med.* 2014;2014:187280. doi:10.1155/2014/187280
- 29. Laires PA, Mesquita R, Veloso L, Martins AP, Cernadas R, Fonseca JE. Patient's access to healthcare and treatment in rheumatoid arthritis: the views of stakeholders in Portugal. *BMC Musculoskelet Disord*. 2013;14:279. doi:10.1186/1471-2474-14-279
- 30. Fautrel B, Benhamou M, Foltz V, et al. Early referral to the rheumatologist for early arthritis patients: evidence for suboptimal care. Results from the ESPOIR cohort. *Rheumatology*. 2010;49(1):147–155. doi:10.1093/rheumatology/kep340
- 31. Russell MD, Galloway JB, Andrews CD, et al. Incidence and management of inflammatory arthritis in England before and during the COVID-19 pandemic: a population-level cohort study using OpenSAFELY. *Lancet Rheumatol*. 2022;4(12):e853–e863. doi:10.1016/S2665-9913(22)00305-8
- 32. Bower H, Frisell T, Di Giuseppe D, et al. Effects of the COVID-19 pandemic on patients with inflammatory joint diseases in Sweden: from infection severity to impact on care provision. *RMD Open.* 2021;7(3):e001987. doi:10.1136/rmdopen-2021-001987
- 33. De Cock D, Van der Elst K, Stouten V, et al. The perspective of patients with early rheumatoid arthritis on the journey from symptom onset until referral to a rheumatologist. *Rheumatol Adv Pract*. 2019;3(2):rkz035. doi:10.1093/rap/rkz035
- 34. Meyfroidt S, Stevens J, De Lepeleire J, et al. A general practice perspective on early rheumatoid arthritis management: a qualitative study from Flanders. Eur J Gen Pract. 2015;21(4):231–237. doi:10.3109/13814788.2015.1084279
- 35. Pollard LC, Graves H, Scott DL, Kingsley GH, Lempp H. Perceived barriers to integrated care in rheumatoid arthritis: views of recipients and providers of care in an inner-city setting. BMC Musculoskelet Disord. 2011;12:19. doi:10.1186/1471-2474-12-19
- 36. Goldenberg DL, DeHoratius RJ, Kaplan SR, et al. Rheumatology training at internal medicine and family practice residency programs. *Arthritis Rheum*. 1985;28(4):471–476. doi:10.1002/art.1780280420
- 37. Stack RJ, van Tuyl LH, Sloots M, et al. Symptom complexes in patients with seropositive arthralgia and in patients newly diagnosed with rheumatoid arthritis: a qualitative exploration of symptom development. *Rheumatology*. 2014;53(9):1646–1653. doi:10.1093/rheumatology/keu159
- 38. Scott IC, Mangat N, MacGregor A, Raza K, Mallen CD, Hider SL. Primary care challenges in diagnosing and referring patients with suspected rheumatoid arthritis: a national cross-sectional GP survey. *Rheumatol Adv Pract*. 2018;2(1):rky012. doi:10.1093/rap/rky012
- 39. Suter LG, Fraenkel L, Holmboe ES. What factors account for referral delays for patients with suspected rheumatoid arthritis?. *Arthritis Rheum*. 2006;55(2):300–305. doi:10.1002/art.21855
- 40. Sinclair D, Hull RG. Why do general practitioners request rheumatoid factor? A study of symptoms, requesting patterns and patient outcome. *Ann Clin Biochem.* 2003;40(Pt 2):131–137. doi:10.1258/000456303763046049
- 41. Miller A, Nightingale AL, Sammon CJ, et al. Estimating the diagnostic accuracy of rheumatoid factor in UK primary care: a study using the Clinical Practice Research Datalink. *Rheumatology*. 2015;54(10):1882–1889. doi:10.1093/rheumatology/kev131
- 42. Cottrell E, Welsh V, Mallen C. Inflammatory arthritis: case review and primary care perspectives. Clin Rheumatol. 2012;31(4):739–744. doi:10.1007/s10067-011-1919-7
- 43. Widdifield J, Paterson JM, Bernatsky S, et al. Access to rheumatologists among patients with newly diagnosed rheumatoid arthritis in a Canadian universal public healthcare system. *BMJ Open*. 2014;4(1):e003888. doi:10.1136/bmjopen-2013-003888
- 44. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis.* 2010;69(9):1580–1588. doi:10.1136/ard.2010.138461
- 45. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988;31(3):315–324. doi:10.1002/art.1780310302
- 46. Boeters DM, Gaujoux-Viala C, Constantin A, van der Helm-van Mil AHM. The 2010 ACR/EULAR criteria are not sufficiently accurate in the early identification of autoantibody-negative rheumatoid arthritis: results from the Leiden-EAC and ESPOIR cohorts. *Semin Arthritis Rheum*. 2017;47(2):170–174. doi:10.1016/j.semarthrit.2017.04.009
- 47. Coffey CM, Crowson CS, Myasoedova E, Matteson EL, Davis JM. Evidence of diagnostic and treatment delay in seronegative rheumatoid arthritis: missing the window of opportunity. *Mayo Clin Proce*. 2019;94(11):2241–2248. doi:10.1016/j.mayocp.2019.05.023

48. American College of Rheumatology. Diseases and conditions; 2022. Available from: https://www.rheumatology.org/I-Am-A/Patient-Caregiver /Diseases-Conditions. Accessed December 27, 2022.

- 49. Sociedade Portuguesa de Reumatologia. Info Doenças; 2022. Available from: https://spreumatologia.pt. Accessed December 27, 2022.
- 50. Hwang AS, Gall V, Liang MH. Evaluation of the internet for finding persons with undiagnosed rheumatoid arthritis and systemic lupus erythematosus. *J Clin Rheumatol.* 2009;15(5):218–222. doi:10.1097/RHU.0b013e3181b126d3
- 51. Machold KP, Köller MD, Pflugbeil S, et al. The public neglect of rheumatic diseases: insights from analyses of attendees in a musculoskeletal disease awareness activity. *Ann Rheum Dis.* 2007;66(5):697–699. doi:10.1136/ard.2006.062422
- 52. Puchner R, Schaffer G, Sautner J, Alkin A, Machold K, Stamm T. Rheumatological care in rural areas: the Rheuma-Bus project 2018. Wien Klin Wochenschr. 2021;133(3-4):131-136. doi:10.1007/s00508-020-01630-z
- 53. Don't delay, connect today. Available from: https://eular.org/dont\_delay\_connect\_today.cfm. Accessed December 27, 2022.
- 54. Harrison AA, Badenhorst C, Kirby S, White D, Athens J, Stebbings S. Comparison of rates of referral and diagnosis of axial spondyloarthritis before and after an ankylosing spondylitis public awareness campaign. Clin Rheumatol. 2014;33(7):963–968. doi:10.1007/s10067-014-2551-0
- 55. Grilli R, Freemantle N, Minozzi S, Domenighetti G, Finer D. Mass media interventions: effects on health services utilisation. *Cochrane Database Syst Rev.* 2000;2:Cd000389. doi:10.1002/14651858.Cd000389
- 56. Stack RJ, Llewellyn Z, Deighton C, Kiely P, Mallen CD, Raza K. General practitioners' perspectives on campaigns to promote rapid help-seeking behaviour at the onset of rheumatoid arthritis. *Scand J Prim Health Care*. 2014;32(1):37–43. doi:10.3109/02813432.2014.900239
- 57. Eberhardt K, Recht L, Wollheim F, Lithman T, Pettersson H, Schersten B. Detection of suspected inflammatory joint disease with a new simple self-administered hand test. *Br J Rheumatol*. 1988;27(6):457–461. doi:10.1093/rheumatology/27.6.457
- 58. Wong AL, Harker JO, Mittman BS, et al. Development and evaluation of a patient self-report case-finding method for rheumatoid arthritis. *Semin Arthritis Rheum*. 2004;34(1):484–499. doi:10.1016/j.semarthrit.2003.12.002
- 59. Liang MH, Couto MC, Duarte CC, et al. An Internet-based technique for the identification of persons with symptoms of inflammatory polyarthritis of less than 12 weeks. *Clin Rheumatol*. 2015;34(3):465–470. doi:10.1007/s10067-014-2796-7
- 60. Deane KD, Striebich CC, Goldstein BL, et al. Identification of undiagnosed inflammatory arthritis in a community health fair screen. *Arthritis Rheum*. 2009;61(12):1642–1649. doi:10.1002/art.24834
- 61. Petrella RJ, Davis P. Improving management of musculoskeletal disorders in primary care: the Joint Adventures Program. *Clin Rheumatol*. 2007;26 (7):1061–1066. doi:10.1007/s10067-006-0446-4
- 62. Fonseca JE, Pereira da Silva JA, Bernardes M, et al. Effectiveness of a referral program for rheumatoid arthritis and axial spondyloarthritis Diagnosis at Primary Care Centers in Portugal SIARA STUDY. Effectiveness of a Referral Program for rheumatoid arthritis and axial spondyloarthritis Diagnosis at Primary Care Centers in Portugal SIARA STUDY. Acta Reumatol Port. 2018;43(1):40-51.
- 63. van Onna M, Gorter S, Maiburg B, Waagenaar G, van Tubergen A. Education improves referral of patients suspected of having spondyloarthritis by general practitioners: a study with unannounced standardised patients in daily practice. *RMD Open.* 2015;1(1):e000152. doi:10.1136/rmdopen-2015-000152
- Bell MJ, Tavares R, Guillemin F, Bykerk VP, Tugwell P, Wells GA. Development of a self-administered early inflammatory arthritis detection tool. *BMC Musculoskelet Disord*. 2010;11:50. doi:10.1186/1471-2474-11-50
- 65. Tavares R, Huang S, Bykerk VP, Bell MJ. A parallel group cohort to determine the measurement properties of an early inflammatory arthritis detection tool. *Rheumatology*, 2013;52(11):2077–2085. doi:10.1093/rheumatology/ket190
- 66. Ten Brinck RM, van Dijk BT, van Steenbergen HW, et al. Development and validation of a clinical rule for recognition of early inflammatory arthritis. *BMJ Open*. 2019;8(11):e023552. doi:10.1136/bmjopen-2018-023552
- 67. Combe B, Landewe R, Daien CI, et al. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis.* 2017;76(6):948–959. doi:10.1136/annrheumdis-2016-210602
- 68. Smolen JS, Landewe RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79(6):685–699. doi:10.1136/annrheumdis-2019-216655
- 69. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis. 2017;76(3):491–496. doi:10.1136/annrheumdis-2016-209846
- 70. Sieper J, Srinivasan S, Zamani O, et al. Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study. *Ann Rheum Dis.* 2013;72(10):1621–1627. doi:10.1136/annrheumdis-2012-201777
- 71. Brandt HC, Spiller I, Song IH, Vahldiek JL, Rudwaleit M, Sieper J. Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. *Ann Rheum Dis.* 2007;66(11):1479–1484. doi:10.1136/ard.2006.068734
- 72. Juanola X, Fernández-Sueiro JL, Torre-Alonso JC, et al. Comparison of 2 referral strategies for the diagnosis of axial spondyloarthritis in Spain. The RADAR study. *Reumatol Clin*. 2013;9(6):348–352. doi:10.1016/j.reuma.2013.02.009
- 73. Fullerton LM, Brooks S, Sweezie R, Ahluwalia V, Bombardier C, Gagliardi AR. Patient, rheumatologist and therapist perspectives on the implementation of an Allied Health Rheumatology Triage (AHRT) initiative in Ontario Rheumatology Clinics. *Pragmat Obs Res.* 2020;11:1–12. doi:10.2147/por.s213966
- 74. Sathi N, Whitehead E, Grennan D. Can a rheumatologist accurately prioritize patients on the basis of information in the general practitioner referral letter?. *Rheumatology*. 2003;42(10):1270–1271. doi:10.1093/rheumatology/keg336
- 75. Harrington T. Improving access to rheumatology care: a continuing challenge. J Rheumatol. 2008;35(7):1233-1234.
- 76. De Coster C, Fitzgerald A, Cepoiu M. Priority-setting tools for rheumatology disease referrals: a review of the literature. *Clin Rheumatol*. 2008;27 (11):1411–1416. doi:10.1007/s10067-008-0938-5
- 77. Speyer I, Hazes JM, Breedveld FC. Recruitment of patients with early rheumatoid arthritis The Netherlands experience. *J Rheumatol Suppl.* 1996;44:84–85.
- 78. van der Horst-Bruinsma IE, Speyer I, Visser H, Breedveld FC, Hazes JM. Diagnosis and course of early-onset arthritis: results of a special early arthritis clinic compared to routine patient care. *Br J Rheumatol*. 1998;37(10):1084–1088. doi:10.1093/rheumatology/37.10.1084
- 79. Govoni M, Sciré CA, Manara M, et al. Does early arthritis clinic organisation improve outcomes? What evidence is there? A systematic review. *Clin Exp Rheumatol.* 2013;31(3):443–451.

Open Access Rheumatology: Research and Reviews

# **Dovepress**

## Publish your work in this journal

Open Access Rheumatology Research and Reviews is an international, peer-reviewed, open access journal publishing original research, reports, editorials, reviews and commentaries on all aspects of clinical and experimental rheumatology in the clinic and laboratory including the following topics: Pathology, pathophysiology of rheumatological diseases; Investigation, treatment and management of rheumatological diseases; Clinical trials and novel pharmacological approaches for the treatment of rheumatological disorders. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

 $\textbf{Submit your manuscript here:} \ \text{https://www.dovepress.com/open-access-rheumatology-research-and-reviews-journal} \\$ 

