Review

Does early arthritis clinic organisation improve outcomes? What evidence is there? A systematic review

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Key words: early arthritis, early rheumatoid arthritis, early arthritis clinic, referral, health care organisation

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ABSTRACT

Objectives. To perform a systematic review aimed to identify studies addressing the effect of the establishment of a structured organisation programme, named early arthritis clinic (EAC), finalised to manage patients with early arthritis (EA) or suspected early rheumatoid arthritis (ERA).

Methods. A literature search was performed until May 2012 using electronic databases. Additional information was obtained through a hand and grey literature search. Primary and secondary outcomes and eligibility criteria have been defined.

Results. The search provided a total of 3367 citations and, after the selection process, 11 non randomised controlled trials were selected, including a total of 8240 participants. The efficacy of EAC did clearly emerge with regard to reduction of the referral lag time and of the time to treatment (secondary outcomes). Only two studies met the primary outcomes: one study demonstrated that the EAC contributed to reducing disease activity and radiographic progression but not functional disability, while another reported a reduction of pain after a 6-12-month period of follow-up.

Conclusion. Whether the establishment of EAC would improve the prognosis of EA in terms of primary outcomes such as clinical, functional and radiologic progression compared to patients managed outside from EAC does appear a still poorly addressed issue in the literature, which should be recognised as an urgent unmet need by the rheumatology community to gain more evidence-based information on this topic.

Introduction

The 'window of opportunity' hypothesis for therapeutic intervention in early rheumatoid arthritis (ERA) and in early

arthritis (EA) is now an established concept, based on the assumption that there is a time frame within which there is a good probability to obtain a smart response to therapy yielding early- and long-term benefits or, even more importantly, the chance of cure (1). Evidence exists that a delay of even a few months before starting conventional DMARD therapy determines a worst pattern of radiographic evolution (2, 3), which begins early (4) and persists after a prolonged follow-up (5). Two meta-analyses of clinical trials and observational studies documented the benefits of early intervention compared with delayed treatment, especially in those patients with more severe disease (3, 6).

For these reasons early referral is recommended by most available guidelines (7) and widely accepted by the rheumatology community (8).

On this background the idea of Early Arthritis Clinics (EACs) emerged in the late 1980s (9) aimed to establish specialist clinics for early assessment of patients with inflammatory arthritis at onset. Such clinics targeted patients with ERA or EA with the potential to evolve into RA, with the mission of early case definition, prognosis assessment and treatment beginning (10).

Prompted by this revolutionary acquisition, a lot of EAC experiences have started worldwide. However, whereas there is no doubt that this new approach has provided a better awareness about early arthritis as a medical emergency, to the best of our knowledge there is no formal demonstration that this organisational effort has provided significant benefits in terms of public health care and improved outcomes. Furthermore, no formal comparison has been made to analyse if different organisational modalities — named EACs — could have provided different results, one of

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them resulting in a better than another. For this reason, solicited by regional healthcare system, a systematic review on this topic has been performed in order to verify what were, if any, the available evidence on this topic.

Objectives

To examine whether or not the organisational model known as EAC improves outcomes of patients with EA or ERA, we reviewed studies that assessed the effect of the establishment of structured programmes finalised to the early referral, early diagnosis and early treatment in patients with EA or suspected RA against clinical, functional and structural outcomes.

Secondary explored outcomes included time to referral, time to diagnosis and time to treatment.

Methods

Information source

A systematic literature review was performed using electronic databases Medline (1966–2012), Embase (1980–2012), ISI Web of Knowledge, Cochrane and DARE (database of abstracts of reviews of effectiveness).

References from retrieved articles were also hand screened and a panel of local experts was asked for unpublished and ongoing study (NM, RM, GS, LM, FM, MP, MG).

Search strategy

To make as broader as possible the search strategy, we searched all registers and databases using terms related to the study population and intervention. No language, publication date, or publication status restrictions were imposed. The search of articles was performed using the following search terms: undifferentiated arthritis, inflammatory arthritis, rheumatoid arthritis, arthritis clinic, early arthritis unit, early arthritis clinic, early referral, early diagnosis, referral and consultation. The last search was

Selection of the studies, eligibility criteria and definition of the primary and secondary outcomes
Two reviewers (C.A.S. and M.M.) independently screened title and abstracts

run on 31st May 2012 (Appendix 1).

Appendix 1 (Search strategy)

MEDLINE (Pubmed)

- 1. "undifferentiated arthritis"
- 2. "inflammatory arthritis"
- 3. "rheumatoid arthritis"
- 4. Arthritis, Rheumatoid/diagnosis [Mesh]
- 5. Arthritis, Rheumatoid/epidemiology [Mesh]
- 6. Arthritis, Rheumatoid/prevention and control [Mesh]
- 7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
- 8. "arthritis clinic"
- 9. "early arthritis unit"
- 10. "early arthritis clinic"
- 11. "early referral and consultation"
- 12. "early referral"
- 13. early Diagnosis[Mesh]
- 14. Referral and Consultation [Mesh]
- 15. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
- 16. 7 AND 15

EMBASE

- 1. 'rheumatoid arthritis'/exp
- 2. 'rheumatoid arthritis'
- 3. 1 OR 2
- 4. 'early referral'
- 5. 'early arthritis clinic'
- 6. 'early diagnosis'/exp
- 7. 'early diagnosis'
- 8. 4 OR 5 OR 6 OR 7
- 9. 3 AND 8

ISI Web of Knowledge

Syntax: TS=(early arthritis) AND TS=(early referral) OR TS=(early arthritis clinic).

DARE

(rheumatoid arthritis) AND (diagnosis)

COCHRANE LIBRARY

- 1. "undifferentiated arthritis" OR
- 2. "inflammatory arthritis" OR
- 3. "rheumatoid arthritis" OR
- 4. Arthritis, Rheumatoid/diagnosis [Mesh]
- 5. Arthritis, Rheumatoid/epidemiology [Mesh]
- 6. Arthritis, Rheumatoid/prevention and control [Mesh]
- 7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
- 8. "arthritis clinic"
- 9. "Early arthritis unit"
- 10. "Early arthritis clinic"
- 11. "Early referral"
- 12. Early Diagnosis[Mesh]
- 13. "Referral and Consultation" [Mesh]
- 14. 8 OR 9 OR 10 OR 11 OR 12 OR 13
- 15. 7 AND 14

of all retrieved papers, and selected the studies to be included in this review, after removing duplicates. All articles selected by at least one of the reviewers were retrieved for examination.

According to an *a priori* protocol, articles fulfilling all the following inclusion criteria were selected: a) participants of age >16 years and without previous diagnosis of definite arthritic condition at the moment of the inclusion (popula-

tion); b) study that assessed the effect of the establishment of structured programs finalised to manage patients with EA or suspected RA (intervention); and c) controlled trials, including both concurrent and historical controls (relevant abstracts were also included).

Primary outcomes of the systematic literature review included: clinical outcome, measured according to any validated disease activity index; functional

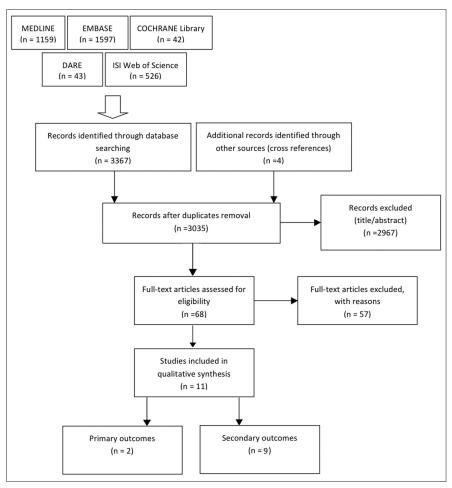


Fig. 1. Literature search flow chart.

disability, measured by the health assessment questionnaire (HAQ); pain, measured on a visual analogue scale or numerical rating score, health-related quality of life, measured by disease specific and generic instruments; structural damage, measured by any validated radiographic damage score; and mortality rates. Secondary outcomes included time to referral, time to diagnosis, and time to first DMARD treatment.

Quality assessment

Given that a number of not randomised studies were expected, we applied the Newcastle-Ottawa quality assessment Scale (NOS) to quantify the overall risk of bias of individual studies (11). Rating was performed by two reviewers (M.M. and C.A.S.) and disagreement were resolved by consensus.

Data extraction

All selected articles were reviewed by two authors (M.M. and C.A.S.), and all

data were extracted using an extraction sheet specifically designed for this review and preliminary tested and validated on ten randomly selected studies reviewed in full-text.

The following data were extracted independently by reviewers: authors, journal, year of publication, study design, inclusion and exclusion criteria, number of participants, setting, intervention and control, outcomes evaluated.

Disagreements were resolved by discussion between the two reviewers; if no agreement could be reached, a third author (M.G.) would decide.

Summary measures and planned methods of analysis

Individual data from primary studies were collected, reporting mean difference MD (95%CI) for continuous outcomes, and risk difference RD (95%CI) for dichotomous outcomes. Mean and standard deviation were estimated assuming normal distribution from avail-

able data, whenever not explicitly reported, only for purpose of qualitative comparison (12, 13). Since methodological flaws and heterogeneity in study design, setting, outcome definition and measurement were expected, thus preventing statistical pooling, we focused on describing the studies and their results on a qualitative synthesis.

Results

Study selection

A total of 11 controlled studies were identified for inclusion in the review (14-24). The search of Medline, Embase, Cochrane library, DARE and ISI Web of Knowledge provided a total of 3367 citations. After adjusting for duplicates and including references from cross-references, 3035 citations remained. Of these, 2967 records were discarded, because after reviewing the abstracts, it appeared that these papers clearly did not meet the inclusion criteria. The full-text of the remaining 68 citations, including a recent systematic review, were examined in more detail (see flow diagram, Fig. 1). After an indepth further analysis it appeared that 57 papers did not meet the inclusion criteria and were discarded (see Appendix 2 for a complete list of these discarded papers). Of the remaining 11 studies, only two (18, 19) addressed some of the selected primary outcomes, while 9 studies examined only secondary outcomes (14-17, 20-24). No unpublished relevant studies were included.

Study characteristics and quality

All eleven finally selected studies were not randomised controlled trials. Two trials used a retrospective (14, 22), while eight a prospective cohort design (15, 16, 18-21, 23, 24); one study used a cross sectional design (17). The setting of intervention group was hospital based in three trials (14, 19, 20), population-based in two trials (22, 24) and mixed hospital/population-based in six (15-18, 21, 23). All control groups were population-based but one (14). The included studies involved a total of 8240 participants. One retrospective study and a prospective one included patients with a diagnosis of early RA (14, 19), while the remaining prospective studies included patients with recent-onset inflammatory arthritis (disease duration <2 years) or other generic musculoskeletal symptoms (15-18, 20-24). The overall quality of the studies in an observational perspective resulted poor or moderate according to the Newcastle Ottawa quality rating scale (average score =4.8/9).

In one retrospective and seven prospec-

tive studies a formalised referral strat-

egy from community to rheumatologic

centres was established (14, 15-17, 20,

Intervention

21, 23, 24), some of them also including education of GPs and dedicated out-patient practice (15-17, 20). In one retrospective study, the intervention was a multicentre project finalised to establish an early arthritis register in the UK (ERAN project) (14). Only one study included disease activity, functional disability and radiographic progression as primary outcome measures (19), while another assessed the level of pain after a 6-12-month period of follow-up (18). Among the secondary outcomes, nine studies assessed the time to referral (time from the onset of symptoms and first rheumatologic consultation) (14-16, 18, 20-24), apart from one study where the time to referral was assessed considering the third available appointment instead of the first access (20). Two studies addressed the time to treatment (time from the onset of symptoms and the beginning of DMARD treatment in

Results of individual studies and synthesis of results

RA patients) (14, 17) (Table I).

Details of primary studies are reported in Table II.

Since the study design, participants, interventions and reported outcome measures varied markedly, we focused on describing the studies, their results, and their methodological quality on a qualitative synthesis, rather than a meta-analysis. All studies addressing the time to referral reported a 14.4-fold average reduction of this lag time (range 2.6–70), one of them yielding impressive results with a contraction of referral time from 10 weeks to one day (22); about the time to treatment,

Appendix 2 Second round discarded papers

- (1) Rheumatology. Hitting hard, hitting fast. Health Serv J 2009; 119(6186): 1p following suppl.
- (2) Too little, too late. Poor GP and public awareness leads to delays in diagnosis and treatment. Health Serv J 2009; 119(6186): Suppl 3.
- (3) Early referral of patients with rheumatoid arthritis. Med Today 2002; 3(8): 8.
- (4) Arndt U, Behrens F, Ziswiler HR, Kaltwasser JP, Moller B. Observational study of a patient and doctor directed pre-referral questionnaire for an early arthritis clinic. Rheumatol Int 2007; 28(1): 21-26.
- (5) Bernatsky S, Feldman DE, Dawes M, Legare J, Mill C, Zummer M, et al. Clarifying the barriers to optimal healthcare for persons with inflammatory arthritis. J Rheumatol 2009; 36(4): 852-3; author reply 853-4.
- (6) Bondin D, Castelino M, Evin S, Gooden A, Peacock C, Teh L. Assessment of outpatient referrals in patients with inflammatory arthritis: An audit. Rheumatology (UK) 2010; 49: i133.
- (7) Bykerk V, Emery P. Delay in receiving rheumatology care leads to long-term harm. Arthritis Rheum 2010; 62(12): 3519-3521.
- (8) Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007; 66(1): 34-45.
- (9) Courtney PA, Wright GD. Referrals to an "early synovitis clinic": are they appropriate? Ann Rheum Dis 2001; 60(10): 991-992.
- (10) Cush JJ. Remodeling a rheumatology practice to facilitate early referral. Rheum Dis Clin North Am 2005; 31(4): 591-604.
- (11) Cush JJ. Early arthritis clinics: if you build it will they come? J Rheumatol 2005; 32(2): 203-207.
- (12) de Rooy DP, van der Linden MP, Knevel R, Huizinga TW, van der Helm-van Mil AH. Predicting arthritis outcomes--what can be learned from the Leiden Early Arthritis Clinic? Rheumatology (Oxford) 2011; 50(1): 93-100.
- (13) Eberhardt K. Very early intervention is crucial to improve work outcome in patients with rheumatoid arthritis. J Rheumatol 2009; 36(6): 1104-1106.
- (14) El Miedany YM, Youssef SS, Mehanna AN, El Gafaary M. Establishment of a Specialized Early Arthritis Clinic using a systematic and specific protocol for referral and management. Arthritis Rheum 2005; 52(9): 237.
- (15) El Miedany Y, Palmer D. Five-Year Outcome of Early Arthritis Clinic: a Nice Effect on the Patients' Outcome. Rheumatology 2010; 49: 1159.
- (16) Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: Evidence based development of a clinical guide. Ann Rheum Dis 2002; 61(4): 290-297.
- (17) Esselens G, Westhovens R, Verschueren P. Effectiveness of an integrated outpatient care programme compared with present-day standard care in early rheumatoid arthritis. Musculoskeletal Care 2009; 7(1): 1-16.
- (18) Esselens GH, De Brabander A, Ovaere L, De Brabanter G, Moons P, Westhovens R. Personal attributes as determinants of timely care in rheumatoid arthritis. Ann Rheum Dis 2006; 65(7): 967-968
- (19) Fautrel B, Benhamou M, Foltz V, Rincheval N, Rat AC, Combe B, et al. Early referral to the rheumatologist for early arthritis patients: evidence for suboptimal care. Results from the ESPOIR cohort. Rheumatology (Oxford) 2010; 49(1): 147-155.
- (20) Feldman DE, Bernatsky S, Haggerty J, Leffondre K, Tousignant P, Roy Y, 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.
- (21) Feldman DE, Schieir O, Montcalm AJ, Bernatsky S, Baron M, McGill Early Inflammatory Arthritis Research Group. Rapidity of rheumatology consultation for people in an early inflammatory arthritis cohort. Ann Rheum Dis 2009; 68(11): 1790-1791.
- (22) Gormley G, Steele K, Gilliland D, Leggett P, Matthews C, Meenagh G, et al. Can triage improve the appropriateness of referrals to an Early Arthritis Clinic? Arthritis Rheum 2001; 44(9): 1608.
- (23) Gormley GJ, Steele WK, Gilliland A, Leggett P, Wright GD, Bell AL, et al. Can diagnostic triage by general practitioners or rheumatology nurses improve the positive predictive value of referrals to early arthritis clinics? Rheumatology (Oxford) 2003; 42(6): 763-768.
- (24) Gough A, Young A, Bacon P. Objectives and outcome of running an early inflammatory arthritis clinic. Baillieres Clin Rheumatol 1992; 6(2): 261-283.
- (25) Harrison BJ, Symmons DP, Brennan P, Bankhead CR, Barrett EM, Scott DG, et al. Inflammatory polyarthritis in the community is not a benign disease: predicting functional disability one year after presentation. J Rheumatol 1996; 23(8): 1326-1331.
- (26) Houssien DA, Scott DL. Early referral and outcome in rheumatoid arthritis. Scand J Rheumatol 1998; 27(4): 300-302.
- (27) Hyrich KL. Patients with suspected rheumatoid arthritis should be referred early to rheumatology. BMJ 2008; 336(7637): 215-16.
- (28) Irvine S, Munro R, Porter D. Early referral, diagnosis, and treatment of rheumatoid arthritis: Evidence for changing medical practice. Ann Rheum Dis 1999; 58(8): 510-13.
- (29) Klareskog L, Nordmark B, Lindblad S. On the organization of an early arthritis clinic. Best-Pract Res Clin Rheumatol 2001 2001; 15(1): 1-15.
- (30) 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 (Oxford) 2010; 49(5): 1005-12.
- (31) Mjaavatten MD, Helgetveit K, Haugen AJ, Nygaard H, Kvien TK. Very early arthritis clinic in Norway: A small proportion of the patients have persistent polyarthritis. Ann Rheum Dis 2006; 65: 111.
- (32) Mjaavatten MD, Nygaard H, Haugen AJ, Helgetveit K, Kvien TK. Disease characteristics and predictors of persistent arthritis after one year in a very early arthritis clinic in Norway. Ann Rheum Dis 2007; 66: 332.
- (33) Mjaavatten MD, Nygaard H, Haugen AJ, Helgetveit K, Kvien T. Performance of criteria for referral of early arthritis to rheumatologist with regard to persistent arthritis after one year: Results from a cohort of very early arthritis patients. Ann Rheum Dis 2007; 66: 331-32.
- (34) Mosher D, Barr S, Fahlman N, Fitzgerald A, Leclercq S, Lupton T, et al. Wait time for Assessment in Early Inflammatory Arthritis Clinic. J Rheumatol 2010; 37(6): 199.
- (35) Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2004; 43(7): 906-14.
- (36) Nell VPK, Machold KP, Eberl C, Stamm T, Uffmann M, Smolen JS. The benefit of very early referral and therapy with disease modifying antirheumatic drugs in patients with early rheumatoid arthritis. Arthritis Rheum 2002; 46(9): S334-5.
- (37) Newman ED, Harrington TM, Olenginski TP, Perruquet JL, McKinley K. "The rheumatologist can see you now": Successful implementation of an advanced access model in a rheumatology practice. Arthritis Rheum 2004; 51(2): 253-57.
- (38) Palm O, Purinszky E. Women with early rheumatoid arthritis are referred later than men. Ann Rheum Dis 2005; 64(8): 1227-28.
- (39) Potter T, Mulherin D, Pugh M. Early intervention with disease-modifying therapy for rheumatoid arthritis: where do the delays occur? Rheumatology (Oxford) 2002; 41(8): 953-55; author reply 955.
- (40) Qian J, Ehrmann Feldman D, Bissonauth A, Menard HA, Panopalis P, Stein M, et al. A retrospective review of rheumatology referral wait times within a health centre in Quebec, Canada. Rheumatol Int 2010; 30(5): 705-707.
- (41) Robinson PC, Taylor WJ. Time to treatment in rheumatoid arthritis: factors associated with time to treatment initiation and urgent triage assessment of general practitioner referrals. J Clin Rheumatol 2010; 16(6): 267-73.
- (42) Saevarsdottir S, Wallin H, Seddighzadeh M, Ernestam S, Geborek P, Petersson IF, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011; 70(3): 469-75.
- (43) Samaranayake M, Bukhari M. An audit of a rheumatology multi disciplinary team (MDT) assessment clinic in early inflammatory arthritis. Rheumatology 2008; 47: II105.
- (44) Sandhu RS, Treharne GJ, Justice EA, Jordan AC, Saravana S, Obrenovic K, et al. Comment on: Delay in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. Rheumatology (Oxford) 2008; 47(4): 559-60; author reply 560.
- (45) Scott DL, Kowalczyk A. Clinical trials: Tight control in early RA pays off in the long run. Nat Rev Rheumatol 2010; 6(11): 623-24.
- (46) Scott J, Goodson N, Thompson R, Brinkley L, Lawrence M, Lamb J, et al. Improving patient care in practice: Results from the aintree early arthritis clinic. Rheumatology 2008; 47: II107.
- (47) Sokka T, Makinen H. An excellent example of an early arthritis clinic What is its clinical value? J Rheumatol 2009; 36(7): 1355-56.
- (48) Symmons DP, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J Rheumatol 1998; 25(6): 1072-77.
- (49) Tam S, Fraser I, Badley E, Young W, Coyte PC. Wait times for likely inflammatory arthritis patients in an early arthritis clinic. J Rheumatol 2006; 33(2): 401.
- (50) Tong C, Joshua FJ. Early diagnosis and treatment of rheumatoid arthritis. Med Today 2007; 8(1): 43-52.
- (51) van der Linden MP, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TW, et al. Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheum 2010; 62(12): 3537-46.
- (52) van der Woude D, Young A, Jayakumar K, Mertens BJ, Toes RE, van der Heijde D, et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. Arthritis Rheum 2009; 60(8): 2262-71.
- (53) Kwok KY, Leung MH. Tight control early rheumatoid arthritis clinic in Hong Kong: a pilot study. Hong Kong Med J. 2012; 18(2): 108-114.
- (54) Muñoz-Fernández S, Carmona L, Collantes E, Mulero J, García-Yébenes MJ, de Miguel E, Almodovar R, Fernández-Carballido C, Llorente JF, Gobbo M; Esperanza Group. A model for the development and implementation of a national plan for the optimal management of early spondyloarthritis: the Esperanza Program. Ann Rheum Dis. 2011; 70(5): 827-30.
- (55) Smith EC, Berry H, Scott DL. The clinical need for an acute rheumatology referral service. *Br J Rheumatol* 1996; 35: 389–91.
- (56) Magnusson CCD. RA diagnosis clinic: an experiment in prioritizing appointments for suspected RA. *J Rheumatol* 2010; 36: 1337.
- (57) Villeneuve E, Nam JL, Bell MJ, Deighton CM, Felson DT, Hazes JM, McInnes IB, Silman AJ, Solomon DH, Thompson AE, White PH, Bykerk VP, Emery P. 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.

the shortening ranged around 1.6 fold average in the intervention group compared with controls.

Discussion

The institution of EACs was initially confined to clinical research units, but through the 1990s, EACs spread worldwide as part of general rheumatology services. The minimum standard core of services offered by an EAC has not yet been formally defined; however, ideally, the clinics should be able to warrant a rapid referral of patients with either signs or symptoms of inflammatory arthritis (IA), to allow early diagnosis and provide a subsequent tight monitoring aimed to assess therapeutic response (10). The exact structure and services offered at such clinics are varied and frequently determined by availability of resources and local health care system organisation. Up to date, several models have been instituted, each of them offering a slightly different approach, although centred on a unifying concept of early case definition and intervention.

One of the first models was the Birmingham one (25), where the service allowed direct referral via long-range pager to a rheumatologist for all patients with possible IA. Urgent patients could be seen on the same or next working day, and all patients could be seen within 2 weeks of referral. Assessments were undertaken in a purpose-built ward with staff including rheumatologists, trainee rheumatologists, a specialist nurse, a physiotherapist and an occupational therapist (OT), and with the capacity to cope with medical students and general practitioners for educational purposes. In the Leeds system, an increased emphasis on imaging was dedicated, with addition of ultrasound and magnetic resonance imaging assessment of joints, to dual energy x-ray absorptiometry and x-ray for all patients (26). The Karolinska system in Sweden is based on a day care programme where all patients receive comprehensive assessment and education by, in turn, a junior doctor, physiotherapist, social worker, OT and co-ordinating nurse, prior to a prognostic and therapeutic decision from the senior physician (27).

Table I. Study characteristics and quality.

Ref.	Author	Year	Design	Inclusion/exclusion criteria	Setting	n°	Intervention / Control	Outcome	NOS
14	Coulson	2007	Cohort retrospective	Early RA	Hospital	729	Early Rheumatoid Arthritis Network vs. Rheumatology Unit at Withy Bush General Hospital	Time to referral Time to treatment	3/9
15	El Miedany	2006	Cohort prospective	Early arthritis / already defined specific rheumatic condition	Mixed (Population/hospital)	108	Early Arthritis Clinic vs. standard approach (historical)	Time to referral	3/9
16	Van der Horst	1998	Cohort prospective	Arthritis and symptoms duration ≤2/ already assessed by a rheumatologist	Mixed (Population/hospital)	474	Early Arthritis Clinic vs. routine Outpatient Clinic	Time to referral	6/9
17	Marcos	2011	Cross-sectional	Arthritis and symptoms duration ≤2 years	Mixed (Population/hospital)	413	Argentin Consortium for Early Arthritis vs. standard approach (historical)	Time to treatment	4/9
18	Gartner	2012	Cohort prospective	N/A	Mixed (Population/hospital)	1036	Immediate Access Clinic (IAC) vs. standard approach (historical)	Time to referral	7/9
19	Descalzo	2012	Cohort prospective	Early RA	Hospital	608	Early Arthritis Units (SERAP cohort) vs. standard approach (PROAR cohort)	DAS 28, HAQ, TSS (total Sharp/van der Heijde score)	8/9
20	Newman	2004	Cohort prospective	Rheumatology patients	Hospital	3340	Referral Strategy vs. standard approach (historical)	Time to third visit Number of RA referrals	4/9
21	Maddison	2004	Cohort prospective	Musculoskeletal symptoms	Mixed (Population/hospital)	N/A	Referral Strategy (targeted early access to musculoskeletal services programme, TEAMS) vs. standard approach (historical)	Time to referral	4/9
22	Pflugbeil (Abstract Eular)	2009	Cohort retrospective	N/A	Population	1212	Rapid Access Clinic (RAC) vs. standard approach (historical)	Time to referral	N/A
23	Edwards (Abstract Eular)	2009	Cohort prospective	Rheumatology patients	Mixed (Population/hospital)	108	Rapid Access and Treatment service (RATS) vs. standard approach (historical)	Time to referral	N/A
24	Speyer	1996	Cohort prospective	Recent-onset arthritis	Population	212	Early Arthritis Clinic vs. Outpatient Clinic	Time to referral	5/9

N/A: not assessed.

The Department of Rheumatology of the Leiden University Medical Centre established an EAC service in 1993 similar to that provided by the Birmingham model, but also linked to basic science institutions yielding additional benefits in terms of better understanding of the pathophysiology of early IA (28).

More recently, an immediate access rheumatology clinic model (IAC) has been instituted in the Vienna General Hospital, providing a considerable waiting time reduction for rheumatology assessment and a substantial lower pain levels after 6–12 months follow-up period in the RA patients who were

followed within the IAC than patients treated elsewhere (18).

Based on the wide available literature, it is intuitive that rapid and early referral is one of the most critical steps of the entire assistance process, allowing to warrant early diagnosis, prognosis, treatment and outcome benefits, being early prognostication – especially if assisted by imaging – the most relevant to guide the most appropriate therapeutic intervention (29-30). However, it is quite surprising that up to date, a very few evidence have been accumulated investigating whether the way to organise early access and the institution of structured EACs translates into a

clear and valuable benefit for both patients and health care system.

The aim of the present systematic review was to search evidence, if any, supporting the notion that an EAC organisation could be advantageous with respect to the traditional patient's referral systems. Conceptually, the entire process of the management of early arthritis can be split in different moments: early referral, early diagnosis, early prognosis, early treatment and evaluation of outcomes.

Data retrieved from our systematic review cover essentially the first and the fourth checkpoints of this process. Only two studies addressed structured outcomes such as disease activity,

Table II. Results of the selected studies.

Ref.	Outcome	Intervention n	Summary measure	Controls n	Summary measure	Association measure
	Time to referral					MD (95%CI) (days)
14	Coulson	467	Median (IQR), months: 5 (3, 11)	160	Median (IQR), months: 14.1 (7.2, 24.8)	-275 (-320, -229)
15	El Miedany	108	Mean, weeks: 3.4	N/A	Mean, weeks: 12	-60 (N/A)
16	Van der Hosrst	233	Median (range), days: 31 (1, 610)	241	Median (IQR) (range) days: 122 (1,727)	-75 (-95, -55)
18	Gartner	1036	Median (IQR), days: 8 (4-13.25)	N/A	>4 months	N/A
21	Maddison	N/A	5 weeks	N/A	35 weeks	-210 (N/A)
22	Pflugbeil	1212	24 hours	N/A	6-10 weeks	N/A
23	Edwards	108	Mean (SD), days: 4.5 (N/A)	N/A	>7 weeks	N/A
24	Speyer	113	Mean (SD), days: 99 (153)	99	Mean (SD), days: 259 (411)	-160 (-242, -78)
	Time to third visit					MD (95%CI) (days)
20	Newman	2003	Mean (SD), days: 25 (N/A)	1337	Mean (SD), days: 40 (N/A)	N/A
	Time to treatment					MD (95%CI) (days)
14	Coulson	485	Median (IQR), months: 8 (4, 13)	131	Median (IQR), months: 12 (6, 21.4)	-121 (-167, -74)
17	Marcos	108	Symptoms duration: mean (SD), months: 8 (6)			
			Time to treatment: all <6 months	N/A	Median (IQR), months: 14 (2.5, 24)	N/A
	DAS28 at 2 years					Adj MD (95%CI)
19	Descalzo	447	N/A	161	N/A	-0.24 (-0.39, -0.08)
	HAQ at 2 years					Adj MD (95%CI)
19	Descalzo	447	N/A	161	N/A	0.01 (-0.03, 0.06)
	Sharp/van der Hei total score at 2 yea					Adj MD (95%CI)
19	Descalzo	447	N/A	161	N/A	-0.05 (-0.09, -0.01)
	Number of new RA	1				RD (95%CI)
20	Newman	2003	194 patients	1337	129 patients	0 (-0.05)

MD: mean difference; Adj MD: adjusted mean difference; N/A: not assessed; RD: risk difference; SD: standard deviation; IQR: interquartile range; CI: confidential interval; HAQ: health assessment questionnaire; DAS28: disease activity score (28 joints).

functional impairment, pain level and radiographic progression (18, 19). The nine studies addressing the time to referral demonstrate that an EAC organisation may warrant a significant average shortening of the time to referral in the intervention group compared with the control group (14-16, 18, 20-24). Only two studies addressed the issue of the time to treatment (14, 17) demonstrating a similar lag time reduction in the intervention group, even though to a lesser extent than it was observed for the time to referral.

It should be underscored that all the studies have considered the time to referral calculated as the time occurring from the symptoms onset and the first rheumatologic consultation. Indeed, delays in help-seeking can occur at different levels, including delays on the part of the patient in seeking medical advice at symptom onset, delays in obtaining an appointment with healthcare professional, and delays in referral to a rheumatologist, achieve a diagnosis, and the commencement of DMARD

therapy (31). In the UK the median delay between symptom onset and rheumatologist's assessment has been reported to be about 23 weeks, most of which is attributed to patient delay in seeking help (median 12 weeks) (32). In other countries, including Austria, Germany and the Netherlands, the delay on the part of the patient is shorter (33, 34).

In a recent study, the median delay across 10 European centres from symptom onset to rheumatology assessment was 6 months, the referral lag time from primary care practitioner to a rheumatologist being an important contributor to overall delay in seven out of the ten participating centre (35).

In a recent systematic review conducted to identify drivers of and barriers to help-seeking behaviour in adults with new onset RA, Stack *et al.* (31) realised that symptom interpretation by the patient himself and the different onset modalities of the arthritis (acute/rapid *versus* slow/vague/intermittent), was central to the patient's decision to seek

help at the onset of the disease. Since ignoring symptoms led people to delay in help-seeking, the authors concluded that strategies to promote help-seeking in RA patients are needed and that targeted public health interventions are required to inform patients about symptom interpretation, in order to reduce delays in referral.

Another systematic review analysed the different strategies adopted to promote early referral and reducing delays in the diagnosis and management of inflammatory arthritis. This review identified main areas of delay to care for patients with inflammatory arthritis and, most importantly, the potential solution for each one, which include: education of the target population about early inflammatory arthritis, education of primary care practitioner who represents the first critical check point for the patient, and the establishment of early arthritis clinics (EAC) (36).

Unfortunately, apart from the efficacy in reducing the referral lag time, scarce evidence-based information is available about the performance of the EAC organisation model in terms of outcome improvement. According to the present systematic review, only two papers addressed this important issue (18, 19). The first one comes from Vienna, where a model providing an immediate access to the rheumatology clinic was tested and evaluated (18). Data regarding diagnostic accuracy, pain levels and care were analysed. In this organisational model patients were referred by their GP, by another specialist or were self-referred. A brief encounter with an experienced rheumatologist was provided to assess disease and for further diagnostic and therapeutic decisions. Patients were then assigned to a group which was referred to a regular clinic work-up, whilst another group was assigned to a work-up out of the clinic. The major results of this approach demonstrated a considerable waiting time reduction for rheumatology assessment with a good diagnostic accuracy of an inflammatory rheumatic disease (>75%) at first evaluation; after a 6-12month follow-up, patients with RA who continued to be cared of in the clinic had substantially lower pain levels than patients managed elsewhere. Advantages in both disease activity measures and satisfaction with health care for patients receiving continuous care in a highly specialised rheumatology clinic (i.e. EAC) have been confirmed in another report by the same group (37).

The second paper refers to an even more recent study from Spain, where two different models of intervention have been compared applied to two different multicentre early RA cohorts (19). The first cohort included 447 early RA patients attending EAC located in 36 reference hospitals in which a specific structured intervention was established (SERAP cohort), the second one was a historical control cohort of patients with early RA attending 34 rheumatology departments (PROAR cohort) and included 161 patients attending regular rheumatology clinics.

Briefly, in the SERAP or intervention cohort, primary care physicians were trained in how to suspect EA and were requested to refer all patients with suspected EA to the Early Arthritis Unit within a maximum of 15 days, according to pre-established definitions and as supported by specific referral protocols and materials. Effectiveness of the intervention was tested by comparing the change in the DAS28, the change in the Health Assessment Questionnaire (HAQ), and the change in the Sharp/ van der Heijde radiologic score after a 2-year follow-up. The results of this study demonstrated a significant reduction of disease activity, as assessed by the DAS28, and less radiographic progression in patients who attended the EA clinics than in those who were cared outside. No significant differences emerged about HAQ changes. Overall, these two studies demonstrate that an EA clinic organisation is effective in improving some important outcomes such as level of disease activity, radiographic progression and mean level of pain, compared to non-protocolised referral setting.

Some limitations in this systematic review must be underscored. The first one is that only two of the selected studies did match some of the primary outcomes of the search strategy. Only two of the secondary outcomes were analysed in nine out of the selected studies.

The second limitation lies in a poor-tomoderate quality of the studies according to the Newcastle Ottawa quality rating scale.

These limitations make any conclusion about the search question, only partially answered. The most clear information retrieved from this review attests that structured approaches in an early arthritis clinical setting do provide a shortening of the lag time to referral and of the lag time to treatment. Although it is intuitive that these steps are fundamental to warrant early diagnosis and early treatment, whether this time shortening translates into better outcomes has been little investigated, with only two studies addressing (one of them in an indirect way) this issue. This result appears quite surprising and disappointing, since public health regulatory institutions involved in the territorial healthcare planning process need to base their decisions primarily on strong available evidence. The core question whether the establishment of EA clinics would improve the prognosis of EA in terms of clinical, functional and radiologic progression compared to patients with EA who do not attend EAC still seems to be a poorly addressed issue in the literature, since most evidence supporting the establishment of EAC is based on studies comparing aggressive and early treatment versus others, but not directly the efficacy of the organisation setting named EAC as a whole versus a not structured programme at all. Fortunately, more recently, this gap seems to be recognised as an urgent unmet need by the rheumatology community. Therefore, further studies as those provided by the Spanish Society of Rheumatology and by Vienna IAC are welcome and to be encouraged.

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References

- 1. O'DELL JR: Treating rheumatoid arthritis early: a window of opportunity? *Arthritis Rheum* 2002; 46: 283-5.
- KORPELA M, LAASONEN L, HANNONEN P et al.; FOR THE FIN-RACO TRIAL GROUP: Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. Arthritis Rheum 2004; 50: 2072-81.
- ANDERSON JJ, WELLS G, VERHOEVEN AC, FELSON DT: Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum* 2000: 43: 22-9.
- LARD LR, VISSER H, SPEYER I et al.: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001; 111: 446-51.
- VAN AKEN J, LARD LR, LE CESSIE S, HAZES JM, BREEDVELD FC, HUIZINGA TW: Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 274-9.
- FINCKH A, LIANG MH, VAN HERCKENRODE CM, DE PABLO P: Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006; 55: 864-72.
- 7. COMBE B, LANDEWÉ R, LUKAS C *et al.*: EULAR recommendations for the management of early arthritis: report of a task force

- of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66: 34-45.
- 8. ALETAHA D, EBERL G, NELL VP, MACHOLD KP, SMOLEN JS: Attitudes to early rheumatoid arthritis: changing patterns. Results of a survey. *Ann Rheum Dis* 2004; 63: 1269-75.
- 9. EMERY P, GOUGH A: Why early arthritis clinics? *Br J Rheumatol* 1991; 30: 241-2.
- QUINN MA, EMERY P: Are early arthritis clinics necessary? Best Pract Res Clin Rheumatol 2005; 19: 1-17.
- 11. WELLS GA, SHEA B, O'CONNELL D *et al*.: The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm [cited 2009 Oct 19].
- HIGGINS JP, GREEN S (Eds). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. London: Cochrane Collaboration: 2011: 1.
- 13. HOZO SP, DJULBEGOVIC B, HOZO I: Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; 20; 5-13.
- 14. COULSON A, NAGASAYI S, MAYES C, and E.R.A.N MEMBERS: Comparison of referral times for management of early rheumatoid arthritis: ERAN vs. a participating centre. BSR Annual Meeting 08-11 May 2007 and BHPR Spring Meeting 09-11 May 2007 ICC, Birmingham, UK. *Rheumatology* (Oxford) 2007; 46 (Suppl. 1): i109 (abstract).
- EL MIEDANY Y, PALMER D, EL GAAFARY M: Diagnosis of early arthritis: outcomes of a nurse-led clinic. *Br J Nurs* 2006; 15: 394-
- 16. 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: 1084-8.
- 17. MARCOS J, WAIMANN C, DAL PRA F et al.; CONAART (CONSORCIO ARGENTINO DE ARTRI-TIS TEMPRANA-ARGENTINE CONSORTIUM FOR EARLY ARTHRITIS): General characteristics of an early arthritis cohort in Argentina. Rheumatology (Oxford) 2011; 50: 110-6.

- GÄRTNER M, FABRIZII JP, KOBAN E et al.: Immediate access rheumatology clinic: efficiency and outcomes. Ann Rheum Dis 2012; 71: 363-8.
- DESCALZO MÁ, CARBONELL J, GONZÁLEZ-ÁLVARO I et al.; SERAP AND PROAR STUDY GROUPS: Effectiveness of a clinical practice intervention in early rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012; 64: 321-30
- 20. NEWMAN ED, HARRINGTON TM, OLENGIN-SKI TP, PERRUGUET JL, MCKINLEY K: "The rheumatologist can see you now": Successful implementation of an advanced access model in a rheumatology practice. Arthritis Rheum 2004; 51: 253-7.
- MADDISON P, JONES J, BRESLIN A et al.: Improved access and targeting of musculoskeletal services in northwest Wales: targeted early access to musculoskeletal services (TEAMS) programme. BMJ 2004; 329: 1325-7.
- 22. PFLUGBEIL S, FUCHS J, SMOLEN JS: Rapid access clinics allow early detection of infl ammatory rheumatic diseases. EULAR Congress 2009 Copenaghen 10-13 June. Ann Rheum Dis 2009; 68 (Suppl. 3): 538 (abstract FR 10559).
- 23. EDWARDS MHRN, HULL RG, LEDINGHAM JM: Rapid access and treatment service a practical model of urgent rheumatology care. EULAR Congress 2009 Copenaghen 10-13 June. *Ann Rheum Dis* 2009; 68 (Suppl. 3): 529 (abstract FR10534).
- 24. SPEYER I, HAZES JM, BREEDVELD FC: Recruitment of patients with early rheumatoid arthritis – the Netherlands experience. *J Rheumatol* 1996; 44 (Suppl.): 84-5.
- GOUGH AKS: Disease Severity and Prediction of Outcome in Early Rheumatoid Arthritis, thesis. London 1993.
- 26. QUINN MA, GREEN MJ, EMERY P: Evaluation and management of early inflammatory polyarthritis. *In* HOCHBERG MC, SILMAN AJ, SMOLEN JS, WEINBLATT ME, WEISMAN MH (Eds.) *Rheumatology*, 3rd ed. St Louis, MO: Mosby, 2003, pp. 885-91.
- KLARESKLOG L, NORDMARK B, LINDBLAD S: On the organization of an early arthritis clinic. Best Pract Res Clin Rheumatol 2001; 15: 1-15.

- VAN AKEN J, VAN BILSEN JH, ALLAART CF, HUIZINGA TW, BREEDVELD FC: The Leiden Early Arthritis Clinic. Clin Exp Rheumatol 2003; 21 (Suppl. 31): S100-5.
- 29. MACCHIONI P, MAGNANI M, MULÈ R et al.: Ultrasonographic predictors for the development of joint damage in rheumatoid arthritis patients: a single joint prospective study. Clin Exp Rheumatol 2012; 31: 8-17.
- GOVONI M, CAPORALI R: Predicting and managing the progression of structural damage in rheumatoid arthritis: where do we stand? Clin Exp Rheumatol 2012; 30: 459-63.
- 31. 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: 493-7.
- 32. 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* (Oxford) 2007; 46: 1438-40.
- 33. VAN DER LINDEN MP, LE CESSIE S, RAZA K *et al.*: Long-term impact of delay in assessment of patients with early arthritis. *Arthritis Rheum* 2010; 62: 3537-46.
- 34. HAY MC, CADIGAN RJ, KHANNA D *et al.*: Prepared patients: internet information seeking by new rheumatology patients. *Arthritis Rheum* 2008; 59: 575-82.
- 35. RAZA K, STACK R, KUMAR K *et al.*: Delays in assessment of patients with rheumatoid arthritis: variation across Europe. *Ann Rheum Dis* 2011; 70: 1822-5.
- 36. 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: 13.22
- 37. NELL-DUXNEUNER V, REZENDE LS, STAMM TA, DUER M, SMOLEN JS, MACHOLD KP: Attending and non-attending patients in a real-life setting of an early arthritis clinic: why do people leave clinics and where do they go? *Clin Exp Rheumatol* 2012; 30: 184-90.