To screen or not to screen: How to find and identify very early arthritis

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Abstract

There is accumulating evidence demonstrating that early treatment leads to better outcomes in rheumatoid arthritis. In order to be treated early, patients thus need to be identified at the earliest possible stage. This means identifying patients with rheumatoid arthritis at their earliest clinical signs but it could also mean screening for healthy individuals at high risk of developing rheumatoid arthritis. The different tools available to screen for these individuals are reviewed here and their relevance is discussed.

Introduction

Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis affecting approximately 1% of the general population. It is characterised by joint destruction, which leads to functional decline and disability as well as increased mortality. There has been accumulating evidence that early disease-modifying anti-rheumatic drug (DMARD) initiation leads to better outcomes [1–3]. However, to be able to treat patients early they need to be identified early, which explains why increasing emphasis has been placed on the early diagnosis and identification of RA over the past few years. Development of the new 2010 American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) criteria for classifying RA is one such example to enable earlier identification. In addition, more centres have established early arthritis...
clinics (EACs) and incorporated new methods of triaging patients [4]. Furthermore, as we move forward, in addition to trying to identify and treat RA early, efforts are increasing to find ways to identify patients at imminent risk of RA in its preclinical stage. Prior to the onset of overt manifestations of RA, patients at risk go through a series of stages beginning with a period during which they only have genetic risk factors. They are then thought to go through a period of autoimmunity but with no apparent inflammation and/or symptoms and then subsequently have symptoms without apparent synovitis. Being able to identify people at risk of RA, particularly those with autoimmunity and early symptoms and/or high genetic risk, could lead to the development of interventions to prevent its development.

**Should we screen for RA?**

Screening is defined as a process of identifying apparently healthy people who may be at increased risk of a disease or a condition. Moreover, screening is usually performed for disease where there is an available intervention which can prevent development of this disease or where an early intervention will lead to better outcomes.

To date, there is no precise way to identify RA at a preclinical stage. However, increasingly more researchers are addressing this issue. However, even if we could identify people at risk of RA, there is still a need to demonstrate that there is an intervention which can halt or prevent disease progression or at least lead to better outcomes than intervention at the earliest sign of synovitis. Although there is no proven effective intervention in preclinical RA, prospective observational data suggest that intervention at this stage could indeed modify future RA risk. Using a national database including 313 RA cases and 1252 controls, Jick et al. have shown a decreased risk of incident RA in patients using statins for hyperlipidaemia (odds ratio (OR) 0.59, 95% confidence interval (CI) 0.37–0.96) [5]. Although screening of preclinical RA remains an area of research for the moment, available data will be reviewed presuming the day when clinicians will be able to effectively screen for preclinical RA and prevent RA is not far off.

Although not all scientists may agree, another way to consider screening is to try to identify an individual at the earliest stage of clinically overt disease. This is warranted in diseases where early intervention is known to lead to better outcomes. This is indeed the case in RA where there is good evidence to support that treatment should be started as soon as possible. In a meta-analysis, patients who received early treatment had sustained benefit in radiographic progression over 5 years [6]. Shorter disease duration was the strongest predictor of improvement in disease activity, and delayed treatment led to more radiographic progression. The proportion of patients achieving remission and low disease activity was also higher in patients with less disease duration at the time of treatment initiation. These data support the hypothesis of a ‘window of opportunity’, a time frame early in the course of the disease where an intervention may result in a disproportionate long-term improvement [7]. Early treatment may alter the disease course and may even cure it. Thus, screening, or more precisely, early identification of people with new-onset RA is of most value as it could not only decrease the disease burden with improved function and survival for patients but also decrease costs for society through a decreased need for more expensive therapy and through maintenance of work productivity.

Data to support early intervention in undifferentiated arthritis (UA), where patients have synovitis and a presentation compatible with RA but they do not fulfil classification criteria, are less abundant. In the PROMPT trial (The PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment study), in UA patients with less than 2 years of synovitis, methotrexate was associated with delayed progression to RA defined by the 1987 ACR RA criteria, with the most benefit seen in anti-cyclic citrullinated peptide (anti-CCP) positive subjects [8]. Another small study using abatacept in UA and very early RA showed a trend towards decreased progression to classifiable RA [9]. Saleem et al. reported that a short course of infliximab in poor-prognosis UA provided modest, short-term relief but did not prevent the development of RA [10]. It is important to note that these trials were done prior to the publication of the 2010 ACR-EULAR RA criteria and that a proportion of patients who were recruited to these trials would now be classifiable as RA instead of as UA. Thus, in the remainder of this discussion the screening of both UA and RA, termed inflammatory arthritis
(IA), is discussed together. What would change is the intervention used once screening has been done.

**In what population and with what tool?**

**Screening for people at risk of RA**

To be able to screen asymptomatic individuals for a specific disease, we need to have a biomarker and perhaps a clinical prediction rule to identify these individuals in this asymptomatic stage of the disease. The current paradigm is that RA develops in three distinct phases [11] (Fig 1). The first phase is a state of susceptibility linked to genetic risk factors, either alone or in combination, that predispose to the loss of self-tolerance. The second is the development of preclinical auto-immunity where an individual at risk develops autoantibodies such as anti-CCP and rheumatoid factor (RF) and other immunologic factors such as increased cytokines, T- and B-cell autoreactivity and/or increased inflammatory markers but no signs or symptoms of RA. The transition from susceptibility to autoimmunity is probably triggered by an environmental event such as an infection, hormonal influence and tobacco exposure. This phase can be of variable length. As phase 1 and 2 are asymptomatic, they may collectively be called preclinical RA. The third phase is the development of clinically apparent disease where synovitis can be detected by physical examination. Defining exactly when the transition from preclinical to clinical disease occurs is not that easy. Most agree that RA-related autoantibodies without joint symptoms or other organ injury represents preclinical RA, but there is less clarity about patients with arthralgia or patients with synovitis who cannot be classified as RA or any other form of inflammatory arthritis. For instance, patients with arthralgia may have reported an episode of swelling, though this may not be visible at a screening visit. It is not clear how to interpret tests using high-sensitivity imaging in patients with arthralgia.

Supporting the concept of preclinical auto-immunity, many studies have demonstrated that anti-CCP and RF can be present years before the development of clinically apparent RA [12–14]. In a study, Nielen et al. found rheumatic factor–immunoglobulin M (RF–IgM) and anti-CCP to be positive in, respectively, 28% and 41% of 79 RA patients with preclinical stored serum [15]. RF was positive a median of 2 years prior to RA diagnosis and anti-CCP, 4.5 years. Similar findings were found by Rantanpää-Dalhlqvist et al., who tested preclinical serum from 83 RA patients collected a median of 2.5 years prior to symptom onset [16]. Thirty-four percent of patients were positive for anti-CCP and 17–34% for the different RF isotypes within 1.5 years prior to diagnosis. The combination of anti-CCP and any RF isotype was highly specific (99%) for future development of RA when patients’ sera were

Proposed phase of RA development

![Proposed phase of RA development](image)

**Fig. 1.** Phase 1 represents the individuals at genetic risk. Environmental triggers can then lead to phase 2 where the individual develops autoantibodies without clinical signs of the disease called pre-clinical autoimmunity. Eventually, some patients will progress to the third phase where they develop overt inflammatory arthritis.
compared with controls. However, they calculated the positive predictive value (PPV) of anti-CCP for the development of RA to be of only 16% and 22% in combination with positive immunoglobulin A–rheumatoid factor (IgA–RF) in the general population.

Apart from low PPV, another problem is that these autoantibodies can be present many years before symptoms and are less useful in isolation for predicting imminent symptomatic or overt disease. Moreover, not all RA patients have detectable pre-RA diagnosis autoantibody positivity. Therefore, it needs to be combined with risk factors other than autoantibodies to be a useful way to identify RA in its preclinical stage. These could include phospholipase A2, multiple cytokine/chemokines and C-reactive protein (CRP) [62]. In one study, Deane et al. used stored samples from 73 military seropositive RA cases and controls from pre-RA diagnosis [17]. Preclinical positivity of anti-CCP and/or two or more RF isotypes was >96% specific for future RA. Interleukin (IL)-1alpha, IL-1beta, IL-6, IL-10, IL-12p40, IL-12p70, IL-15, fibroblast growth factor-2, Fms-related tyrosine kinase 3 ligand (flt-3 ligand), tumour necrosis factor-alpha (TNF-alpha), interferon gamma-induced protein-10, granulocyte macrophage colony-stimulating factor and CRP were positive in a significantly greater proportion of RA cases versus controls. The number of positive cytokines increased near the time of RA diagnosis and this seemed to be even greater for older individuals. In regression modelling, increasing number of cytokine/chemokines predicted decreased time to diagnosis, and the predicted time-to-diagnosis based on cytokine/chemokines was longer in older (>40 years old) compared to younger cases. Several other studies have reported similar findings demonstrating a preclinical rise in serum cytokines or other inflammatory markers [16,18]. Nielen et al. found that the appearance of anti-CCP and RF shortly preceded a rise in CRP levels [19]. However, this finding could not be replicated in another study [20].

Researchers have also looked at another way to overcome the problem that autoantibodies can be present for years before the development of RA by trying to characterise the evolution of the antibody response in the preclinical phase of RA. Sokolove et al. used a novel multiple autoantigen array to evaluate development of the different epitopes comprising anti-CCP, also known as anti-citrullinated protein antibodies (ACPAs) [21]. They tested the stored serum of 81 RA patients, which was available from 1 to 12 years prior to the disease onset for ACPA sub-types and numerous cytokines. They observed a time-dependent expansion of ACPA specificity with the number of ACPA sub-types, which strongly predicted elevations in many inflammatory cytokines. Combining different epitopes and cytokines, authors identified a profile which displayed moderate sensitivity (58.2%) but significant specificity (87%) for identifying patients who were within 2 years of RA clinical onset. This profile includes autoantibodies targeting epitopes derived from citrullinated fibrogen as well as citrullinated enolase and whole citrullinated vimentin. Cytokines identified as predictors included IL-12p70, IL-1beta, IL-5, IL-7 and TNF-beta.

Adding genetic factors known to increase the risk of RA such as the shared epitope and protein tyrosine phosphatase, non-receptor type 22 (lymphoid) (PTPN22) to these profiles could also help improve their performance in predicting RA development. Thus, it is foreseeable that in patients with a higher genetic susceptibility of RA (e.g., having numerous family members with auto-immunity and/or RA) would be candidates for more intense screening that would include close clinical monitoring and regular assessment for other laboratory signs of auto-immune dysregulation and inflammatory cytokine up-regulation.

We need to be cognizant of the fact that many of these studies are limited by the fact that translational studies were performed on stored serum from biobanks and are not truly prospective as participants were not subjected to detailed baseline and follow-up joint examination. These findings thus still need to be tested in a true prospective manner. The question that remains is in whom we should test for these autoantibodies’ and cytokines’ profiles. Testing the general population would definitely not be cost-effective due to the low prevalence of RA. These profile tests could be applied to a test population presumed to be at high risk such as first-degree relatives (FDRs), as they have a five- to seven-fold increased risk of incident RA, or those with early musculoskeletal complaints [22].

At the moment, at least two cohorts using FDRs of probands with RA are being followed prospectively [23–25]. These cohorts will help study the evolution of RA auto-immunity and inflammation over time in order to develop better profiles of autoantibodies, cytokines, chemokines and/or other factors which could predict the transition from the preclinical to the clinical phase of RA. This could
even allow for the identification of factors implicated in the transition from phase 1 (genetic risk) to phase 2 (asymptomatic auto-immunity).

There is also a cohort of individuals with arthralgia and positive ACPA and/or IgM–RF being followed up prospectively in The Netherlands. The authors demonstrated that the presence of ACPA but not IgM–RF predicted arthritis development [26]. After a median follow-up of 28 months, 29 out 147 patients developed arthritis with a hazard ratio (HR) of 6.0 (95%CI 1.8–19.8) compared to 1.4 (95%CI 0.6–3.1) for RF. In ACPA-positive patients, the risk of developing arthritis was further enhanced by the presence of RF and high ACPA levels. In a further study, patients with an extended ACPA repertoire were found to have a higher risk of developing arthritis, which is in line with the finding of the increasing number of recognised ACPA epitopes prior to the development of RA from blood-bank studies [27]. However, arthritis development was not associated with recognition of a specific citrullinated peptide in this cohort. Other interesting findings coming from the same cohort have been the identification of gene signatures relevant to the development of RA [28]. Signatures significantly associated with arthritis development were involved in interferon-mediated immunity, haematopoiesis and chemokine/cytokine activity. Genes involved in B-cell immunology were associated with protection against progression to arthritis. Ultrasonography has also been tested for predicting arthritis but has not had concluding results; hence, further research will be needed [29]. Although these findings are very interesting, testing for gene signature and ACPA repertoire is not readily available. To overcome this issue, van de Stadt et al. have developed a prediction rule for the development of arthritis using their cohort of patients with seropositive arthralgia, which included 374 patients at the time of the study [30]. A total of 131 patients (35%) developed arthritis after a median of 12 months. They developed a score ranging from 0 to 13 that can be calculated for each patient using nine variables: RA in an FDR, alcohol non-use, duration of symptoms <12 months, presence of intermittent symptoms, arthralgia in upper and lower extremities, visual analogue scale ≥50, presence of morning stiffness for ≥1 h, history of swollen joints as reported by the patient and antibody status. Patients can then be categorised in three risk groups: low (0–4 points), intermediate (5–6 points) and high risk (7–13 points). The intermediate group and high-risk group had, respectively, a HR of 4.53 (95%CI 2.42–8.77) and 14.86 (95%CI 8.40–28.32) compared to the low-risk group. This prediction rule could help select high-risk individuals for intervention studies, especially if combined with ACPA repertoire, gene signature and possibly cytokine/chemokine testing.

**Screening for IA/RA**

Although there are still significant challenges and lack of good rationale to routinely screen for preclinical RA, it is worthwhile to step up efforts to identify clinical IA as early as possible as early treatment leads to better outcomes. This type of screening can be done in different populations: 1) the general population that may have joint symptoms but have not yet sought medical help for it, 2) patients presenting to general practitioners (GPs) with joint pain and 3) patients being referred to rheumatologists for suspicion of arthritis.

**General population**

Arthralgia is very common in the general population and people may not always seek medical help as they consider their symptoms to be ‘normal’ aches and pains. However, a small proportion of them may already have RA or UA or could be nearing the end of the preclinical phase and at risk of developing arthritis.

A group of researchers have tried identifying these patients through a community health fair. People who had joint pain, family history of RA or were just curious about their health were invited to fill in a questionnaire and have RA-related autoantibody testing performed [31]. This was followed by joint examination by a trained professional (rheumatologist or nurse practitioner). A total of 601 subjects were screened; 84 (14%) had IA (at least one swollen joint) that had never been diagnosed, of whom nine (1.5%) had RA by the ACR 1987 RA criteria. As many as 41 subjects were positive for RF and/or anti-CCP and had no findings of IA: 27 were only RF-positive, 11 were only anti-CCP-positive and three were positive for both RF and anti-CCP. The diagnostic accuracy of the combination of the questionnaire and
autoantibody testing to identify IA yielded maximal sensitivity, specificity and PPV and negative predictive value of 95.3%, 99.2%, 71.4% and 97.7% respectively.

Other attempts at identifying IA in the general population include public awareness programmes, self-administered tests and Web-based questionnaires [32]. Unfortunately, most of the time either their effectiveness has not been assessed or they are too sensitive and lack specificity which means that numerous patients need clinical review. In a time when there is a lack of rheumatologists in many countries, these strategies are not helpful.

Patients presenting to GPs

People presenting with musculoskeletal complaints comprise 10–30% of visits to family physicians’ offices [33]. Although the majority of them will present with mechanical joint problems, a proportion will have a form of IA and need to be seen by a rheumatologist as early as possible in order to start treatment in a timely fashion. Hence, GPs must be able to identify patients with possible RA to then refer them. There can also be other health professionals such as physiotherapists who often encounter people with joint pain. Tools to help GPs and health professionals identify patients with arthritis include self-administered questionnaires that can be given to patients and a musculoskeletal (MSK) screening examination.

Patient self-administered questionnaires. Self-administered questionnaires to be handed by health professionals to patients presenting with MSK complaints to their office or filled in on the Web prior to the visit have been developed as a guide to detect IA [34–37]. Unfortunately, not many have been validated in this population. Maksymowych developed a Web-based screening tool for RA called the E-triage RA Study in Early Arthritis (ERASE) based on patients’ self-reported pattern of joint involvement, symptom duration and the absence of symptoms of fibromyalgia [35]. It was tested in 124 newly referred patients. Using logistic regression, the different items of the questionnaire were identified as being significantly positively or negatively associated with RA: self-reported distribution of joint involvement (odds ratio (OR) for metacarpophalangeal (MCP) joint = 1367, for wrist = 73), duration of symptoms (weeks/months vs. years, OR = 34) and presence of any two of jaw pain, irritable bowel syndrome, chronic fatigue, daily headaches grouped together as fibromyalgia symptoms (OR = 0.02). ERASE was further developed as a screening index based on a weighting of these items ((4 for any MCP involvement) + (2 for any wrist involvement) + (2 for duration weeks/months) + (3 for any two of four of fibromyalgia-related symptoms)). Receiver operating characteristic (ROC) analysis based on the ERASE scoring tool revealed an area under the curve (AUC) of 0.93 and a sensitivity of 95% and specificity of 76%, using a cut-off score of 2.5.

MSK screening examination. The Gait, Arms, Legs, and Spine (GALS) locomotor screening examination was developed to address the high prevalence and underdetection of MSK disorders [38]. This 3-min examination consists of three parts: three questions addressing pain, difficulty dressing and difficulty with stairs; assessment of gait; and a physical examination of the appearance and movement of the arms, legs and spine. Although the GALS was not developed specifically as a screening examination for RA, Beattie et al. have shown that it can be used by various health professionals (physiotherapists, nurse practitioners and GPs) to identify signs and symptoms consistent with IA [39,40]. Sensitivity and specificity for detecting RA varied from 50% to 100% and from 70% to 100%. Following a very short training period, family physicians, nurse practitioners and physiotherapists could use the GALS examination as a screening tool for RA; individuals with positive results will then benefit from further investigation or rheumatology referral.

Other potential tool. Singh et al. have developed a computer-based program that could predict the probability of an individual patient to have RA based on nine items (six symptom-related and three based on laboratory results) that the GP enters in the program [41]. It has yet to be tested to check whether it would improve identification of RA by GPs.

Although educational programmes including workshops, joint consultation with GPs and rheumatologists, teleclinics and educational material are not screening tools per se, they can improve awareness and knowledge of IA leading to improved ability to detect IA and quality of the referral process [32].
These tools can help GPs screen for RA in people with MSK complaints, but we need to remember that for screening to be of value, an intervention that will improve the disease course/prognosis must be made. In the case of early RA, the intervention is the initiation of treatment and this should probably be made by a rheumatologist. Indeed, a UK National Audit Office report and many studies have suggested that RA patients managed by rheumatologists achieve better outcomes with better cost-effectiveness [42–44]. Hence, whenever there is a suspicion of RA, using these tools or not, GPs should refer the patient to a rheumatologist as soon as possible.

**Patients referred to rheumatologists**

Once a patient has been identified as a potential case of IA by a primary care health professional, he needs to be seen by a rheumatologist to confirm the diagnosis and start treatment as soon as possible. However, many patients with other MSK conditions are also being referred to rheumatologists and, in an era where there is a shortage of rheumatologists in many countries, this leads delays before the initial visit. In order to ensure that patients with IA are being seen in a timely fashion, many rheumatology clinics will triage or screen their referrals. This is another group of patients where we need to screen for patients most likely to have RA.

**Triage of referrals.** Some rheumatologists have developed triage systems where they review information provided in the referral letter in order to make a broad presumptive diagnosis and assign a grade from A to C/D, where A is assigned to urgent cases including individuals with new IA, to be seen within 2–4 weeks. These systems were shown to help prioritise appointments for patients with IA and reduce unnecessary referrals. These grading systems are usually developed empirically and rely entirely on the rheumatologist’s attempt at a diagnosis which is largely dependent on the information provided in the referral letter [45,46]. In the study by Graydon et al., 35 cases (17%) were upgraded to urgent status after consultation, reflecting inappropriately triaged, truly urgent patients [46]. The absence of basic historical, examination and laboratory markers accounted for inappropriate triage of urgent cases. Another paper reported that reviewing patients’ records to help prioritise appointments was another effective form of triage [47]. However, this requires the patients’ records, which are not always easily available.

Unfortunately, triage is dependent on the quality of the referral letter, which often lacks important information. In their study, Jack et al. reported that just 17% of consults indicated symptom duration [48]. Only 2% mentioned any circadian rhythm of symptoms (such as morning stiffness) and only 6% provided information about functional status. Almost two-thirds (62%) of consults specified only ‘joint pain’ in the referral letter. In order to overcome this problem, many groups have designed referral forms.

**Referral forms.** The use of referral forms has helped standardise information provided and has improved triage [49,50]. Forms include various combinations of elements of history (duration of symptoms, joint distribution, morning stiffness duration, obvious swelling, benefit from non-steroidal anti-inflammatory drugs (NSAIDs) or steroids and functional impact), specific co-morbidities (psoriasis, irritable bowel disease (IBD), etc.) and family history, physical examination (distribution of joint swelling, MTP squeeze test), laboratory tests (RF, sedimentation rate, CRP, full blood count (FBC) and antinuclear antibody (ANA), etc.) and X-rays and some ask for an attempt at diagnosis. The use of referral forms ensures that all the information useful to assess the urgency of the referral is present and each patient can be seen within an appropriate time frame. Use of referral forms together with triage was shown to significantly increase the ability to detect urgent referrals [49] and reduce waiting time for appointments compared to triage alone [50].

Instead of a referral form, Bell et al. have developed an 11-item patient self-administered questionnaire which can help prioritise patients referred to the rheumatology clinic [34]. This questionnaire includes questions about symptoms of arthritis, functional ability, personal and family history of RA and a diagnosis of psoriasis. It was tested in 143 patients newly referred to two rheumatology outpatient clinics [51]. The best-fit model included younger age, male sex, ‘trouble making a fist’, ‘morning stiffness’, “ever told you have RA,” and ‘psoriasis diagnosis’. The refined tool had a mean predictive performance (standard error, SE) of 0.915 (0.002), a sensitivity of 0.855 (0.005) and a specificity of 0.873 (0.003). This questionnaire could potentially also be used by GPs to help them decide if a patient should be referred to a rheumatologist, but it has not yet been tested in this population.
Triage clinics. Triage can also be done by a trained individual (GP or another health professional) before an appointment with a rheumatologist. In one study, trained GPs and rheumatology nurses reached sensitivity, specificity and PPV and negative predictive value between 87% and 92% [52]. No data are available on improving time to diagnosis or initiation of treatment, which is the ultimate goal.

Screening referral letters to identify individuals most likely to have IA has been shown to improve the time for patients with IA/RA to be seen by the rheumatologist, especially when used in conjunction with referral forms or self-administered questionnaires. Triage clinics are also likely to help prioritise individuals who are more likely to benefit from early treatment and help to take advantage of the window of opportunity in early disease. It is of note that this process will only be effective if identified patients can be rapidly seen by rheumatologists, which is usually facilitated through rapid access services or EACs [32].

Early access clinics. Rapid or immediate access clinics have also been developed [53–55]. These clinics ensure that patients are seen within 1 or 2 days of being referred for a brief assessment prior to appointment scheduling or further recommendation. This is very similar to the triage clinic but is performed by rheumatologists. Other groups developed rapid access services where a member of staff is available at all times for telephonic discussion and where arrangements are made for patients who need to be seen or where urgent new referrals are seen in a designated twice-weekly session [56,57]. EACs where patients with one or two swollen joints, depending on the clinic's inclusion criteria, can be referred is another setting which enables rheumatologists to identify patients with RA as early as possible. It has been shown that patients with IA seen in EACs have a shorter symptom duration than patients seen in routine care [58].

What is the cost-effectiveness of screening?

The total cost of RA is substantial, especially in patients with high levels of disease activity and disability [59]. It includes both direct costs such as cost of health-care utilisation and drugs and indirect costs, including loss of productivity, premature mortality and burden for caregivers. The introduction of biological agents has significantly raised direct medical costs. Although they have improved disease outcomes and lowered RA-related use of health-care resources, their use in early disease has not been shown to be cost-effective compared to a treat-to-target approach using conventional DMARDs [60]. Although we could not find a study demonstrating the cost-effectiveness of early treatment, we can extrapolate that early treatment, at least with conventional DMARDs, is likely to be cost-effective as several studies have demonstrated disease severity and functional disability, both improved by early treatment, to be significant predictors of increased direct and indirect costs [59]. Screening patients presenting to their GPs and patients referred to a rheumatology department to identify patients with RA as early as possible can be assumed to be cost-effective as these patients have a disease that warrants treatment which we know to be most effective if started early.

However, community-wide screening for RA in the healthy population has not yet been proven to be a cost-effective or a time-effective way to identify patients with IA due to the low prevalence of RA. In the Deane et al. study, the cost of screening one individual was $42 for laboratory testing and paperwork, not including manpower to complete the screening process and follow-up contact [30]. Adding these costs, the screen cost goes up to $2000 per person of interest identified when defined as RA or individuals with one swollen joint and positive RF or anti-CCP and of 400$ if we also include patients synovitis but no autoantibodies or autoantibodies without clinical synovitis. Thus, the number needed to screen would have to be justifiable to prevent or halt a case of RA in a safe and cost-effective manner.

The cost-effectiveness of identifying individuals at risk of RA is far from certain. Following probands of RA is an option but as the majority of patients with RA do not have a family history of the disease, screening only these individuals will miss most RA cases. The other option currently available is to perform autoantibody testing in all patients with arthralgia. Cost-effectiveness evaluation of testing for ACPA in individuals with MSK complaints not believed to have RA by their GP to identify preclinical disease is currently underway in the UK (Paul Emery, personal communication). However, for this screening to be of value outside a research setting, we first need an intervention (which moreover should be safe and inexpensive) that would prevent individuals at high risk of RA to develop the
disease. In a small study, 83 patients with arthralgia and positive ACPA or IgM–RF were given one dose of 100 mg intramuscular (IM) dexamethasone or placebo at baseline and 6 weeks [61]. Although patients in the dexamethasone group had reductions of antibody levels at 1 month, arthritis development at 6 months was similar in both groups (20% vs. 21%). Therefore, before considering screening for people at risk of RA, we have yet to determine which intervention can effectively prevent disease development.

Summary

Screening for both preclinical RA and new-onset RA remains an area of research. Many advances have been made in terms of finding effective ways of screening for RA earlier, enabling more patients to have access to early DMARD therapy. In addition, findings that have identified cytokine/chemokine profiles that can predict the transition from preclinical to clinical disease may also have future clinical applications when very early interventions are found that are safe and cost-effective. Although further studies are needed, the day when scientists and clinicians will be able to effectively predict the development of RA does not seem far off. Better understanding of the events leading to the development of clinical RA can potentially also inform appropriate interventions and treatment strategies which, in turn, could prevent development of RA in high-risk individual. Thus, there is justification for screening persons with newly symptomatic RA and people at risk of RA.

Due to the improved outcomes with early treatment, the identification of patients with RA in their clinical phase is warranted. Various tools are available, which may help identify these individuals. Questionnaires and MSK screening examination can be used by GPs and other health professionals who may encounter patients presenting with arthralgia. In patients being referred to rheumatologists, the combined use of triage and referral forms as well as triage clinics can help identify individuals most likely to have RA and prioritise them so that diagnoses can be confirmed and treatment initiated as early as possible. However, management of individuals with UA remains a question as a substantial

Practice points

- Screening for people at risk of RA remains an area of research at the moment.
- As early treatment leads to better outcomes, patients’ general physicians should refer them to arthritis specialty care as soon as they have a suspicion of IA.
- Screening tools in the form of questionnaires as well as MSK screening examination are available to help health professionals in primary care identify patients with IA.
- The use of referral forms combined with triage or triage clinics are an effective means for rheumatologists to identify patients who are most likely to have IA and thus need to be seen as early as possible.

Research agenda

- Results from blood-bank studies of pre-RA serum have helped identified factors that could be used to identify RA at a preclinical stage, but prospective studies are needed to define which tests will be of most value in which populations.
- Intervention studies in the preclinical RA group are needed before we can determine the value of screening for preclinical RA in the general population.
- Although it is agreed that early treatment is more effective, the best initial treatment strategy for RA is still a question of debate and even more so for the management of UA that can have a variable course. Better predictive biomarkers and strategy trials are needed in this scenario.
proportion of them may remit spontaneously while others will progress to develop RA. Hopefully, the new ACR-EULAR criteria will overcome this problem as they were designed using initiation of methotrexate at 1 year as the gold standard.

Conflict of interest

The author declares no conflict of interest.

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