Early rheumatoid arthritis

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Background: This review outlines current knowledge of diagnosis, assessment, treatment and risk factors for early rheumatoid arthritis (RA).

Methods: Selective review of current literature was obtained by searching the terms ‘rheumatoid arthritis’ and ‘early’.

Results: Three issues dominate the current views on early RA. First, its recognition may be difficult. Many experts consider that early inflammatory arthritis should only be classified as RA after several months’ of observation. Secondly, there is emphasis on early intensive treatment with conventional disease-modifying drugs or biologics, especially tumour necrosis factor inhibitors. Thirdly, there is a debate on the risk factors with evidence of genetic risks and environmental factors like smoking that may trigger RA. Developing citrullinated proteins followed by anti-cyclic citrullinated peptide antibodies, specific for RA, appears to be a crucial pathogenetic step.

Discussion: Early RA needs immediate specialist assessment and review. Early intensive therapy is effective but needs to be focussed on patients mostly at risk of severe progressive disease.

Keywords: Rheumatoid arthritis/early assessment/disease-modifying drugs/biologics

Synopsis of established rheumatoid arthritis

The key issues in early rheumatoid arthritis (RA) need to be considered with the overall context of established RA. This disorder remains the commonest long-term inflammatory disease in the UK and other developed countries. It affects about 1% of adults, and has a marked female preponderance in the region of 3:1. RA lasts for many years and is characterized by joint inflammation, progressive joint destruction—mainly due to bone erosions—and increasing disability. A substantial minority of patients have systemic features. These include rheumatoid nodules and lung disease. There are also increased risks of coronary artery disease and infection. Severe RA shortens life expectancy.
Patients have symptoms of pain and stiffness, which is relieved by non-steroidal anti-inflammatory drugs and simple analgesics. They need access to a range of non-drug treatment modalities including education, psychological approaches, occupational therapy, exercise and physical treatment and, in late disease, joint replacement surgery.

Patients also need treatment with disease-modifying drugs (DMARDs). These improve symptoms and change the course of the disease by reducing erosive joint damage. The classic DMARD, injectable gold, was first used to treat RA in the 1930s; it is rarely given today. The main DMARDs widely used include sulfasalazine, leflunomide and methotrexate. In addition to conventional drugs, two other therapeutic classes improve symptoms and reduce or stop erosive progression. These are the biologics and corticosteroids. There is a debate on the extent to which biologics such as tumour necrosis factor (TNF) inhibitors and corticosteroids should be used owing to a combination of concerns about costs (with biologics) and adverse events (with corticosteroids). Within the UK only a minority of patients with RA receive either of these drugs, but there are marked variations between practices in different countries.

Methods

The search terms ‘rheumatoid arthritis’ and ‘early’ were used to identify relevant publications in Medline from January 1990 to March 2007. Key publications dealing with definition, assessment, treatment and risk factors were retrieved. Those publications considered crucial to the topic were included within the review; a full systematic search was not undertaken.

Defining early RA

What is early RA?

Historically, early RA was considered as less than 5 years disease, but by the early-1990s this had decreased to 24 months or less, with greater emphasis on the first 12 months.1 Currently, many rheumatologists wish to see patients with early RA at the first available opportunity. The proportion of rheumatologists who wish to see patients within 6 weeks from symptom onset doubled from 9% in the year 1997 to 17% in 2003,2 though not all patients were seen so rapidly.

Despite this emphasis on rapid referral there are often profound problems in recognizing early RA. The classification of RA is based on
criteria introduced in 1987—the American College of Rheumatology criteria.\(^3\) Unfortunately, these criteria do not perform well in early RA.\(^4\) This is hardly surprising as the criteria was developed using patients attending specialist RA clinics with average disease durations over 7 years and the comparison group had other established diagnoses like osteoarthritis and lupus. Like other criteria sets, the 1987 ACR criteria used ‘physician’s opinion’ as the gold standard. However, in early RA, physicians often cannot recognize it on clinical grounds alone. The extensive experience gained in the Norfolk Arthritis Register (NOAR) has been used to produce a modern synthesis about early arthritis,\(^5\) which is put forward in a review by Dixon and Symmons.\(^6\) They suggest that patients with early inflammatory arthritis should not be immediately classified and, only after they have been followed for some months or longer, it is possible to decide who has seropositive or seronegative RA or if they have other disorders. They suggested the ‘life cycle’ of RA falls into four phases. First, there is the period leading up to the onset of arthritis. Secondly, there is a period during which persistence or remission is determined. Thirdly, there is the evolution into a specific form of arthritis, and finally the outcome of arthritis. In some patients these phases follow in rapid succession but in others the course is prolonged over months or years. Rather than the concept of early RA they suggest that patients should be considered as having either established RA or an undifferentiated inflammatory arthritis. Their views are shown in Figure 1.

Most experts have experienced similar problems in defining early RA. For example, an evaluation of the first 1000 patients seen in the early arthritis clinic in Leiden found that at 2 weeks only 10% fulfilled the criteria for RA and about one-third of the patients presented with an undifferentiated arthritis.\(^7\) The overall assessment of several inception cohort studies suggests that about one-third of patients with such an undifferentiated arthritis develop RA while some remit

![Fig. 1 The onset of early RA (after Dixon and Symmons).\(^6\)](https://academic.oup.com/bmb/article-abstract/81-82/1/97/283483/823763)
spontaneously and the rest remain undifferentiated or develop other rheumatological diagnoses.

The importance of early RA

Although all patients need early assessment and early treatment, there are specific reasons for focusing on the need for prompt specialist involvement in early RA. The main rationale, which has been elegantly expressed by Emery over the years, is that inflammation in patients presenting with RA should be suppressed as early as possible. Leaving patients with early RA either undiagnosed or untreated increases the risk of persisting inflammation and progressive joint damage. At the same time, treating patients with mild early disease who are unlikely to progress is equally unhelpful; it exposes patients to risks without any definite benefits and represents the obverse side of early effective care. The reason for caution is that many patients with early arthritis enter a period of remission irrespective of whether or not they have been treated, and patients with mild disease are most likely to achieve spontaneous remission.

Remission

As a substantial proportion of patients with early arthritis enter remission, it is important to consider exactly what this constitutes. As with the diagnosis of early RA, the definition of remission is contentious. Many experts use the criteria of the American Rheumatism Association. These involve patients having less than 15 min morning stiffness, no fatigue, no joint pain, no joint tenderness motion, no soft tissue swelling in joints or tendon sheaths and a low erythrocyte sedimentation rate (ESR) (<30 mm/h for men and <20 mm/h for women). A variety of less-stringent definitions of low-disease activity states have also been used to define remission in early RA. A compounding problem is that remission can occur by itself, in which case it is often termed ‘natural remission’; or it can be due to effective treatment with drugs, when it is, in essence, a state of persisting low-disease activity.

Although about one-third of patients with early, undifferentiated arthritis experience natural remission, the rate is lower in patients with early RA. Most studies suggest that about 10% of early RA patients enter a natural remission. For example, a US study by Wolfe found 14% of 458 RA followed-up for over 1000 patient years achieved remission without being treated, and a Dutch study by Prevoo et al. found 10% of 227 RA patients followed-up for 4 years...
achieved remission. It is important to interject a note of caution about
treatment and remission as mild early arthritis, especially if the diagno-
sis of RA is uncertain, will often end in remission and it is important
not to over-treat mild cases that would have entered remission without
the need for drug therapy.

Assessing early RA

Disease activity

Persisting disease activity is an important consequence of early RA and
is closely linked to symptoms such as pain. Initially, assessments of
disease activity in RA have focused on separate measurements of rel-
vant variables including symptoms such as the duration of early
morning stiffness, the number of swollen and tender joints and
measures of the acute-phase response such as the ESR.

However, composite measures are now often used to give an overall
assessment of disease activity. The most commonly used composite
measure is the Disease Activity Score (DAS). Calculating DAS requires
an assessment of four specific variables—tender joints, swollen joints,
visual analogue score for patient global assessment and ESR. These are
entered into a relatively complex calculation that gives a score between
1 and 10. The commonly used DAS-28 specifically assesses 28 joints
(shoulders, elbows, wrists, hands and knees). Using DAS-28, a score of
\( \geq 5.1 \) indicates high disease activity, a score of \( \leq 3.2 \) indicates low
disease activity and a score of \( \leq 2.6 \) indicates that the patient is in
remission. DAS-28 calculators are available, together with a detailed
description of the DAS from Professor van Riel.\(^{13}\)

One Dutch observational study by Welsing \textit{et al.}\(^{14}\) showed that after
improvement in the early months of treatment, DAS scores remain
stable over the ensuing course of RA. The mean initial DAS was 3.6,
and this fell to around 3.0 by 6–9 months and remained at this level
subsequently. A similar pattern was found in an Austrian early RA regist-
ry, in which DAS scores fell from an initial mean of 5.5 to a mean of
3.2.\(^{15}\) Studies examining changes in single disease activity measures,
such as articular indices or acute-phase response measures, show a
similar picture. Initially, active disease is suppressed by treatment but
does not enter remission. For example, a report of 684 patients from the
UK by Wiles \textit{et al.}\(^{16}\) showed that an initial average swollen joint count
of 6 fell to 2 after 12 months and thereafter remained at this level.

When patients are seen very early in the course of their disease, there
are potentially greater improvements in DAS scores. A small group
of patients with very early RA from Austria,\(^{17}\) who were seen within
3 months and received disease-modifying drugs as needed, showed
DAS improved by 2.8 when compared with an improvement in DAS of
1.7 in patients seen within 12 months who received similar treatment.

Joint damage

Patients with early RA show erosive joint damage, which can be
assessed using conventional X-rays or modern imaging methods such
as magnetic resonance imaging (MRI) or ultrasound. Almost 30 years
ago Brook and Corbett\textsuperscript{18} summarized radiological changes in 94
patients with early RA followed for 5 years. X-ray damage appeared
early and involved 73\% of patients. Erosive changes preceded joint-
space loss and were particularly marked in the feet. Since then many
groups have reported the frequency of erosive changes in early RA
patients followed for up to 12 years of disease. On average, 44\% of
patients have erosions at the beginning of these observational studies.
After an average of 4 years of follow-up, the mean percentage of
patients having erosions has increased to 63\% with considerable vari-
ation between studies.\textsuperscript{19} For example, Machold \textit{et al.}\textsuperscript{20} reported find-
ings in 108 patients with very early arthritis seen within 3 months of
their first symptoms and found that 13\% had erosions at their first
assessment; after 2 years of follow-up this had increased to 28\%.
In contrast, the largest UK study, the Early Rheumatoid Arthritis Study
(ERAS), reported experience in an inception cohort of 866 RA patients.
They found that initially 32\% had erosive damage and 3 years later
this had increased to 70\% of cases receiving conventional treatment.\textsuperscript{21}

X-ray erosions remain the key structural outcome measure in early
RA and their use is recommended by an Expert Committee of
European rheumatologists following detailed review of all the available
evidence.\textsuperscript{22} MRI and ultrasonography are promising techniques that
may become valuable in monitoring early RA. There are many enthu-
siasts who promote their use,\textsuperscript{23} though the balance of expert opinion is
that they are still experimental and findings can be controversial, and
their merits in routine clinical practice have yet to be defined.

Disability and quality of life

Both disease-specific measures like the Health Assessment
Questionnaire (HAQ) and generic measures like the SF-36 can be used
to assess the impact of RA on disability and quality of life. HAQ is the
most widely studied assessment. It measures disability over eight
domains including walking and everyday household tasks. Disability
increases with disease duration with an average annual increase of 1–2% in patients followed prospectively, though there is a rather different pattern in early RA. Results from many observational studies including the Norfolk Arthritis Register and a Swedish observational cohort, both show examples of a ‘J-shaped’ curve, which means an initial fall in HAQ scores is followed by an increase over the ensuing years.

There is less information about generic measures in early RA such as SF-36 scores, which assess quality of life across several domains, including pain and function. Unlike most measures, in which high scores represent poor function, SF-36 has an inverse scoring system and high scores represent good quality of life and vice versa. SF-36 scores show broadly similar patterns to HAQ scores. This is shown in a study by West and Jonsson who reported SF-36 scores in patients with early RA followed for 2 years. Initially patients showed lower (worse) values for all eight subscales of the SF-36 when compared with controls. After 2 years patients reported improvements in many subscales including pain and physical function.

**Developing concepts about treating early RA**

**General treatment options**

Patients need to have symptoms of pain and stiffness relieved by NSAIDs and simple analgesics. They also need to access a range of non-drug treatment modalities such as education, psychological approaches, occupational therapy, exercise and physical treatment and, in late disease, joint replacement surgery.

**Disease modification**

Many patients also need to be treated with DMARDs. These improve symptoms and also change the course of the disease, which implies that they reduce erosive joint damage. The first and most classical DMARD was injectable gold. This drug was first used to treat RA in the 1930s. It is not often used today. There are several other conventional drugs that are classified as DMARDs. These include sulphasalazine, leflunomide and methotrexate, which are the most widely used DMARDs.

In addition to conventional drugs, two other therapeutic classes can be classified as DMARDs, because they reduce symptoms and reduce or stop erosive progression. These are biologics and corticosteroids.
Currently, the dominant biologics used for RA are anti-cytokine agents directed against TNF. Some biologics target IL-1 and IL-6 and others target T and B cell surface molecules. The first biologics to be introduced into clinical practice were TNF-inhibitors. Three TNF-inhibitors are available—infliximab, etanercept and adalimumab. Anakinra, which is an IL-1 receptor antagonist, is available but is less commonly used. New biologics that will soon be available include tocilizumab, an anti-IL-6 antibody; abatacept, a fusion protein that interferes with T cell activation; and rituximab, which targets B cells.

Corticosteroids, though previously given in high doses in RA, are now used only in low-dose treatment schedules, with the exception of a rapidly reducing treatment plan used in some studies.

**Early treatment**

The conventional conservative approach starting cautiously with NSAIDs and only giving DMARDs when these have been shown to fail entirely is unsatisfactory. With such a conservative approach many patients will have progressive disease. The early use of DMARDs, given as sequential monotherapy, is more effective at least in the short term.

Observational studies are one way to evaluate the benefits of early DMARDs. The Norfolk Arthritis Register, a large observational study in early arthritis from one area of England, evaluated DMARD therapy in 353 consecutive RA patients followed for 5 years. As patients with mild arthritis inevitably have good outcomes without DMARDs the results required careful analysis. However, after adjusting for baseline severity, early DMARD therapy in severe RA gave the most beneficial outcomes at 5 years.

Randomized controlled trials support the observational findings. For example, one study showed early treatment with sulphasalazine-reduced disease activity and X-ray progression over 12 months when compared with persisting NSAIDs alone.

The situation is more complex. Verstappen et al. reported 5-year follow-up results from an earlier trial involving 238 patients with recently diagnosed RA. Some patients had received anti-inflammatory drugs only for at least 12 months and waited an average of 14 months before starting DMARDs. Most patients received early DMARDs. Five-year results in 44 patients given delayed treatment with DMARDs and 145 patients given early DMARDs showed no prolonged clinical advantages from early DMARDs. In the first 12 months there had been many advantages from early DMARDs; most clinical variables showed...
better responses. However, the benefits of early DMARDs became less obvious with time.

As a consequence of these concerns rheumatologists have embraced the concept of early aggressive therapy more than the DMARD monotherapy. Given the sensitivity of patients towards the concept of being treated ‘aggressively’, a more rational term for such an approach is ‘intensive’ treatment. Some experts talk of ‘a window of opportunity’ in early RA.

**Which patients need early intensive treatment?**

Many patients with RA get worse over time and fail to respond to DMARD monotherapy. However, a substantial minority respond well and may even enter prolonged remission with or without a short period of DMARD treatment, as outlined in the section on remission. These good responses are more likely in patients with mild early disease, in particular patients who are seronegative on testing for rheumatoid factor and have no erosive changes on X-rays.

Rheumatoid factor has been studied for over 50 years and it is well known as a predictor of severe disease. More recent interest has focused on anti-cyclic citrullinated peptide antibodies (anti-CCP), which are a relatively new entrant in the assessment of RA. Antibodies to citrullinated peptides have been known to precede the development of RA by several years and anti-citrulline immunity has increasingly been suggested to be causatively involved in the development of RA. There is growing evidence that anti-CCP is predictive of more severe early RA and may indicate the need for early treatment.

Identifying those patients with severe disease who are most likely to progress unless treated early and intensively remains an inexact art. As well as rheumatoid factor and anti-CCP there is good evidence about the importance of disease activity measures, including joint counts and the ESR and other acute-phase measures together with early erosive disease, and there is even a prediction model available based on the work in the Netherlands. Other groups have taken a more long-term view, particularly the Early Rheumatoid Arthritis Study group, and they have shown that over 5 years high initial HAQ scores are indicative of poor long-term functional outcomes. In simple terms if patients have over four to six swollen joints or more, a similar number of tender joints, an ESR of 30 mm/h or higher and have any evidence of erosive damage in their hands and feet they are likely to merit intensive treatment. High HAQ scores, especially over 1.5 is also indicative of the need for intensive treatment. Despite the persisting interest in prediction it remains difficult to accurately define prognosis; and
additional analysis of data from the Netherlands suggests that the majority of patients with early arthritis (54%) cannot be classified as to whether or not they have severe disease.\textsuperscript{33}

**New treatment approaches in early RA**

**Combining steroids with DMARDs**

It has been known for 50 years that high-dose oral steroids rapidly improve synovitis and reduce radiological progression. However, this approach gives excessive toxicity. Low-dose steroids have less effect on symptoms, but they reduce erosive damage and have little toxicity. The first trial to examine this in detail\textsuperscript{34} gave strong evidence that 7.5 mg of daily oral prednisolone with DMARD monotherapy reduced erosive damage over 2 years. Subsequent research showed that the effects of steroids were independent from taking DMARDs.\textsuperscript{35} Other groups have confirmed the benefits of low-dose steroids combined with DMARDs in reducing erosive damage in early RA.\textsuperscript{36}

An alternative approach was devised by Boers and his Dutch collaborators.\textsuperscript{37} They combined methotrexate with sulphasalazine and gave oral prednisolone in an initial high dose of 60 mg daily that was tapered rapidly in a ‘step-down’ manner to 7.5 mg daily—the so-called COBRA regimen. In comparison with DMARD monotherapy this triple therapy approach improved symptoms and reduced erosive damage to 12 months. Its benefits persisted for over 5 years.\textsuperscript{38}

**DMARD combinations**

Initial trials of combination DMARDs used combinations that were either too toxic, such as injectable gold and hydroxychloroquine, or had limited efficacy, such as methotrexate–azathioprine. None of the initial combinations had favourable effective/toxicity ratios.\textsuperscript{39} Subsequent research, using less toxic and more effective combinations like methotrexate–sulfasalazine–hydroxychloroquine gave better results, and a recent systematic review of 41 randomized trials of high quality concluded that they had benefits, although they also increased toxicity.\textsuperscript{40}

The best way to use combinations of DMARDs in early RA may be as part of a treatment strategy. A study from Finland compared combination therapy (sulphasalazine, methotrexate, hydroxychloroquine and prednisolone) with single DMARDs that were given with or without prednisolone.\textsuperscript{41} It showed that over 2 years, combination therapy was
better and not more hazardous than single treatment. For example, after 2 years 37% of patients receiving combination therapy had entered remission; in contrast, only 18% of patients receiving DMARD monotherapy had entered remission.

Another study from Scotland, evaluated the benefit of what was termed tight control in early RA. Intensive management centred on triple therapy with methotrexate, sulfasalazine and hydroxychloroquine together with low-dose steroids. Compared with routine care, this study showed patients treated intensively were more likely to have a good response or be in remission; 65% of intensively treated patients entered remission when compared with 16% treated routinely. The effect on intensive therapy on the DAS is shown in Figure 2. Radiographic progression and physical function were also reduced by tight control at no additional cost.

**Early biologicals**

Although giving etanercept monotherapy in early RA is effective, it is no improvement over methotrexate monotherapy in terms of its effect on clinical features of joint inflammation; both treatments show similar efficacy. Both treatments reduce symptoms of joint inflammation to a similar extent. Although etanercept is slightly more effective in reducing radiological progression this is a minimal advantage.

Four trials subsequently studied the effects of combinations of these biologics in patients with early RA comparing methotrexate–TNF inhibitor combinations with methotrexate monotherapy. They were all large studies and between them they enrolled nearly 4000 patients. All showed better clinical and radiological outcomes with methotrexate–TNF-inhibitor combinations. The number of patients who showed an

![Fig. 2 Changes in DAS with intensive conventional treatment in early RA (from the TICORA trial).](image-url)
improvement of 50% across a range of seven clinical and laboratory variables was 38% with methotrexate monotherapy when compared with 60% with TNF-inhibitor combination therapy. The effects of biologics on disease activity in early RA are shown in Table 1. More impressive was their rapid effects on radiological progression. Although some patients did progress with combination therapy, the median rate of progression in these studies in patients receiving combination treatment was zero.

**Table 1** Responses in trials of TNF-inhibitors for early RA

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>Months</th>
<th>Randomized Cases</th>
<th>Receiving Key Treatments</th>
<th>Percent ACR-20 Responders</th>
<th>Percent ACR-50 Responders</th>
<th>Percent ACR-70 Responders</th>
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<tr>
<td>Bathon41</td>
<td>2000</td>
<td>Etanercept</td>
<td>12</td>
<td>217</td>
<td>DMARD mono 207 Anti-TNF mono –</td>
<td>59</td>
<td>39</td>
<td>20</td>
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<tr>
<td>St Claire42</td>
<td>2004</td>
<td>Infliximab</td>
<td>12</td>
<td>282</td>
<td>Anti-TNF mono – 359</td>
<td>54</td>
<td>32</td>
<td>21</td>
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<tr>
<td>Klareskog43</td>
<td>2004</td>
<td>Etanercept</td>
<td>12</td>
<td>228</td>
<td>Anti-TNF/MTX – 223</td>
<td>75</td>
<td>43</td>
<td>19</td>
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<tr>
<td>Goekoop-Ruiterman44</td>
<td>2005</td>
<td>Infliximab</td>
<td>12</td>
<td>508</td>
<td>Anti-TNF/MTX – 128</td>
<td>65</td>
<td>48</td>
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<td>2006</td>
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<td>24</td>
<td>799</td>
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ACR, American College of Rheumatology; ACR-20/50/70 responders show ≥20, 50 or 70% improvement, respectively, in ACR core set of seven clinical and laboratory measures.

Conventional or biological combinations

Only one study has directly compared conventional combinations with biologic combinations. This is aptly named as BeSt trial.44 This study compared four different treatment strategies in 508 RA patients with...
early disease. These strategies comprised sequential DMARD monotherapy, step-up combination DMARD therapy, initial combination therapy with tapered high-dose prednisone (the COBRA regimen) and initial combination therapy with a TNF-inhibitor (infliximab). The study showed that initial combination therapy including either prednisone (in the COBRA regimen) or infliximab gave earlier functional improvement and less radiographic damage after 12 months of either sequential monotherapy or step-up combination therapy. The percentage of patients showing 20% overall improvements were similar with both intensive DMARD therapy (the COBRA regimen) and methotrexate–TNF-inhibitors; both improved 79% of patients. However, TNF-inhibitors resulted in 40% of patients achieved 70% improvements and 81% entering a period of remission, while with combination DMARDs, only 28% achieved 70% improvements and 73% entered a period of remission. While TNF-inhibitors combined with methotrexate appear better with the most stringent measures like remission, the impact of one type of intensive treatment is almost the same as another.

New concepts of autoimmunity in early RA

Smoking and citrullation

Klareskog et al.⁴⁸ have highlighted the complex relationship between smoking and RA. Although the cause of RA is unknown, there is growing information about the factors that can trigger its onset. One of these is cigarette smoking. It has been known for some years that smoking is a risk factor for the development of RA.⁴⁹ Smoking is associated with more joint destruction, particularly the development of erosive disease, and extra-articular features such as vasculitis. Anti-CCP antibodies (see above) indicate more aggressive early RA.

Fig. 3 The relationship of smoking to anti-CCP and genetic risks on the chance of developing RA (after Klareskog et al.).⁴⁶
The relationship of smoking to antibodies and genetic risks in the development of RA is shown in Figure 3.

Citrullination means changing one of the widely distributed amino acids arginine to a slightly different compound citrulline. The conversion of arginine to citrulline is controlled by an enzyme called peptidylarginine deiminase, often shortened to its acronym, PAD. This enzyme is hormonally controlled. Although the change is a minor chemical modification, it results in a change in the charge of the protein containing arginine. The process of citrullination is an early step in the process of cell death, and is crucial to remodelling normal and inflamed tissues.

Klareskog et al. showed that cells from the bronchoalveolar lavage fluid of ‘healthy’ smokers contained cells expressing citrulline. But fluids from non-smokers did not have citrulline-containing cells. They also found many smokers with lung inflammation had citrulline-positive cells in their bronchoalveolar lavage fluids and there were far more of these cells in smokers with lung disease. In essence, smoking is an environmental exposure that causes citrullination of cells.

Citrullination is important because the most specific immunological test for RA is the presence of anti-citrulline antibodies, in what is now called the anti-cyclic citrullinated peptide, usually called by its acronym anti-CCP, which predicts more severe disease. By showing that an association between smoking, citrullination of proteins and a key immunological feature of RA—anti-CCP antibodies, this work helps us understand the development of the disease.

This research returns the investigation of early RA towards the earlier interest in infective triggers. Chest infections with smoking and possibly oral infections too, could be potent triggers for the disease in genetically predisposed individuals. It is possible that RA has several causes, one of which is infection and the development of anti-CCP antibodies. Cigarette smoking is therefore an indirect trigger of RA. As RA is far more frequent in females, any increase in cigarette smoking among young women should be a cause of great concern and may result in an increase in the frequency and severity of RA in later life.

Anti-CCP testing

Should this test be used in routine clinical practice? Most clinicians are familiar with measuring rheumatoid factor and it would be unhelpful to stop doing so. But measuring anti-CCP in arthritis, especially early arthritis, is becoming routine in many centres. It is invariably an additional test over and above rheumatoid factor measures. It is more specific for RA and when positive is a better indicator of severe
disease. It seems likely that over the next decade its use will gradually spread. Given the enormous medical and social costs of RA it seems foolish not to measure another antibody in the early stages of the disease if this gives more prognostic information.

**Stopping smoking**

The dangers of smoking are well known, though often overlooked. Most clinicians emphasize the importance to patients of stopping smoking. The relationship of smoking with RA represents yet another reason of not to smoke. When patients develop RA there is every reason for them to be persuaded to stop. Indeed, it could be argued that clinicians should routinely refer their patients with RA to programmes set-up to stop smoking. It is intriguing that the rise of RA in the 20th century may have been in part attributable to the rise in cigarette smoking and also of interest that a public health measure—stopping smoking—of general value may also be helpful in preventing RA.

**Conclusions**

Despite many recent advances, early RA is difficult to recognize, its cause remains unknown and it can be complex trying to decide whether or not a patient merits intensive treatment with several DMARDs or with biologics. At present, it seems sensible to focus on trying to rapidly identify patients with the most severe early RA, particularly patients who are seropositive for rheumatoid factor and have early erosive damage, and given them intensive treatment. There is some evidence, albeit incomplete, that combination therapy using TNF-inhibitors is most effective. However, its high cost and uncertain long-term risks may dissuade some experts from using it. A key uncertain question when and in whom these high-cost new treatments should be started.

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