EARLY ARTHRITIS: DIAGNOSIS AND MANAGEMENT

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LEARNING OUTCOMES

At the end of the module participants should be able to:

- Discuss the term Early Arthritis and its significance
- Describe and evaluate the diagnostic measures used in the diagnosis of Early Arthritis (clinical, radiological & laboratory)
- Describe and discuss the prognostic factors in Early Arthritis
- List, outline and evaluate the treatment modalities (pharmacological and non-pharmacological) available for the management of Early Arthritis
- Discuss the aims of treatment and the outcome measures used to evaluate the treatment of the disease

I INTRODUCTION

Amongst the chronic inflammatory joint diseases, rheumatoid arthritis (RA) is the most common and most serious. Untreated it results in joint destruction, functional impairment and increased mortality[1], predominantly due to accelerated cardiovascular disease [2]. The outcome of the disease, however, has improved considerably in recent years with the availability of effective therapies and the recognition that early aggressive treatment strategies result in better outcomes[3-7].

In practice, patients with inflammatory arthritis should be seen early and treated appropriately at the earliest opportunity. Clinicians need to differentiate between the early features of RA (or an inflammatory arthritis that has the potential to become progressive and/or destructive), from diseases that may present with similar clinical features, e.g. systemic lupus erythematosus (SLE) or the spondarthropathies, and from those that will remit spontaneously. Decisions with regards optimal therapeutic strategies are also imperative. The goal of treatment is early suppression of inflammation and establishing remission[8] in order to prevent joint damage, disability, and the long-term complications of the disease.

This module will provide some background and an approach to the diagnosis and treatment of EARLY ARTHRITIS.
II BACKGROUND

II-1 The Clinical Rationale For Early Management [9]

Spontaneous remission in true RA is rare. Although definitions vary, remission implies a low disease activity state that if sustained is neither damaging nor disabling. In a cohort of 458 patient with RA followed up for 1131 patient years, 14% achieved remission without treatment [10]. In another study of 183 RA patients with a follow-up of 5 years, a remission rate of 20% was described; 11% were in spontaneous remission and 9% was drug-induced[11]. In the majority of patients, untreated, persistent inflammation results in joint damage, functional decline and premature mortality.

There is evidence that radiographic damage, loss of bone mineral density[12] and loss of function [13] occur early in the disease process. Radiological outcome studies have shown that 70% of patients with recent onset RA develop bony erosions within the first 3 years [14]. Furthermore, within 3 months of disease onset 25% of patients have erosions evident on X-ray[15]. Early erosions also predict the future development of severe radiographic lesions. Other newer imaging techniques such as magnetic resonance imaging (MRI) and ultrasound (US) have confirmed evidence of damage within weeks on onset of symptoms [16, 17]. Moreover these lesions correlate reliably with later radiographic erosions [18].

A delay in treatment is associated with poorer outcomes. In a meta-analysis of 12 studies with 1133 RA patients, disease duration less than 2 years, an average delay of 9 months in starting DMARDs significantly increased subsequent radiographic progression [19].

II-2 How Early Is Early?

The concept of a ‘window-of-opportunity’ [20, 21] suggests that there is a timeframe early in the course of the disease where there may be a disproportionate response to therapy . Rather than just a quantitative improvement, early treatment may have a qualitative effect and alter the longterm disease process. Previously, studies used a cut-off of less than 5 years to define early disease, however, by the 1990s, symptom duration of less than 12 to 24 months was considered early. This duration was chosen because at the end of this period, most patients have incurred significant damage when treated conventionally. It is now recognised that this period may be limited to weeks or months.
There is increasing evidence that very early RA, i.e. within the first 12 weeks, may be an immunopathologically distinct phase compared to later disease[22]. Therapy during this period may have different effects than treatment at a later stage. Studies have tested this very early window of opportunity. An unblinded study of a single dose of corticosteroid in 63 patients with mild early inflammatory arthritis (median duration 20 weeks) found the strongest predictor of disease remission at 6 months was disease duration less than 12 weeks at time of therapy[23]. Clinical and radiological outcomes were significantly better at 3 years among a cohort of 20 patients who started DMARD therapy 3 months after disease onset (very early) compared to 20 with a median 12 months disease at treatment start (early)[15]. Remission was achieved in 50% in the very early group compared to only 15% in the early group. Importantly, the major differences between the two groups occurred within the first year and especially during the first 3 months of treatment. This suggests that treatment in very early arthritis may have a greater effect on disease progression.

Evidence for the disease process also exists in the preclinical stage i.e. before the onset of symptoms. Rheumatoid factor (RF) [24] and anti-cyclic citrullinated peptide (anti-CCP) antibodies [25, 26] have been detected in patients with rheumatoid arthritis (RA) years before the onset of symptoms. Elevated levels of highly sensitive C-reactive protein (CRP) have also been shown before onset of clinical disease [27]. Complementary to the serologic changes, imaging with ultrasound and MRI, and arthroscopy detect synovitis in clinically normal joints of patients with early RA [28].

II-3 The Challenges Of Early Disease

The first few weeks or months of symptoms, therefore, represent a potentially important therapeutic window in patients with very early synovitis destined to develop RA. However, treating patients within this phase presents several challenges:

1. Assessing patients with inflammatory arthritis early
2. Predicting which patients with early synovitis will develop RA and thus require treatment
3. Determining how such patients should be treated

As there is no single diagnostic test, a combination of clinical features and laboratory tests are used to make the diagnosis RA. The American College of Rheumatology classification criteria are often used to define RA [29]. However, as they were developed in populations with long-standing definite disease, they do not perform as well for the diagnosis of recent-onset RA[30]. In a recent systematic analysis of literature published between 1988 and December 2006, the sensitivity and specificity of the 1987 American College of Rheumatology (ACR) criteria to predict RA in unclassified early arthritis was found to be 67% and 75% respectively[31].
Due to the poor sensitivity early in the disease course, patients with RA may not fulfil the classification criteria and may therefore be misdiagnosed. The relatively low specificity means that other conditions such as postviral arthropathies, early spondyloarthritis, and other self-limiting arthritides that may satisfy the ACR criteria.

Moreover, as rheumatologists continue to see patients earlier in the course of disease, it has also become clear that a sizable proportion of patients who present with an inflammatory arthritis, may have an undifferentiated arthritis (UA) [32] – a form of arthritis that does not fulfil the classification criteria for a more definitive diagnosis. The outcome of these patients varies and the diagnosis may change in the first years of follow-up. Some patients will progress to RA, and some to other rheumatic diseases such as spondyloarthropathy. Others will remain undifferentiated or enter into remission. Estimates from studies reporting outcomes for UA vary widely: 13 % to 60% of patients with UA have been documented to experience remission, 7 to 65 % evolving into RA or another definable disease and 10% to 40% having persistent disease activity, but remaining undifferentiated [33]. The disparities may be explained by the differences in inclusion criteria and the definitions used for UA and RA. Using more stringent criteria, in cohorts that required arthritis to be present at inclusion and RA defined by the ACR criteria, the proportion of patients that developed RA within one year has been documented to range from 17% to 32% [34].

The key issue facing clinicians seeing patients with UA or early arthritis, therefore, is the prognosis of early arthritis. Differentiating patients with ‘self-limiting disease’ from those at risk of developing ‘persistent inflammatory non-destructive’ or ‘persistent inflammatory and erosive arthritis’[35] will allow the initiation of appropriate therapeutic measures for those that will progress and prevent unnecessary treatment for those that will resolve.
III AN APPROACH TO EARLY ARTHRITIS

There is currently no single best way to manage patients with early arthritis. Rather, the use of the following principles may guide management strategies:

- Early recognition and treatment of patients with persistent erosive arthritis result in better longterm clinical outcomes.
- Furthermore, regular monitoring of disease activity and treating to target, aiming for remission, improves outcomes.

The following steps have been suggested as an approach to for the evaluation and treatment of patients with early arthritis [36]:

- Recognise the presence of inflammatory arthritis.
- Exclude diseases other than RA or UA that present with an inflammatory arthritis (e.g. systemic lupus erythematosus (SLE), psoriatic arthritis or a spondyloarthropathy).
- Estimate the risk of developing persistent or erosive irreversible arthritis in patients with RA or UA. This remains a challenge; however a combination of clinical features, laboratory tests and imaging techniques may help to predict the outcome of arthritis with acceptable accuracy.
- Institute therapy and monitor disease activity, escalating treatment as required in order to achieve a favourable outcome.

The clinical evaluation remains the cornerstone for evaluating early arthritis; determining whether arthritis is present or not, differentiating between inflammatory or non-inflammatory disease and deciding aetiology of the arthropathy. Articular symptoms may be the presenting manifestation of many infectious, inflammatory or malignant conditions. The clinical feature may also provide clues to identify those at risk of developing persistent erosive disease (see table 1).

A thorough history should be documented, detailing the distribution of the symptomatic joints, duration of symptoms and early morning stiffness, response to non-steroidal anti-inflammatories, any prodromal illness and associated symptoms. Family, personal and past medical histories including smoking history should also be noted. A comprehensive examination of all systems should be performed.

Laboratory investigations and imaging are ancillary measures for the diagnosis and prognosis of patients presenting with early arthritis and should be tailored to the individual. It is important, to be aware of their limitations when interpreting the results (e.g. avoid false reassurance that pathology is absent when test results are normal). Imaging techniques are potentially helpful in this setting.
IV IDENTIFICATION OF INFLAMMATORY JOINT DISEASE

The clinical finding of joint swelling not caused by trauma or bony swelling should suggest a diagnosis of early arthritis, especially if it includes involvement of at least two joints and/or early morning stiffness lasting 30 minutes or more. Hand or foot involvement is common in inflammatory arthropathies and is suggested by a positive metacarpophalangeal (MCP) or metatarsophalangeal (MTP) ‘squeeze test’.

Figure 2: Metacarpophalangeal squeeze test

All new patients with symptoms of an inflammatory arthritis should be referred to a rheumatologist during the early more treatable phase of the disease. As a proportion of patients that will develop severe persistent inflammatory arthritis will have normal/ negative results at disease onset, this should be done regardless of blood test results or radiographic findings. It has been suggested that tests done in primary care may be counterproductive, delaying referral whilst waiting for results. The referral should ideally be within 6 weeks of symptom onset [36].

V IDENTIFICATION OF A DEFINITIVE CAUSE OF AN INFLAMMATORY ARTHROPATHY

V-1 Clinical Features

Whilst joint symptoms predominate early in RA, extra-articular manifestations of RA (nodules, keratoconjunctivitis sicca etc.) are seldom present early in disease. In other forms of polyarthritis, extra-articular manifestations maybe present early and may precede the onset of synovitis, providing clinical clues to the diagnosis. This is particularly true with systemic lupus erythematosus (malar rash, serositis), reactive arthritis (urethritis, conjunctivitis), psoriatic arthritis (psoriasis, nail pitting) and sarcoidosis (lung involvement, fever)[37]. See table 1.
Figure 3: Malar rash in a patient with systemic lupus erythematosus

![Malar rash](image1.png)

Figure 4: Psoriatic plaques

![Psoriatic plaques](image2.png)

V-2 Investigations

Most cases of suspected inflammatory arthritis will warrant a complete blood count, inflammatory markers, basic serology including RF, anti-CCP antibodies and antinuclear antibodies, renal and liver function tests and a urine analysis.

More specific tests may be directed by the clinical presentation including tests for uric acid, cultures where infection may be suspected, serology for atypical infections e.g. Lyme disease, virology e.g. hepatitis B, C or parvovirus, serum angiotensin-converting enzyme, specific autoantibodies and genetic markers. In cases of suspected crystal arthropathy or infection, an aspirate of a joint effusion will be of value in making a definitive diagnosis. Findings on X-rays may further assist in making the diagnosis of a specific arthropathy e.g. the presence of cartilage calcification in calcium pyrophosphate dihydrate deposition disease (CPPD).
**Figure 5:** Calcification of the triangular fibrocartilage of the wrist in calcium pyrophosphate dihydrate deposition disease
# Table 1: Differentiating diseases that present as an early arthritis

<table>
<thead>
<tr>
<th>Arthritis</th>
<th>Personal history</th>
<th>Typical pattern of joint involvement</th>
<th>Joints affected</th>
<th>Associated Features</th>
<th>Laboratory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated Arthritis (nonprogressive)</td>
<td>F&gt;M</td>
<td>Insidious Oligoarthritis</td>
<td>PIP, MCP, wrist, MTP, knee, ankle</td>
<td></td>
<td>↑CRP/ESR</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>F&gt;M; 35-50 years</td>
<td>Insidious, progressive symmetrical</td>
<td>PIP, MCP, wrist, MTP, knee, ankle</td>
<td>EMS</td>
<td>↑CRP/ESR, RF+, CCP+</td>
</tr>
<tr>
<td>Spondyloarthropathy</td>
<td></td>
<td>Persistent, asymmetric oligoarticular</td>
<td>DIP, PIP, knee, feet, spine</td>
<td>Psoriasis</td>
<td>CRP may be normal More severe course in HLA B27 +</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>F &gt; M, young</td>
<td>Polymarticular, symmetric, usually nonerosive</td>
<td>PIP, knee</td>
<td>Rash, serositis</td>
<td>ESR, CRP, proteinuria, ANA+, dsDNA+</td>
</tr>
<tr>
<td>Viral (HBV, HCV)</td>
<td>Hepatitis risk factors</td>
<td>Acute polyarthiritis</td>
<td>PIP, MCP, wrist, knee, ankles</td>
<td>Jaundice</td>
<td>↑ESR/CRP, ↑ LFTs Hepatitis B and C serology</td>
</tr>
<tr>
<td>Septic Arthritis (nongonococcal)</td>
<td>Peak incidence in elderly Reduced host immunity Joint prostheses</td>
<td>Acute Monarticular Often extremely painful (Beware may be polyarticular)</td>
<td>Knee – most common Hip, shoulder, ankle, wrist</td>
<td>Systemic symptoms common</td>
<td>Commonest cause Staphylococcus aureus Synovial fluid is gram stain positive in 50% and culture positive in 90%</td>
</tr>
<tr>
<td>Gonococcal</td>
<td>F &gt; M, young, sexually active</td>
<td>Acute oligo- or polyarthritis</td>
<td>Wrist, knee</td>
<td>Fever Rash Skin blisters/pustules, Tenosynovitis</td>
<td>↑ESR/CRP, ↑WBC Synovial fluid gram stain positive in 25% and culture positive in 50% of cases</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>F &gt; M, Men with knee or hip involvement ↑ age</td>
<td>Progressive oligo- or polyarticular asymmetric or symmetric, bony swelling</td>
<td>DIP, PIP, first CMC1, knee, hip, MTP, spine</td>
<td>Normal laboratory tests</td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td>Men, Postmenopausal women, Diuretic use (especially in elderly)</td>
<td>Sudden onset, severe pain with attacks oligoarticular early, polyarticular later</td>
<td>MTP, toes, ankle, knees</td>
<td>Tophi</td>
<td>Synovial fluid – urate crystals ↑ uric acid level – (normal levels in 40% of acute attacks)</td>
</tr>
<tr>
<td>Pseudogout</td>
<td>M=F, ↑ age</td>
<td>Chronic Oligo- or polyarticular Acute monarticular (25%)</td>
<td>Knee, wrist, finger, MTP</td>
<td>Associated conditions include: Hypomagnesaemia Hypophosphataemia Haemochromatosis Wilson’s disease Hyperparathyroidism</td>
<td>↑CRP, ↑WBC</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>M = F, older Caucasian</td>
<td>Prolonged morning stiffness</td>
<td>Hip and shoulder girdle PIP, wrist, knee occasionally</td>
<td>RS3PE</td>
<td>Anaemia, ↑ESR/CRP</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>F&gt;M</td>
<td>Acute symmetrical Chronic uncomon</td>
<td>Knees, ankles</td>
<td>Fever, Erythema nodosum &amp; hilar lymphadenopathy with acute sarcoid</td>
<td>↑ESR/CRP, Serum ACE</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>F&gt;M</td>
<td>Acute or occasionally insidious symmetric or asymmetric</td>
<td>MCP, PIP Tendon friction rubs (diffuse disease)</td>
<td></td>
<td>↑CRP/ESR ANA +, ScI-70+, ACA+</td>
</tr>
</tbody>
</table>

RA, rheumatoid arthritis; UA, undifferentiated arthritis; F, female; M, male; PIP, proximal interphalangeal joint; MCP, metacarpophalangeal joint; CMC1, first carpometacarpal joint; MTP, metatarsophalangeal joint; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; HBV, hepatitis B virus; HCV, hepatitis C virus, WBC, white blood cells; ANA, antinuclear antibody; ACA, anticitrulline antibody; LFT, liver function test; IBD, inflammatory bowel disease
VI PREDICTION OF OUTCOME OF UNDIFFERENTIATED AND EARLY RHEUMATOID ARTHRITIS

After other diseases are excluded and a diagnosis of probable RA or UA is made, the third step is to determine which patients are at risk of developing persistent and/or erosive arthritis. This prognostic assessment is important for guiding optimum treatment strategies. Predictors of persistence and disease progression include demographic, genetic, clinical, serological and radiological factors.

VI-1 Assessment of Disease Persistence

The frequent spontaneous remission of synovitis in patients with early arthritis (especially those with symptoms of less than 3 months duration) means that a therapeutic approach which targets all patients with very early synovitis will needlessly expose many patients to potentially toxic therapies. The ability to distinguish resolving disease from synovitis that persists and develops into RA is thus essential. Female gender, cigarette smoking, duration of symptoms, the tender and swollen joint count, hand involvement, the level of acute phase response, presence of RF and anti-CCP antibodies, and the fulfilment of 1987 ACR diagnostic criteria for RA are factors associated with disease persistence. See table 2.

An alternative approach is to look at patients more likely to enter spontaneous early remission. Seronegativity for rheumatoid factor (RF) and fewer active joints at baseline in early RA have been cited as markers of a favourable outcome[11]. Other studies have shown a relationship with male gender and absence of erosions with remission rates [10].

<table>
<thead>
<tr>
<th>Table 2: Candidate predictors of disease persistence in early arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Female gender</td>
</tr>
<tr>
<td>• Duration of symptoms (more than 12 weeks)</td>
</tr>
<tr>
<td>• High tender and swollen joint count</td>
</tr>
<tr>
<td>• Hand involvement</td>
</tr>
<tr>
<td>• Cigarette smoking</td>
</tr>
<tr>
<td>• Acute phase response</td>
</tr>
<tr>
<td>• Rheumatoid factor</td>
</tr>
<tr>
<td>• Anti-CCP antibodies</td>
</tr>
<tr>
<td>• Fulfilment of 1987 ACR diagnostic criteria for RA (sensitivity 88%; specificity 73%)</td>
</tr>
</tbody>
</table>
VI-2 Assessment of Disease Severity

In clinical practice, treatment of early RA is often commenced and increased according to the disease activity. An alternative approach would be to initiate the most appropriate treatment based on prognostic stratification, differentiating between those with a more benign disease from those at risk of developing severe erosive disease who would benefit from more aggressive, and more expensive, treatment early on to prevent severe outcomes.

Many of the factors predicting disease persistence are also markers of disease severity. Joint damage and functional disability are the two most common outcome measures of disease severity. The most reliable prognostic factors of radiological damage are a high acute phase response, the presence and titre of RF and anti-CCP antibodies at baseline, the HLA-DRB1*0401 allele subtype, and early erosions or radiological score at disease onset. Factors that have been found to predict future disability include a baseline HAQ score, Ritchie index, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and presence (or absence) of erosions [38]. Female gender, older age, the number of damaged joints, RF positivity and the presence of nodules (although usually a later finding in RA) at baseline are other documented factors [39]. See table 3.

<table>
<thead>
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<tbody>
<tr>
<td>• Female gender b</td>
</tr>
<tr>
<td>• High tender b and swollen joint a count</td>
</tr>
<tr>
<td>• HAQ score b</td>
</tr>
<tr>
<td>• Acute phase reactants a,b</td>
</tr>
<tr>
<td>• Rheumatoid factor a</td>
</tr>
<tr>
<td>• Anti-CCP antibodies a</td>
</tr>
<tr>
<td>• Shared Epitope a</td>
</tr>
<tr>
<td>• Erosive disease a, b</td>
</tr>
</tbody>
</table>

a  Predictors of joint damage
b  Predictors of functional disability
VI-3 Individual Factors Predicting Persistence and Disease Severity

VI-3-1 Disease duration

Several studies have shown symptom duration at first visit to be a good predictor of disease persistence[40, 41]. In a study by Green et al 63 patients with mild untreated early inflammatory arthritis were given a single dose of corticosteroids at presentation. At 6 months 49 patients (78%) had persistent inflammatory joint disease and 14 (22%) had clinical disease remission. The strongest predictor of persistence was disease duration of 12 weeks[23]. With disease less than 12 weeks, the chance of remission was increased five-fold. The 1987 ACR classification criteria for RA were found to be less helpful in predicting persistence in those with shorter disease duration: of those fulfilling the ACR criteria presentation, 53% with disease duration of less than 12 weeks had persistent disease 6 months later compared to 94% who presented with symptoms greater than 12 weeks.

A further study examined the use of a similar protocol of intra-articular corticosteroid injections in patients with early oligoarthritis (i.e. four or less joints) followed by an early review to assess for the presence of persistent synovitis[42]. At least 50% of patients with oligoarthritis had complete response at 2 weeks and the best predictor of response at 12 and 26 weeks was the presence or absence of synovitis on examination at 2 weeks follow-up. Failure to respond by 2 weeks indicated a high likelihood of persistent disease and the need for DMARD therapy.

VI-3-2 Early morning stiffness

Early morning stiffness (EMS) is an early symptom of an inflammatory arthritis. It is a complex symptom and may be difficult to interpret and to discriminate from pain and functional limitation. Despite this, it remains a useful clinical marker of disease persistence. [43],[44].

VI-3-3 Joint involvement

In a cohort of 121 patients with early arthritis followed up for a median duration of 5 years, those with polyarticular disease and hand involvement were more likely to have persistent disease [41]. These findings have been confirmed by several other studies [45, 46].

Persistent joint inflammation leads to joint destruction; a high joint count is also a marker of disease severity. The number of swollen joints probably correlates better with radiographic progression than the number of tender joints.
VI-3-4 Functional disability

Functional disability as measured by the Stanford Health Assessment Questionnaire disability index (HAQ) is one of the most reliable predictor of disease outcomes in early arthritis [47]. A high baseline HAQ is an important risk factor for the development of future functional disability and predictive of both all-cause and cardiovascular mortality in patients with early disease. Analysis from a primary care-based inception cohort of patients with recent-onset polyarthritis has found the 1 year HAQ score to be a better predictor of subsequent outcome than the baseline HAQ score[48].

The baseline HAQ score has also been shown to be the best predictive factor of quality of life and work disability[49] in patients with early RA.

VI-3-5 The acute phase response

A rise in the level of acute-phase reactants such as the ESR and CRP provide surrogate measures of inflammation.

Highly sensitive CRP (hs-CRP) assays may be used to identify mild disease activity that is not detectable by routine CRP testing [50]. Hs-CRP is also superior to ESR in predicting disease activity and disease severity.

Both elevated ESR and CRP levels, especially if sustained, have also been shown to be predictive of long term radiographic progression[36]. In a study of 130 patients with early RA (median disease duration 3 months), logistic regression analysis of baseline variables revealed that a high CRP level (≥ 20mg/l) was an independent predictor of radiographic severe progressive joint damage at 1 year (odds ratio, 3.59; 95% CI 1.53, 8.39)[51]. CRP levels at presentation have also been found to be an independent predictor of functional ability assessed by the Health Assessment Questionnaire (HAQ).

VI-3-6 Rheumatoid Factor

RF is perhaps the most consistent prognostic marker in early inflammatory arthritis as a predictor of disease persistence and progression with radiological damage in patients with inflammatory arthritis. In a large series of UA patients, a stepwise logistic model was used to determine factors predisposing to development of RA, Wolfe et al found that RF was the best predictor of persistence[52]. The 1987 ACR criteria for RA and disease duration were other significant factors.
In a study of 65 patients where factors predicting persistent or self-limiting symmetrical polyarthritis were analysed, RF positivity emerged as the strongest variable, with a positive predictive value of 85%. Combining this with an erythrocyte sedimentation rate (ESR) of > 30 mm/hour carried a relative risk for persistent synovitis of 4.33[40].

RF positivity is also a strong predictor of radiographic progression [53, 54]. The association between RF and functional disability is less consistent. In a review, RF positivity or more specifically a high RF titre was found to be a predictor of disability in some studies, but in others this association was not significant [38, 55].

VI-3-7 Anti-cyclic citrullinated peptide antibodies

Research into autoantibodies in sera of RA patients distinct from RF led to the discovery of antiperinuclear factor the 1960s and anti-keratin antibodies in the 1970s. Subsequent studies showed that these antibodies recognized a similar antigen, citrulline. This non-standard amino acid is generated by the post-translational modification of arginine residues by the enzyme peptidylarginine deiminase (PAD).

Anti-CCP antibodies are present early in the disease course and can precede onset of symptoms by up to 10 years, particularly in the 2 years prior to symptom onset [26, 56]. In a study by van Gaalen et al, 93% of patients with early UA who were anti-CCP positive at baseline were diagnosed with RA at 3 years. Conversely, only 25% anti-CCP negative patients had a diagnosis of RA at followup [57].

Studies of patients with less than 6 months of joint symptoms, have shown that anti-CCP antibodies have a similar sensitivity to RF, ranging from 39% to 63%, but a much greater specificity, of 93% to 98%, for distinguishing RA from other inflammatory disease in patients with early undifferentiated arthritis [58] These antibodies may be of particular value in detecting the seronegative group of patients with RA. However, because of their relatively low sensitivities, relying on this autoantibody tests alone will miss a proportion of patients who will develop the disease.

The presence of anti-CCP antibodies is an independent predictor of radiological damage and progression[59] The titre of anti-CCP antibodies is also related to disease severity[60].
VI-3-8 Genetic markers

Genetic factors are the ideal prognostic markers because they are present at disease onset and unchanged by treatment. The shared epitope (SE), a group of HLA-DRB1 alleles that share a similar amino acid sequence, is strongly associated with RA. Several studies have shown a correlation between SE and disease persistence [23, 61]. This was found to be a particularly useful marker among patients who were seronegative for RF [23]. Others, however, have found the presence of SE of less value as an independent predictor of disease persistence [39, 44] but rather of disease severity once the diagnosis of RA is made [39, 62].

Among the different HLA-DRB1 alleles examined, HLA-DRB1*401 and DRB1*0404 are consistently associated with radiographic erosions in different ethnic groups. This association appears to be dose dependant since patients with two RA-associated alleles (DRB1*04 or DRB1*01) have more radiographic erosions and more joint replacement than patients with non-disease associated-alleles [63]. Studies have shown that individuals who were homozygous for HLA-DRB1*0404 were 4 times more likely to develop erosions than those who were SE negative[61, 64]. (Further discussion on the association with the SE and smoking and the development of anti-CCP antibodies can be found in the module on the pathogenesis of RA).

In recent years, the association between PTPN22, a negative regulator of T-cell activation, and RA has been described by several groups[65, 66]. This is the first non-HLA (human leucocyte antigen) genetic variation consistently associated with the susceptibility to a number of autoimmune diseases including RA The abnormality is a missense single nucleotide polymorphism (SNP) in this haematopoietic-specific protein tyrosine phosphatase gene. In a study examining sera of blood donors pre-RA, a strong association was documented between the PTPN22 1858T variant and the future development of RA [67].

Several other genetic polymorphisms have been studied in patients with early RA. Amongst theses are the 150V IL4[68] single-nucleotide polymorphism and the TNFA-308[69] polymorphism which have been shown to be markers for early radiographic bone erosions. Since these genes encode for cytokines, these studies suggest that functional alterations in cytokine regulation are involved in the disease pathogenesis and may have an effect on disease persistence and damage.
VI-3-9 Smoking

Smoking is a well established risk factor for the development of RA[70, 71] The risk increases proportionally with the number of pack years. There is also a strong association between smoking and the development of rheumatoid nodules in early seropositive rheumatoid arthritis[72].

Recent studies have gained insights into the potential role of smoking in the pathogenesis of RA . Smoking increases the risk for the development of anti-CCP antibodies. In the presence of shared epitope alleles, this risk is further increased – up to 20 times as compared to shared epitope negative non-smokers[73, 74] It is possible that, smoking, in a genetically predisposed individual, induces apoptosis and protein-citrullination, followed by an anti-citrulline specific immune response.

The outcomes of studies on effect of smoking on disease severity, however, vary. Several studies have demonstrated significant associations between radiographic joint damage and smoking[75, 76]., Others, however, including a large observational study of 2004 RA patients[77], have found no effect of overall current or past smoking [78, 79], suggesting that smoking may be more important in the initiation of RA than in the perpetuation of the erosive disease process. A suggested explanation for the differences in results is the differences in study design. (Those that showed a positive correlation were cross sectional analyses. As these types of studies are unable to establish the temporality of events, they cannot make causal inferences.)

VI-3-10 Imaging

Conventional radiographs

X-rays remain the conventional imaging modality in many centres. Radiographic erosions have a high specificity in discriminating between self-limiting and persistent arthritis[43] and changes seen within the first year of disease are strong predictors of disease progression. Radiographic examination should include the assessment of the hands and feet as erosions often start in the feet and in approximately 14-18% of cases are only detected in the feet [80].
Figure 6: Conventional radiograph of the foot showing erosions of the fifth metatarsal head.

Radiographic damage at baseline also represents the best predictive factor of poor structural outcome. Irrespective of the scoring systems (e.g. Larsen or Sharp scores) used, the initial radiographic score consistently predicts future radiographic damage[51].

Joint erosions and joint space narrowing seen on X-rays, however, are generally late findings. Newer imaging modalities have shown to provide additional diagnostic and prognostic information at an earlier stage.

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) can assess all structures of the inflamed joint. It is more sensitive than clinical examination and radiography for the detection of synovitis and erosions in early rheumatoid arthritis. There is also evidence that MRI findings (for example, synovitis, bone oedema, and bone erosions) may predict subsequent radiographic progression. However, changes resembling mild synovitis or small bone erosions are occasionally found in the joints of healthy subjects, raising the question about the specificity of the technique. Issues of standardisation and reliability of MRI have been addressed and are ongoing. Other disadvantages of MRI are high costs, long examination times and low availability.
Ultrasound

Ultrasonography and power Doppler is also useful for detecting synovitis of the small joints of the hands and feet with greater sensitivity than clinical examination. It is also more sensitive for visualising synovitis and bone erosions in the finger joints than conventional X-rays. Considering the early and frequent involvement of these joints, evaluation by US may be of major importance in the diagnosis of early arthritis. The advantages of US are that it is relatively inexpensive, non-invasive and allows many joints to be assessed at any one time. The main disadvantage is its dependency on the skills of the operator and potential problems with reproducibility.

Figure 7: Rheumatoid arthritis.

Second metacarpophalangeal joint. A. Conventional radiography shows iuxta-articular osteoporosis. B. Sonographic examination, in the longitudinal dorsal scan, reveals proliferative synovitis with marked intra-articular power Doppler signal. m = metacarpal bone; p = proximal phalanx; t = extensor tendon

Further discussion on the use of MRI and US in early arthritis can be found in in-depth discussion 1.
VI-3-11 Hand bone densitometry

With newer therapies for RA, the rates of erosion progression are less therefore more sensitive measures are required to assess treatment outcomes. In RA, bone loss, particularly in the hands, takes place early in the disease process. Measuring hand bone loss may therefore be useful for diagnosis and as a marker of disease activity. Dual energy x-ray absorptiometry (DEXA) measures bone density with high precision, making it sensitive enough to detect even small changes in bone mass. Studies in RA assessing bone mineral density (BMD) have shown a good correlation between BMD loss in the spine [12] and hand[81] with disease activity. In a study comparing the role of hand DEXA and radiography in 58 patients with early RA (mean disease duration 8.5 months), DEXA was found to be a more sensitive tool than radiology for measuring disease related bone damage. 50% of patients demonstrated significant loss of hand BMD after 24 weeks compared to only 22% showing radiographic deterioration as measured by the modified Sharp score at 48 weeks[82].

VI-3-12 Histology

Studies using arthroscopy have confirmed imaging findings of subclinical synovitis examining asymptomatic joints of newly diagnosed RA[83]. Distinct macroscopic vascular patterns have been seen in early RA and psoriatic arthritis [84]. Comparison of histopathological features of synovial tissue in early RA and non RA synovitis has shown subtle differences in histological features, cytokine and protease expression patterns, and apoptosis. An analysis of synovial biopsies of 95 patients with early arthritis showed that the higher scores for the number of CD38+ plasma cells and CD 22+ B cells in RA were the best discriminating markers comparing RA to non-RA patients. The number of CD68+ macrophages in the synovial tissue of patients with RA was also increased [85]. Thus far, however, the clinical value of the histopathological characteristics of synovial tissue in early arthritis is yet to be proven [86].

Figure 8: Arthroscopy showing Rheumatoid synovitis. Hypertrophic, rounded, polypoid-like villi with an opaque, ill-defined background due to congestion and oedema.
VI-4 Predictors of Persistence and Disease Severity: Practical Points

In practice, the clinical features and investigations listed in tables 2 and 3 may be used to identify patients with early inflammatory arthritis who are at risk of a persistent and more severe disease course. Conventional radiography is the mainstay imaging modality although the use of US, MRI (see issue 1) and DEXA are coming to the fore. At present, non HLA genetic markers and histology remain more research based tools rather than investigations for day to day patient care.

VI-5 Predictive Models for the Progression of Early Arthritis

In general, a combination of predictive factors has been found to be superior to single variables in predicting those who will develop a persistent erosive arthritis. Several reports have developed prediction models with a combination of the most reliable markers. Although they hold promise, many still require validation using larger cohorts. Further discussion can be found in-depth discussion II.

VII TREATMENT [36, 87]

Patients with early arthritis will require a combination of pharmacological and non-pharmacological therapy. The first principle of pharmacological therapy for early arthritis is that of early intervention with effective / appropriate treatment. The second is one of ‘tight control’ of disease activity. In practice, tight control for RA means that therapy is increased if disease activity is not suppressed below a predefined level (ideally remission). A suggested algorithm for the management of early arthritis is shown in figure 9.

Figure 9: AN ALGORITHM FOR THE MANAGEMENT OF EARLY INFLAMMATORY ARTHRITIS

![Algorithm Diagram]
VII-1 Nonpharmacological Treatment and Lifestyle Measures

As discussed earlier in this review, lifestyle factors, such as smoking, increase the risk of developing RA. These factors impact on the progression of the disease and lead to an increase in the associated pain and functional limitations of RA [88]. The reduction or cessation of smoking is therefore advised. Ensuring an appropriate body weight by following a healthy diet and maintaining physical activity can also influence pain in RA.

Several non-pharmaceutical interventions—such as dynamic exercises, occupational therapy, and hydrotherapy—have shown beneficial symptom relieving effects in established RA. These are recommended as adjuncts to pharmaceutical interventions in patients with early arthritis.

VII-2 Patient Education

As part of the management of any chronic disease, patients should be provided with information concerning the disease and its treatment. Education programmes may be used as adjunctive measures, aimed at coping with pain and disability and the maintenance of work ability. In general interventions have only shown short term benefits. Specific objectives in early arthritis are still to be developed[36].

Patients with an inflammatory arthritis who do not meet criteria for a specific diagnosis and do not have poor prognostic factors are much more likely to do well. Approximately fifty percent of unclassified cases, often those with fewer joints involved, less symmetry, and more lower-extremity disease, have been found to be in remission at follow-up. Although patients may feel disappointed when a specific diagnosis is lacking, they may be reassured of a better outcome [41].

VII-3 Pharmacological Treatment

VII-3-1 Symptomatic treatment

Simple analgesics may be required for pain management. These are often employed in combination with other therapies to control the inflammatory process.

There is substantial evidence in established RA that both classical and COX-2 selective, non-steroidal anti-inflammatory drugs (NSAIDS) are more effective than simple analgesics in relieving the signs and symptoms of active disease. These observations have been extrapolated to early arthritis with the recommendations that NSAIDS be considered in symptomatic patients after evaluation of gastrointestinal, renal, and cardiovascular status[36]. (Further discussion may be found in the module on the Treatment of Rheumatoid Arthritis.)
VII-3-2 Glucocorticoids

An approach for patients who present with very early inflammatory arthritis (less than 12 weeks of symptoms) may be to give a single dose of corticosteroid to provide rapid improvement symptoms and demonstrate the reversibility of disease[23]. Results of an open study of 100 patients with undifferentiated arthritis suggest that a single dose of intramuscular or intra-articular steroids may induce remission [89]. Two ongoing European placebo-controlled randomised trials (STIVEA and SAVE) are comparing the effects of low dose intramuscular depomedrone in patients with very early synovitis. The STIVEA trial is assessing the effects of 240mg of depomedrone given over 3 weeks to patients with synovitis of less than 10 weeks duration. In the SAVE trial the effect of 120mg depomedrone is being assessed in patients with synovitis of less than 16 weeks. The aim is to assess whether the early use of steroid can induce remission and the results are still awaited. It has been noted that these studies target a broad range of patients, a large proportion of whom may have a self-limiting disease.

In established RA, several randomised controlled trials and systematic reviews[90] have shown that systemic low dose glucocorticoids, typically prednisone ≤ 10mg/day, were effective in relieving short term signs and symptoms in patients. Despite controversial data [91, 92], several studies have shown that glucocorticoids – either alone or in combination with other DMARD therapy – are effective in slowing radiographic progression in early and established RA[3, 4, 93, 94]. Their effect on functional outcome is still to be established.

Patients on glucocorticoid therapy should be monitoring for potential side effects - including hypertension, diabetes, cataracts, and osteoporosis – and where advocated, preventative measures instituted.

VII-3-3 Disease modifying antirheumatic drugs (DMARDs)

Patients at risk of developing persistent and/or erosive arthritis should be start treatment with DMARDs as early as possible even if they do not yet fulfil established classification criteria for inflammatory rheumatologic diseases.

There is strong evidence that patients with recent onset polyarthritis who receive earlier DMARD treatment have better outcomes with regards to radiographic progression, function, and ability to work than those in whom DMARD treatment is delayed by a few months [15].Disease duration at the time of DMARD initiation was shown to be the main predictor of response to treatment in the meta-analysis of 14 RCTs by Anderson et al.
The best response was seen in those with less than 1 year of symptoms at commencement of therapy [95]. Another recent meta-analysis of 12 studies examined the effect of early DMARD therapy on the long-term radiographic progression in patients with early RA (less than 2 years at presentation). Six were open-label extensions of randomised control trials (RCTs) in which placebo patients later started DMARD therapy and 6 were observational cohort studies. The average delay between early and late therapy was 9 months. After a median of 3 years of observation, those patients who received early treatment had 33% less radiologic progression compared to those with delayed treatment [96].

DMARDs have an effect on the disease process within weeks to months. Methotrexate, sulphasalazine, and leflunomide [97] are commonly used DMARDs which have been shown to improve clinical outcomes and delay radiological progression. Less commonly used agents include azathiaprine, gold and cyclosporine. (Details of these drugs can be found in the module on the treatment of RA). Among the DMARDs, methotrexate (MTX) is considered the anchor drug and is generally used first in patients at risk of developing persistent disease or erosive disease because of its relatively beneficial safety profile [98], clinical and radiological efficacy [99], and its beneficial properties in treatment combinations with biologic agents [5, 6, 100]. Leflunomide and sulphasalazine have similar clinical efficacy and are considered best alternatives.

Despite early treatment, substantial structural damage may still occur in some early RA patients treated with DMARDs alone [54]. In a cohort of very early RA patients with symptom duration of less than 3 months, 64% developed erosive disease by 3 years.

In the PROMPT study, the first double-blind RCT addressing early DMARD therapy in patients with UA before the stage of fulfilling ACR criteria for RA, 110 patients were randomised to treatment with methotrexate or placebo for 12 months. Outcomes at 30 months showed that MTX delayed but did not prevent the progression to RA [101]. Most benefit was seen in the subgroup of patients (22%) that were anti-CCP antibody positive.

**VII-3-4 Combination DMARD therapy [102]**

Another therapeutic strategy in the treatment of RA is the early use of combination therapy with conventional DMARDs or biologic agents. Most of the evidence is based on studies of patients with early or established RA and has been extrapolated to the management of early arthritis.
Several studies have addressed the issue of whether initial combination therapy of early RA confers benefit over more conservative strategies. In the COBRA trial, a combination of Methotrexate (7.5mg weekly), sulphasalazine (2g/day) and prednisolone (starting with 60mg/day and tapering over 6 months) resulted in long-term effects on radiographic progression, compared with sulphasalazine monotherapy in 155 patients with RA of duration under 2 years [3, 103]. These results were consistent with those from the FIN–RACo study, in which 197 patients with onset of RA within 2 years were randomly assigned to receive either four-drug regimen, with methotrexate, sulphasalazine, hydroxychloroquine, and prednisolone (maximum doses: 1mg/week, 2g/day, 300mg/week and 10mg/day) or a single DMARD[4, 104, 105] for 2 years. After 18 months, a greater proportion of the combination group were less likely to have radiographic progression, and the work disability rate was lower compared with patients on monotherapy. In neither study was there an arm with DMARD monotherapy plus steroids. Although in the latter study, steroid was permitted in the single treatment group, this was introduced later, at up to 93 weeks from baseline.

Benefits of the more aggressive approach over ‘conservative’ treatment have been demonstrated by other studies[106]. However, studies comparing sulphasalazine/ methotrexate combination versus single agents [107, 108] were unable to identify better outcomes for any treatment arm over the other. An explanation for the differences in study finding may relate to the choice of DMARDs used. Sulphasalazine and methotrexate have similar characteristics in terms of time of onset of treatment effects as well as efficacy in established RA. Moreover, recent data have indicated that the combination of sulphasalazine and methotrexate should yield little benefit because of their biologic interactions [109].

Taken together, a benefit not only of early but also of aggressive treatment in patients with arthritis of short duration, at least for the clinical course, seems achievable particularly when highly active DMARDs (methotrexate, sulphasalazine or possibly leflunomide) are combined with steroids. However, unequivocal benefit of combination therapy with conventional DMARDs is yet to be demonstrated. In most of the trials using aggressive approaches to initial treatment of arthritis, patients – including those treated with DMARD (and steroid) regimens - deteriorated with respect to radiological scores. Only the COBRA [3] and FinRACo [104] trials reported radiographic benefits in the more aggressive treatment groups.
VII-3-5 Biologic therapy

An alternative approach to treating patients with early arthritis is to target the subgroup of patients with very early synovitis who are at high risk of developing RA with potent anti-inflammatory therapy. Tumor necrosis factor alpha (TNF-α) is a cytokine that is central to the inflammatory cascade. It has pleiotropic effects driving the immune response, with powerful modulatory effects on many aspect of cellular and humoral immunity and has an important role in persistence of early RA [110].

In a placebo controlled study, Quinn et al [6] demonstrated that early RA patients with poor prognostic factors treated with infliximab and MTX developed less erosions at 12 months than patients treated with MTX alone. The benefits obtained in patients treated with infliximab after 1 year was sustained at 2 years without further infliximab infusion.

The concept that intensive interventions early in the course of persistent arthritis may improve clinical activity and profoundly affect long term radiographic progression is supported by several recent RCTs with TNF blockers in early rheumatoid arthritis. In patients with a disease duration of less than three years, the use of a TNF blocking drug (adalimumab, etanercept, or infliximab) – especially in combination with methotrexate – revealed an increased rate of clinical remission and slowing of radiographic progression compared with methotrexate monotherapy[6, 100, 111, 112]. In addition, at least for infliximab, it has been demonstrated that, even in cases in which clinical activity was not optimally suppressed (‘poor response’), radiographic progression appeared to be significantly retarded in comparison with methotrexate [113].

The BeSt study, a multi-centre single blinded trial of 508 RA patients with less than 2 years of symptoms, compared four treatment strategies including a sequential monotherapy (group1), step-up combination therapy (group2), a triple step-down strategy with methotrexate, sulphasalazine, and high dose prednisone(group3), and infliximab plus methotrexate(group4) [7]. Treatment was adjusted at 3 monthly intervals with a goal of achieving a DAS44 of 2.4 or less. The two groups with initial intensive treatment (groups 3 and 4) showed a more rapid clinical response and a better radiographic outcome than groups 1 and 2. Progression of joint damage remained better suppressed in groups 3 and 4 (median Sharp-van der Heijde scores of 2.0, 2.0, 1.0 and 1.0 in groups 1, 2, 3 and 4 respectively (p=0.004)). In addition, less treatment adjustments were required in groups 3 and 4 to achieve suppression of disease activity and, after 2 years of treatment approximately 50% of patients in group 4 were able to stop treatment with infliximab and maintain remission. No significant differences in toxicity were noted between the groups.
TNF-blocking agents, therefore, provide rapid control of inflammation and have proven efficacy both in terms of clinical outcomes and structural damage in early disease. They are, however, substantially more expensive than traditional DMARDs, limiting their widespread use in early disease. Selecting patients with poor prognostic factors may improve this cost-benefit balance[114].

VII-4 Treatment Strategies: Practical Points

- Nonpharmacological and lifestyle measures form part of the treatment strategy. Of these, reduction or cessation of smoking is a known factor that could and prevent the development of early RA and decrease the risk of cardiovascular complications of the disease and should therefore be strongly encouraged.
- Early institution of effective therapy is the cornerstone of treatment for early arthritis. Delaying treatment may be considered (if at all) only in those with very mild disease less than 3 months from onset. A single dose of intramuscular steroid therapy may be advocated in this group. Arthritis that is persistent for more than 12 weeks is unlikely to spontaneously resolve [89]: many of these patients will progress to develop RA. If ACR criteria are fulfilled after this period they are unlikely to remit.
- Disease modifying therapy should be commenced in all early arthritis patients in whom the disease is likely to develop into a destructive arthritis classifiable as RA. The biologic agents, in particular TNF blockers, have been shown to confer additional benefits.
- Regarding the risk –benefit ratio and the cost effectiveness of these strategies, a reasonable course of action in early arthritis should be initial DMARD therapy with NSAIDS and steroids as adjunctive therapy. In most cases MTX is generally considered the first DMARD of choice. Other DMARDs e.g. sulphasalazine and leflunomide are suitable alternatives.
- In patients with significant disease activity and/ or risk factors for adverse outcome e.g. (high titre) rheumatoid factor or anti-CCP antibodies, early use of a more intensive strategy including the use of TNF blockers may be necessary.

VIII MONITORING OF DISEASE ACTIVITY AND TIGHT CONTROL

The objective of therapy is to achieve remission in order to prevent structural damage and long-term disability. Regular monitoring of disease activity is therefore necessary, increasing treatment if disease is not controlled. Imaging may further assist with decisions with regards therapeutic escalation. The ‘best' initial treatment may be less of a matter of drug choice and more of a question of whether treatment aims (‘remission' or low disease activity’) as defined by available scores [115-118] are strictly followed.
In the TICORA [119] ('tight control in RA') study, 110 patients with RA of less than 5 years duration were randomly assigned to an intensive treatment in order to reach a low activity state (DAS44 < 2.4) close to remission, or to regular clinical care. Patients in the TICORA group were examined monthly and DMARD therapy was escalated according to a predefined strategy if the DAS44 was above 2.4. Those in the routine care group were seen every 3 months without formal assessment or feedback on disease activity scores and therapy adjusted according to the clinical judgement of the rheumatologist. The intensive treatment group had significantly more remissions and developed less radiographic damage than the control group after 18 months of follow up. Of note, this intensive monitoring strategy resulted in higher treatment retention rate, a lower rate of discontinuations due to side effects, and lower costs per patient (based on lower admission costs) than routine care over the 18 month of observation.

Further trials have also shown better outcomes where intensive care was based on regular monitoring of disease activity and treatment to target[7]. In the PREMIER [100], ASPIRE [111] and TEMPO [5, 120] studies (despite the fact that they were done in established RA) clinical remission was achieved in some patients and higher remission rates were associated with arrest of radiographic progression (maybe even repair) and better physical function.

Regular monitoring of disease activity and adverse events, therefore, should guide decisions on choice and changes in treatment strategies. This includes both traditional DMARDs and biologics. Monitoring of disease activity should include tender and swollen joint count, patient's and physician's global assessment, ESR & CRP. Arthritis activity should be assessed at one to three month intervals, for as long as remission is not achieved. Structural damage should be assessed by X-rays every 6 to 12 months during the first few years. Functional assessment (for example the HAQ) can be used to complement the disease activity and structural damage monitoring.

**Figure 10: EULAR RESPONSE CRITERIA**

<table>
<thead>
<tr>
<th>DAS at Endpoint</th>
<th>DAS28 at Endpoint</th>
<th>Improvement in DAS28 From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.4</td>
<td>≤ 3.2</td>
<td>&gt; 1.2</td>
</tr>
<tr>
<td>2.4 &gt; 3.7</td>
<td>&gt; 3.2 and ≤ 5.1</td>
<td>&gt; 0.6 and ≤ 1.2</td>
</tr>
<tr>
<td>&gt; 3.7</td>
<td>&gt; 5.1</td>
<td>≤ 0.6</td>
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</tbody>
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Remission: DAS 28 ≤ 2.6 ; DAS ≤ 1.6
IX SUMMARY

- Early diagnosis and treatment can prevent or delay the joint destruction, functional impairment and mortality associated with Rheumatoid Arthritis.
- Early recognition of an inflammatory arthritis is therefore imperative.
- Patients with an inflammatory arthritis should be referred as early as possible to a rheumatologist for further management...
- A combination of clinical, imaging and laboratory measures will allow the clinician to differentiate different causes of an inflammatory arthritis from Rheumatoid arthritis. In the earliest stages the arthritis may be undifferentiated.
- Patients with rheumatoid arthritis or an undifferentiated arthritis must be evaluated in terms of risk of disease progression and severity.
- Early therapy should be instituted for those at risk of developing a persistent erosive arthritis.
- Therapy includes both pharmacological and nonpharmacological measures.
- The best treatment is a combination of optimal drug therapy and regular monitoring and intervention to achieve remission or low disease activity.

A summary of the recommendations for the management early arthritis are summarised in table 4.
Table 4 EULAR recommendations on the management of early arthritis [36]

1. Arthritis is characterised by the presence of joint swelling, associated with pain or stiffness. Patients presenting with arthritis of more that 1 joint should be referred to, and seen by, a rheumatologist, ideally within 6 weeks after onset of symptoms.

2. Clinical examination is the method of choice for detecting synovitis. In doubtful cases, ultrasound, power Doppler, and MRI might be helpful to detect synovitis.

3. Exclusion of disease other than rheumatoid arthritis requires careful history taking and clinical examination, and ought to include at least the following laboratory tests: complete blood cell count, urinalysis, transaminases, and antinuclear antibodies.

4. In every patient presenting with early arthritis to the rheumatologist, the following factors predicting persistent and erosive disease should be measured: number of swollen and tender joints, ESR or CRP, level of rheumatoid factor and anti-CCP antibodies, and radiographic erosions.

5. Patients at risk of developing persistent or erosive arthritis would be started with DMARDs as early as possible, even if they do not yet fulfil established classification criteria for inflammatory rheumatological diseases.

6. Patient information concerning the disease and its treatment and outcome is important. Education programmes aimed at coping with pain, disability and maintenance of work ability may be employed as adjunct interventions.

7. NSAIDs have to be considered in symptomatic patients after evaluation of gastrointestinal, renal, and cardiovascular status.

8. Systemic glucocorticoids reduce pain and swelling and should be considered as adjunctive treatment (mainly temporary), as part of the DMARD strategy. Intra-articular glucocorticoids injections should be considered for the relief of local symptoms of inflammation.

9. Among the DMARDS, Methotrexate is considered to be the anchor drug, and should be used first in patients at risk of developing persistent disease.

10. The main goal of DMARD treatment is to achieve remission. Regular monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment strategies (DMARDs including biological agents).

11. Non-pharmaceutical interventions such as dynamic exercises, occupational therapy, and hydrotherapy can be applied as adjuncts to pharmaceutical interventions in patients with early arthritis.

12. Monitoring of disease activity should include tender and swollen joint count, patient’s and physician’s global assessments, ESR and CRP. Arthritis activity should be assessed at one to three month intervals, for as long as remission is not achieved. Structural damage should be assessed by radiographs of hands and feet every 6-12 months during the first few years. Functional assessment (for example, HAQ) can be used to complement the disease activity and structural damage monitoring.

CRP, C reactive protein; DMARD disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MRI, magnetic resonance imaging.
X FURTHER RESEARCH

Areas for further research include:

- The development of accurate classification and diagnostic criteria for early arthritis.
- The development and validation of diagnostic tests and strategies that enable GPs to recognise and refer patients with persistent and/or erosive forms of arthritis early.
- The development of a prediction model that is usable in clinical practice and predicts persistent (erosive) arthritis well enough to direct treatment decisions.
- The validation of ultrasonography and magnetic resonance imaging for the diagnosis of early synovitis, showing early erosions and for the prognosis of further joint destruction.
- The role of glucocorticoids in very early arthritis should be evaluated.
- The effect of the temporary use of intensive treatments, such as biological agents in early arthritis should be investigated to test whether prevention of erosions and cure (in terms of long-term, possibly drug-free, remission) of the disease is possible.
- Studies with an appropriate design to determine to comparative effectiveness and cost-effectiveness of different therapeutic strategies are required.
REFERENCES – **Main references in bold**


