The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Rheumatoid arthritis

Manfred Herold

1 Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disorder causing irreversible joint damage and significant disability. Its aetiology is still unknown but genetic factors, environmental influences as well as lifestyle modalities like smoking all impact on disease susceptibility.

RA is the most common chronic, inflammatory rheumatic disease with a prevalence in developed countries of between 0.5 % and 1 % and an estimated annual incidence of about 40 cases per 100 000 persons. People can be affected at any age but most frequently the onset of disease occurs between the ages of 40 and 70 years; the incidence increasing with age [1]. Women are affected about three times more often than men [2].

2 Diagnostic criteria

The diagnosis cannot be established by a single laboratory test or radiographic findings but is the summarised conclusion of a spectrum of disease manifestations.

Until recently, the 1987 RA classification criteria of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) were widely used. These criteria were developed by evaluating patients with established RA and had a diagnostic sensitivity of 91 % and a specificity of 89 %. The criteria include the presence of morning stiffness, arthritis of three or more joint areas, arthritis of the hand joints, symmetric arthritis, rheumatoid nodules, elevated levels of serum rheumatoid factor, and radiographic changes (Table 1). The 1987 ACR criteria are excellent to differentiate an established RA from a non-RA arthritis but have a lack of sensitivity in early disease. A rethinking of diagnostic classification to allow effective treatment in early RA resulted in the new classification criteria defined in 2009 and published 2010 [3].

Nowadays the classification as 'definite RA' is based on the confirmed presence of synovitis in at least one joint and a total score of 6 or more from a possible 10

Table 1. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis published in *Arthritis Rheum 1988; 31: 315–24.*
For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks.

Signs & symptoms	Comments
morning stiffness	lasting at least 1 hour before maximal improvement
arthritis of 3 or more joint areas	PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
arthritis of hand joints	at least 1 area swollen in a wrist, MCP, or PIP joint
symmetric arthritis	simultaneous involvement of the same joint areas on both sides of the body
rheumatoid nodules	subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
serum rheumatoid factor	tested by any method for which the result has been positive in < 5 % of normal control subjects
radiographic changes	radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints

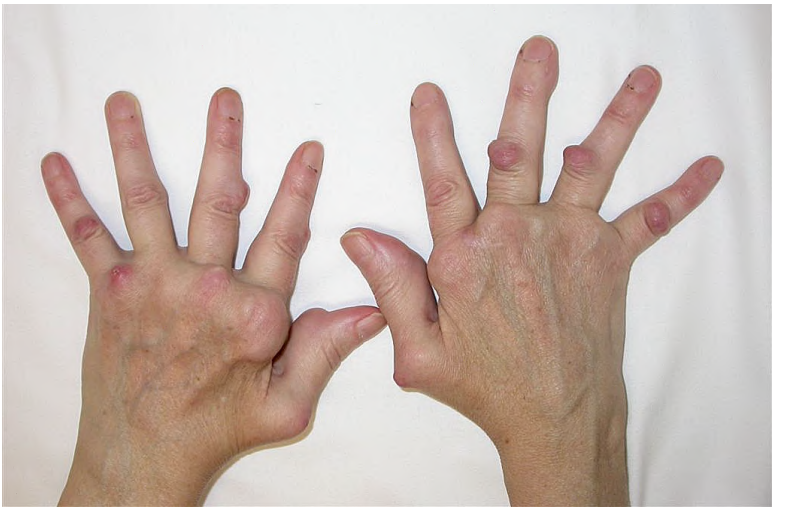

Figure 1. Long-standing rheumatoid arthritis with typical signs including swollen MCP joints, ulnar deviation of fingers, atrophy of musculii interossei and rheumatoid nodules (picture M. Herold 2009).

Table 2. 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria [4]. Comparing to the ACR criteria of 1987 classification of symptoms as RA is possible in a very early phase of the disease. A maximum of 10 points is possible. Patients with 6 or more points are classified as RA.

Signs & symptoms	Points
Joint involvement	***0–5***
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
Serology	***0–3***
negative RF *and* negative ACPA	0
low-positive RF *or* low-positive ACPA	2
high-positive RF *or* high-positive ACPA	3
Acute-phase reactants	***0–1***
normal CRP *and* normal ESR	0
abnormal CRP *or* abnormal ESR	1
duration of symptoms	***0–1***
< 6 weeks	0
≥6 weeks	

point score being determined as the sum of single scores in four domains (Table 2) which are:

- number and site of involved joints (range 0–5),
- serological abnormality (range 0–3),
- elevated acute-phase response (range 0–1) and
- symptom duration (range 0–1).

3 Requirements for family practitioners

A broad range of clinical signs and symptoms (Fig. 1) is seen in patients with RA (Table 3) predominantly pain, stiffness especially in the morning, swelling of peripheral joints and decreased range of motion. But RA is a systemic disease and untreated patients have increased morbidity and mortality compared to the general population. The higher mortality is largely attributed to an increased incidence of cardiovascular diseases with a more than 3 fold higher risk of myocardial infarction. The risk of malignancy from lymphomas and certain carcinomas is

Table 3. Signs and symptoms of RA*.

Symptoms
– joint swelling
– pain & stiffness (commonly in the morning and lasting > 1 hour)
– weakness
– deformity
– general symptoms of sickness (fatigue, malaise, weight loss, depression)
Articular characteristics
– palpation tenderness
– synovial thickening
– erythema & effusion (early on)
– decreased range of motion (later on)
– ulnar deviation of fingers (later on)
– subluxation (later on)
– ankylosis (later on)
Distribution
– symmetrical (especially later on)
– distal more common than proximal
– PIP, MCP/MTP, wrist/ankle more common than elbow/knee, shoulder/hip

* modified from Lee & Weinblatt 2001 [1]

also slightly increased. Early, aggressive and effective treatment is the goal in the management of RA patients.

RA usually begins with the painful swelling of several joints caused by an inflammation of the synovial membrane. Most often the small joints of hands (Fig. 2) and feet such as proximal interphalangeal (PIP) and metacarpophalangeal (MCP) or metatarsophalangeal (MTP) joints are involved, but sometimes also the larger joints of hands and feet, elbows, shoulders and knees. Affected joints are swollen, tender and warm, and stiffness limits their movement. Morning stiffness up to several hours is a commonly mentioned clinical characteristic which affects quality of life and ability to function in the morning. According to an international recommendation [4], rapid referral to a rheumatologist with a noted clinical suspicion of RA is advised in the presence of 3 or more swollen joints, a positive squeeze test indicating inflamed adjacent joints like MTP or MCP and a morning stiffness of more than 30 minutes until major improvement occurs (Table 4).

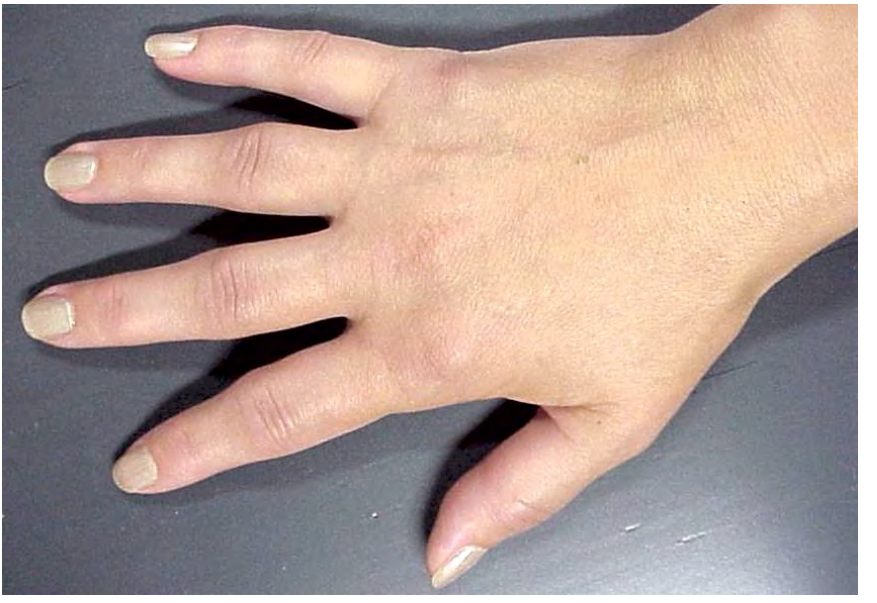

Figure 2. Very early RA with swollen and painful PIP joints (picture M. Herold 2003).

Table 4. Early signs and symptoms which are highly suspicious for a beginning RA [3].

1. ≥ 3 swollen joints
2. MTP/MCP involvement, Squeeze test positive
3. morning stiffness of ≥ 30 minutes

Early diagnosis is vital as permanent structural damage occurs within the first weeks of active RA and only intervention with disease modifying antirheumatic drugs (DMARDs) slows the progression of structural and irreversible joint damage and improves long term outcome, as well as overall patients' quality of life.

4 Diagnostic measurements for experts

Diagnosis is mainly based on clinical signs and symptoms. In addition, blood tests are useful in classifying the collection of symptoms as RA and helpful in estimating disease activity. Several autoantibodies have been detected in RA patients but two major antibody systems dominate in RA, the rheumatoid factors (RFs) and antibodies against citrullinated peptides or proteins (ACPAs). Rheumatoid factor

is the most common and best known antibody. RFs are immunoglobulins with activity directed to the Fc part of immunoglobulin G (IgG). RFs may be of any immunoglobulin type. For diagnosis of RA usually RF of the immunoglobulin class IgM (IgM RF) is measured. IgM RF is present in about 80 % of RA patients. At the time of first symptoms of RA, patients are often RF negative but develop RF activity within the first year of disease. Up to 20 % of RA patients remain negative for RF throughout the course of their disease. These patients are classified as seronegative RA. The diagnostic sensitivity of RF is around 69 %, the specificity about 85 %. RF is also seen in patients with other autoimmune diseases such as Sjögren's syndrome (present in 70 %) or systemic lupus erythematosus (up to 30 %) and also in patients with chronic inflammation including hepatitis or chronic bacterial and other viral diseases. IgM RF was one of the diagnostic criteria in the ACR criteria of 1987 (Table 1) and is also one of the laboratory markers in the new 2010 EULAR/ACR criteria (Table 2), where not only antibody positivity is considered as a diagnostic feature but also the serum concentration. In the new diagnostic criteria RF is equal to ACPA.

ACPAs are antibodies targeting citrullinated peptide or protein antigens. Several commercially available assay systems are available for ACPA testing. The most frequently used tests are the anti-CCP (anti-cyclic citrullinated peptides) and the anti-MCV (anti mutated citrullinated vimentin) tests both with comparable sensitivity of about 67 % and a specificity of about 95 %. Sensitivity of ACPA is comparable to RF, specificity is significantly higher. High positive RF and/or ACPA predict an erosive course of the disease.

Other autoantibodies are also found in the sera of RA patients. These RA non-specific antibodies include antinuclear antibodies (ANA), antiphospholipid antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), antibodies to type II collagen and others. They have neither diagnostic nor prognostic importance.

Non-specific markers of inflammation such as ESR and CRP are usually elevated in active disease and correlated with the numbers of involved joints and with disease activity.

Imaging plays a key role in diagnosis and management of RA. Standard radiography of hands and feet at the time of diagnosis and in follow-up are the first choice of imaging RA. Juxta-articular osteopenia is an early sign. Erosions characterise established disease and are usually irreversible and untreatable. Increasing number of erosions in follow-up radiographs suggests inadequately controlled RA and that correction and intensifying of drug therapy is necessary. Ultrasound and magnetic resonance imaging (MRI) provide a more accurate assessment, as well as earlier detection of lesions and are used in addition to plain radiography in the early stages of disease when erosions are not seen and RA is suspected.

5 Management

The management of RA is based on drug treatment with disease-modifying antirheumatic drugs (DMARDs), glucocorticoids (GCs) and nonsteroidal anti-inflammatory drugs (NSAIDs) as well as non-pharmacological interventions such as physical, occupational and psychological therapeutic approaches.

NSAIDs reduce pain and stiffness, are more efficacious than analgesics and are widely used in times of active disease. NSAIDs relieve symptoms but do not influence the long term course of disease. Non-selective as well as COX-2 selective NSAIDs are used. There are concerns over NSAIDs' gastrointestinal, renal, and cardiovascular side effects. COX-2 selective drugs or the addition of gastroprotective agents (misoprostol, double doses of H2 blockers, and proton pump inhibitors) to non-selective NSAIDs significantly reduce gastrointestinal complications. For some of the COX-2 selective drugs, long term use has been associated with increased cardiovascular risk and for all non-selective NSAIDs the same risk cannot be excluded. Consequently, the US Food and Drug Administration and the European Medicines Agency recommend the shortest possible treatment duration with NSAIDS and contraindications for patients at risk.

Glucocorticoids (GCs) have widespread use in RA. GCs quickly improve symptoms such as pain and stiffness and decrease joint swelling and tenderness. They are given in early disease as bridging therapy until DMARDs exert their anti-inflammatory effects. The usual dose of prednisone is 5 to 10 mg daily. Initial doses up to 25 mg daily may be used, but should be tapered as rapidly as clinically feasible. Short term use of GCs is also indicated to treat acute flare-ups of disease activity. GCs are also useful as chronic adjunctive therapy in patients with severe disease that is not well controlled on NSAIDs and DMARDs. If GC therapy of 3 or more months is required, calcium and vitamin D supplementation should also be prescribed to avoid glucocorticoid-induced osteoporosis. The need for accompanying anti-resorptive therapy with bisphosphonates depends on risk factors including the results of bone-mineral density (BMD) measurement.

Intra-articular glucocorticoid injections are effective for controlling a local flare in a single active joint.

The mainstay of RA treatment is the early and continuous application of DMARDs. The term DMARDs comprises a group of drugs which are defined by their use in RA but are otherwise unrelated. DMARDs slow down progressive joint damage, reduce synovial joint swelling and pain and prevent loss of joint function. DMARDs should be started as soon as the diagnosis of RA is made. Methotrexate (MTX) is the gold standard and is recommended as the first treatment strategy in patients with active RA. MTX is given as a single dose between 7.5 and 30 mg once a week usually orally or subcutaneously. Besides MTX, leflunomide (orally, 20 mg daily) and sulfasalazine (orally, between 2 and 3 g daily) are also widely used. Antimalarials like chloroquine (orally, 250 mg daily) and hydroxychloroquine (orally, 200 mg daily) have DMARD-like properties and may be preferentially given in

milder forms of RA with low disease activity. DMARDs are sometimes combined to increase efficacy.

If synthetic DMARDs have failed, a biological DMARD (so called biological) in addition to the synthetic DMARD may be applied. Biologicals are biotechnologically produced drugs which are administered parenterally either by subcutaneous or intravenous application. Biologicals reduce or suppress inflammation by targeting molecules involved in the inflammatory response (such as pro-inflammatory cytokines) or by blocking pro-inflammatory cellular activity by targeting molecules on lymphocyte surfaces. To date, 9 biologicals have been launched for RA treatment. Infliximab, etanercept, adalimumab, golimumab and certolizumab pegol are so-called tumour necrosis factor (TNF) inhibitors. Other biological agents with different targets are anakinra (interleukin-1 receptor antagonist), tocilizumab (anti-interleukin-6 receptor antibody), abatacept (T-cell costimulation modulator) and rituximab (anti-CCD20 antibody). These biological agents are usually combined with methotrexate or other DMARDs to improve efficacy.

DMARDs have shown their ability to slow disease progression and to prevent joint destruction. They are given as early as possible in the disease process.

6 Follow up

The aim of treatment is remission or sustained low disease activity. Monitoring of disease activity should be regularly performed and treatments switched if treatment goals are not attained.

Disease activity is estimated by counting tender and swollen joints and using visual analogue scales (VAS) to evaluate patient and physician global scoring. Questionnaires such as the health assessment questionnaire are also helpful to evaluate treatment success. Measurement of ESR and CRP is necessary to determine inflammation activity.

Various composite scores have been designed for use in studies and in daily routine. The most common are the disease activity score measured on 28 joints (DAS-28), SDAI (simple disease activity index) and CDAI (Clinical Disease Activity Index).

DAS-28 is calculated by a complex mathematical formula, which includes the number of tender (TJ) and swollen joints (SJ) out of a total of 28, the ESR, and the patient's global assessment (PGA) of global health measured on a VAS between 0 ($\hat{=}$ very good) and 10 ($\hat{=}$ very bad). A DAS-28 score greater than 5.1 implies active disease, less than 3.2 well controlled disease, and less than 2.6 remission.

SDAI is a similar estimation of disease activity but calculation is easier. SDAI also includes physician's global assessment (MDGA) of disease activity on a VAS similar to the patients' VAS between 0 and 10 and uses CRP instead of ESR. SDAI is the sum of TJ, SJ, MDGA, PGA and CPR in mg/dl. SDAI value of > 40 constitutes

high disease activity, SDAI of 20–40 indicates moderate RA activity, and SDAI of < 20 mild disease.

CDAI is the only index that does not include a measure of acute-phase response. CDAI is the sum of TJ, SJ, MDGA and PGA. CDAI < 10 represents low disease activity, > 22 (up to a maximum of 76) high disease activity.

A special feature of rheumatoid arthritis is Felty's syndrome which is defined as rheumatoid arthritis and the presence an enlarged spleen (splenomegaly), and an abnormally low white blood count. Felty's syndrome is a very rare disease of unknown origin seen in less than 1 % of RA patients who usually have long standing RA. It is supposed that patients with this syndrome are more at risk of infection because of their low white blood cell count.

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