EXTENDED REPORT

EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)

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Objective: To formulate EULAR recommendations for the management of early arthritis.

Methods: In accordance with EULAR's ''standardised operating procedures'', the task force pursued an evidence based approach and an approach based on expert opinion. A steering group comprised of 14 rheumatologists representing 10 European countries. The group defined the focus of the process, the target population, and formulated an operational definition of ''management''. Each participant was invited to propose issues of interest regarding the management of early arthritis or early rheumatoid arthritis. Fifteen issues for further research were selected by use of a modified Delphi technique. A systematic literature search was carried out. Evidence was categorised according to usual guidelines. A set of draft recommendations was proposed on the basis of the research questions and the results of the literature search.. The strength of the recommendations was based on the category of evidence and expert opinion.

Results: 15 research questions, covering the entire spectrum of ''management of early arthritis'', were formulated for further research; and 284 studies were identified and evaluated. Twelve recommendations for the management of early arthritis were selected and presented with short sentences. The selected statements included recognition of arthritis, referral, diagnosis, prognosis, classification, and treatment of early arthritis (information, education, non-pharmacological interventions, pharmacological treatments, and monitoring of the disease process). On the basis of expert opinion, 11 items were identified as being important for future research.

Conclusions: 12 key recommendations for the management of early arthritis or early rheumatoid arthritis were developed, based on evidence in the literature and expert consensus.

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The definition of rheumatoid arthritis is sometimes imprecise, but the term is normally used to describe a symmetrical, persistent, and destructive polyarthritis often associated with rheumatoid factor or with positive results in tests for anti-cyclic citrullinated peptide (anti-CCP) antibodies. An early diagnosis is complicated by the absence of specific tests and diagnostic criteria.[1] In practice, early inflammatory arthritis is often undifferentiated.[2] Early arthritis may develop into established rheumatoid arthritis or into another definite arthropathy, may resolve spontaneously, or may remain undifferentiated. For an improved evaluation of the diagnosis and outcome in arthritis, it has been proposed that the first step should be to recognise the presence of inflammatory arthritis, the next should be to exclude definite diagnoses of arthritis (for example, systemic lupus erythematosus (SLE), psoriatic arthritis, seronegative spondylarthropathies, and so on), and the final step should be to estimate the risk of developing persistent or erosive irreversible arthritis and to propose an optimal therapeutic strategy.[2] [3] Although the prognosis of early arthritis is still a difficult issue to address, a combination of clinical biological and radiographic indices may help to predict the outcome of arthritis with acceptable accuracy.

In the past few years the development of effective new treatments and the validation of new concepts have highlighted the need to develop guidelines for the management of early arthritis. New disease modifying antirheumatic drugs (DMARDs) and DMARD combinations have shown their ability to slow disease progression.[4–7] Furthermore, biological treatments have resulted in rapid and sustained disease control, associated with an impressive prevention of joint destruction.[8–10] There is now a body of evidence about early rheumatoid arthritis to support the very early use of effective DMARDs—preferably before the first radiographic evidence of erosions—to prevent further joint damage and disability.[11–13] The assessment and close monitoring of patients with early arthritis seem crucial for the optimisation of therapeutic strategies.[7] [14] In addition, management of early arthritis includes more than drug treatment alone, and an ideal treatment proposal should be based on an appropriate assessment of the prognosis in the individual case.

A potential limitation is that management of early rheumatoid arthritis varies widely among countries, doctors (rheumatologists or general practitioners), and settings (university hospital, private practice, and so on), owing to differences in

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Abbreviations: ACR, American College of Rheumatology; ASPIRE, Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ESCISIT, European Standing Committee for International Clinical Studies Including Therapeutics; EULAR, European League Against Rheumatism; RCT, randomised controlled trial; TEMPO, Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes; TICORA, Tight Control for Rheumatoid Arthritis study; TNF, tumour necrosis factor

culture, health care reimbursement policies, patients' and physicians' preferences, and similar issues.

The objective of this task force was to formulate, and obtain consensus on, a set of recommendations aiming at improving the management of early arthritis. The European League Against Rheumatism (EULAR) standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations[15] has served as a framework to achieve this goal.

METHODS

The EULAR standardised operating procedures prescribe a discussion among experts in the field about the focus, the target population, and an operational definition of the term "management", followed by consensus building based on currently available literature (evidence based), as well as on expert opinion, in order to arrive at a consensus on a set of recommendations.[15] An international expert committee should be formed as a platform for these discussions.

The expert committee

The expert committee comprised 14 rheumatologists and one research fellow (CL) from 10 European countries. All these experts have been involved in early arthritis clinics or early arthritis trials, or both, for many years. After discussion, the group voted to define the focus of the process (early undifferentiated arthritis, with a certain propensity to become persistent and erosive arthritis), and the target population (rheumatologists, GPs, medical students), and to obtain an operational definition of the term "management" ("All organisational, diagnostic, medical and educational procedures related to patients seeking help for arthritis of a peripheral joint").

Fifteen specific issues for further research were selected by use of a modified Delphi technique. The selected topics included recognition of arthritis, referral, diagnosis, prognosis, classification, information, education, non-pharmacological interventions, pharmacological treatments, and monitoring of the disease process (table 1). These research questions were adjusted for further literature research if appropriate, and key index terms were derived by three of us (BC, RL, CL).

Evidence based approach

A systematic search of PubMed, Medline, Embase, CINAHL, and the Cochrane library was carried out. All publications in English language up to January 2005 were included. A further selection was based on reading the title or the abstract. As the topics varied widely, no systematic scoring system was used.

Categories of evidence were applied according to Shekelle *et al*.[16] They include a hierarchy of evidence in descending order by study design (table 2). Questions posed were answered with the use of the best available evidence. An estimation of treatment effect was assessed when possible, by calculating the effect size and 95% confidence interval (CI) for validated continuous outcome measures of disease activity and structural damage compared with placebo or active control. We considered an effect size around 0.2 as small, around 0.5 as moderate, and greater than 0.8 as large.

Expert opinion approach

The results of the literature search were summarised, aggregated, and disseminated to the expert committee with the accompanying levels of evidence. A set of 15 draft recommendations was prepared by three of us (BC, RL, CL), which was a compilation of the research questions (expert opinion) and the results of the literature search (evidence based). This set of draft recommendations formed the basis for discussion during a second meeting. After discussion, voting, and adjusting the

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Table 1 Selected research questions for a literature search

- What is the clinical presentation of early arthritis that a GP should recognise in order to refer to the rheumatologist?
- How early should patients with arthritis be referred to a medical specialist?
- What are the diagnostic procedures that need to be undertaken in order to confirm early synovitis?
- What are the minimum diagnostic procedures necessary in a patient with early arthritis in order to exclude other diseases?
- What are the prognostic procedures that need to be carried out in a patient with confirmed early arthritis?
- Can we substitute distinct disease classifications (rheumatoid arthritis, psoriatic arthritis) with prognostic eponyms such as "persistent" or "persistent and erosive"?
- What is the efficacy of non-pharmaceutical interventions compared to efficacy of drug treatment in early arthritis? (Note: most findings are in *established* rheumatoid arthritis.)
- How should information be given (route of administration) in early arthritis?
- Are NSAIDs (classical and/or coxibs) more efficacious (efficacy in relation to toxicity) than analgesics (including opioids) in early arthritis? (Note: there have been no trial in early arthritis.)
- Is there a place for (intra-articular and/or systemic) corticosteroids in the treatment of early arthritis?
- Is an early treatment start with DMARDs better than a delayed treatment start in early arthritis?
- Is aggressive treatment (for example, combination therapy with or without corticosteroids) better than less aggressive treatment (monotherapy) in early arthritis?
- Can an optimal starting point (for example, X weeks of arthritis) be defined in early arthritis? (Is the starting point dependent on the prognosis?)
- Can consensus be obtained with regard to the choice of DMARD strategies in early arthritis?
- Can consensus be obtained on whether or not disease activity, radiographic progression, and function should be monitored, and if yes, how (by what instruments) and how often?

DMARD, disease modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug.

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formulation, the expert committee eventually arrived at 12 final recommendations for the management of early arthritis. Further, the expert committee proposed topics for a research agenda. The recommendations are presented in brief sentences. The strength of the recommendations, according to the category of evidence (table 3) and the knowledge of the experts, was proposed by two members of the committee (BC, RL), graded from A (highest) to D (lowest),[16] and ratified by the expert committee.

The relevance of the recommendations was checked according to the AGREE instrument (www.agreecollaboration.org).

RESULTS
Evidence based approach

The general search identified a large number of publications related to arthritis. After deleting publications and articles irrelevant to the research questions, 284 manuscripts were further evaluated. They included reports of meta-analyses, randomised controlled trials (RCTs), controlled trials, observational studies, comparative studies, case–control studies, cross

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Table 2 Categories of evidence[16]

Ia Evidence from meta-analyses of randomised controlled trials
Ib Evidence from at least one randomised controlled trial
IIa Evidence from at least one controlled study without randomisation
IIb Evidence from at least one type of quasi-experimental study
III Evidence from descriptive studies, such as comparative, correlation, or case–control
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

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sectional surveys, systematic reviews, and expert reports or opinions. As original publications about early arthritis or early rheumatoid arthritis were missing on some topics such as non-pharmacological treatment or symptomatic treatments, some publications relevant to established rheumatoid arthritis, including 10 Cochrane reviews, were also examined.

Assessment of propositions
Table 4 summarises the final set of 12 recommendations as proposed by the expert committee. The strength of each recommendation is presented in table 5. The recommendations are ordered by topic, with no weighting according to order.

The recommendations
Recommendation 1

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

Although the level of evidence supporting the content of this recommendation is rather low (category III or IV), there was general agreement that a recommendation regarding the recognition of arthritis and about early referral should be included. Joint swelling not caused by trauma or bony swelling should suggest a diagnosis of early arthritis, preferably if it includes involvement of at least two joints, with or without morning stiffness of more than 30 minutes' duration, and/or involvement of metacarpophalangeal and/or metatarsophangeal joints.[17–19] Involvement of hand and foot joints is suggested by a positive ''squeeze test''[18 20] (category III).

One systematic review,[21] several randomised controlled studies,[22–25] and a number of prospective observational studies[11–13 26] showed a better outcome of arthritis when treatment is started earlier. Evaluation of the impact of a delay in the start of treatment on the outcome of arthritis is difficult. From evidence in published reports and the clinical experience of the members of the committee, it was recommended that drug treatment by a rheumatologist should start within a relatively short period after the onset of complaints, which justifies to the committee the wording ''ideally within six weeks'' in this recommendation. Several comparative studies[27–33] have shown a better functional status and earlier DMARD start in cases treated by rheumatologists, which further supports the view that patients with clinical presentations suggestive of arthritis should be referred to a rheumatologist early.[18]

Recommendation 2

> Clinical examination is the method of choice for detecting arthritis. In doubtful cases, ultrasound, power Doppler, and MRI may be helpful in detecting synovitis.

Table 3 Strength of recommendations[16]
A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendations from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category II or III evidence

The expert committee was unanimous in their view that clinical examination is still the gold standard in detecting synovitis. This does not mean that imaging methods are incapable of detecting synovitis, and may even do so with greater sensitivity. Ultrasonography and power Doppler techniques allow the assessment of synovitis, by detecting thickening of the synovial membrane of inflamed joints and bursae or tendon sheaths. Two controlled studies have suggested that ultrasonography is more sensitive than clinical examination for detecting synovitis in knee joints.[34 35] However, ultrasonography and power Doppler have hardly been used at all for detecting synovitis of the small joints of the hands and feet[36] (category III), and scientific evidence of the clinical value of ultrasonography in early arthritis is limited. In one controlled study and in a few comparative studies, MRI has been shown to be more sensitive than clinical examination and radiography for the detection of synovitis and erosions in early rheumatoid arthritis.[37–39] There is evidence that MRI findings (for example, synovitis, bone oedema, and bone erosions) may predict subsequent radiographic progression.[40 41] However, the level of evidence is rather low, and changes resembling mild synovitis or small bone erosions are occasionally found in the joints of healthy subjects, raising questions about the specificity of this technique.[42] Issues of standardisation and reliability of MRI have been addressed and are ongoing.

Altogether, the expert committee thought that MRI and ultrasonography are promising techniques that may become valuable in the diagnosis, prognosis, and therapeutic monitoring of early arthritis. However, their use is still experimental and sometimes controversial, and their merits in routine clinical practice have yet to be defined.

Recommendation 3

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

This recommendation is entirely expert based. As experimental evidence from appropriately designed clinical trials was unavailable, the group considered that ''good clinical practice'' and a ''high level of training'' sufficed to address this topic, so no literature search was carried out. In order to exclude patients in whom the arthritis has differentiated into diseases other than rheumatoid arthritis which may have a different prognosis and treatment (such as connective tissue diseases, reactive arthritis, infectious arthritis, and others), the group proposed that the minimum diagnostic procedures should include a careful history and clinical examination, a complete blood cell count, transaminase analysis, urinary analysis, and anti-nuclear antibody testing.

The diagnostic procedure may also include tests for uric acid and Lyme disease, parvovirus infection, urethral or cervical swab cultures, anti-bacterial serology, tests for hepatitis B or C, or chest x ray, according to the context and the country. Tests for erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor, and anti-cyclic citrullinated peptide (anti-CCP) antibodies were excluded here, as these tests are related to the extent of the inflammation and the (prognostic) severity of the arthritis rather than to other diagnoses.

Recommendation 4

> In every patient presenting with early arthritis to the rheumatologist, the following factors predicting persistent

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Table 4 Final set of 12 recommendations on the management of early arthritis based on both evidence and expert opinion

- Arthritis is characterised by the presence of joint swelling, associated with pain or stiffness. Patients presenting with arthritis of more than one joint should be referred to, and seen by, a rheumatologist, ideally within six weeks after the onset of symptoms.
- Clinical examination is the method of choice for detecting synovitis. In doubtful cases, ultrasound, power Doppler, and MRI might be helpful to detect synovitis.
- Exclusion of diseases 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, urinary analysis, transaminases, antinuclear antibodies.
- 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, levels of rheumatoid factor and anti-CCP antibodies, and radiographic erosions.
- Patients at risk of developing persistent or erosive arthritis should be started with DMARDs as early as possible, even if they do not yet fulfil established classification criteria for inflammatory rheumatological diseases.
- 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.
- NSAIDs have to be considered in symptomatic patients after evaluation of gastrointestinal, renal, and cardiovascular status.
- Systemic glucocorticoids reduce pain and swelling and should be considered as adjunctive treatment (mainly temporary), as part of the DMARD strategy. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.
- Among the DMARDS, methotrexate is considered to be the anchor drug, and should be used first in patients at risk of developing persistent disease.
- 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).
- Non-pharmaceutical interventions such as dynamic exercises, occupational therapy, and hydrotherapy can be applied as adjuncts to pharmaceutical interventions in patients with early arthritis.
- 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 to 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.

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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.

After exclusion of diseases other than rheumatoid arthritis, the third step in the diagnostic procedure should be to try to determine the patients at risk of developing persistent or erosive arthritis. This prognostic typing was considered crucial to guide the optimal therapeutic strategy. Forty five studies that evaluated the prognostic factors in early arthritis (n = 5) or early rheumatoid arthritis (n = 40) were examined. They are all observational or case–control studies (category III). Most prognostic factors were analysed in a multivariate manner in these studies, so that their independent contribution could be tested. In many of the studies, the variable to predict (dependent variable) was radiographic progression. The presence of IgM or IgA rheumatoid factor,[20 43–59] high ESR or CRP level,[41 43 44 47 49 50 53 55 57 59] and early radiographic evidence of erosions,[20 43 44 49 52 54 56 58 61] according to most of the reports, independently predict long term radiographic progression. The number of swollen joints probably correlates better with radiographic progression than the number of tender joints.[20 44 46–49] Recently, several studies have shown that presence of anti-CCP antibodies is also an independent prognostic factor for radiographic progression in early arthritis and early rheumatoid arthritis.[20 54 60–64] The presence of HLA-DRB1*0401 and DRB1*0404 is also consistently associated with joint damage in different ethnic groups.[43 49 61] This association appears to be dose dependent, as patients with two rheumatoid arthritis associated genes show more radiographic evidence of destruction than those with non-associated alleles.[43 61] HLA-DRB1*01 genes alone are not associated with the severity of rheumatoid arthritis. However, when DRB1*04 genes are included in logistic regression analyses, they do not often

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Table 5 Strength of the recommendations

Recommendations	No of studies evaluated	Level of evidence	Strength of recommendation
1 Early referral	35	Ib	B
2 Diagnosis of early synovitis	30	IIb	C
3 Minimum diagnostic procedure	–	–	D
4 Prediction of persistent and erosive arthritis	45	III	C
5 Early treatment start	27	Ia	A
6 Patient information	26	Ia/Ib	B
7 NSAIDs	11	Ia	B
8 Systemic and intra-articular glucocorticoids	21	Ia	A
9 Methotrexate is the anchor drug	24	Ia	A
10 Treatment strategies	22	Ib	B
11 Non-pharmaceutical interventions	32	Ia	B
12 Regular monitoring	11	Ia	A

NSAID, non-steroidal anti-inflammatory drug.

contribute to explaining variation in the model, which makes DRB1 genotyping a less suitable tool for prognostic purposes. The duration of cigarette smoking has also been shown to be an interesting susceptibility factor and a determinant of disease progression in rheumatoid arthritis, but this variable was not often investigated or selected as an independent variable in multivariate studies.

Abnormalities seen on MRI may be of prognostic interest.[40 41] In general, single variables have shown limited prognostic value, and several reports have tried to develop prediction models with a combination of the most reliable markers.[20 43 48 53] Though some of these models seem promising, the development and (cross)validation of a robust model, easy to use in all settings in clinical practice, is still pending.

Recommendation 5

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

Four studies (category III) have shown that early arthritis is frequently undifferentiated at presentation,[65–68] and six studies (category III) have shown that classification criteria for established diseases have little discriminant value during the early months of the disease.[50 69–73] Recent studies have demonstrated that joint erosion occurs early in rheumatoid arthritis, and that more than 80% of patients with a disease duration of less than two years may already have radiographic evidence of joint damage. The concept of a ''window of opportunity'' for effective treatment of recent onset rheumatoid arthritis has been supported by one meta-analysis,[21] six RCTs,[22–25 74 75] and several comparative or observational studies.[11–13 26 76 77] Among patients with recent onset polyarthritis, those who received DMARD treatment early had a better outcome with regard to radiographic progression, function, and ability to work than those in whom DMARD treatment was delayed by a few months.[11–13 23 26 74] Results of a meta-analysis of 1435 patients also support this concept: disease duration at the time of DMARD initiation was shown to be the main predictor of the response to DMARD treatment.[21]

Recommendation 6

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

Provision of information should be an integral part of the management of any chronic disease. The expert committee considered that patient information concerning arthritis, its treatment, and its outcome was important. Three RCTs demonstrated that written information may increase knowledge about the disease.[78–80] One systematic review,[81] four RCTs,[82–85] and two controlled trials[86 87] showed that a self management education programme resulted in improved clinical outcome in rheumatoid arthritis, producing short term effects on disability, joint count, and patient global assessment, anxiety, and depression, but without any evidence of long term benefit.[81] There is only weak evidence that group education is better than individual education (category IV).[87 88]

In summary, patient information was considered important, and the benefits of educational interventions have been shown in clinical trials. In the opinion of the expert committee,

however, it is difficult to prioritise a single educational intervention, because all interventions have only shown short term benefits, and are subjected to cross national and cultural variation. It is important to bear in mind that specific objectives in early arthritis have not been achieved, and that further evaluation is needed.

Recommendation 7

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

Substantial evidence, including a Cochrane review in established rheumatoid arthritis but not in early (rheumatoid) arthritis, indicates 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 (category Ia).[89 90] Some data were missing to calculate the effect size of NSAIDs versus analgesics in rheumatoid arthritis.

However, there are concerns over the gastrointestinal, renal, and cardiovascular side effects of NSAIDs. Replacement of conventional NSAIDS by COX-2 selective drugs, or the addition of gastroprotective agents (misoprostol, double doses of H_2 blockers, and proton pump inhibitors) to classical NSAIDs can significantly reduce gastrointestinal complications such as the incidence of gastrointestinal bleeding (category Ia).[91] However, the long term use of COX-2 selective drugs has been associated with increased cardiovascular risk.[92 93] Probably, this increased cardiovascular risk is not limited to COX-2 selective drugs, but extends to all NSAIDs. Consequently, the US Food and Drug Administration and the European Medicines Agency have published recommendations for the use of these drugs. Among others, they recommend the shortest treatment duration possible and contraindications for at-risk patients. The expert committee felt there is no reason to assume that these observations should not be extrapolated to early arthritis. Symptomatic patients presenting with early arthritis should therefore be treated with NSAIDs after careful evaluation of gastrointestinal, renal, and cardiovascular status.

Recommendation 8

Systemic glucocorticoids reduce pain and swelling and should be considered as a (mainly temporary) adjunct to the DMARD strategy. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.

Several RCTs and three systematic reviews have shown that systemic low dose glucocorticoids, typically prednisone $\leqslant 10$ mg/day, were effective in relieving short term signs and symptoms in patients with rheumatoid arthritis.[94–99] Results of a recent open study of 100 patients with undifferentiated arthritis suggested that a single dose of intramuscular or intra-articular steroids may even induce remission,[100] although formal evidence for this strategy is lacking.

In addition, and despite controversial data, steroids are probably effective in slowing radiographic progression in early and established rheumatoid arthritis. In an RCT involving rheumatoid arthritis patients with a disease duration of less than two years, Kirwan[101] reported the superior efficacy of two years of continuous treatment with prednisolone, 7.5 mg daily, with respect to radiographic progression compared with standard care without prednisolone. In an RCT involving

patients with rheumatoid arthritis of less than one year duration, van Everdingen et al[102] compared treatment with prednisone 10 mg daily and NSAIDs. Only sulfasalazine was allowed in this study, but only after six months, and only as a rescue drug. The prednisone group showed significantly less radiographic progression at 12 and 24 months. The effect size of low dose steroids on the Larsen score compared with symptomatic treatments in these two studies was only 0.28 and 0.26, respectively, at 24 months. These data are supported by data from another RCT[103] and from two trials in early rheumatoid arthritis, which indicated that combination therapy including steroids was more effective in terms of radiographic progression than single DMARD therapy, but it is not possible to determine the specific benefits provided by steroid administration in these trials.[5 6 104] The published data have not all been positive. Paulus et al[105] were unable to show an effect of prednisone, ⩽ 5 mg/day, in radiographic progression in a subgroup analysis of a three year RCT comparing etodolac and ibuprofen in 824 patients. A recent RCT by Capell et al[106] failed to demonstrate any significant difference in two year radiographic progression between prednisone, 7 mg/day, and placebo. In addition, subanalysis of two recent trials with new DMARDs did not show any added benefit of low dose prednisone with respect to radiographic progression.[4 107]

The positive short term effects of intra-articular corticosteroid administration in relieving local symptoms of inflammation in rheumatoid arthritis were shown in two RCTs.[108 109] Among the intra-articular corticosteroids, there is some indication that triamcinolone hexacetonide is the most effective.[110]

In summary, systemic glucocorticoids—either alone or as part of a DMARD combination strategy—are effective in the short term relief of signs and symptoms, and are probably effective in retarding radiographic progression in early and established rheumatoid arthritis. The systemic use of glucocorticoids in early arthritis has not yet been formally investigated. Preferably, treatment with glucocorticoids is temporary because of the risk of side effects—including weight gain, hypertension, diabetes, cataracts, and osteoporosis—which justify careful monitoring and appropriate prevention. Furthermore, the long term safety of low dose glucocorticoids is largely unknown. Intra-articular steroids may be effective as an adjunct to DMARDs in relieving local joint symptoms. There is still no evidence that intra-articular or intramuscular steroids alter the course of early arthritis.

Recommendation 9

> Among the DMARDs, methotrexate is considered the anchor drug and should be used first in patients at risk of developing persistent disease.

At the root of this statement is the observation of a meta-analysis of patients with established rheumatoid arthritis, showing a significantly lower discontinuation rate of methotrexate as compared to other DMARDs (but leflunomide and tumour necrosis factor (TNF) blockers were not evaluated).[111] Several RCTs have proven the clinical efficacy of methotrexate. These RCTs were followed by observational studies clearly establishing that methotrexate is effective over long periods, and that it has a better toxicity profile than other DMARDs.[112–115] Importantly , methotrexate is one of the first conventional DMARDs with proven efficacy on radiographic progression in rheumatoid arthritis.[4] In early rheumatoid arthritis, two RCTs (of 12 and 18 months' duration) failed to demonstrate the superiority of methotrexate over other DMARDs such as sulfasalazine.[116 117]. However, recent RCTs with TNF blocking drugs have shown that methotrexate is almost as effective as

TNF blocker monotherapy in patients with early (less than three years' duration) severe rheumatoid arthritis.[107 118]

An important argument for considering methotrexate as an anchor drug is that it can be combined with biological treatments if necessary. This has emerged from RCTs showing greater efficacy for the combination of TNF blocking drugs with methotrexate than for monotherapy.[9 118–120] The combination of methotrexate with TNF blockers appears to convey the maximum therapeutic effect currently obtainable, both in established and early rheumatoid arthritis. The combination of methotrexate with sulfasalazine has not been shown to be superior to single drug treatment.[116–117] Despite interesting reports,[5 7 104 121–128] whether the combination of methotrexate with other DMARDs is more efficient than monotherapy needs further investigation.

Leflunomide, and to a lesser extent sulfasalazine, have a similar clinical efficacy to methotrexate in established and recent rheumatoid arthritis (category Ia).[124] Leflunomide is as effective as methotrexate in slowing radiographic damage.[4] Sulfasalazine, in contrast, may be inferior to leflunomide and methotrexate in the long term.

In summary, methotrexate appears to be an anchor drug in rheumatoid arthritis, both as monotherapy and in combination with conventional DMARDs or TNF blocking drugs for most patients with rheumatoid arthritis.

Although formal evidence that prioritises methotrexate as the first DMARD in early arthritis or early rheumatoid arthritis is lacking, the expert committee recommends that treatment should be started with methotrexate (unless contraindicated) in patients at risk of persistent or erosive disease. This recommendation is based on its clinical and radiological efficacy in combination with the relatively beneficial safety profile, and on its beneficial properties in treatment combinations. Leflunomide, and to a lesser extent, sulfasalazine are considered the best alternatives.

Recommendation 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)

The introduction of new drugs that can control disease progression, and the demonstration that DMARDs are more effective if used early rather than later in disease progression, have led to crucial changes in management goals in early arthritis and early rheumatoid arthritis. The objective should now be to achieve remission in order to prevent structural damage and long term disability.

One recent therapeutic strategy in the treatment of rheumatoid arthritis is the early use of combination therapy with conventional DMARDs (''intensive'' therapy). Some RCTs have evaluated the combination of two DMARDs (mainly methotrexate-sulfasalazine or methotrexate-ciclosporine) in early rheumatoid arthritis, with controversial results both for clinical efficacy and for radiographic evidence of progression.[116 117 121 123 125 126] However, a combination of methotrexate and sulfasalazine with high dose steroids in a step-down therapeutic strategy (COBRA) resulted in protracted effects on radiographic progression, compared with sulfasalazine monotherapy in 155 patients with early rheumatoid arthritis (category 1b).[5 104] These results are consistent with those from the FIN-RACo study, in which 197 patients with onset of rheumatoid arthritis within the previous two years were randomly assigned to receive either a four-drug regimen, with methotrexate, sulfasalazine, hydroxychloroquine, and

prednisolone (5 mg/d), or a single DMARD.[6 127 128] After 18 months, a greater proportion of the combination therapy group were in remission. After five years, the combination group were less likely to have radiographic progression, and the work disability rate was lower compared with the patients on monotherapy. However, in neither study was there an arm with DMARD monotherapy plus steroids.

The concept that intensive interventions early in the course of persistent arthritis may profoundly affect long term radiographic progression is also supported by four 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.[118–120 129] The effect size of such a combination versus methotrexate alone on total radiographic score in patients with early rheumatoid arthritis varied from 0.42 to 0.96. These data are consistent with those from several RCTs in established rheumatoid arthritis, showing that intensive treatment with a combination of conventional DMARDs plus steroids or with biological therapy in combination with methotrexate may provide superior clinical and radiological efficacy than monotherapy.[8–10]

In addition, a recent RCT compared four treatment strategies in early rheumatoid arthritis, including a progressive step-up regimen, sequential monotherapy, a triple step-down strategy with methotrexate, sulfasalazine, and high dose prednisone, and infliximab plus methotrexate.[7] The two groups with initial intensive treatment (combination and infliximab group) showed a more rapid clinical response and a better radiographic outcome than the sequential monotherapy or the step-up DMARD therapy groups.

In the TICORA study,[14] patients with early rheumatoid arthritis were randomly assigned to an intensive treatment in order to reach a low disease activity state (DAS44 <2.4) close to remission, or to regular clinical care The intensive treatment group developed less radiographic damage than the control group after 18 months of follow up, suggesting an association between remission (or low disease activity) and further joint destruction (category Ib). Other data support the need to achieve clinical remission in order to control the disease process, including the long term follow up of two Dutch cohorts which found a positive relation between disease activity score (DAS) and 28 joint disease activity score (DAS28) and radiological progression, after adjustment for time effects and baseline predictors of radiological destruction and their interactions with time[130] (category III). In the PREMIER study,[118] the ASPIRE study,[119] and the TEMPO study (despite the fact that it was done in established rheumatoid arthritis),[9 131] 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.

In summary, initial intensive treatment provides a better outcome than DMARD monotherapy including methotrexate in patients with recent onset chronic arthritis, but mainly in a subset of patients with severe disease.[119] Consequently, regarding the benefit to risk ratio and the cost-effectiveness of these strategies, a reasonable course of action should be initial DMARD monotherapy with methotrexate (or leflunomide or sulfasalazine). However, the expert committee felt that there is ample evidence that with modern treatment combinations with or without biological agents clinical remission is an achievable goal. There is also indirect evidence from various RCTs and observational studies that remission is associated with better radiographic outcome and better preservation of physical function. As there is emerging evidence that maintaining

remission is as important as achieving remission, it is obvious that disease activity should be closely monitored in order to change DMARD therapy and strategy if necessary ("benchmarking"). The first studies supporting this view have just been published.[14]

Recommendation 11

> Non-pharmaceutical interventions such as dynamic exercises, occupational therapy, and hydrotherapy can be applied as treatment adjunct to pharmaceutical interventions in patients with early arthritis.
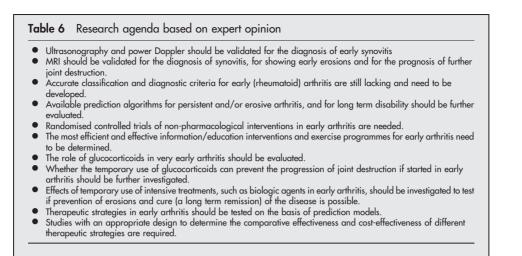
The effect of non-pharmaceutical treatments has not been investigated in early arthritis and can only be extrapolated from the results of several RCTs and eight Cochrane reviews in established rheumatoid arthritis. RCTs have shown that joint specific dynamic exercises may improve strength and physical function in rheumatoid arthritis, but without a clear effect on pain or disease activity.[132 133] However, the optimal exercise programme has not yet been determined. One recent RCT and a Cochrane review reported a positive effect of occupational therapy on functional ability and self management, but without an effect on disease activity.[134 135] Hydrotherapy in rheumatoid arthritis has been evaluated in two recent meta-analyses,[136 137] with positive findings but insufficient evidence to support a strong recommendation.

Nine RCTs have been undertaken to investigate the efficacy of diets. The results are controversial—the diets and the study designs varied widely, and most of the trials with diets only included highly selected and motivated patients. A one year study randomised 66 patients to receive a vegetarian diet free of gluten or a well balanced non-vegan diet. The vegetarian diet group experienced significantly better effects in most of clinical variables, including the ACR 20 response, as compared with the non-vegetarian group.[138] Two other RCTs found a positive effect of a vegetarian diet on pain and indices of disease activity.[139 140] Numerous other non-pharmaceutical interventions have been investigated in patients with rheumatoid arthritis. Acupuncture, laser therapy, use of compression gloves, transcutaneous electrical nerve stimulation (TENS), ultrasound, thermotherapy, use of splints or ortheses, and homoeopathy are examples of non-pharmaceutical interventions with which controversial effects have been reported in RCTs.[141–144] When positive, the RCTs showed short term relief of pain only, rather than an effect on disease activity.

In summary, some non-pharmaceutical interventions—such as dynamic exercises, occupational therapy and hydrotherapy—have shown indisputable, often symptom relieving effects in established rheumatoid arthritis. There is limited evidence that a vegetarian diet may have a modest effect on symptoms. The efficacy of non-pharmaceutical interventions in early arthritis has not been formally tested, and there is no indication that they improve long term outcomes such as radiographic progression. The expert committee therefore felt that non-pharmaceutical interventions should only be applied as an adjunct to pharmaceutical treatment in patients with early arthritis.

Recommendation 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 x rays

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Table 6 Research agenda based on expert opinion

- Ultrasonography and power Doppler should be validated for the diagnosis of early synovitis
- MRI should be validated for the diagnosis of synovitis, for showing early erosions and for the prognosis of further joint destruction.
- Accurate classification and diagnostic criteria for early (rheumatoid) arthritis are still lacking and need to be developed.
- Available prediction algorithms for persistent and/or erosive arthritis, and for long term disability should be further evaluated.
- Randomised controlled trials of non-pharmacological interventions in early arthritis are needed.
- The most efficient and effective information/education interventions and exercise programmes for early arthritis need to be determined.
- The role of glucocorticoids in very early arthritis should be evaluated.
- Whether the temporary use of glucocorticoids can prevent the progression of joint destruction if started in early arthritis should be further investigated.
- Effects of temporary use of intensive treatments, such as biologic agents in early arthritis, should be investigated to test if prevention of erosions and cure (a long term remission) of the disease is possible.
- Therapeutic strategies in early arthritis should be tested on the basis of prediction models.
- Studies with an appropriate design to determine the comparative effectiveness and cost-effectiveness of different therapeutic strategies are required.

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every 6 to 12 months during the first few years. Functional assessment (for example, HAQ) can be used to complement the disease activity and structural damage monitoring.

This statement is supported by at least three RCTs.[7 14 145] In the TICORA study, patients with recent onset rheumatoid arthritis were randomly assigned to receive routine DMARD treatment at the discretion of the treating rheumatologist, or intensive treatment with monthly assessment of clinical disease activity.[14] In this latter group, the treatment was intensified or drug combinations were used if the effect on disease activity was insufficient, as defined by a DAS44 <2.4. This intensive strategy appeared to be significantly more effective at all follow up visits throughout the first 18 months, in terms of both clinical symptoms and radiographic progression.

Intensive care based on regular monitoring of DAS28 or DAS44 was associated with better outcome in two recent trials,[7 145] and other validated composite indices can be used to monitor disease activity equally reliably.[146] No evidence from an appropriately designed clinical trial exists to support monitoring of radiographic progression. The expert committee considered monitoring of radiographic progression useful in view of the objective of the management of early arthritis (to prevent joint destruction), the observation that radiographic progression is greatest during the first two years after disease onset, and the appreciation that radiographic progression is clinically meaningful in case of a change of 4 Sharp units (during six months follow up) and can be reliably established at the group level after a three to six months interval[147] (category III). In order to facilitate radiographic monitoring, it could be desirable to use the simple erosion and narrowing score (SENS), a scoring method based on the van der Heijde modified Sharp score and validated for use in clinical practice.[148]

DISCUSSION

These 12 recommendations, presented in short sentences, are based on recent research evidence up to January 2005 and on expert opinion. The task force has followed the EULAR standardised operating procedures for formulating recommendations.[15] Similar methods have been also used to develop the EULAR recommendations for the management of knee and hip osteoarthritis.[149 150] Early arthritis is frequently undifferentiated, and the major issues of interest are diagnosis, prognosis, and treatment. As these issues cannot be considered independently, the expert committee has decided to focus its work on "early undifferentiated arthritis with a certain propensity to become

persistent and erosive", and to use an operational definition for "management" that covers the entire process, including referral, diagnosis, prognosis, and treatment. As a result, these recommendations are not aimed only at rheumatologists but also at GPs and potentially at medical students. Types of arthritis that do not fit the framework outlined above were excluded in this exercise.

As mentioned already by others,[149] the expert committee did not find it helpful to score the quality of the studies, both because the topics that were examined varied widely and because of the heterogeneity of the studies that were found The committee chose to grade the level of evidence provided by every study, which was based on the methodology of the study, and took this grading into consideration when discussing the content and the strength of the recommendations. An important consideration in the discussions always was whether the type of study fitted the content of the research question that was at the basis of the literature search. Besides evidence obtained from published reports, expert opinion and the clinical experience of the expert committee turned out to be very important for reaching consensus, and for formulating and weighing the strength of the recommendations. The expert committee had to face an important limitation in that most of the published data from which the recommendations were derived were based on studies in patients with early rheumatoid arthritis or established rheumatoid arthritis, rather than on studies in early arthritis. Nevertheless, the expert committee considered the data in early rheumatoid arthritis robust enough and relevant enough to be extrapolated to "early arthritis with a certain propensity to become persistent and/or erosive". By doing so, the expert committee has implicitly subordinated the classification of rheumatoid arthritis to a clinical diagnosis of potentially persistent erosive arthritis, which can be interpreted as a novelty. This new line of thinking enabled the task force to highlight key points in the management of early arthritis, including the need for early referral to a rheumatologist; the prediction of persistent and erosive disease; the requirement for an early start of efficient DMARD treatment in all patients at risk of developing persistent or erosive arthritis; the key role of methotrexate as the first and anchor drug; the objective of the therapeutic strategy in inducing remission and preventing joint destruction; and the need for regular monitoring to adapt the strategy as necessary and detect adverse events.

Reviewing the literature, the committee felt that there was a need to develop new tools for early and accurate diagnosis and prognosis. These include new imaging and serological measures

and also prediction algorithms for long term outcome. Also lacking is information about the effectiveness of non-pharmacological interventions, the role of glucocorticoids, and the comparative effectiveness and cost-effectiveness of different strategic modes in early arthritis. The task force proposed 11 items considered the most important for future research according to current available evidence (table 6).

New effective treatments for rheumatoid arthritis and new strategic concepts in the treatment of the disease have definitely changed thinking about the management of early arthritis.

The current EULAR recommendations on the management of early arthritis value the recent therapeutic developments, but they also point to the variety of available treatment, and the heterogeneity of patients in whom these treatment should be applied. Management according to protocols will become increasingly difficult, and every health professional should choose the most appropriate management strategy for every individual patient. The recommendations should be considered a reflection of current thinking in the field of early arthritis, supported by firm evidence if possible, and dressed up by expert opinion if necessary, in order to serve as an aid for health professionals and patients who have to make decisions about the most appropriate individual management strategy. To that end, it is hoped that the recommendations will be widely disseminated and discussed within the rheumatological community and other physicians taking care of patients with early arthritis, and that they will help improve the standard of care for patients with arthritis across different health care systems. Obviously these recommendations will need an update after few years, in order to incorporate new scientific evidence.

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