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2016 update of the EULAR recommendations for the management of early arthritis

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Abstract

Objectives: Since the 2007 recommendations for the management of early arthritis have been presented, considerable research has been published in the field of early arthritis, mandating an update of the 2007 EULAR recommendations for management of early arthritis.

Methods: In accordance with the 2014 EULAR Standardised Operating Procedures, the expert committee pursued an approach that was based on evidence in the literature and on expert opinion. The committee involved 20 rheumatologists, 2 patients and 1 health professional representing 12 European countries. The group defined the focus of the expert committee and target population, formulated a definition of "management" and selected the research questions. A systematic literature research (SLR) was performed by 2 fellows with the help of a skilled librarian. A set of draft recommendations was proposed on the basis of the research questions and the results of the SLR. For each recommendation the categories of evidence were identified, the strength of recommendations was derived and the level of agreement was determined through a voting process.

Results: The updated recommendations comprise 3 overarching principles and 12 recommendations for managing early arthritis. The selected statements involve the recognition of arthritis, referral, diagnosis, prognostication, treatment (information, education, pharmacological and non-pharmacological interventions), monitoring and strategy. Eighteen items were identified as relevant for future research.

Conclusion: These recommendations provide rheumatologists, general practitioners, health professionals, patients and other stakeholders with an updated EULAR consensus on the entire management of early arthritis.

Peripheral inflammatory arthritis is among the most common features with which patients present in clinical rheumatology. Identifying the underlying disease can be difficult, particularly at an early stage. In clinical practice, early inflammatory arthritis is frequently undifferentiated (1). Early arthritis can develop into established rheumatoid arthritis (RA) or another definite arthropathy, can resolve spontaneously, or may remain undifferentiated for indefinite periods. To better evaluate diagnosis and outcome in arthritis, it has been proposed to first recognize inflammatory arthritis; then search for a definite diagnosis (e.g., peripheral or axial spondyloarthritis; psoriatic arthritis [PsA]; systemic lupus erythematosus…), and finally estimate the risk of developing persistent and/or erosive arthritis and propose an optimal therapeutic strategy (2, 3). Although the prognosis of early arthritis is still difficult to define, a combination of clinical, laboratory and radiographic parameters may help to predict patients' outcomes with acceptable accuracy.

The management of early arthritis has changed considerably in the past few years under the influence of new concepts for diagnosis and new effective therapies. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) have been shown to slow disease progression in chronic inflammatory arthritides such as RA and PsA (4–6). Furthermore, biological (b) DMARDs have demonstrated rapid and sustained disease control associated with an arrest of joint destruction (7,8). A large body of evidence points to the usefulness of very early DMARD-start for early chronic inflammatory arthritis, preferably before the onset of erosions, in order to reduce or even prevent the risk of (further) joint damage and disability (5,9,10). Also, the assessment and tight monitoring of patients with early arthritis serves to better adapt therapeutic strategies (9,11). Beyond doubt, the treatment goal of early arthritis should now be: clinical remission and prevention of joint destruction.

Patients with early arthritis should be identified and referred to rheumatologists to confirm the presence of arthritis, the (potential) diagnosis and its prognosis and initiate appropriate

treatment strategies based on these findings. Furthermore, management of early arthritis should include more than drug treatment alone, with education, shared decision making and the role of allied health professionals as important themes.

A set of recommendations for the management of arthritis should address all these different aspects.

The EULAR recommendations for the management of early arthritis have been published in 2007 (9). In 2010, EULAR has presented recommendations for the management of RA with synthetic and biological DMARDs, which have been updated in 2013 and 2016 (12,13); in addition, recommendations for the management of PsA were recently published (6). While the latter recommendations focused on the pharmacological treatments of PsA and RA, both in advanced and in early disease, the 2007 recommendations for the management of early arthritis covered the entire spectrum of management of early arthritis, including the recognition of arthritis, referral, diagnosis, prognosis, classification, information, education, non-pharmacological interventions and monitoring of the disease process as well as pharmacological treatment. The systematic literature review (SLR) that has guided the 2007 EULAR recommendations included publications up to January 2005 (9). Between 2005 and 2015 research in early arthritis has been a major focus, and many studies have appeared in the peer-reviewed literature. This literature includes - but is not limited to - topics such as diagnosis and classification criteria, window of opportunity, imaging, prognostication, treatments and therapeutic strategies.

These developments mandated an update of the existing EULAR recommendations on early arthritis, which is reported here.

METHODS

The update of the EULAR recommendations for the management of early arthritis has followed the 2014 EULAR Standardised Operating Procedures (14). The definitions (e.g., management and early arthritis) of and the target populations (rheumatologists, general practitioners, medical students, healthcare professionals, patients) addressed by the 2007 expert committee (9) were considered. Briefly, the term "management" was defined as "all organisational, diagnostic, medical and educational procedures related to patients seeking help for arthritis of a peripheral joint "and" early arthritis" was restricted to "early inflammatory joint disease".

The expert committee

The expert committee comprised 20 rheumatologists, including 2 research fellows (CD and CH), 1 health professional and 2 patients, from 12 European countries.

Fifteen research questions derived from the 2007 process were proposed by the convenor (BC) and the methodologist (RL), and subsequently amended and approved by the whole committee. The selected topics included recognition of arthritis, referral, diagnosis, prognostics, classification, information, education, non-pharmacological interventions, pharmacological treatments, monitoring of the disease process, strategy and prevention.

Evidence-based approach

The research questions were adjusted for further literature research if appropriate, and structured according to the Patients – Intervention – Comparator - Outcome (PICO) systematic by 4 of the authors (CD, CH, BC, RL). Eligible study types were also defined.

A systematic search of PubMed, Medline, Embase, CINAHL and the Cochrane library was performed, with the help of a skilled librarian (Louise Falzon, Columbia University Medical Centre, USA). All articles published in English up to December 2015 were included. Abstracts from the 2014 and 2015 EULAR and American College of Rheumatology (ACR)

conferences were also considered. The search was completed by a hand search and by questioning experts for additional references. The SLR process is reported in detail in two separate articles (15,16).

Expert opinion approach

Each member of the expert committee obtained insight into the results of the literature search and the accompanying levels of evidence before a meeting in January 2016. During the meeting, the results of the SLR were presented to the committee in aggregated format. Three break-out groups, chaired by one expert, were formed to amend the 2007 recommendations (1-4; 5-8 and 9-12) and to propose new recommendations if considered appropriate. Each group then reported its proposals and wording to the entire committee for discussion and consensus, and the final formulation of the recommendations was obtained after a vote with at least 85% agreement for each item's final wording.

After the meeting the recommendations were circulated by email to all expert committee members for further minor amendments if necessary. Categories of evidence and grades of recommendations were then determined (by CD, CH, RL, BC) according to the standards of the Oxford Centre for Evidence-Based Medicine (17). To determine the level of agreement with recommendations, an anonymized email-based voting on a 0–10 scale was performed, a vote of 0 indicating complete disagreement with a particular recommendation and 10 indicating complete agreement. The means and SDs for scores from the whole group were calculated. The recommendations are presented as a bulleted list and as a flow diagram of the various management steps (table 1; figure 1).

RESULTS

The discussions of the expert committee resulted in 3 overarching principles and 12 recommendations (Table 1) (in 2007, 12 recommendations were formulated).

Overarching principles

The expert committee considered that some of the principles on the care of patients with early arthritis are generic and should be stated first and separated from individual recommendations on diagnosis, prognosis and treatment. The committee decided unanimously on the following 3 overarching principles (Table 1).

Principle A:

Management of early arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.

The term "best care" is obviously a major principle in medicine. The wording "shared decision between the patient and the rheumatologist" is more than informing the patient; it rather refers to the comprehensive process of communication, knowledge exchange and achieving consensus that should lead to a treatment decision that is optimal from the perspectives of both patient and clinical care provider.

Principle B:

Rheumatologists are the specialists who should primarily care for patients with early arthritis.

This statement, which was part of recommendation 1 in the 2007 recommendations, was also highlighted in the EULAR recommendations for the management of RA (14) and PsA (6). Its basis is evidence that patients with chronic arthritis under rheumatologists' care receive an earlier diagnosis, start treatment earlier, and have better outcomes, in particular with respect to joint damage and physical function (18–20). Rheumatologists have the expertise to establish an accurate diagnosis of early arthritis, are familiar with monitoring disease activity and with the potential severity of the disease in their patients with inflammatory arthritis, and

are well aware of the indications, contraindications and adverse effects of specific therapies. However, the expert committee intentionally added the term "primarily" to this statement for three reasons: 1) the management of patients with early arthritis includes the care by primary care physicians and other health professionals in a multidisciplinary approach; 2) in some places care by rheumatologists is not always available and accessible. Some countries have a shortage of rheumatologists, and in such situations patients should receive treatment from other health care providers with experience in the care of patients with inflammatory arthritis. 3) in some countries, task shifting from rheumatologists to other health professionals is actively supported in order to facilitate early access and optimal quality of care, and to make care cheaper. Such care is still primarily under the responsibility and supervision of rheumatologists, but may be provided by other care providers.

Principle C:

> *A definite diagnosis in a patient with early arthritis should only be made after a careful history taking and clinical examination, which should also guide laboratory testing and additional procedures.*

In the 2007 recommendations, this important statement was included as bullet point 3. It was considered that "good clinical practice" and a "high level of training" suffices, an opinion that was entirely expert-based. The expert group was of the unanimous opinion that the statement is so generic that it represents an overarching principle rather than a recommendation. To establish a definite diagnosis in a patient with early arthritis, the group proposed that the minimum diagnostic procedures should include careful history taking and clinical examination, keeping the different possible causes of inflammatory arthritis in mind. After excluding other causes of joint swelling and pain (e.g., septic arthritis, trauma, osteoarthritis, gout) particular attention should be paid to age, geographical area and travel history, number and pattern of involved joints, axial/entheseal involvement and extra-

articular features (e.g., eye, skin, genito-urinal and gastrointestinal symptoms), including recent infections (1). A minimal laboratory testing panel was proposed in the 2007 recommendations and should include testing for C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR), full blood cell count, transaminase levels, renal function, and urine analysis, rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA) and anti-nuclear antibodies. In addition, the diagnostic procedure may be expanded with microbiology and/or serological tests (reactive arthritis, synovial fluid microbial culture, Lyme disease, parvovirus infection, hepatitis B or C), uric acid testing, synovial fluid analysis (cell count and polarized light microscopy if needed), chest and joint radiographs, but dependent on the context and the country.

Table 1: 2016 update of the EULAR recommendations for management of early arthritis: Final recommendations based on evidence and expert opinion

Overarching principles

A. Management of early arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B. Rheumatologists are the specialists who should primarily care for patients with early arthritis
C. A definitive diagnosis in a patient with early arthritis should only be made after a careful history taking and clinical examination which should also guide laboratory testing and additional procedures

Recommendations

1. Patients presenting arthritis (any joint swelling, associated with pain or stiffness) should be referred to, and seen by, a rheumatologist, within six weeks after the onset of symptoms.
2. Clinical examination is the method of choice for detecting arthritis, which may be confirmed by ultrasonography.
3. If a definite diagnosis cannot be reached and the patient has early undifferentiated arthritis, risk factors for persistent and/or erosive disease, including number of swollen joints, acute phase reactants, rheumatoid factor, ACPA and imaging findings, should be considered in management decisions.
4. Patients at risk of persistent arthritis should be started on DMARDs as early as possible (ideally within 3 months), even if they do not fulfil classification criteria for an inflammatory rheumatologic disease.
5. Among the DMARDs, methotrexate is considered to be the anchor drug and, unless contraindicated, should be part of the first treatment strategy in patients at risk of persistent disease.
6. NSAIDs are effective symptomatic therapies but should be used at the minimum effective dose for the shortest time possible, after evaluation of gastrointestinal, renal, and cardiovascular risks.
7. Systemic glucocorticoids reduce pain, swelling and structural progression, but in view of their cumulative side effects, they should be used at the lowest dose necessary as temporary (less than 6 months) adjunctive treatment. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.
8. The main goal of DMARD treatment is to achieve clinical remission, and regular monitoring of disease activity, adverse events and comorbidities should guide decisions on choice and changes in treatment strategies to reach this target.
9. Monitoring of disease activity should include tender and swollen joint counts, patient and physician global assessments, ESR and CRP, usually by applying a composite measure. Arthritis activity should be assessed at one to three month intervals until the treatment target has been reached. Radiographic and patient-reported outcome measures, such as functional assessments, can be used to complement disease activity monitoring.
10. Non-pharmacological interventions, such as dynamic exercises and occupational therapy, should be considered as adjuncts to drug treatment in patients with early arthritis.

11. In patients with early arthritis smoking cessation, dental care, weight control, assessment of vaccination status and management of comorbidities should be part of overall patient care.
12. Patient information concerning the disease, its outcome (including comorbidities) and its treatment is important. Education programs aimed at coping with pain, disability, maintenance of ability to work and social participation may be used as adjunct interventions.

NSAIDs, non-steroidal anti-inflammatory drugs; ACPA, anti-citrullinated peptide antibodies; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

Recommendations

The discussions of the expert committee culminated into 12 recommendations (Table 1). In comparison with 2007, the previous recommendation 3 was transformed into overarching principle C, while a recommendation for prevention (No. 11) was added. In addition, the order of the bullet points was slightly amended in order to better assure a logical sequence (and not for reasons of prioritization). Table 2 displays the levels of evidence and grades for the following recommendations based on the Oxford Levels of Evidence assessment as well as level of agreement after anonymized voting by the expert committee.

Recommendation 1:

Patients presenting with arthritis (any joint swelling, associated with pain or stiffness) should be referred to, and seen by, a rheumatologist, within six weeks after the onset of symptoms.

This recommendation is almost identical to its 2007 counterpart, but with subtle changes in the wording. After 2005, 2 studies have confirmed that patients with inflammatory arthritis in general, and those with suspected RA in particular, should be referred to rheumatologists as early as possible (19,20). A delay in referral is one of the most important causes of late diagnosis and late start of effective treatment. Patients with early arthritis referred to a

specialist within 3 months show better outcomes in terms of drug-free remission, radiographic damage and (less) need for orthopaedic surgery than those with late referral.(15). This is also fully in line with standards of care developed for patients with RA and quality indicators as established by European Expert committees (21).On the basis of these data as well as the clinical experience of the committee members it was recommended that diagnosis and start of treatment, both by a rheumatologist, should be established within a relatively short period after the onset of complaints which justifies the wording "within 6 weeks" in this recommendation.

Joint swelling not due to trauma or bony swelling suggests early inflammatory arthritis, especially if associated with pain and morning stiffness >30 min (22). Several referral questionnaires evaluating swelling, pain and stiffness have been developed to aid in the detection of early arthritis (15). These questionnaires have a good sensitivity (86-90%) and specificity (90%), but have been tested only in small patient samples and lack confirmation in independent validation cohorts. The committee was of the opinion that an appropriately validated tool to help general practitioners in adequately diagnosing and referring patients with early arthritis is currently lacking. The strength of this recommendation was considered 'good' (category B) (Table 2).

Table 2: Updated EULAR recommendations for management of early arthritis, with level of evidence (LoE), grade of recommendation (GoR) and level of agreement (LoA)

		LoE*	GoR*	LoA*
A.	Shared decision	na	na	9.87 ± 0.46
B.	Rheumatologists	na	na	9.78 ± 0.67
C.	Diagnosis	na	na	9.78 ± 0.67
1.	Early referral	Ib	B	9.43 ± 1.16
2.	Clinical examination	IIb	C	9.48 ± 0.99
3.	Prognosis	IIb	C	9.83 ± 0.49
4.	Early treatment start	Ia	A	9.35 ± 1.07
5.	MTX, the anchor drug	Ia	A	9.52 ± 0.99
6.	NSAIDs	IV	D	9.00 ± 1.13

7.	Glucocorticoids	Ia	A	9.00 ± 1.28
8.	Remission and treatment strategies	Ib,IV**	A,D	9.52 ± 0.9
9.	Regular monitoring	Ia,IV	A,D$	9.13 ± 1.06
10.	Non-pharmaceutical interventions	1a	B	8.96 ± 1.26
11.	Prevention	IIb,IV	C,D$	8.96 ± 1.19
12.	Patient information	Ia,Ib	B	9.35 ± 0.98

* LoE and GoR are based on the recommendations of the Oxford Centre for Evidence-Based Medicine. LoA was based on an anonymized email voting system with a 0-10 scale by all members of the expert committee (data are mean ± SD; 100% of voters)
** The general statement is evidence-based.
$ The place in the treatment algorithm is based on expert consensus.
na, not applicable; MTX, methotrexate

Recommendation 2:

Clinical examination is the method of choice for detecting arthritis, which may be confirmed by ultrasonography.

The expert committee unanimously appreciated the pivotal role of clinical examination. Clinical examination is still the cornerstone of detecting synovitis. This appreciation does not preclude that imaging modalities may be more sensitive in the detection of synovitis. Ultrasonography (US), including power Doppler techniques, may suggest synovitis by showing thickening of the synovial membrane, bursae and/or tendon sheaths with enhanced vascularity (15). Several controlled studies have suggested a greater sensitivity of US than clinical examination in detecting synovitis in the knee and in small joints. US has been evaluated in detail in the "EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis" (23). The expert committee did not recommend a more prominent role for US in the detection of synovitis, since it was broadly felt that potentially decreased specificity and lack of knowledge regarding the long-term consequences of positive US in individual patients did not currently justify a more prominent position for US. Further, wording specifically referring to power Doppler was deleted,

because the group considered that power Doppler should be part of every US joint examination anyway.

MRI has also been suggested to be more sensitive than clinical examination in the early detection of synovitis (23-25) but may face a lack of specificity as suggested by the prevalence of MRI abnormalities in the normal population (26). In contrast with US, which is now a common tool in many rheumatologist practices, the long scanning time, limited access and the relatively high costs limit the widespread use of MRI. Therefore, the expert committee considered that MRI should be proposed only in very difficult cases or in patients with specific forms of arthritis, and that further research is needed to better determine the place of this imaging modality in the diagnosis of patients with early arthritis. MRI was part of the 2007 recommendations but was deleted from the current set.

Recommendation 3:

> *If a definite diagnosis cannot be reached and the patient has early undifferentiated arthritis, risk factors for persistent and/or erosive disease, including number of swollen joints, acute-phase reactants, rheumatoid factor, ACPA and imaging findings, should be considered in management decisions.*

This recommendation was slightly rephrased because the group wanted to highlight that early undifferentiated arthritis should be clearly differentiated from early RA. In addition, "imaging" was used instead of "radiographic" to show that imaging modalities other than plain radiographs may provide prognostic information. For patients with early arthritis, after the exclusion of specific forms of arthritis, the working diagnosis is often undifferentiated arthritis. The next step in the diagnostic procedure is to evaluate the risk of persistent and/or erosive arthritis, usually corresponding to the definition of RA, in an individual patient (27). This prognostic typing is now considered crucial to guide the optimal therapeutic strategy.

Since the 2007 exercise, many observational studies have evaluated the prognostic value of laboratory and imaging procedures for early arthritis. Most prognostic factors were analysed

in a multivariate manner in these studies, to test their independent contribution. Commonly tested dependent variables were persistence, erosiveness or radiographic progression.

In most of the studies, ACPA- and RF-positivity and ACPA- and RF-levels have shown some predictive value for the development of persistent and erosive arthritis. This observation was clearly highlighted by EULAR and ACR since ACPAs, in addition to RF, have obtained an important weight in the 2010 ACR/EULAR classification criteria for RA (27,28). In addition, several recent studies have confirmed the independent association of ACPAs with a diagnosis of RA as well as with radiographic progression in patients with early arthritis (29-33). RF has been assigned a similar weight as ACPAs in the 2010 ACR/EULAR classification criteria for RA, although recent publications stemming from early arthritis cohorts and observational studies have suggested a lower predictive and diagnostic value of RF compared to ACPAs but RF has a stronger association with disease activity independent of the presence of ACPA (15). The combination of RF and ACPAs does not provide additional value to RF or ACPAs alone (28). In addition to ACPA, the number of swollen joints and the level of CRP and ESR are independent contributory factors.

Early erosion typical of RA is still a major prognostic factor in early arthritis and automatically leads to a classification of RA (27,34). Synovitis and erosion detected by MRI or US may predict further joint damage in early arthritis, but false positivity has been reported (26, 35). MRI-detected bone marrow oedema and osteitis are independent predictors of radiographic progression in early RA (23,24), but data are limited in early arthritis. Finally, 2 recent studies have shown that hand flexor or extensor tenosynovitis on US (36) or MRI (25) may be a specific- though not very sensitive - marker for RA classification.

Several combinations of diagnostic markers have been evaluated but no one has been formally validated (15). In addition, multibiomarker tests have been proposed to evaluate disease activity, prognosis and response to therapy, but current data are not convincing and

further research is warranted (15). Finally, it has been reported that substituting MRI for clinical examination in the 2010 ACR/EULAR criteria increases the sensitivity but decreases the specificity for a diagnosis of RA (15). MRI is therefore of limited value in making a diagnosis of RA and is not recommended as a standard procedure.

Recommendation 4:

> *Patients at risk of persistent arthritis should be started on DMARDs as early as possible (ideally within 3 months), even if they do not fulfil classification criteria for an inflammatory rheumatologic disease.*

This recommendation was slightly reworded and reiterates the unanimous opinion of the committee that an early treatment start is pivotal in the management of patients with early chronic arthritis such as early RA, early PsA, or those at risk to develop persistent and erosive disease. The wording "RA" is not used in this statement, but the implicit meaning is that persistent and/or erosive disease is factually synonymous to RA (see previous item) and justifies an early start with DMARDs. A new element is the maximum delay of 3 months after the onset of symptoms before starting the first DMARD. The expert committee was of the opinion that this time frame constitutes a 'window of opportunity' that should be considered to provide an optimal outcome in the patients at risk. Eight recent studies have endorsed an early treatment start. Four studies showed that introducing DMARDs within 3 months after the onset of symptoms leads to better outcome (remission, response to treatment, Health Assessment Questionnaire [HAQ] disability score or radiographic progression) (37-40). Very recently, van Nies et al. have suggested, based on data in the ESPOIR and Leiden early-arthritis cohorts, that 12 to 14 weeks represent an appropriate window within which therapy should be started in order to prevent arthritis persistence (41). In addition, disease duration at the time of DMARD initiation was the most important determinant of response to DMARD therapy in another study (15). This statement may raise questions about the best definition for 'early RA'. A duration of 3 months after the onset of

symptoms may be the longest allowable delay in prescribing the first DMARD. However, this maximum delay is still difficult to meet in daily practice, while most of the recent 'early RA-cohorts' allowed a delay of 6 months from the onset of symptoms (joint swelling usually) for inclusion (28,29,41). A delay of not more than 6 months was also proposed in recent RA guidelines (42). A delay of more than one year from symptom onset must not be considered "early" anymore.

Recommendation 5:

Among the DMARDs, methotrexate is considered the anchor drug and unless contraindicated, should be part of the first treatment strategy in patients at risk of persistent disease.

This recommendation (previously No. 9) remains almost unchanged. Previous SLRs have confirmed the clinical and structural efficacy as well as the good safety profile of methotrexate (MTX) (4,43,44). An important argument to consider MTX an anchor drug as part of the first treatment strategy in patients at risk of persistent arthritis (e.g., at risk of RA) is its good efficacy in early RA, and its 'practicability', both as monotherapy and in combination with glucocorticoids, other csDMARDs and bDMARDs) (4,13,45). Recent trials in early DMARD-naïve RA patients have evaluated MTX monotherapy versus csDMARDs combined with different dosages and routes of administration of glucocorticoids. Verschueren et al. have recently reported similar 16-week remission rates in high-risk early-RA patients receiving MTX-monotherapy, MTX plus sulfasalazine (SSZ) or MTX plus leflunomide (LEF), all in combination with high-dose prednisone bridging strategies (46). In another trial MTX plus temporary high-dose prednisone was not less effective than MTX plus SSZ plus temporary high-dose prednisone after 26 weeks (47). The tREACH trial suggested short lived superiority of MTX combined with SSZ, hydroxychloquine (HCQ) and glucocorticoids versus MTX and glucocorticoids, but this superiority was not seen in all aspects, was not clinically meaningful and did ultimately not sustain after 1 year (48). The

TEAR trial did not support a benefit of an intensive csDMARDs combination regimen over MTX-monotherapy either (49). In the absence of clear signals for superiority of a csDMARDs combination regimen, and guided by a trend towards lower tolerability for csDMARD-combination (16), the committee was of the opinion that the first treatment strategy should be MTX monotherapy with or without short term high dose glucocorticoids as bridging therapy for most patients. In that regard, dose optimization is an important aspect of first-line DMARD strategy, as previously reported (4,45) (MTX should be titrated rapidly to 20-30 mg/week, depending on clinical response and tolerability; parenteral administration should be considered in case of inadequate clinical response or intolerance).

The superiority of bDMARDs plus MTX over MTX monotherapy has been proven in many randomized controlled trials (RCTs) and was confirmed by 8 recent studies in the current SLR (16). In addition, 2 targeted synthetic DMARDs have recently demonstrated superiority to MTX, both used as monotherapy, in patients with early RA (50,51). Nevertheless, because the benefit-to-risk ratio of these biologic and targeted synthetic DMARDs was not convincingly favourable in patients with early disease, because tight monitoring is anyway part of the current treatment strategy to identify those in need of adding biologics and also because of their high cost, the expert committee considered their use as a first treatment strategy inappropriate, except in rare situations.

Recent RCTs comparing other csDMARDs to MTX were lacking. The clinical efficacy of LEF, and to a lesser extent SSZ, is similar to MTX in established and recent RA (9). LEF is as effective as MTX in slowing radiographic damage, and its therapeutic maintenance is similar to that of MTX (9) In contrast, SSZ may be inferior to LEF and MTX in the long term. Although formal evidence prioritizing MTX over other csDMARDs as the first DMARD used in early arthritis and/or early RA is lacking, the expert committee does recommend MTX as first-choice treatment (unless contra-indicated) in patients at risk of

persistent disease. LEF and (to a lesser extent) SSZ are considered the best alternatives. Of note, SSZ is considered safe during pregnancy in contrast to MTX and LEF. Finally, the committee is of the opinion that antimalarial drugs, which have shown less clinical efficacy and may not retard radiographic progression in patients with RA but may have positive metabolic effects, can be considered as partner in combination therapy or as DMARD monotherapy in patients with mild disease and comorbidities or with persistent arthritis other than RA (52)**.**

Recommendation 6:

NSAIDs are effective symptomatic therapies, but should be used at the minimum effective dose for the shortest time possible, after evaluation of gastrointestinal, renal and cardiovascular risks.

The SLR did not yield new data on NSAIDs in patients with early arthritis. The expert committee felt that symptomatic therapy with NSAIDs is still of value in patients presenting with early arthritis, but only after a careful consideration of gastrointestinal, renal and cardiovascular contraindications. In addition to the previous item no 7 about NSAIDs, the group now reinforces the need to follow US Food and Drug Administration and European Medicines Agency guidelines about NSAIDs, that now includes wording about the shortest possible treatment duration, the minimum effective dose and the contra-indications for patients at risk (www.fda.gov; www.ema.europa.eu).

Recommendation 7:

Systemic glucocorticoids reduce pain, swelling and structural progression, but in view of their cumulative side effects, they should be used at the lowest dose necessary as temporary (less than 6 months) adjunctive treatment. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.

The expert committee has intensively debated the role of glucocorticoids in the management of early arthritis. This discussion was based on expert opinion and on new information obtained by the SLR (16). Recently, one meta-analysis of 14 RCTs in patients with RA and 2

RCTs in patients with 'early RA' has confirmed that systemic glucocorticoids (GC) improve clinical and radiographic outcomes (16, 53, 54). Preferably, therapy with systemic GC is temporary because of the risk of side-effects, including weight gain, hypertension, diabetes, cataracts and osteoporosis, which justify careful monitoring and appropriate prevention. New data stemming from registries, observational studies and extensions of RCTs have also suggested an increased risk of severe infections, cardiovascular events and mortality (16, 55-60). In addition, there is evidence that intra-articular steroids may be an effective adjunct to DMARDs in relieving joint symptoms in patients presenting with early arthritis and may improve disease activity up to 24 months (16).

The committee has reworded this item (No. 8 in the previous recommendations) in order to highlight the effectiveness of systemic GC for relieving symptoms and disease progression but also in order to point to the risks of cumulative side effects in the medium to long term. The committee is of the opinion that GC can only be justified if used at the lowest possible cumulative dose, and for the shortest possible duration, and exclusively as adjunct (or: bridge) therapy to csDMARDs. GC monotherapy may mask disease activity before a diagnosis has been established and should be avoided in patients with early arthritis, in order to expedite a proper diagnosis, and secure an adequate prognosis and a prompt DMARD treatment start. Despite a fierce debate this recommendation was finally approved by 95% of the members and obtained a high level of agreement (mean of 9.00 ± 1.28) with anonymous voting. The wording "low dose" and the optimal regimen (low daily dose or high dose then step-down or parenteral boosts) in early arthritis are still under debate and will be mentioned in the research agenda (table 3).

Recommendation 8:

The main goal of DMARD treatment is to achieve clinical remission, and regular monitoring of disease activity, adverse events and comorbidities should guide decisions on choice and changes in treatment strategies to reach this target.

The 2007 recommendations for patients with early arthritis were among the first guidelines to highlight clinical remission as the main objective in the care of these patients. In the past 10 years, accumulating data have supported this as a major goal for the treatment of RA and other inflammatory arthritides (6,9,11,13,61).

The expert committee has decided to keep the wording of the previous recommendation No. 10 unchanged. A few new studies have confirmed that achieving clinical remission as early as possible results in better clinical outcomes and quality of life, and helps to prevent further structural damage, functional disability and job-loss in patients with early arthritis and early RA (62). Which particular remission criteria should be used in practice remains unclear. Composite scores (DAS, DAS28, CDAI, SDAI) should be used, and the ACR-EULAR remission criteria (Boolean or SDAI) is likely the most stringent (63). An interesting definition for daily practice is "the absence of signs and symptoms of significant inflammatory disease activity"(11). Recent evidence has suggested that remission leads to a better outcome than low disease activity (LDA) (62, 64, 65), and the committee was of the opinion that clinical remission according to the ACR-EULAR Boolean or index-based definition is the target for every patient presenting with early arthritis. A low disease activity state (LDA) could be an appropriate alternative goal only in cases in which remission is considered unfeasible. In this respect, factors such as comorbidities, age or adverse events must be considered, and may determine the desired treatment target, which will form the basis for the process of shared decision making with the patient.

The expert committee also discussed whether imaging remission should be included in the target, as suggested by some recent recommendations (23). Studies have suggested that on-going inflammation seen by US, and to a lesser extent by MRI, in patients with clinical remission may predict structural progression. However, the significance thereof and its clinical utility are questionable and is associated with significant overtreatment and thus

potential waste of societal resources (66); the SLR did not yield new information (15,16). Therefore, the expert committee suggested that the value of imaging remission should be part of the research agenda.

Finally, the committee felt that disease activity should be closely monitored in order to allow a timely change in DMARD therapy when necessary. The benefits of the treat-to-target approach have now amply been shown in patients with RA and PsA (11, 67)) and there is no reason to assume that the situation is different for early arthritis.

Recommendation 9:

> *Monitoring of disease activity should include tender and swollen joint counts, patient's and physician's global assessments, ESR and CRP, usually by applying a composite measure. Arthritis activity should be assessed at one to three month intervals until the treatment target has been reached. Radiographic and patient reported outcome measures, such as functional assessments can be used to complement disease activity monitoring.*

In every patient with active arthritis, closely monitoring disease activity is now considered of particular importance in the therapeutic strategy to provide a good outcome and this is highlighted by all of the most recent recommendations (6, 9, 11, 13, 42, 61). Monitoring disease activity should be as frequent as the level of disease activity mandates, usually every 1 to 3 months, then potentially less frequently (such as every 6 to 12 months) once the treatment target has been achieved.

Nevertheless, three changes were proposed to this item (previously No. 12). First, a composite measure was recommended as the method of choice to monitor disease activity; second, a specific time frame for monitoring structural damage was deliberately left out; and third, patient-reported outcomes were expanded beyond functional assessments.

Swollen joint count and progression of joint damage have been consistently found to be associated (68, 69). In addition, many trials have supported the use of a tight control of disease activity assessed via composite measures that include joint count evaluation (11,16, 67, 70). Although it is difficult to formally investigate, the expert committee was of the

opinion that monitoring the occurrence of radiographic progression is useful in view of one of the key objectives of managing early arthritis: the prevention of joint destruction. The determination of an optimal window for monitoring progression was added as an item for the research agenda (table 3).

Finally, patient-reported outcomes such as quality of life, fatigue and physical function are key to evaluate outcome (71, 72) and the committee has mandated them as part of disease monitoring.

Table 3: Research agenda for management of early arthritis

Diagnosis and prognosis
1. Which tools could help general practitioners to diagnose early arthritis and prioritise referral?
2. Can we better define the diagnostic and prognostic value of ultrasonography in early arthritis?
3. Can we better define the diagnostic and prognostic value of MRI in early arthritis?
4. What is the diagnostic value of the systematic screening of antinuclear antibodies in early arthritis?
5. Which new biomarkers / multibiomarkers may help to better evaluate disease activity, the prognosis and arthritis?

Treatment and outcome
1. Can we develop prediction models to better define the therapeutic strategy in early arthritis?
2. Can we define at what level of risk (for developing persistent arthritis) different pharmacological interventions have a favorable benefit to-risk ratios?.
3. Do combinations of csDMARDs provide a better benefit / risk ratio than csDMARD monotherapy in early arthritis ?
4. Can we better define "low dose", and "short term" use of glucocorticoids for an optimal medium to long term benefit to risk ratio?
5. What is the optimal regimen (low daily dosage or high dose then step-down, or parenteral boosts) of glucocorticoids for better outcome in early arthritis ?
6. Does imaging remission have an added benefit to clinical remission in treatment decisions?
7. What is the optimal interval at which to monitor radiographic progression in early chronic inflammatory arthritis?
8. What is the effectiveness of different non-pharmacological interventions in early arthritis ?
9. Can physical activity/exercise reduce cardiovascular risk in early chronic arthritis?
10. Which study designs can best be used to investigate the comparative effectiveness and cost-effectiveness of different therapeutic strategies?
11. Is smoking cessation, oral hygiene, diets, or psychological interventions beneficial for the outcome of patients with early arthritis ?
12. What are the most efficient and effective information and education interventions and exercise

programs for early arthritis?

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Recommendation 10:

Non-pharmacological interventions, such as dynamic exercises and occupational therapy, should be considered as adjuncts to drug treatment in patients with early arthritis.

This recommendation has remained almost unchanged. The efficacy of non- pharmacological therapy has not been investigated in early arthritis and can only be extrapolated from the results of several RCTs in established RA. Hydrotherapy in patients with RA has been evaluated in some studies (73, 74) but with insufficient evidence to support a strong recommendation; consequently, hydrotherapy was not included in the current statement but may be considered at the individual patient level. Previous RCTs have shown that joint-specific dynamic exercises may improve strength and physical function in RA, but the current SLR identified some controversial effects on disease activity (16, 74). Occupational therapy may improve functional ability and self-management but does not have a positive effect on disease activity; recent studies were not found (75).

Finally, psychological counselling can be considered in selected patients, but trials investigating the efficacy of psychological interventions are lacking, and the committee did not include counselling in the statement. Furthermore, the SLR did not identify appropriate trials that evaluated the effectiveness of diets.

Since dynamic exercises, occupational therapy and to a lesser extent hydrotherapy have been associated with symptom relief in patients with established RA, the expert committee has decided to include them as adjunct therapies to pharmaceutical therapies in patients with early arthritis.

Recommendation 11:

In patients with early arthritis smoking cessation, dental care, weight control, assessment of vaccination status and management of comorbidities should be part of overall patient care.

This recommendation is new and largely based on expert opinion. The expert committee felt that during the last decade evidence has accumulated that highlights the importance of the management of comorbidities (e.g. cardiovascular diseases, metabolic conditions (e.g., hyperlipidaemia, diabetes), lung diseases, infections, malignancies, osteoporosis and depression) in the context of the management of early arthritis (76-82). Comorbidities may affect life expectancy and outcomes (physical function, quality of life) independently of disease activity in patients with inflammatory arthritis. In addition, coexisting diseases may affect the efficacy and safety of anti-rheumatic therapies (82). Obesity and smoking may affect the response to treatment in inflammatory arthritis (80). Prevention is now considered key in the management of chronic inflammatory rheumatic diseases, but comorbidities are still not optimally managed (76). Smoking is the best-established modifiable risk factor in the development of RA and spondyloarthritis (83,84). Furthermore, tobacco use has been associated with the presence of extra-articular manifestations such as rheumatoid nodules but also serum RF and ACPAs. While smoking does not seem to be associated with the perpetuation of disease activity or progression of RA (85), it may affect the outcome of spondyloarthritis (84).

RA is associated with periodontal disease, although the direction of the relationship still remains unclear (86). The microbiome may play a role in chronic arthritis risk and progression, and *Porphyromonas gingivalis* infection could promote aberrant citrullination and a local breach of tolerance to citrullinated peptides. The potentially beneficial contribution of oral hygiene has been put on the research agenda.

Although current data do not prove that risk-factor modification is beneficial to patients, the modifiable risk factors identified in the SLR are so generic in nature that the committee was

unanimously of the opinion that a recommendation aiming at abolishing their potential influence on arthritis (and general health) would not harm patients and may convey some benefits.

In addition, the expert committee noted that fewer patients with chronic arthritis than recommended are currently vaccinated (87), and that this should be specifically mentioned.

Recommendation 12:

> *Patient information concerning the disease, its outcome (including comorbidities) and its treatment is important. Education programs aimed at coping with pain, disability, maintenance of ability to work and social participation may be used as adjunct interventions.*

This recommendation was very similar to the previous item no. 6. Obviously, full transparency about the disease and its treatment options should be an integral part of the management of any chronic disease, and constitutes the core of overarching principle A. Other healthcare providers share the responsibility in the provision of information. Studies have suggested that adherence to treatment is dependent on the quality of information exchange and the quality of the interaction between the patient and health professionals, including rheumatologists (16).

EULAR has recently recommended that "people with inflammatory arthritis should have access to and be offered patient education throughout the course of their disease, including as a minimum, at diagnosis, at pharmacological treatment change and when required by the patient's physical or psychological condition" (88). The content and delivery of patient education should be individually tailored, with individual and group sessions representing different approaches to delivery. It is impossible to prioritise a single educational intervention since all tested interventions have only short-term benefits and feature cross-national and cultural variations (16). Improved quality of life is a major aim for patients and the committee proposed to add "social participation" as one of the objectives of these education programs.

The expert committee also felt that patients should be aware that comorbidities may affect the outcome and treatment of inflammatory arthritis, and that their screening and management should be part of the global management of early arthritis.

DISCUSSION

The update of the EULAR recommendations for the management of early arthritis followed the 2014 EULAR Standardised Operating Procedures (14). The committee has proposed an important revision of the items, but obviously most major recommendations have remained intact. These updated recommendations for management of early arthritis contain 3 overarching principles, 12 recommendations and 2 algorithms that integrate all the recent developments in the management of early arthritis. The definition of the term "management" was unchanged and includes all spectra of management of early arthritis, including referral, diagnosis, prognosis, classification, information, education, non-pharmacological interventions, and pharmacological treatments and monitoring of the disease. The term "early arthritis" was restricted to "early inflammatory arthritis" and mainly, but not only, focused on the risk of chronic arthritis.

The expert committee had to face a limitation in that most of the published data on treatment and strategy on which they could build their recommendations involved studies in patients with early RA or established RA, rather than specific studies of early arthritis. Despite this limitation, the committee considered much of the data for early RA sufficiently robust and relevant for extrapolating to "early arthritis with a certain propensity to become persistent." The scope was different compared to the EULAR recommendations for the management of RA (13), which focussed on the use of DMARDs in both early and established disease. However, there are overlaps with regard to the first line therapy for early arthritis at risk of persistence (figure 1) and for early RA (DMARD naïve and usually less than 6 months

disease duration). Not surprisingly, the 2 sets of recommendations are very congruent on these specific points.

These recommendations have important strengths including the composition of the expert committee comprising 20 rheumatologists, including 2 research fellows, from 12 European countries and new addition of 1 health professional and 2 patient-representatives. 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 was always whether the type of study fitted the content of the research question that was at the basis of the literature search. The recommendations were based on the most recent evidence but also on expert opinion. For example, the expert committee felt that evidence supported comorbidities as possibly affecting the outcome of arthritis but also treatment efficacy and safety and should be considered in the management of all early arthritis cases. Despite the sparse evidence, the expert committee also wanted to indicate that smoking cessation and dental care could be proposed to patients with early arthritis, and that both patients and health professionals should be aware of the importance to improve vaccination coverage. In this respect, a new recommendation on prevention was added (item 11). Of note, the level of agreement among the experts was high for each item (means of 9.0 to 9.9), which support the appropriateness and validity of the recommendations.

In light of the current literature and despite important recent advances, the committee felt that further development of new tools is needed for early and accurate diagnosis and prognosis, including new biomarkers, better understanding of the added value of US and MRI, and creation of prediction algorithms for long-term outcome (table 3). Finally, the expert committee felt that the comparative effectiveness and cost-effectiveness of the different

strategic modalities in early arthritis, including the effectiveness of non-pharmacological interventions, need additional research.

While these “recommendations” are deliberately not called “guidelines”, they do reflect a strong view of many European experts including patient representatives. They should provide rheumatologists, general practitioners, medical students, health professionals, health authorities and patients a practical approach to the management of early arthritis, even though each healthcare professional should choose the most appropriate management strategy for each individual patient. To that end, it is hoped that the recommendations will be widely disseminated and discussed within the community of rheumatologists and other health professionals caring for patients with early arthritis and that they will help improve the standard of care for patients with arthritis across different healthcare systems. Obviously, these recommendations will probably need amendment after about 5 years to incorporate new scientific evidence.

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