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EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria

Désirée van der Heijde,[1] Annette H M van der Helm-van Mil,[1] Daniel Aletaha,[2] Clifton O Bingham,[3] Gerd R Burmester,[4] Maxime Dougados,[5] Paul Emery,[6] David Felson,[7,8] Rachel Knevel,[1] Tore K Kvien,[9] Robert B M Landewé,[10] Cédric Lukas,[11] Iain McInnes,[12] Alan J Silman,[13] Josef S Smolen,[2] Ewa Stanislawska-Biernat,[14] Angela Zink,[15] Bernard Combe[11]

Handling editor Hans Bijlsma

For numbered affiliations see end of article.

Correspondence to
Professor Désirée van der Heijde, Department of Rheumatology, Leiden University Medical Center, PO Box 9600, Leiden 2300 RC, The Netherlands; mail@dvanderheijde.nl

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ABSTRACT

The aim of this report was to propose a definition for erosive disease in the context of inflammatory arthritis in light of the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) rheumatoid arthritis (RA) criteria for use in clinical practice and studies. A EULAR task force was formed including 16 rheumatologists and one rheumatology fellow. The process was both evidence based and consensus based, and included, between March 2010 and April 2012, analyses of data from two cohorts, two face-to-face meetings, one online voting and one teleconference. The Leiden Early Arthritis Cohort and the French ESPOIR cohort were used for the evidence-based part. The outcome measures, which were initiation of methotrexate therapy, or any disease-modifying antirheumatic drug therapy within the first year of disease and arthritis persistency over 5 years, were studied with the aim to give the best definition of erosive disease. A decision was made to select a definition with a high specificity and focus on patients who did not otherwise fulfil the 2010 ACR/EULAR RA criteria (<6 points). By a unanimous vote the following definition was selected: erosive disease for use in the 2010 ACR/EULAR RA classification criteria is defined when an erosion (defined as a cortical break) is seen in at least three separate joints at any of the following sites: the proximal interphalangeal, the metacarpophalangeal, the wrist (counted as one joint) and the metatarsophalangeal joints on radiographs of both hands and feet. A highly specific definition for erosive disease has thus been formulated.

INTRODUCTION

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) rheumatoid arthritis (RA) classification criteria were recently published.[1] The main reason for the development of this new scoring system was the low sensitivity of the 1987 ACR criteria in early disease. These new criteria focus on features at early stages of arthritis that are associated with persistent and/or erosive disease.

Because the aim of the new classification criteria was to enable diagnosis and treatment earlier in the course of disease in order to prevent disease complications and particularly joint destruction, erosions were not considered for inclusion in the scoring system. However, as stated by the working group, patients with erosions typical of RA were deemed to have prima facie evidence of RA and can be classified as such.[1] It was also acknowledged that a definition was needed of what is meant by significant erosive disease either in terms of the size, site or the number of erosions. The group decided that future work would be needed to define what evidence of erosions is acceptable to be considered 'typical' of RA. It was also considered that such agreement could be the task for further consensus, although current evidence suggests that such a definition should be highly specific.[2]

In the official presentation of the 2010 ACR/EULAR RA criteria on the websites of the ACR and EULAR, it is not recommended to obtain radiographs for the mere purpose of classification as these are not required for scoring by the 2010 ACR/EULAR classification criteria.[3 4] One exception, however, is the unclassified patient in whom long-standing but inactive disease is suspected as they might have been misclassified as not having RA. Furthermore, if radiographs are already available (eg, taken by the general practitioner before referral) in an early arthritis patient, their information can be taken into consideration for classification purposes. In these circumstances, the presence of typical erosions should allow a classification of RA even with a score of less than 6/10.

In 2010 a task force was established by EULAR to propose a definition for erosive disease ('typical erosions') in light of the 2010 ACR/EULAR RA criteria. It was decided to have the recommendation evidence based as far as possible. The current report presents the final recommendation from this task force, while the data analyses that formed the basis for the evidence are being published as a companion paper.[5]

METHODS

A project group was formed by the authors of this paper under the auspices of EULAR and consisted of 16 rheumatologists and one rheumatology fellow. The members of this task force came from seven European countries and the USA. The ACR had been invited to participate but ultimately did not join this activity due to procedural reasons and therefore it was commonly agreed that the project

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would be carried out by EULAR. The process, which took place between March 2010 and April 2012, was based on both evidence and consensus, and included analyses of two databases, two face-to-face meetings, one online voting and one teleconference. The EULAR procedures on the development of recommendations were followed and the EULAR executive committee approved the final paper. The analyses of two cohorts, the Leiden Early Arthritis Cohort and the French ESPOIR cohort, with the aim of best defining erosive disease with the outcome measures being the initiation of methotrexate therapy, or any disease-modifying antirheumatic drug therapy within the first year of disease and arthritis persistency over 5 years, are published separately.[5–7] Erosion for this work was defined as a break in the cortex on a radiograph.

RESULTS

The aim of the task force was to derive and recommend a definition of erosive disease, which could be applied both in clinical practice and in studies. The two circumstances, as defined by the working group on the 2010 ACR/EULAR classification criteria for RA, in which there is a need for the definition of erosive disease, refer to patients who may have clinical RA but who do not meet the current classification. This could include patients with long-standing but inactive disease, and patients with (frequently early) undiagnosed disease in whom radiographs are available. The first group of patients are unlikely to be included in clinical trials of RA, the situation in which classification criteria will mostly be used. So the most important scenario seems to be the undiagnosed patient who has active disease and has radiographs available. Consequently, the task force decided to focus on the group of early arthritis patients for the evidence-based part of the recommendation.

The task force agreed to provide a highly specific definition for erosive disease, in line with the recommendation of the working group on the 2010 ACR/EULAR classification criteria for RA, stating that it should be possible to classify patients as having RA based on erosive disease on radiographs alone. Consequently, the likelihood of a false-positive classification based on a too non-specific definition of erosive disease should be very low. Lack of sensitivity is not a major issue here, as patients can still fulfil the criteria according to the usual classification. It was decided that the specificity should be at least 0.80 but preferably 0.90 or greater.

Data obtained from the analyses of the two early arthritis cohorts were discussed by the members of the task force, additional analyses were performed and the final data were shared. Finally, an online voting was set up in which each member of the task force could vote for a definition of the cut-off for erosive disease. Members were asked to select both their first and their second choice for a cut-off. It was decided before the online vote took place that in the case of lack of concordance (at least two out of three of the votes), the outcome of the vote would be discussed by teleconference, and a final decision would be made.

The preferred cut-off selected by six (50%) of the task force members was two erosive joints; one member voted for one erosive joint in an appropriate clinical context, otherwise two joints; another member voted for three erosive joints, two members voted for four erosive joints, and one member for five erosive joints. One member did not make a choice. The responses to their second choice for the cut-off showed more members selecting a higher cut-off; 10 members voted for a cut-off of three joints or higher.

Box 1

Erosive disease for use in the 2010 ACR/EULAR rheumatoid arthritis classification criteria is defined when an erosion (defined as a cortical break) is seen at at least three separate joints at any of the following sites: the PIP joints, the MCP joints, the wrist (counted as one joint) and the MTP joints on radiographs of both hands and feet.

During the following teleconference, there was a unanimous vote for at least three erosive joints. An erosive joint can have one or more erosions. These joints can be at one or more of the following sites: proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, wrist (counted as one joint) and metatarsophalangeal (MTP) joints on radiographs of both hands and feet. If bilateral joints are affected, these count as two joints; three joints in the same joint group (eg, MCP) fulfil the definition. So every combination of joints can be used to arrive at the sum of three joints (see box 1).

DISCUSSION

The analyses of the two early arthritis cohorts provided useful data to make an evidence and consensus-based definition possible. There are several strengths in the use of these two cohorts. First, both cohorts had a large number of patients included, comprised patients with (relatively) short symptom duration and included patients who did and did not fulfil the 2010 ACR/EULAR RA classification criteria, had several outcomes available that could be used as an external standard, are representative of patients referred to rheumatologists, and all radiographs were scored by one person per cohort. Possible limitations are the fact that the radiographs were scored by a trained observer, which reduces the generalisability for use in clinical practice by untrained observers. Moreover, the joints included in the Sharp–van der Heijde method are the only joints that could be included in the analyses. On the other hand, these are the joints that are most frequently involved in RA, which is also the reason for their being included in the score. Moreover, the wrist was counted as only one joint in the analyses, which may spuriously have limited the contributory influence of the wrist. Finally, we used ‘erosive joint’ as the unit of measurement and not ‘an erosion’. The reason for this was that an erosion score of, for example, ‘2’ in a joint could be based on one large erosion or two smaller erosions, which could not be distinguished in the cohorts without rescoring all the films. However, it is well known that joints that are erosive are prone to further (erosive) destruction, so the count of different joints with erosions leads to a more specific definition, which was our aim.[8 9]

A strength of the outcome is the consistency of the data: both cohorts and all different outcome measures provided the same results for the various cut-offs of erosive joints tested. The specificity of the sites of the involved joints could be tested: for example, is an erosive joint in the MTP more or less specific in comparison to an erosive joint in the PIP. This turned out not to be the case and therefore the recommendation can be given for all joint sites in the hands and feet.

As already published in a limited analysis of the Leiden Early Arthritis Cohort, a high number of erosive joints is needed to reach the predefined minimum of specificity, with fulfilment of

the 1987 RA criteria and persistent disease as external standards.[2] Only with a cut-off of at least three erosive joints does the specificity consistently exceed 0.80 and frequently reach over 0.90 in all the different settings tested. A possible reason that one erosive joint is not very specific is that an erosion can also be seen in other types of arthritis. Moreover, there is always measurement error involved, which is reduced with a cut-off of three erosive joints (it is more likely that the patient indeed has true erosions when having three erosive joints as compared to a patient with one erosive joint).

The task force paid most attention to the group of patients that did not fulfil the ACR/EULAR 2010 criteria, due to not having a total of six points. Especially in this group of patients the cut-off of at least two erosive joints resulted in specificity of less than 0.80 in several settings, while the cut-of of three erosive joints led in all settings to a specificity greater than 0.85 and in all but one greater than 0.90.

The proposed definition is indeed highly specific, which is expectedly at the cost of sensitivity. Depending on the setting, the sensitivity ranges from 0.15 to 0.29. This was a deliberate choice made by the task force, and in line with the recommendation of the working group for the 2010 ACR/EULAR RA classification criteria. Consequently, only a few patients (3.3% of the studied early arthritis patients from both cohorts) will be classified as RA based solely on the presence of erosive disease, while not fulfilling the six points needed for the regular classification. This is probably higher in the second target group: patients with long-standing, inactive disease. However, we did not test this, which is a research question for further studies. It should be stressed, however, that the current definition is for use with the 2010 ACR/EULAR RA classification criteria, which is mostly needed for clinical trials. In clinical practice, when sensitivity is more important, rheumatologists might consider patients with fewer erosions already as having erosive disease for the purpose of treating the patients.

In conclusion, we present a definition of erosive disease in light of the 2010 ACR/EULAR RA classification criteria. This is a highly specific definition, consequently with few misclassifications of patients having RA based solely on the presence of erosive disease. The use of this definition in different settings will provide further insight into the proportion of patients with a 2010 ACR/EULAR RA classification based solely on the presence of erosive disease.

Author affiliations
[1]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[2]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria
[3]Division of Rheumatology, Johns Hopkins University, Baltimore, Maryland, USA
[4]Department of Rheumatology and Clinical Immunology, Charité—University Medicine, Berlin, Germany
[5]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France
[6]Section of Musculoskeletal Disease, Leeds MSK Biomedical Unit LTHT, Leeds University, Leeds, UK
[7]Boston University School of Medicine, Boston, Massachusetts, USA
[8]University of Manchester, Manchester, UK
[9]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[10]Department of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam and Atrium Medical Center, Heerlen, The Netherlands
[11]Department of Rheumatology, Lapeyronie Hospital, UMR 5534, Montpellier I University, Montpellier, France
[12]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK
[13]Arthritis Research UK, Chesterfield, Manchester, UK
[14]Rheumatology Clinic, Institute of Rheumatology, Warsaw, Poland
[15]Department of Epidemiology, German Rheumatism Research Centre Berlin, Berlin, Germany

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Notes