Management of contemporary early undifferentiated arthritis: data on EULAR's recommendation on the risk of persistent disease

Hollander, N.K. den; Verstappen, M.; Huizinga, T.W.J.; Helm-van Mil, A. van der

Management of contemporary early undifferentiated arthritis: data on EULAR's recommendation on the risk of persistent disease

Early treatment initiation is crucial to improve long-term outcomes in rheumatoid arthritis (RA). This may also apply to undifferentiated arthritis (UA), patients at high risk of persistent arthritis/RA. Therefore, the EULAR recommendations for early arthritis recommend assessing the following risk factors for disease persistency in early UA: number of swollen joints, acute phase reactants (ie, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), rheumatoid-factor (RF), anti-citrullinated protein antibodies (ACPA) and imaging findings/erosions.[1 2] This recommendation was based on markers identified as predictive in a systematic literature review.[2] Importantly however, prognostic research in UA is based on an outdated definition of UA: not meeting 1987-RA-classification criteria and having no alternative diagnosis ('conventional UA'). A proportion of these patients with conventional UA meet the 2010-RA-criteria and is currently considered to have RA.[3–5] Contemporary UA, in contrast, is defined as neither meeting the 1987-RA-criteria nor the 2010-RA-criteria and having no other clinical diagnosis. In addition, for some of the recommended risk factors data were lacking in the systematic literature review (polyarthritis) or it was concluded that adequately designed studies were lacking (CRP and ESR).[2] Since predictors may be disease stage or population dependent, and because predictors for persistent disease identified in conventional UA may not be applicable to contemporary UA, we conducted a large cohort study in contemporary UA to assess risk factors for persistent disease mentioned in the current EULAR recommendation. Conventional UA was studied for comparison.

In short, 710 patients with contemporary UA, not fulfilling 1987-RA-criteria or 2010-RA-criteria and having no alternative diagnosis, consecutively included in the Leiden Early Arthritis Clinic cohort between 2006–2019, when disease-modifying anti rheumatic drug (DMARD) start in UA was recommended, were studied (online supplemental figure 1). The cohort is described in detail elsewhere.[6] At inclusion swollen joint counts and laboratory procedures were performed, including: ACPA (EliA CPP (anti-CCP2),

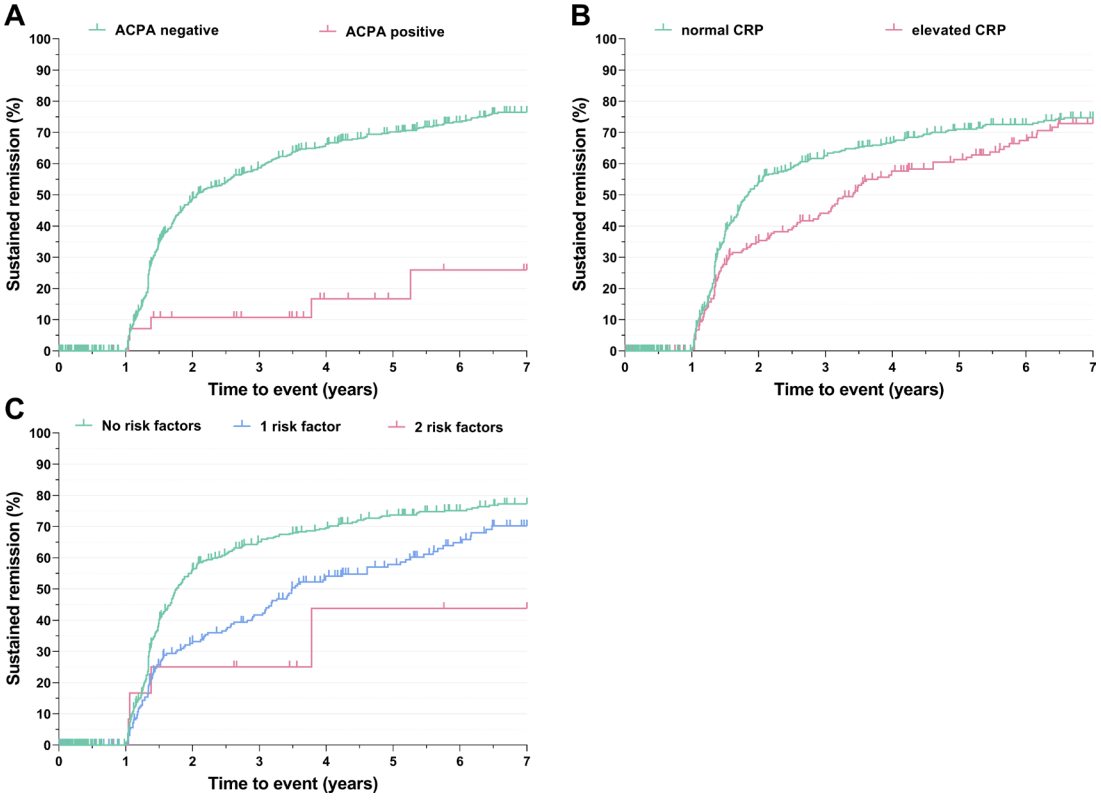

Figure 1 Cumulative incidence of sustained remission in contemporary undifferentiated arthritis for presence of ACPA positivity (A), elevated CRP (B), 0, 1 and 2 of these factors (C). (1A) Of all the patients with contemporary UA, 5% was APCA positive (≥10 U/mL); (1B) in total 31% of the patients with contemporary UA had an elevated CRP (≥10 mg/L); (1C) of all the patients with contemporary UA 67% had no risk factors, 31% had one risk factor and only 2% had two risk factors. ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; UA, undifferentiated arthritis.

Phadia, the Netherlands, elevated ≥10 U/mL)), IgM-RF (in-house ELISA, elevated ≥5.0 IU/mL), CRP (elevated ≥10 mg/L) and ESR. Patients were assessed after 4 months, 12 months and yearly thereafter. The outcome was sustained remission, thus absence of disease persistence, defined as sustained absence of clinical synovitis without DMARDs (including corticosteroids) for at least 1 year and the entire follow-up. The cumulative incidence was visualised using Kaplan-Meier. Cox regression analysis was used to test risk factors. Radiographic erosions at baseline were rare (1.8%) and not included in analyses. Within the same inclusion period, 1004 patients with conventional UA were included (not fulfilling the 1987-RA-criteria and having no other diagnosis); analyses were also performed in this population.

Patients with contemporary UA presented with a median of two swollen joints and were mostly ACPA-negative (online supplemental table 1 for baseline characteristics). The median follow-up was 6 years (IQR 3–9 years). DMARDs were started by 48% of the patients. Sustained remission after a median of 1.5 years (IQR 1–3) was achieved by 60% of the patients with UA, after which they were followed for another 5.5 years (IQR 3–8) without recurrence of arthritis, demonstrating the sustained absence of disease. Univariable analyses showed that CRP, ESR, ACPA and RF were associated with time to sustained remission (HR 0.77 (95% CI: 0.62 to 0.95), HR 0.79 (95% CI: 0.64 to 0.97), HR 0.18 (95% CI: 0.08 to 0.44) and HR 0.49 (95% CI: 0.31 to 0.77), respectively), while polyarthritis (HR 0.76 (95% CI: 0.57 to 1.01)) was not statistically significant. In multivariable Cox regression ACPA (HR 0.095 (95% CI: 0.03 to 0.32); figure 1A) and CRP (HR 0.67 (95% CI: 0.50 to 0.91); figure 1B) remained significantly associated (online supplemental table 2). Assessing the number of these remaining two risk-factors (0, 1, 2 factors; figure 1C) showed that patients with UA without any of these two factors (67% of patients with UA) achieved sustained remission in 77%. Patients with two risk-factors in contrast, were rare (2%) and had persistent disease in 56%.

For comparison, patients with conventional UA were more often ACPA positive (online supplemental table 1 for baseline characteristics). Multivariable Cox regression analysis in these patients with UA revealed that ACPA, RF, CRP and polyarthritis were associated with sustained remission (online supplemental table 2).

Concluding, the population with contemporary UA is different from conventional UA and risk factors for disease persistence are partly dissimilar. ACPA and CRP remain to be predictive in contemporary UA. Other factors included in the current EULAR recommendation are uninformative (RF, ESR and polyarthritis) or rare (erosions). Further prognostic studies in contemporary UA are warranted, after which risk factors recommended in future EULAR recommendations may require revision.

Nikolet K den Hollander [1], **Marloes Verstappen** [1], **Tom WJ Huizinga** [1], **Annette van der Helm-van Mil** [1,2]

[1]Rheumatology, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands
[2]Rheumatology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence to Nikolet K den Hollander, Rheumatology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands; n.k.den_hollander@lumc.nl

Handling editor Josef S Smolen

Contributors All authors contributed to the conception and study design. NKdH contributed to acquisition of the data and analysed the data. All authors contributed to interpretation of the data and the development of the manuscript. All authors approved the final version of the manuscript.

Funding The research leading to these results has received funding from the Dutch Arthritis Foundation and the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (starting grant, agreement No 714312).

Disclaimer The funding source had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or decision to submit the manuscript for publication.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by 'Commisie Medische Ethiek' of the Leiden University Medical Centre (B19.008). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-221821).

To cite den Hollander NK, Verstappen M, Huizinga TWJ, *et al*. *Ann Rheum Dis* 2022;**81**:740–741.

Received 9 November 2021
Accepted 12 January 2022
Published Online First 27 January 2022

Ann Rheum Dis 2022;**81**:740–741. doi:10.1136/annrheumdis-2021-221821

ORCID iDs
Nikolet K den Hollander http://orcid.org/0000-0002-5066-2251
Marloes Verstappen http://orcid.org/0000-0002-7850-5063
Tom WJ Huizinga http://orcid.org/0000-0001-7033-7520
Annette van der Helm-van Mil http://orcid.org/0000-0001-8572-1437

REFERENCES

1 Combe B, Landewe R, Daien CI, *et al*. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis* 2017;76:948–59.
2 Hua C, Daien CI, Combe B, *et al*. Diagnosis, prognosis and classification of early arthritis: results of a systematic review Informing the 2016 update of the EULAR recommendations for the management of early arthritis. *RMD Open* 2017;3:e000406.
3 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
4 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
5 Krabben A, Huizinga TWJ, van der Helm-van Mil AHM. Undifferentiated arthritis characteristics and outcomes when applying the 2010 and 1987 criteria for rheumatoid arthritis. *Ann Rheum Dis* 2012;71:238–41.
6 de Rooy DPC, van der Linden MPM, Knevel R, *et al*. Predicting arthritis outcomes--what can be learned from the Leiden Early Arthritis Clinic? *Rheumatology* 2011;50:93–100.