Article:
Emery, P orcid.org/0000-0002-7429-8482 and Duquenne, L (2020) It's never too soon to treat rheumatoid arthritis: finally, some supportive evidence. The Lancet Rheumatology, 2 (6). E311-E313. ISSN 2665-9913

https://doi.org/10.1016/s2665-9913(20)30103-x

Commentary
“It’s never too soon to treat RA”: finally, some supportive evidence

Paul Emery FMedSci[1,2]
Professor of Rheumatology Versus Arthritis,

Laurence Duquenne[1,2]

[1]Leeds Institute Rheumatic and Musculoskeletal Medicine University Leeds
[2] Leeds NIHR Biomedical Research Centre, The Leeds Teaching Hospitals Trust, Leeds UK

For many years early arthritis clinics have been promoted as a means of improving long-term outcome for patients (1), the logic being that early therapy minimises structural damage, (which correlates with longer term functional loss), induced by inflammation both locally and systemically (2). Furthermore, there is the long-term belief in the, at least theoretical, window of opportunity whereby early intervention permits a qualitatively better outcome than the same intervention applied at a later date(1). A recent focus on individuals “at risk” has led to the realisation that multiple pathological mechanisms are taking place prior to clinical arthritis, for example objective evidence of sub-clinical inflammation on sensitive imaging (3-5)or immunological abnormalities in T-cell subsets (6).

These data led to the maxims that “the earlier the better” and “never too soon to treat RA”. Indeed, expert opinion led EULAR to the recommendation that patients should start treatment within 6 weeks after “any joint swelling associated with pain or stiffness” (7). Using extensive inception cohort data from Leiden and France Niemantsverdriet et al (8) have produced the best evidence so far to address this question. Their findings show in a meta-analysis of two cohorts that a time to encounter (TtE) of ≤6weeks was 1.7 times more likely to achieve sustained drug-free remission (SDFR) compared to both 7-11weeks TtE (HR 1.69; 95% CI 1.10-2.57; p=0.02) and ≥12weeks TtE (HR1.67; 95% CI 1.08-2.58; p=0.02). Leiden’s results showed significant results in multivariable but not in univariable analysis, whilst ESPOIR showed the reverse; it is unclear why this was the case.
In this study, TtE was defined as “any pain or swelling”. This suggests some heterogeneity in the group categorisation, as swelling could have occurred later than pain, raising the issue of which type of pain without swelling led to the referral. Categorisation of the timeline between symptoms, swelling and TtE should decrease analysis bias. Also, as Leiden, quite logically, is conducting “at-risk of RA” studies, GPs have been offered guidance for early referral since 2013 (9), alerting them to the concept of “clinically significant arthralgia” (10). This may explain the big difference in RA diagnosis at first visit between the EAC (36%) and

the ESPOIR cohort (78%). Additionally, the large sample size with its' statistical power should permit analysis of TtE as a continuous variable and define an optimal cut-off point (11). Also, it would be interesting to see if the large sample size could enable an internal cross-validation (12).
The end-point of SDFR might have selected patients with a milder disease who were more likely to have a better outcome. Although, this was not supported by baseline data which showed the ≤6weeks TtE, compared to other TtE, had mostly equivalent measures of disease activity. Nevertheless, SDFR is a highly desirable outcome, and its prevalence in the Leiden cohort maybe partly due to the remission-induction trials undertaken in the Netherlands. Were the patients who achieved SDFR more likely to have had such treatment? If so, it could provide evidence that has been sought for so long, to support a more aggressive approach to early disease. Notwithstanding this, as SDFR is an extreme end point rarely achieved in routine practice, it would be very helpful to see the data of clinical remission on therapy, (say at 5 years) and for this end point the ESPOIR data representing routine clinical practice (albeit with smaller numbers) could be more relevant for answering the role of TtE.

What about radiology? Structural damage reduction, once the Holy Grail for rheumatologists, would have been expected to be observed in the early treated patients, especially as they had an improved outcome. However, there was little difference in radiological damage between the different TtEs. This lack of correlation between X-ray changes and SDFR suggests that in patients well treated early, the small level of structural damage becomes less important for outcome.

This important study confirms the importance of rapid referral clinics and immediate therapy, if these findings are accepted, the implications are considerable. Seeing patients so rapidly is a logistics and cost challenge, but may be justified by a long-term health-economic analysis from a societal viewpoint. The study also raises the question of whether treating earlier could produce even better outcomes. To date, only one abstract has showed that individuals diagnosed with RA while being followed in an "at-risk" cohort had milder disease activity than those diagnosed through standard referral (13). Meanwhile, intervention studies in "at risk" populations which have so far looked at delaying/preventing clinical disease, may wish to focus more on SDFR once disease has occurred.

1. Emery P, Gough A. Why early arthritis clinics? Br J Rheumatol. 1991;30(4):241-2.
2. Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. Lancet (London, England). 1994;344(8914):23-7.
3. Nam JL, Hensor EMA, Hunt L, Conaghan PG, Wakefield RJ, Emery P. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody-positive patients without clinical synovitis. Ann Rheum Dis. 2016;75(12):2060-7.
4. van Steenbergen HW, Mangnus L, Reijnierse M, Huizinga TW, van der Helm-van Mil AH. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Ann Rheum Dis. 2016;75(10):1824-30.
5. Mankia K, D'Agostino MA, Rowbotham E, et al. MRI inflammation of the hand interosseous tendons occurs in anti-CCP-positive at-risk individuals and may precede the development of clinical synovitis. Ann Rheum Dis. 2019;78(6):781-6.

6. Hunt L, Hensor EM, Nam J et al. T cell subsets: an immunological biomarker to predict progression to clinical arthritis in ACPA-positive individuals. Ann Rheum Dis. 2016;75(10):1884-9.
7. 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(6):948-59.
8. Niemantsverdriet E, Dougados M, Combe B, Van der Helm-van Mil AHM. Referring early arthritis patients within 6 weeks versus 12 weeks after symptom onset: an observational cohort study to search for evidence of the first EULAR recommendation for early arthritis. Lancet Rheumatol. 2020.
9. van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction rule for the development of arthritis in seropositive arthralgia patients. Ann Rheum Dis. 2013;72(12):1920-6.
10. Ruta S, Prado ES, Chichande JT et al. EULAR definition of "arthralgia suspicious for progression to rheumatoid arthritis" in a large cohort of patients included in a program for rapid diagnosis: role of auto-antibodies and ultrasound. Clin Rheumatol. 2020.
11. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med. 2006;25(1):127-41.
12. Ollier W, Muir KR, Lophatananon A, Verma A, Yuille M. Risk biomarkers enable precision in public health. Per Med. 2018;15(4):329-42.
13. Duquenne L, Pentony P, Mankia K., et al. At diagnosis of rheumatoid arthritis, at-risk patients followed in CCP+ clinic showed milder disease activity than conventionally referred patients. Ann Rheum Dis. 2018;77(supplement Suppl, year 2018):A93.