

EULAR Standing Committee of Investigative Rheumatology:

The EULAR Synovitis Study Group

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Identification of biomarkers associated with response to treatment in rheumatoid arthritis.

A variety of methodological studies has been performed by the EULAR Synovitis Study Group, showing specific effects of targeted interventions as well as a consistent relationship between the change in the intensity of sublining macrophage infiltration and the magnitude of the clinical response, independent of the specific mechanism of action (1;2). In previous years, the merit of using the number of sublining macrophages as a candidate biomarker was tested across a range of discrete interventions and kinetics. There was a significant correlation between the change in the number of macrophages and the change in DAS28. The change in sublining macrophages could explain 76% of the variation in the change in DAS28 (3). The sensitivity to change of the biomarker was high in actively treated patients while the ability to detect changes in placebo treated patients was weak (4). The close correlation was clearly independent of the mode of action of the individual therapies. More recently, more data became available from different centers on compounds that were not clinically effective, confirming the consistent relationship between the DAS28 and the number of sublining macrophages and, importantly, the absence of placebo effects on biological markers in studies of relatively short duration. Together, the available data suggest that therapies, which fail to reduce the number of sublining macrophages and/or fail to affect the specific molecules to which the compound is directed, are unlikely to be clinically effective.

Consistency across centers

Recently, we determined whether the correlation between the mean change in disease activity and the mean change in synovial sublining CD68 expression could be demonstrated across different academic centers (5). Synovial biopsies obtained at arthroscopy from patients with rheumatoid arthritis before and 160 days after rituximab therapy were selected and coded. Paired sections were processed independently at Amsterdam Medical Center (AMC) and at St. Vincent's University Hospital (SVUH), Dublin. Digital image analysis (DIA) was employed at both centers to quantify CD68 sublining expression. After decoding, inter- and intra-center variations in quantification of CD68sl expression, Δ CD68sl, and the relationships between Δ CD68sl and Δ DAS were determined. Determination of the sensitivity of biomarker expression to detect change was based on the standardized response mean (SRM).

After analysis of sublining CD68 expression at centers in two different countries, high levels of intra-center and inter-center agreement were observed. For the pooled sections stained at AMC, the correlation between two investigators was $R=0.942$, $P<0.0001$ and for sections stained at SVUH $R=0.899$, $P=0.001$. Similarly, the intra-center correlations for Δ CD68sl expression after treatment were $R=0.998$, $P<0.0001$ for sections stained at AMC and $R=0.880$, $P<0.0001$ for sections stained at SVUH. The inter-center correlation for the pooled scores of sections stained at AMC was $R=0.85$, $P<0.0001$ and for the sections stained at SVUH $R=0.62$, $P=0.001$. Weak agreement between centers in Δ CD68sl expression was explained by methodological issues which were resolved. The consistent correlation between Δ DAS and Δ CD68sl expression across different studies (Pearson correlation = 0.895, $P < 0.001$) was confirmed. The SRM values for Δ CD68sl, calculated from analyses at both AMC and SVUH were consistently 0.5 or greater, indicating a moderate to high potential to detect change.

Thus, the correlation between mean Δ DAS and mean Δ CD68sl expression was confirmed across two centers after appropriate standardisation of techniques, which is critical. Examination of serial biopsy samples can be used reliably to screen for interesting biological effects at the site of inflammation in rheumatoid arthritis at an early stage of drug development.

Identification of biomarkers associated with response to treatment in psoriatic arthritis.

We also determined which of the changes in synovial tissue correlates best with clinical response associated with effective therapy (adalimumab) to facilitate the planning of future studies with therapeutic agents for psoriatic arthritis (6). Twenty-four active psoriatic patient patients were randomized to receive adalimumab (n=12) or placebo (n=12) for 4 weeks. Synovial biopsies were obtained before and after 4 weeks of treatment. Immunohistochemical analysis was performed to characterize the cell infiltrate, expression of cytokines and matrix metalloproteinases (MMPs), and vascularity. Sections were analyzed by digital image analysis. Statistical analysis was performed using covariance analysis.

The mean DAS28 after 4 weeks was 1.92 units lower (95% confidence interval (CI) 1.07 - 2.77) after adalimumab therapy compared with placebo. Paired pre- and post-treatment synovial samples were available from 19 patients. Many cell types were reduced after adalimumab treatment compared to placebo. After applying a ranked ANCOVA model to correct for baseline imbalances, a significant effect of treatment was observed on CD3 positive cells: there was a median reduction of 248 cells/mm² after adalimumab versus placebo treatment (P = 0.035). In addition, the expression of MMP-13 was significantly reduced after active treatment: the integrated optical density (IOD)/mm² was 18,190 lower after adalimumab treatment as compared to placebo (P = 0.033).

Thus, adalimumab therapy in psoriatic arthritis is associated with a marked reduction in T cell infiltration and MMP-13 expression in synovial tissue, suggesting that these parameters could be used as biomarkers that are sensitive to change after active treatment in small proof of concept studies in psoriatic arthritis. Of importance, other investigators within the EULAR Synovitis Study Group have independently confirmed the specific decrease in CD3+ T cells in the synovium after initiation of TNF blockade in patients with PsA (7).

Other research

The EULAR Synovitis Study Group works closely together on standardisation and dissemination of technology, as described above. It should be noted, however, that the participants are also highly active in the development of new technologies as well as in more basic research focused on synovial biology.

Inflammatory Arthritis Fellowship Program

Two participants in the EULAR Synovitis Study Group, the University of Glasgow and the AMC/University of Amsterdam have together created a new dynamic Fellowship Program that started in 2008. This program is designed to attract and train talented young clinical scientists, as well as foster excellent translational and clinical research. With the Fellowship program we support talented clinicians who have shown originality and dedication, have a marked capacity for self-direction, and who are seeking an opportunity to establish skills in the conduct of translational and clinical science in the field of inflammation medicine. Fellows are trained in the needed skills 'for trade and life' necessary for an outstanding career in rheumatology including good clinical practice, clinical trial design and conduct, needle arthroscopy, musculoskeletal ultrasound and core laboratory techniques. Contact persons are Professor Iain McInnes (ibmi1w@clinmed.gla.ac.uk) and Professor Paul-Peter Tak (P.P.Tak@amc.uva.nl).

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