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Chapter 11

Absence of changes in synovial sublining macrophages after ineffective anti-rheumatic treatment: Implications for the use as a biomarker.

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A previous study designed to identify optimal biomarkers associated with therapeutic efficacy in patients with rheumatoid arthritis (RA) has shown that the number of CD68 positive sublining macrophages in arthroscopic synovial biopsies could be used to differentiate between active and placebo treatment (1). A subsequent study confirmed the highly significant relationship between changes in synovial macrophage infiltration and clinical efficacy across a wide range of therapies (2). Such a biomarker could facilitate decisions in relatively small proof of concept studies to continue or discontinue development of novel antirheumatic drugs towards large clinical trials aimed at evaluation of clinical efficiency. Obviously, there needs to have sufficient sensitivity to detect change. This was determined by the standardized response mean (SRM), which is calculated by dividing the mean change by the standard deviation of the mean change. An SRM of > 0.8 is usually considered to indicate high potential to detect changes, an SRM of 0.5 as moderate, and an SRM of 0.2 as low potential to detect changes.

According to the SRM, the number of sublining macrophages is highly sensitive to change after active treatment (2). Of importance, the synovial biomarker exhibited a very low SRM for placebo treatment, indicating that the number of CD68 positive cells in the synovium is perhaps not susceptible to placebo effects in proof of concept studies of relatively short duration. Together, these data support the notion that quantification of the changes in sublining macrophage numbers could be used to predict potential efficacy of novel anti-rheumatic drugs in an early stage of drug development.

For a biomarker to pass the “discrimination criterion” of the so-called OMERACT filter, it should not only exhibit a high sensitivity to change, but it should also distinguish between effective and ineffective treatment (3). So far the data on the effects of ineffective experimental and placebo therapies on synovial biomarkers that could be included in the formal calculation of the SRM have been very limited. Therefore, we included in our analysis data that were obtained in 2 recently performed randomized, controlled clinical trials, with strategies that were shown to be ineffective in RA patients: MCP-1 blockade (4) and C5a receptor (C5aR) blockade (5;6).

In the first study 27 (20 verum, 7 placebo) RA patients underwent serial synovial biopsy before and 43 days after treatment with an anti-CCL2/MCP-1 antibody (4). In the second study 18 (11 verum, 7 placebo) RA patients underwent serial synovial biopsy before and 28 days after treatment with F-[OPdChaWR], an oral C5a receptor antagonist (5). Synovial biopsies were obtained by mini-arthroscopy under local anesthesia from an actively inflamed joint. Biopsies were taken from 6 or more sites within the joint to minimize sampling error [methodology reviewed in (7)].

The data from these 2 studies were added to the previously described dataset consisting of 2 placebo treated control groups on stable disease-modifying antirheumatic drugs (DMARDs) and 5 groups treated with efficacious antirheumatic drugs (2). The SRM was calculated for the
number of CD68 positive macrophages in the synovial sublining and the DAS28 to determine
the sensitivity to change for both placebo and verum treated groups, using exactly the same
methodology as previously described (1;2). The sensitivity to change of the synovial biomarker
was high in the patients who received effective therapies (SRM > 0.8), whereas the ability to
detect changes was low in patients treated with the ineffective drugs. The mean change (±
SEM) in DAS28 for the anti-MCP1 treated group was -0.11 ± 0.32 with an SRM of -0.07. The mean
change in number of sublining macrophages was 51 ± 59, corresponding with an SRM of 0.19.
In the anti-C5aR treated group the mean change in DAS28 was -0.34 ± 0.14 with an SRM of -0.71.
The mean change in number of sublining macrophages was 85 ± 117, with an SRM of 0.22.

To account for the precision by which the SRM has been measured in each study we calculated
the weighted mean of the SRM and its standard error (SE). The weighted mean of the SRM for
the CD68 sublining macrophages was -0.89 (± SE 0.12) for the effective, 0.20 (± SE 0.18) for the
ineffective, and 0.11 (± SE 0.18) for the placebo group (Figure 1A). The difference between the

![Figure 1. A)](image)

**Figure 1. A)** The weighted average of the standardized response means (SRM) was calculated for the
change in DAS28 and the number of CD68+ sublining macrophages. This is shown for studies with
effective drugs (-0.89 ± SE 0.12), in the placebo arms of studies (0.11 ± SE 0.18) and studies with ineffective
experimental drugs (0.20 ± SE 0.18). The biomarker showed good sensitivity to change and was not
susceptible to placebo effects in small proof of concept studies of relatively short duration. **B)** Correlation
between the mean change in CD68 positive sublining macrophages and the mean change in DAS28
for each substudy (Pearson correlation = 0.895 (P < 0.001), weighted linear regression P < 0.001, R² =
0.801, 95% confidence interval 0.002-0.004). There was a consistent relationship between the change in
macrophage numbers and clinical improvement after treatment. (t = time in days between first and second
biopsy; n = number of patients; the group that received stable DMARD therapy (O) was treated with
methotrexate (MTX), sulphasalazine, hydroxychloroquine, leflunomide, or a combination of these drugs).
effective and ineffective group was significant for CD68 sublining macrophages as well as the DAS28 (Z-value -5.06 and -4.20, respectively, P < 0.01). Hence, a clear distinction between effective and ineffective treatment was possible. Linear regression showed that the mean change in sublining macrophages could predict 80% of the variance in the mean change in DAS28 grouped for each study group ($R^2 = 0.801$, 95% confidence interval 0.002-0.004, $P<0.001$), (Figure 1B). As expected, in contrast to the results obtained using the synovial biomarker, the DAS28 was susceptible to placebo effects, as shown by the weighted mean of the SRM of $-0.30$ ($\pm$ SE 0.18) for the combined ineffective treatment group (Figure 1A).

In conclusion, the change in synovial sublining macrophages can be used to discriminate between effective treatment on the one hand and ineffective and placebo treatment on the other. In addition, the change in the synovial biomarker appears to be less susceptible to placebo effects compared to clinical evaluation. These findings further validate observations in independent patient groups from our center (8) as well as other centers (9;10) and add to the validity of the use of the synovial biomarker in relatively small, high density of data, proof of concept studies to screen for potential efficacy in an early stage of drug development. Of interest, these data also point to a common mechanism by which different effective therapeutic approaches ultimately influence the numbers and activation status of synovial macrophages, which are associated with clinical signs and symptoms. Preliminary data suggest that this is also true after B cell depletion in RA (Thurlings R et al. Oral presentation. EULAR 2007, abstract number OP0229).
REFERENCE LIST


