Does functional MRI convincingly explain the fast effect of TNF-α blockade?

Hess et al. (1) recently reported that nociceptive stimuli-activated brain areas, revealed by functional MRI (fMRI), were significantly reduced within 24 h after an infusion of a monoclonal antibody to TNF-α in their patients with rheumatoid arthritis (RA). Together with evidence from accompanying animal experiments, the authors concluded that neutralization of TNF-α could rapidly inhibit pain responses in the CNS. Although the investigation represented an important attempt to understand fully the fast therapeutical effect of TNF-α blockade, the conclusion should be accepted with caution. In my opinion, two major concerns with fMRI experiments in the patients need to be adequately addressed.

First, no placebo treatment was included. It has been recognized that placebo effects are genuine psychobiological events attributable to the overall therapeutical context, and that these effects can be robust in both laboratory settings and clinical practice (2). Indeed, fMRI experiments in humans showed that placebo analgesia was related to decreased activity in pain-sensitive brain regions (3). It is unclear whether and how the patients with RA were informed about the actions of infliximab before it was i.v. infused. For these patients, on whom chronic pain and suffering had been inflicted, the i.v. infusion itself might subconsciously be considered a clinical procedure with potent placebo effects. To clarify the neural mechanism underlying the fast effect of TNF-α neutralization, an i.v. infusion of a placebo is necessary, although the use of a placebo may be regarded as unethical if an effective treatment is available. Ideally, infliximab-induced changes in nociceptive stimuli-elicited brain activation should be contrasted with placebo-induced alterations; otherwise, the placebo effects cannot be excluded.

Second, no correlation analysis between infliximab-induced changes in brain activation and subjective rating of pain intensity was conducted. Although the sample size is rather small (n = 5), such analysis is especially valuable when a placebo control is unavailable in practice. If neutralization of TNF-α was capable of relieving nociceptive stimuli-elicited pain rapidly through inhibition of brain activation, infliximab-induced changes in brain activation by compression of the affected metacarpophalangeal joints should be correlated with subjective ratings of pain intensity across individuals.

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Reply to Hou: Central nervous system effects of TNF-α blockade

Hou is correct in pointing to the lack of a placebo group in the human part of the study on functional magnetic resonance imaging (fMRI) in patients with rheumatoid arthritis (RA) receiving tumor necrosis factor inhibition (TNFi) therapy (1). However, to run a placebo group in this setting would have been an ethical problem: All patients with RA studied had active disease requiring rapid and effective treatment. Because effective treatment modalities are available, placebo treatment could not have been justified. Even in clinical trials of RA, inclusion of a placebo arm has become difficult, despite the fact that additional symptomatic treatment with glucocorticoids and nonsteroidal antiinflammatory drugs (NSAIDs) is allowed. In our study, we needed to avoid such symptomatic treatment, because both glucocorticoids and NSAIDs affect the CNS, especially the perception of pain.

Placebo responses are a familiar observation in rheumatology, and minor responses, such as a 20% improvement of signs and symptoms of RA [American Colleague of Rheumatology (ACR)], are found in up to 30% of the patients, whereas more pronounced responses are rare. For the following reasons, however, we think that our results are not based on placebo responses:

i) fMRI changes were highly consistent among mice and men, and vehicle (placebo) treatment had no effect on fMRI responses in mice (2). Moreover, as pointed out by Diamond and Tracey (3), animal studies support the concept that TNF-α affects central nervous functions.

ii) In addition, responses remained stable over weeks in all patients, in contrast to a placebo-based effect, which is spurious at best, not leading to long-lasting antinociceptive effects in a chronic disease like RA.

iii) There was good correlation between the visual analog scale (VAS) for pain and the total area size of the bold signal (Spearman’s ρ = 0.43, P < 0.05), although one has to consider that the standardized VAS question for pain in RA refers to pain experienced during the past week rather than the same day, which weakens this association.

iv) Finally, large number of studies with TNFi in patients with RA used a placebo control but did not observe rapid pain relief or a “feeling of well-being” in the placebo group. In contrast, countless patients with RA experienced rapid improvement immediately after the start of TNFi, and rheumatologists became quite familiar with this phenomenon.

These observations prompted us to perform this study, which provides an understandable neurophysiological explanation for the rapidity of onset of pain relief and a “feeling of well-being” before any change in the objective parameters of joint inflammation occurs. This finding is important because key outcome parameters in RA—as well as in ankylosing spondylitis, Crohn’s disease, and psoriasis—are based on completely or partly patient-related outcomes, such as the ACR20 response, the Disease Activity Score 28 (DAS28), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Crohn Disease Activity Index (CDAI), and the Psoriasis Area and Severity Index (PASI), respectively. All these scores are greatly affected by the early perception of improvement of pain and/or the overall disease state reported by the patient.

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