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WHY most (but perhaps not all) DMARDs work equally well

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ABSTRACT

Biological- or targeted-synthetic DMARD-responses reported in randomized clinical trials, placebo-controlled or head-to-head, in patients with rheumatoid arthritis, psoriatic arthritis or spondyloarthritis are unbelievably similar, when looking across trials performed in the same disease and applying the same primary outcome measures. The exception to this rule may be the response to Janus-kinase-inhibitors, which seem to work 10 % better in all trials (JAK-bonus) This article provides a potential explanation for this remarkable phenomenon, including an explanation for the JAK-bonus. It seems as if JAK-inhibitors exert some inflammation-independent effects on pain, fatigue and wellbeing, and that drug treatment of rheumatic diseases is more than the inhibition of inflammation alone.

The paradigm of chronic inflammation underlying many rheumatic musculoskeletal diseases (RMD) states that all signs and symptoms of patients with an inflammatory RMD, such as pain, stiffness, fatigue and joint swelling, are attributable to the inflammatory process. DMARDs, including biological (b)- and targeted synthetic (ts)-DMARD, among which the *Janus kinase inhibitors* (JAKi), may via abrogation of inflammation lead to resolution of symptoms and normalization of long-term outcome. Many successful randomized trials have in principle proven the validity of this paradigm. The primary endpoints in these trials were usually validated response criteria, composed of several separate measures aggregated into a composite index. Examples are the American College of Rheumatology (ACR)-response criteria (ACR20-50-70) for rheumatoid arthritis (RA) and the Assessment in Spondyloarthritis International Society (ASAS)-response criteria (ASAS40) for axial spondyloarthritis (axSpA). That ACR- and ASAS-response criteria contain substantial patient- and assessor-reported ('subjective') information (the authors' estimation is 60–70 % for the ACR- and 90–100 % for the ASAS-response-criteria) is a relatively underexposed feature. Subjectivity adds face validity to response criteria, but also opens the gate to perception-biases (beliefs), rampant among patients and assessors too. Causal theory teaches that well-designed RCTs provide an unbiased estimate of the *specific* anti-inflammatory treatment effect. The same level of unbiasedness, however, does not pertain to *non-specific* treatment effects, often referred to as placebo-or nocebo-effects. Such effects are considered unwelcome 'side-effects' of drug trials, but have undeniably become more impactful over time and are constituting a threat for the interpretability of modern RCTs.

All bDMARDs work equally well; The 60–40–20 rule

There is the idea held among key-opinion-leaders that all b/tsDMARDs work equally well. By this they mean that ACR20, −50 and −70 response-rates of effective drugs in placebo-controlled RA-trials are said to approximate 60 %, 40 % and 20 %, respectively, regardless of the drug (class) under study. A similar phenomenon exists in psoriatic arthritis (PsA)- and axSpA-trials. Even more striking in this regard is the observation from several head-to-head (H2H) trials comparing two (or more) active bDMARDs, that the response-curves for two active drugs

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are literally superimposable, and that this pertains to other indices with patient-reported content (eg. disease activity score (DAS), health-assessment questionnaire (HAQ)-score) too [1,2]. Nobody can really prove the veracity of this biologically rather implausible phenomenon, nor can anybody explain it, but it seems that the field has accepted it as a fact. Right or wrong, the fact that any trial result with bDMARDs is apparently predictable from the onset of the trial, and seemingly independent of the drug or drug-class under study, echoes in our treatment recommendations, which still refrain from giving priority to any particular (class of) b/tsDMARD [3,4].

How expectations influence trial outcomes

Recently, Kerschbaumer et al. have shed more light on the relevance of trial-information that patients and their assessors possess *before* a trial really starts for the likelihood that patients will respond [5]. They compared all placebo-controlled RCTs with H2H-trials testing the same bDMARD and showed 50–67 % better responses for the same bDMARD, when applied as comparator in a H2H- vs. a placebo-controlled trial! Apparently, pre-trial reassurance that there is no chance of receiving a placebo-treatment increases the likelihood of a clinical response during the trial. ACR20, −50 and −70 response rates were similarly affected. A pharmacodynamic explanation, such as better suppression of inflammation, does not satisfy here, since the same drugs, dosages, time points and patient populations were analyzed. Only the *context* differed; a clear indication that non-(drug)specific mechanisms are at work. It seems as if a patient's perception of the chance to experience a successful treatment course in the trial is based on pre-trial information and perhaps on early trial experiences, and that this must be juxtaposed as non-specific effect to the specific drug-effect that is sought for in the trial. The measured patient- and physician-response in the trial is then the resultant of the non-specific and the specific effects of the drug (Fig. 1). Even if the latter is fixed, because there is no residual inflammation present anymore, variable and context-dependent non-specific effects may perfectly explain the *within-trial*-variability (many patients with ACR20, fewer with ACR50, and fewest with ACR70) as well as *between-trial*-variability (lower ACR-response rates in placebo controlled- vs. H2H-trials (Fig. 2) [5]. That optimal inhibition of inflammation is already reached by current b-and tsDMARDs for most patients is a plausible supposition, when comparatively looking across trials at biomarkers of residual inflammation (eg. C-reactive protein) or subsequent radiographic joint damage (RA, PsA): both seem to be fully inhibited in most trials. Factors that may explain variability in non-specific trial-responses are trial-design features, patients' personality characteristics (eg. 'sensitive' vs. 'insensitive' patients, 'anxious' vs. 'confident' patients), and also to

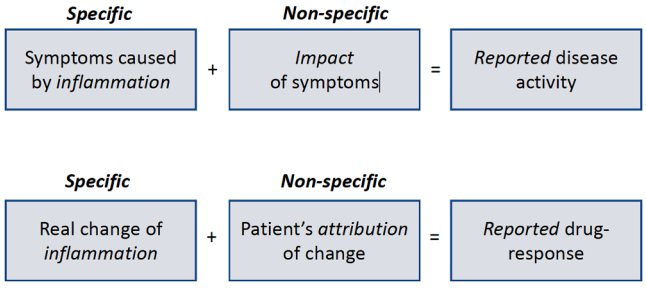

Fig. 1. Conceptualization of reported disease activity status (upper) and reported improvement on a trial-drug in an RCT with a composite patient- and assessor-reported response measure (such as ACR-response in RA). Just as the reported level of disease activity constitutes the summation of symptoms attributable to inflammation (specific) and the impact of those symptoms on the patient (non-specific), the reported response on a trial drug, either placebo or effective treatment, constitutes the summation of real change of inflammation (specific) and patients' and physicians' attribution or perception of change (non-specific).

what extent trial-investigators, who motivate patients for - and monitor them during - the trial, communicate (or: raise) expectations about success and failure.

bDMARDs and JAKi compared: a JAK-bonus

Experts and recommendations committees are in agreement that bDMARDs and JAKi suppress inflammation and joint damage similarly well [4–6]. When looking at ACR-responses, however, there is some room for doubt. Starting with the RA-Beam trial in 2017 [7], that compared the JAKi baricitinib with the TNF-inhibitor adalimumab, several subsequent H2H-trials comparing different JAKi and different bDMARDs consistently showed approximately 10 % higher ACR20, −50 and −70 response-rates for the JAKi vs. the bDMARD, a *'JAK-bonus'* (to date, there is no indication for any JAKi-specificity here). The JAK-bonus disappeared when comparing changes in CRP, swollen joint count or Sharp-scores, but persisted when looking at Boolean remission, a remission index with a substantial amount of subjective information. To date, a JAK-bonus is (still) ignored in treatment recommendations, since better suppression of inflammation, the present paradigm, does not satisfactorily explain the slightly superior responses, and key-opinion-leaders fear a methodological artifact being responsible. In light of the argumentation above, however, it could be that JAKi do more than only suppress chronic inflammation; JAKi may convey beneficial secondary effects, particularly on patients' feelings of being unwell ('feeling sick'). The pleiotropic JAKi may, for instance, interfere with pain-processing and central pain-perception, topics that currently rejoice broad interest among pain-researchers who try to unravel *central sensitization* [8,9], or they may alternatively interfere with chronic fatigue and mood disorder in a manner that differs from how the often single-target bDMARDs act. The best analogy may be the pleiotropic effects of glucocorticoids (GC); GC have not only profound effects on inflammation, but also have (as 'stress hormones') less well-established central effects on pain, arousal, cognition and memory. Experienced rheumatologists appreciate these central effects of GC on top of their anti-inflammatory effects, which make them popular drugs in the clinic, in spite of their feared toxicity.

Potential clinical implications of JAKi-selectivity

There is accruing evidence that JAKi exert certain effects on top of suppressing inflammation alone, but so far this seems to be a class-effect rather than an effect that is attributable to one particular JAKi. Trial results suggest that effective bDMARDs and JAKi already maximally suppress inflammation, in spite of suboptimal ACR70- and remission-rates. Mechanisms such as central sensitization may act partly independently of inflammation and explain why optimal treatment successes stay behind, while residual inflammation is absent. This requires dedicated approaches, pharmacological, non-pharmacological or a combination thereof. The prevailing paradigm of inflammation needs updating in order to better explain quality of life and outcome in patients with inflammatory RMD; the paradigm should expand, but without losing the accomplishments achieved. Scientific research in RMDs must become more expansive and 'allow' less familiar and comfortable phenomena, such as pain, fatigue and sensitization, to be addressed with similar scientific rigor as chronic inflammation.

The 'JAK-bonus', true or false, may give way to the realization that the treatment of inflammatory RMD is more than inhibition of inflammation alone. The fact that two or more separate mechanisms of action may be combined into one drug-class (JAKi) is promising and may be a prospect of better response-rates in future.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:RL

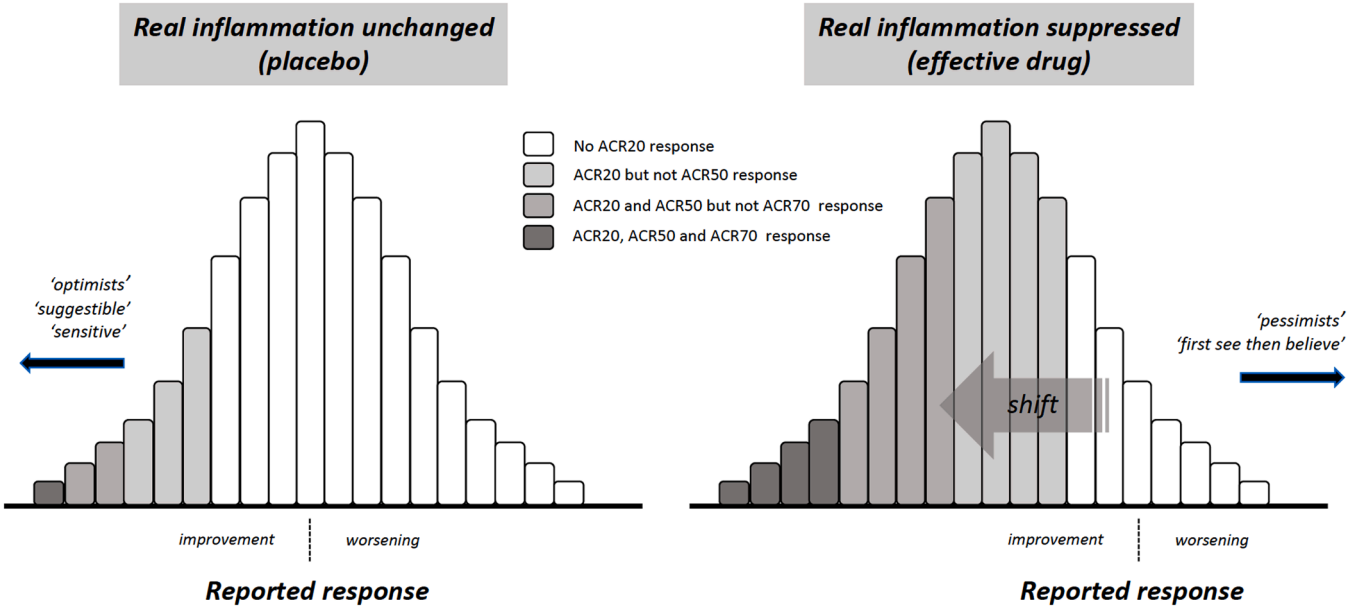

Fig. 2. Histograms of putative ACR 20,50 and 70-response distributions in groups of patients with RA in a double-blind randomized trial comparing an effective drug with a placebo drug. Patients and assessors are fully informed before the start of the trial about the potential virtues and toxicities of the tested drug and the chance of receiving a placebo treatment. Assuming that ACR-responses in a trial arm follow a (close to) normal distribution, like in panel A (placebo-group), with low but increasing numbers of patients reporting an ACR70, −50 or −20 response, as observed in most placebo-controlled RCTs, then the response distribution of the effective treatment arm (panel B) can be interpreted as a *shift* of the entire distribution toward improvement. One interpretation of this hypothetical scenario is that patients primarily report that they feel better when inflammation is suppressed by active drug versus not feeling better (or even worse) if inflammation is unchanged by placebo. The significant variability of ACR-responses seen within most trial arms is then a reflection of differences in non-specific patient-traits, and not necessarily of a graded difference in a drug's ability to inhibit inflammation. Another interpretation of this hypothetical scenario is that it provides a satisfactory explanation for the observation that all effective b/tsDMARDs work similarly (and predictably) well on inflammation (maximum suppression) in the context of (H2H and placebo-controlled) RCTs. Only when a drug has additional secondary effects independent of inflammation, better responses can be achieved.

received honoraria for participating in adboards of- or giving lectures for- AbbVie, Eli-Lilly, Galapagos, Jansen Pharma, Novartis, Pfizer and UCB.RL is owner of Rheumatology Consultancy BV, a small business under Dutch law.

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