DMARDs for mental health symptoms in RA

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Rheumatoid arthritis

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Standfirst

Mental health symptoms are a common and functionally impairing feature of rheumatoid arthritis, and increasingly seem to represent an integral part of the inflammatory process. Could treatment with DMARDs affect physical as well as mental health outcomes?

Refers to Matcham, F. et al. The impact of targeted rheumatoid arthritis pharmacological treatment on mental health: A systematic review and network meta-analysis. *Arthritis Rheumatol.* https://doi.org/10.1002/art.40565 (2018)

Main text

Once considered an area of niche interest, the role of inflammatory processes, such as those observed in rheumatoid arthritis (RA), in the aetiology of common mental illnesses, particularly depression, has emerged to become a major psychiatric research priority[1]. Central to this rise in interest is the potential to develop or repurpose immunotherapies for use in mental health, a specialty that has been starved of new drug classes since the development of selective serotonin reuptake inhibitors (SSRIs) more than 30 years ago[2]. In a timely systematic review, Matcham et al.[3] used pairwise and network meta-analyses to assess and compare the actions of both biologic DMARDs (bDMARDs) and conventional synthetic DMARDs (csDMARDs) on broadly defined mental health outcomes in adult patients with RA.

After reviewing 71 studies of DMARDs in RA that recorded mood outcomes, Matcham et al.[3] identified 57 studies (representing 23,535 patients) where mental health outcomes could be obtained from publication, contact with the authors or statistical imputation. All but two of the studies used the 36-item Short Form Health Survey (SF-36). Using two inter-related SF-36 summary scores, the Mental Component Summary (MCS) and Physical Component Summary (PCS) as their primary and secondary outcomes, Matcham et al.[3] report that DMARDs as a group had only a small effect on mental health outcomes (standardised mean

difference (SMD)=0.21). The effects on physical health outcomes were somewhat larger, but still modest (SMD=0.41). Similar small effects on mental health outcomes were also observed when comparing bDMARDs to placebo (SMD=0.27) and to csDMARDs (SMD=0.19–0.30). The authors conclude that "effective pharmacotherapy alone is unlikely to substantially improve mental health outcomes for most RA patients"[3].

At first glance these findings[3] could be viewed as disappointing and as evidence that bDMARDs have only a marginal therapeutic benefit on RA-associated mental health conditions and perhaps more generally, for depression occurring in a pro-inflammatory milieu. However, as ever the devil lies in the detail. Unlike the situation for the physical health outcomes (all participants by definition had active RA), only 6 of the 57 studies included in the meta-analysis[3] reported a mean MCS score of ≤38, the recommended threshold for screening for either depression or anxiety in RA[4]. Pharmaceutical trials typically screen participants on the basis of suicidality, with the result being that patients with severe depression and/or mental health difficulties are likely to have been excluded. Further, the acknowledged 17% prevalence of depression in patients with RA[3] means that 80–85% of patients within this meta-analysis will not have met formal diagnostic criteria for major depression. Consequently, the potential antidepressant effects of DMARDs are likely to have been underestimated. Further compounding this issue, even in patients diagnosed with depression, conventional antidepressants perform no better than placebo when depression is mild[5]. Interestingly, even in the face of these limitations, the authors report an effect size of bDMARDs on mental health outcomes of 0.27[3], which is not dissimilar to the mean effect size of 0.31 reported in FDA reviews of trials of conventional antidepressants conducted in individuals with major depression[6].

A further issue highlighted by this meta-analysis[3] is the paucity of *reporting* of mental health outcomes in trials of DMARDs in RA even when such data was measured (an issue that also plagues trials of DMARDs across medical diseases). Of the 71 studies recording mental health outcomes, only half (50.7%) specifically reported these outcomes in publications, supplementary material or online data summaries. Furthermore, only two studies used a tool specifically designed to record and monitor depression and anxiety symptoms (in both instances the Hospital Anxiety and Depression Scale was used, which was specifically designed to avoid 'somatic' symptoms such as insomnia and fatigue). All other studies relied on the SF-36, a tool that measures health status and is commonly used to calculate cost-

effectiveness of interventions rather than changes in discrete components relevant to mental health. Why so few studies (including those published within the last 5 years) use bespoke tools to index specific mental health outcomes, particularly given their importance to patients with RA, is a question that needs addressing[7]. Is this a result of the separation of health services into physical and mental health? Or does it reflect an ingrained Cartesian dualism that views the mind as separate from the body and brain and consequently supports a view of depression as an 'understandable' reaction to physical disease? Evidence from human experimental medicine studies is beginning to refute this idea. Many studies have now convincingly demonstrated that even modest increases in pro-inflammatory cytokines act on the brain to induce many of the motivational, cognitive and emotional features of depression including insomnia and fatigue[8]. So rather than being an 'emotional reaction' to disease, it is becoming increasingly apparent that mental health symptoms are likely to be an intrinsic component of the pathology of RA and other inflammatory disorders.

A final result reported by Matcham et al.[3] relates to their use of a network meta-analysis to indirectly compare csDMARDs and bDMARDs with different modes of action on mental health outcomes, even in the absence of direct head-to-head trials. Using this approach they demonstrated that regardless of the mode of action, bDMARDs (including TNF inhibitors, B cell inhibitors, T cell inhibitors, IL-6 blockers and Janus kinase inhibitors) performed better than csDMARDs for improving mental (and physical) health[3]. Although the authors detected no notable differences in mental health outcomes between different bDMARDs, they performed a surface under the cumulative ranking curve (SUCRA) analysis to estimate the probabilities that each mode of treatment was the best, the second best and so on. This approach revealed that although abatacept had an 83% probability of being the most effective treatment for improving physical health, biologic agents targeting anti-IL-6 had a 90% probability of being the most effective DMARD for mental health outcomes[3]. This finding is noteworthy, as increased levels of IL-6 have been repeatedly reported in idiopathic depression, whereas findings for TNF are more variable[9]. Whether these apparent mental health benefits of anti-IL-6 therapies hold up in clinical trials will become clearer following reporting of two on-going phase II trials of tocilizumab and sirukumab in major depression[10].

Whether perceived as a comorbidity or as an integral part of the inflammatory process that underlies RA, mental health symptoms remain poorly recognized and managed in these patients. This problem might relate to a lack of diagnostic tools, relevant clinical expertise or

suitable care pathways. Further investment in both basic and clinical research in this domain, enhanced training of healthcare professionals and development of innovative services that re-unite physical and mental health might be required to help resolve this problem.

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