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Title: **Efficacy of tumour-necrosis factor-inhibitor in moderate disease activity rheumatoid arthritis: sub-analysis of the 'VEDERA' trial**

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Dear Editor,

Until recently in the UK, targeted therapies including biologic disease modifying anti-rheumatic drugs (bDMARDs) and Janus Kinase inhibitors (JAKi) have only been available for use in patients with rheumatoid arthritis (RA) in high disease activity (HDA) following the failure to at least two conventional synthetic DMARDs (csDMARDs) including methotrexate (MTX). Filgotinib, an oral selective inhibitor of JAK-1, in combination with MTX if tolerated, has recently been approved in the UK by the National Institute for Health and Care Excellence (NICE) for use in RA patients with moderate or high disease activity (1), representing a key milestone in improving treatment options for patients in the UK. This was followed by NICE approval of tumour necrosis factor inhibitors (TNFi) in the treatment of moderate RA (2).

There are however, a paucity of controlled trial data to inform on outcomes in patients with early RA and in MDA who are escalated to targeted therapies. We report on a post-hoc analysis of the Very early Etanercept (ETN) and MTX versus MTX with Delayed ETN in RA (VEDERA) trial (3). The VEDERA trial was a pragmatic, investigator-initiated study of patients with very early RA (VERA; $\leq$ 12 month symptom duration) who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism RA classification criteria (4). Participants were randomised 1:1 to first- line ETN+MTX or first-line MTX-treat to target (MTX-TT) for a total duration of 48 weeks. ETN was added to MTX-TT at week 24 if patients were not in DAS28-ESR remission (< 2.6). The trial did not meet its primary endpoint of a larger than standard effect size (30%) in VERA compared to TT strategy, although demonstrated a 14% difference, consistent with previous studies (5). Protocoled cumulative corticosteroid exposure did not differ between the two treatment arms.

In the MTX-TT group (n=60), following TT csDMARD escalation at week 24, 21 (35%) patients were in MDA (14 and 7 in HDA and MDA respectively at baseline) and escalated to ETN+MTX. After 24 weeks of ETN+MTX, at week 48, only 3/21 (14%) achieved remission, 9 (43%) improved to LDA, and 9 persisted in MDA. Thus, the target of remission or LDA was achieved in 57% of patients in MDA following escalation to ETN+MTX while just under half did not improve. Interestingly, of the 19 patients in MDA at baseline and randomised to first-line ETN+MTX group, 14 (74%) improved to LDA or remission by week 24 and this improved to 16 (84%) by week 48. The main difference in this group appears to be numerically higher MDA score prior to starting ETN+MTX (table 1).

Several studies have shown MDA is heterogeneous (6) and is not a benign state (7)(8). The approval of filgotinib and TNFi in moderately active RA is an important step towards achieving the goal of remission and puts our practice on a par with the rest of Europe. The hope is timelier escalation to targeted therapies, rather than after prolonged periods of unabated DA, will lead to better achievement of treatment target. Our data demonstrate that whilst tighter control of DA may be achievable in VERA patients with MDA, a proportion persist in MDA, highlighting the challenges in achieving the treatment target even with highly efficient DMARD escalation in patients with VERA. This response appears to be poorer compared to patients in (higher spectrum) MDA at time of diagnosis and treated with first-line ETN+MTX. As such, escalating all moderate RA patients to advanced therapies may be not be appropriate. We would suggest wider clinical assessment guide this decision – such as overall level of MDA, relative change in DA and functional capacity, and review of the individual components driving MDA. Persistent swollen joint(s) and/or acute phase would be key basis for escalating to advanced therapy although evaluating for mild levels of inflammation in the absence of these may be necessary.

The introduction of a targeted synthetic JAKi for the MDA patient population and the imminent availability of TNFi bDMARD therapies represent vital steps to improve MDA treatment options in the UK. This report emphasises the need for a better understanding of MDA and the ability to tailor available treatment options in order to improve outcomes for patients with RA.

Key message*:* Persistent moderate disease despite TNF-inhibitor in half of rheumatoid arthritis patients warrants more treatment options.

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Table 1: Characteristics of moderate disease activity MTX-TT group at week 24 and ETN+MTX group at baseline

	MTX-TT MDA week 24 (35%, n/N = 21/60) – escalated to ETN+MTX	**First-line ETN+MTX MDA baseline (32%, n/N = 19/60)**
Age (mean, SD)	53(11.5)	51(11.9)
Female %(n/N)	81(17/21)	58(11/19)
RF positive %(n/N)	81(17/21)	68(13/19)
ACPA positive %(n/N)	88(18/19)	84(16/19)
RF and/or ACPA neg %(n/N)	29(6/21)	32(6/19)
TJC (median, Q1-Q3)	5(3-8)	5(4-7)
SJC (median, Q1-Q3)	1(0-2)	3(2-4)
ESR (median, Q1-Q3)	12.4(9-19)	20(13.5-32.5)
CRP (median, Q1-Q3)	0.9(0.6-7)	2.26(0.58-9.8)
VAS-PAIN (mean, SD)	39.4(21.5)	50.3(23.4)
VAS-DA (mean, SD)	40.5(22.1)	49.3(20.5)
DAS28-ESR (mean, SD)	3.88(0.51)	4.66(0.32)

ACPA: anti-citrullinated protein antibody; CRP: C-reactive protein; DA: disease activity; ESR: erythrocyte sedimentation rate; ETN: etanercept; GS: greyscale; LDA: low disease activity; MDA: moderate disease activity; MTX: methotrexate; PD: power Doppler; RF: rheumatoid factor; SJC: swollen joint count; TJC = tender joint count; TT: treat to target; VAS: visual analogue score.