RHEUMATOLOGY

Letters to the Editor

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Is radiographic progression a downside of stopping TNF-inhibitor in RA patients with low disease activity, if this is followed by flare? A sub-study of the POET-US trial

Rheumatology key message

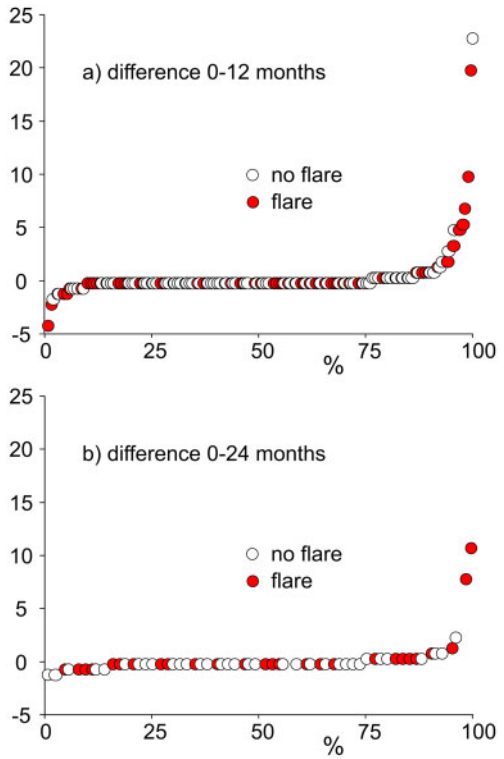
- RA flare during the first year following TNFi cessation does not cause additional radiographic progression.

Dear Editor, Half of patients with RA, who are in sustained low disease activity (LDA) or remission, can discontinue TNF-inhibitor successfully, without experiencing a flare within 1 year after stopping [1]. This implies that 50% does have flare; unfortunately, we are not yet able to predict at the moment of stopping TNFi which patient is at high risk of flaring. However, soon after restarting TNFi again, at least LDA is achieved [1]. The aim of our study was to establish whether flaring in this situation would be associated with more radiographic progression [2], compared with no flaring.

This is a sub-analysis of the POET-US study [3], in which patients had been included who had RA (ACR 1987 OR 2010 criteria), were older than 18 years, had been using TNFi and csDMARD >1 year and had DAS28 < 3.2 for 6 months prior to inclusion. The study was approved by a central ethics commission and participants gave their written informed consent according to the Declaration of Helsinki. TNFi was stopped and patients were followed for 52 weeks thereafter. In case of a flare, TNFi was restarted within a short period in most patients. Flare was defined as >0.6 increase of DAS28 since study start AND (Boolean) an actual DAS28 ⩾ 3.2, according to OMERACT [4]. X-rays of hands and feet were made at, or <12 months before, inclusion and at 12 and 24 months after stopping TNFi. These were scored by two independent readers using the Sharp van der Heijde score (SvdH); their inter-rater reliability was 0.97 (95%CI: 0.96, 0.98) and their average score was used, unless only one reading was available. Cumulative probability plots of radiographic joint progression for those flaring *vs* those not flaring were drafted [5].

Complete X-ray data were available of 141 of 256 POET-US patients at 12 months after stopping TNFi, and of 84 at 24 months. During the first year, 69 (49%) patients experienced a flare. Baseline characteristics did not differ between patients with or without complete X-ray data. Linear regression (outcome: radiographic progression over 1 year, predictors baseline SvdH-score and flare y/n) was performed to establish whether flare would independently predict radiographic progression, but it did not. In contrast, a higher baseline SvdH-score predicted more radiographic progression (R^2 0.123, P = 0.0000). After one year there was no significant difference in mean (s.d.) radiographic progression between RA patients who flared and those who did not: respectively 0.74 (3.0) and 0.53 (2.8) SvdH units, P = 0.94 (Mann–Whitney U test). The cumulative probability plot (Fig. 1a) shows that 86% (121/141) of patients in both groups had no radiographic progression over one year. Although at 24 months a major part of X-rays were missing, we also plotted a cumulative probability plot for

Fig. 1 Cumulative probability plots of radiographic progression



Cumulative radiographic progression plots showing the change in Sharp van der Heijde score (*y*-axis) during the first year after stopping TNFi and continuing csDMARD (**a**, n = 141) and during the first two years after stopping TNFi and continuing csDMARD (**b**, n = 84). No flare: patients who did not experience a flare of RA during the first year after stopping TNFi, Flare: patients who experienced a flare of RA during the first year after stopping TNFi.

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radiographic progression over two years with similar results (Fig. 1b).

Although these outcomes are reassuring, it should be noted that flare occurred after a mean (S.D.) of 21 (14) weeks after stopping TNFi, leaving a relatively short period in which progression could be increased, but in both groups, we found minor radiological progression also over two years. Minor radiological progression has been reported before in patients with LDA; it might be explained by subclinical disease activity in some [6]. In conclusion: flare in the first year after TNFi cessation in RA patients with LDA seems not to cause additional radiographic progression.

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References

1 Smolen JS, Landewe R, Bijlsma J *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.

2 Henaux S, Ruyssen-Witrand A, Cantagrel A *et al*. Risk of losing remission, low disease activity or radiographic progression in case of bDMARD discontinuation or tapering in rheumatoid arthritis: systematic analysis of the literature and meta-analysis. Ann Rheum Dis 2018;77:515–22.

3 Lamers-Karnebeek FB, Luime JJ, Ten Cate DF *et al*. Limited value for ultrasonography in predicting flare in rheumatoid arthritis patients with low disease activity stopping TNF inhibitors. Rheumatol 2017;56:1560–5.

4 van der Maas A, Lie E, Christensen R *et al*. Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. Ann Rheum Dis 2013;72:1800–5.

5 van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999;26:743–5.

6 Saleem B, Brown AK, Keen H *et al*. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: a clinical and imaging comparative study. Arthritis Rheum 2009;60:1915–22.

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Inhibition of IFNα secretion in cells from patients with juvenile dermatomyositis under TBK1 inhibitor treatment revealed by single-molecular assay technology

Rheumatology key message

- Detection of IFNαs proteins secreted by cells from JDM patients opens new perspective for drug discovery.

Dear Editor, A type 1 IFN gene signature has been previously demonstrated in the peripheral blood and muscle of patients with JDM, correlating with disease activity scores. However, direct measurement of IFN alpha (IFNα) protein in samples from patients has remained a challenge until recently. We addressed this limitation by optimizing an ultrasensitive single-molecule array (Simoa) digital ELISA utilizing high affinity autoantibodies isolated from APECED patients that recognize all human interferon-α species [1]. Using this technology, we were able to detect and quantify serum IFNα in the blood of JDM patients [2], and the blood, cerebrospinal fluid, cell supernatant and tissues from patients with other complex and monogenic interferonopathies [2, 3]. Interestingly, the median serum concentration of IFNα was at 56 fg/ml in JDM patients, almost 100 times below the limit of detection of classical anti IFNα ELISAs.

In the present study, we evaluated the ability of anti-inflammatory drugs, particularly the TBK1 inhibitor BX795, to control IFNα secretion from cells of JDM patients. Previous studies have shown that TBK1 inhibition controls disease activity in a mouse model of SLE, and interferon signalling in fibroblasts from lupus patients [4] and PBMCs isolated from patients with gain-of-function of STING [3]. TBK1 inhibitors are currently in preclinical evaluation for their use in inflammatory diseases such as SLE.