Influenza vaccination and interruption of methotrexate in adult patients with rheumatoid arthritis in the COVID-19 era: an ongoing dilemma

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With the COVID-19 pandemic continuing unabated and the advent of the influenza season, public health authorities have emphasised that influenza vaccination is of paramount importance[1]. Vaccination can reduce the severity of influenza infection and prevent hospitalisations[1], which may help to conserve already strained healthcare resources. EULAR recommend that annual influenza vaccination should be strongly considered for most patients with chronic autoimmune inflammatory rheumatic diseases (AIIRD), as these patients are at increased risk of infection, due to inherent and/or iatrogenic immunocompromise[2]. There is no optimal formulation (valency or dose) of the inactivated influenza vaccine for patients with AIIRD. Patients with AIIRD require potentially life-long immunosuppression. Short-term interruption of treatment may sometimes be necessary to restore immune responses, e.g. with severe infection or major surgery. Anecdotally, some clinicians temporarily discontinue methotrexate (MTX) (e.g. one week before/after immunisation) in patients with rheumatoid arthritis (RA) to optimise the efficacy of influenza vaccination, although this approach is not supported by guidelines. Here we consider the evidence-base for and implications of this strategy in the COVID-19 pandemic.

Seasonal influenza is a major global cause of morbidity, mortality and burden on healthcare services. Influenza may be clinically confused with COVID-19 and co-infection carries a worse prognosis[3]. Influenza vaccination reduces the incidence, complications, hospital admissions and mortality from influenza and pneumonia in AIIRD[2]. The host immune system (including immunosenescence with ageing) may influence vaccine effectiveness. MTX is the most commonly prescribed first-line disease modifying anti-rheumatic drug (DMARD) for RA alone or in combination with biologic therapy. The immunosuppressive effect of MTX is beneficial in RA to reduce biologic-associated immunogenicity (anti-drug antibodies)[4], but may compromise vaccine responses[5].

The effects of temporary discontinuation of MTX on antibody titres to the trivalent influenza vaccine, were investigated in a prospective, randomised parallel-group, single-blind, single-centre pilot study of patients with RA (n=199) taking stable MTX doses[6]. Patients were randomised to continue MTX (group 1; n=54); suspend MTX four weeks before vaccination

(group 2; n=44); suspend MTX two weeks before and after vaccination (group 3; n=49); or four weeks after vaccination (group 4; n=52)[6]. All groups demonstrated similar frequency of satisfactory vaccine responses (≥four-fold increase in antibody titre), however group 3 achieved significantly higher vaccine responses compared with group 1. Withholding MTX four weeks prior (group 2) was not associated with significantly different antibody titres, whereas discontinuing MTX for four weeks after vaccination (group 4) resulted in improvement compared with group 1. To reduce the risk of RA flares, whilst achieving adequate vaccine response, a shorter MTX discontinuation period was investigated in a prospective, multicentre study, where patients with RA on stable MTX doses, were randomised to continue MTX (n=156) or withhold MTX for two weeks (n=160) after the quadrivalent influenza vaccine[7]. Significantly more patients in the MTX-hold group, achieved satisfactory vaccine responses (≥fourfold increase in antibody titre in ≥2/4 influenza antigens) compared with the MTX-continue group (75.5% vs 54.5%, p<0.001; difference 21.0%, 95% CI 10.6-31.7%). Neither of these studies demonstrated a significant increase in RA flares following discontinuation of MTX[6,7]. A recent post-hoc analysis of these studies compared disease activity between the MTX-hold groups (for four weeks before[6] [n=44] or two weeks after[7] [n=161] vaccination) with a pooled MTX-continue group (n=210)[8]. The analysis concluded that short-term discontinuation of MTX for 2 weeks was safe, whereas discontinuation for 4 weeks was associated with a transient increase in disease flares although adjusted flare rates were 2.90 (2-week hold) and 3.94 (4-week hold) [8]. However, only one arm (group 2) from the first study was included and, furthermore, flare rate was based on disease activity measured at a single fixed time-point, four weeks after methotrexate interruption. This corresponded to the end of the four week interruption period in the first study and two weeks after MTX resumption in the second. The original studies did not demonstrate significantly increased flare rates with methotrexate interruption, and transient disease activity increases were readily controlled; vaccine responses were >70% higher in the second study, even with MTX continuation (Table).

It is unclear whether antibody titres to influenza vaccines (often used sole surrogate outcomes for efficacy) translate into protection from infection, or if there are better correlates in immunocompromised patients e.g. T-cell responses[9]. Whilst the risks of RA flare and need for glucocorticoids appears small, both can increase infection risk. Patients with AIIRD receiving ≥10mg prednisolone had significantly poorer outcomes with COVID-19[10]. Furthermore, the generalisability of these studies (both from Korea) with low baseline MTX doses (10-15mg

weekly) is unknown[6,7]. The influence of patient age, MTX dose and administration route, duration and degree of RA disease activity and other confounders (including smoking/alcohol) is unclear. A large multi-centre, international study would be required to confirm whether transient MTX interruption peri-vaccination reduces incidence/severity of influenza, as well as the optimal strategy to achieve this.

Whilst a two-week discontinuation of MTX post-vaccination in patients with quiescent disease may improve influenza vaccine responses, without a significant impact on RA disease activity[6-8], currently there is insufficient evidence to alter clinical practice or guidelines. Due to restricted access to healthcare during the initial COVID-19 pandemic some patients experienced RA flares, and interrupting MTX may risk destabilising disease control. Nonetheless, we feel available evidence merits individualised discussions with patients with well-controlled disease, regarding the potential benefits and risks of omission of 1-2 doses of MTX, regarding influenza vaccine efficacy, and perhaps COVID-19 vaccination when available.

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