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EDITORIAL

Should we stop methotrexate or not for vaccination?

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The COVID-19 pandemic has brought the debate about methotrexate (MTX) discontinuation and vaccine response back to the forefront. This issue cannot leave the rheumatology community indifferent.

This debate involves a difficult decision weighing the need to continue effective immunosuppressive treatment of chronic inflammatory rheumatism such as rheumatoid arthritis (RA) against the need to protect our patients through effective vaccination.

By its action, low-dose MTX has been shown to impair responsiveness to pneumococcal and influenza vaccine.[1–3] Recently, several studies have explored the humoral response after the COVID-19 vaccine in MTX-treated patients. The article published by Habermann *et al* clearly indicates a reduction in humoral response under MTX after COVID-19 vaccination and a 1-week break from MTX allows this response to be restored.[4] Araujo *et al* showed that in 138 patients with RA treated with MTX continuously or interrupted for 2 weeks, the seroconversion rate and antibody titre was higher in the pause group.[5] The same decrease of antibody production was also confirmed by Abhishek *et al* in the prospective VROOM study.[6] It is important to note that Haberman and Abishek analysed the booster dose and not after basic immunisation. MTX discontinuation was not only evaluated after COVID-19 vaccine since Park *et al* had previously recommanded such intervention for influenza vaccination.[7] These authors have also evaluated the optimal time between the last MTX dose and the vaccine and recommended that a 2 week interval could be optimal.[8]

The first consideration is whether the lowest antibody response evaluated by different assay in these studies can be interpreted as a good and validated predictive marker of vaccine protection. The rationale is simple and refer to the association of dose response of antibody titres after vaccination and protection against symptomatic SARS-CoV-2 infection.[9] In a prospective cohort of patients with autoimmune disease, COVID-19 infection occurred in 7.4% of patients (threefold increased risk) and were associated with nonresponders to the vaccine defined by no antibody titres.[10] They reported that MTX was associated with lower antibody titres but not with breakthrough infection in contrast with other treatment such as mycophenolate mofetil, rituximab and glucocorticoid.[11] In two studies reported by Arumahandi de Silva *et al* and Stahl *et al*, age was the major determinant to explain the decrease in the humoral response in MTX-treated patient with RA.[12 13] This was recently confirmed in the study published by Frommert *et al* by a negative impact of age, MTX, type of vaccine and dosage interval on vaccine antibodies response.[14] Withholding MTX after the second dose of COVID-19 vaccine resulted in a similar humoral response in a randomised controlled trial.[15] Therefore, pausing MTX could be proposed for the second vaccine dose and in patients over 65 years of age.

A difficult issue is to define the threshold of the humoral response as a surrogate biomarker of clinical significance since the titre is influenced by the assay and the vaccine. This mean that there is uncertainty whether monitoring of anti-S response after COVID-19 vaccine might guide individual patient management. Moreover, even if we could define a validated value, the access to the test and its interpretation will not be feasible for all patients in daily care. An additional difficulty is the virus mutation and the absence of correlation between antibody response and severe COVID-19 infection, hospitalisation and death. In the VROOM study, only 4 patients (1%–2%) were hospitalised, which confirm that MTX and RA are not associated with severe COVID-19 infection and limit the data interpretation.[6]

It should also be remembered that for any vaccination, the protective response involves B and T lymphocytes, CD4+and CD8+ and is,

therefore, not explained only by the humoral but also the cellular response. Few articles have analysed the cellular response in inflammatory arthritis. Schmiedeberg *et al* reported an equivalent T cell response in a treated RA population compared with healthy controls after the COVID-19 vaccine.[16] They observed also in this study that only anti-COVID-19 IgG were lowered and IgA and IgM levels were maintained. Interestingly, Kapetanovic *et al* demonstrated that despite a decreased total immunoglobulin level following pneumococcal vaccination, the numbers of circulating total and vaccine-specific IgG or IgA producing plasmablasts did not differ between patients with RA with or without MTX.[17] MTX used at a dose below 25 mg/week could not be considered as an immunosuppressant but that its effect is more immunomodulatory, anti-inflammatory by increasing the level of adenosine. MTX may inhibit proliferation of cells responsible for synovial inflammation in RA but it has become clear that its antiproliferative effects are not the main mechanism of action in RA. The main effect of low weekly doses MTX is an anti-inflammatory action explained by an increase of extracellular adenosine by inhibiting aminoimidazole-carboxamide ribonucleoside. The accumulation of adenosine leads to a decrease secretion of TNF, IFN and IL-6 and increase secretion of IL10.[18 19] The combination of the antiproliferative and anti-inflammatory actions may explain the disease modifying action of MTX. Supporting an immunomodulation rather that an immunosuppressive action of MTX, the vaccine response on MTX treatment could not be considered ineffective and the lowered antibody titre observed may not perfectly reflect the vaccine efficacy.

The second consideration is the consequence of stopping MTX in our patients. The Korean study published by Park *et al* clearly demonstrated the risk of a rebound of the disease (10.6% RA flare if MTX is interrupted for 2 weeks compared with 5.1% in the MTX maintenance group) and the need to use glucocorticoids.[7] A higher rate of flare after the second dose of vaccine was also observed by Araujo *et al*.[5] In the VROOM study, an absolute 25% increased risk of flare with a more frequent use of glucocorticoids in the group pausing MTX was reported.[6] This is not in line with the results of a pharmacological study in which pausing temporary MTX for one tot wo weeks has no influence on the intracellular polyglutamate dosage of MTX.[20] To limit the risk of flare, factors such as the duration of MTX administration and the dose, the disease activity in the last months, the severity of RA and the comedication should be globally analysed before taking a decision. Another concern is related to the observation that vaccination against COVID-19 could influence RA symptoms and disease activity. A recent review published by Xie *et al* showed a flare rate in RA ranging from 7.8% to 11.3% but the resolution occurred very shortly within 7 days.[21] In 2019, the EULAR updated their recommendation for vaccine and one of them indicate that vaccination in patients should be promoted during a quiescent state of disease to avoid flare-ups and favour a good immune response.[22] Pausing MTX recommendation could therefore be problematic in patients with early or active disease. An alternative for not discontinuing MTX could be to propose a booster dose in patients. This approach was evaluated in two studies which demonstrate that an additional vaccine dose to patients with inflammatory disease contribute to strong and sustained immune-responses comparable to healthy controls.[23 24]

The last consideration is potentially the more relevant since the vaccination coverage in RA is not optimal. The COVID-19 pandemic and its 6 million deaths reminded us of the need for vaccination. Our patients with RA are at increased risk of infections due to inherent dysregulation of the immune system and treatment with immunosuppressive agents.[25] For this, the EULAR task force publication is a good tool to review the different vaccine in RA.[22] Despite this, we know that the rate of full vaccinated patients with RA is not optimal. The COMORA study found that only 25% of patients with RA were adherent to current vaccine recommendations.[26] To analyse this, Sandler *et al* conducted a survey to assess vaccination rates in the RA population and reported vaccination rates of 79% for influenza and 53% for pneumococcus in an academic centre.[27] This reflects that a large number of patients with RA do not accept the vaccine for several reasons and speaking about a lack of antibody response could increase the vaccine hesitancy. To improve this, EULAR has published recommendations on the management of inflammatory rheumatism and RA during the COVID-19 period.[28] Numerous cohorts were analysed during the COVID-19 pandemy, severe COVID-19 and mortality was not associated with the diagnosis of RA but related to the risks observed in the general population such as age, male sex, obesity and hypertension. Among treatments, only glucocorticoids and some immunosuppressants such as rituximab, mycophenolate mofetil were associated with increased severity and mortality from SARS-CoV-2 infection. Recently, EULAR published an update to strongly encourage patients to receive full SARS-CoV-2 vaccination.[29] A recent survey in physicians indicates that the rheumatologist should be responsible for the vaccination and 96.7% considered the vaccination very important. Despite this, only 37% of the physician reported vaccinating the majority of their patients.[30] In the RA clinic of one of us in Brussels, the rate of vaccination willingness in patients with RA improve from 69% in 2020 to 81% in 2021.[31] This mean that we have improved the process but still 19% of my RA population are not protected against severe infection. Optimising vaccination with MTX pausing is therefore an important but a secondary objective and need further analyses to better determine the target population and the way we could apply this easily in our standard of

care. Pausing immunosuppressive agent to improve vaccine protection is not limited to MTX and will be extended to the risk of other infection such as herpes zoster and JAK inhibitor. The debate is still open and vaccination in RA has the objective to protect patients against severe infection and mortality. EULAR and all rheumatologists have worked hard to promote vaccination. It is indeed undeniable that vaccination has drastically reduced the severity, hospitalisation rate and mortality of COVID-19 infection. Despite these efforts, vaccination rates are not optimal.

The arguments to stop MTX or not could be summarised as :

PRO : Vaccination is an important measure to protect our patients with chronic inflammatory rheumatism such as RA and the temporary discontinuation of MTX helps to optimise the vaccine response.

CON : Discontinuation of MTX has not shown superior protection to vaccination against severe COVID-19 infection and may increase the risk of disease relapse.

In summary, the first objective should be to propose the recommended vaccinations in every patients with inflamatory arthritis. The second objective should be to optimise these vaccinations. In this respect, pausing MTX (1 or 2 weeks) is an interesting option and should be proposed at least to elderly patient. The alternative is to recommend an additional booster dose without pausing MTX. Our role should be after evaluating each patient (age, comorbidities, disease activity and severity…) to define at the individual level the best balance between disease control and prevention of severe infection.

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