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LETTER TO THE EDITOR

Reply: Treatment of anti-MDA5 autoantibody-positive juvenile dermatomyositis using tofacitinib

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Sir,

In their letter, Sabbagh *et al.* report two refractory juvenile dermatomyositis (DM) patients with anti-MDA5 autoantibodies who significantly improved muscle and skin but also lung disease, following treatment with a Janus Kinase 1 and 3 (JAK 1/3) inhibitor (tofacitinib). This observation extends case reports published previously (Aeschlimann *et al.*, 2018; Papadopoulou *et al.*, 2019) reporting the improvement in two other refractory juvenile DM (JDM) cases using another JAK inhibitor (baricitinib).

The rationale of JAK inhibitor use is supported by the strong interferon (IFN) pathway activation in the peripheral blood, muscle and skin biopsies (Wong *et al.*, 2012; Huard *et al.*, 2017; Uruha *et al.*, 2017) of DM patients and the demonstration *in vitro* of the pathogenic role of IFN on both vascular and muscular cells (Ladislau *et al.*, 2018). Indeed, the JAK family plays an important role in the intracellular signalling of multiple cytokines including IFN signalling transduction (Schwartz *et al.*, 2017).

Importantly, Sabbagh *et al.* report for the first time the successful effect of tofacitinib in two cases of anti-MDA5 JDM associated with interstitial lung disease (ILD). This observation is in line with previously published cases in adult anti-MDA5 DM patients (Kurasawa *et al.*, 2018; Kato *et al.*, 2019).

Severe ILD in anti-MDA5 JDM patients has been reported in East-Asian patients (Sato *et al.*, 2009; Kobayashi *et al.*, 2015) and is associated with poor prognosis. In juvenile Caucasian populations, a lower frequency of milder ILD has been reported (Tansley *et al.*, 2014). Nonetheless, the cases reported by Sabbagh *et al.* illustrate that severe ILD in anti-MDA5 JDM can occur and underlines the necessity of finding therapeutic options for these cases at high risk of morbidity and fatality.

A few cases of anti-MDA5 JDM patients associated with severe ILD have also been observed in our cohort and these cases are challenging to manage. Since our publication (Ladislau *et al.*, 2018), we have treated four adult anti-MDA5 DM patients with JAK inhibitors. We only observed a limited beneficial effect. Indeed, only a single patient improved, while three others worsened and died of respiratory failure in the intensive care unit (ICU). Of note, two of these four patients were treated when they were already in respiratory failure in the ICU. One of them improved and was successfully weaned off the non-invasive ventilation, while the other died. These observations raise the question whether the use of JAK inhibitors earlier may have prevented the development of respiratory failure in the presence of anti-MDA5 ILD.

Anti-MDA5 DM has also been associated with a severe vasculopathy (Fiorentino *et al.*, 2011). We previously demonstrated *in vitro* that endothelial cells exposure to type I IFN disrupted vascular network organization and

this effect was reversed by JAK inhibitor therapy (Ladislau *et al.*, 2018). Interestingly, the second patient reported by Sabbagh *et al.* demonstrated a complete resolution of digital ulcers following tofacitinib.

An association between calcinosis and the presence of vascular injury has also been reported (Wendel *et al.*, 2019). Along that line, it must be underlined that the second JDM case displayed an improvement of the calcinosis. Of note, the absence of progression of calcification was reported in other JDM patients treated with JAK inhibitor (Aeschlimann *et al.*, 2018; Papadopoulou *et al.*, 2019). Nonetheless, this is the first JDM case reporting an improvement of calcinosis. Similarly, two other adult DM cases treated with tofacitinib were recently reported and also demonstrated an improvement of extensive calcifications (Valenzuela *et al.*, 2014).

Sabbagh *et al.* demonstrated that in both patients treated with tofacitinib, STAT1 phosphorylation in CD4+ T cells and monocytes stimulated with multiple cytokines (IFNα, IL-6, IL-21, and IFNγ) improved to levels comparable to healthy controls, showing the broader immunomodulatory effect of JAK inhibition other than type I IFN (Schwartz *et al.*, 2017). The pathomechanisms involved in the ILD of anti-MDA5 DM remain to be clarified, and the report of Sabbagh *et al.* suggest the presence of several putative pathways may be involved in addition to IFN-induced lung injuries (e.g. vascular damages) (Liu *et al.*, 2014).

This broad effect of JAK inhibitors is also reflected by its efficacy in many other inflammatory diseases that are not IFN-dependent such as rheumatoid arthritis, psoriasis and psoriatic arthritis and ulcerative colitis (Schwartz *et al.*, 2017). Of note, one of the patients reported by Sabbagh *et al.* developed herpes simplex meningitis following tofacitinib. Prospective trials are needed to clarify the infection risk and safety profile associated with these molecules especially in refractory DM patients previously exposed to several lines of immunosuppressants (Cohen *et al.*, 2014).

If JAK inhibitors take advantage of the important number of cytokines mediating signals via the JAK-STAT pathway to control immune responses, one must not forget that JAK-STAT pathway is also involved in non-immune systems. In the context of juvenile patients, one must consider that JAK2 also transduces the growth hormone signals (Brooks *et al.*, 2014; Schwartz *et al.*, 2017). Nonetheless, previously published cases have not reported growth delays in children treated with JAK inhibitors for JDM or genetic interferonopathies (Frémond *et al.*, 2016; Aeschlimann *et al.*, 2018; Sanchez *et al.*, 2018; Papadopoulou *et al.*, 2019).

To conclude, JAK inhibitors represent a promising therapeutic option for the treatment of juvenile and adult DM. Emerging data suggest its potential beneficial effect on calcinosis and anti-MDA5 related ILD. Prospective clinical trials are needed to confirm these encouraging observations.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Competing interests

The authors report no competing interests.

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