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Letter to the Editor

Dimethyl fumarate induced migrating polyarthralgias

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Dimethyl fumarate (DMF) is a first-line treatment employed in relapsing-remitting multiple sclerosis (MS) [1]. It belongs to the group of fumaric acid esters that have been used since 1958 for treating psoriasis, (particularly in Germany) [1].

The main undesirable effects known are gastrointestinal, hepatic (cytolysis), and hematological disorders like leukopenia or lymphopenia, as well as hot flashes, skin rash, and pruritus. While its mechanism of action is still poorly understood, the agent is assumed to act by limiting the passage of lymphocytes through the blood-brain barrier, thus reducing expression of adhesion molecules and production of pro-inflammatory cytokines [1].

We hereby report the case of a 19-year-old patient female followed-up at the University Hospital of Clermont-Ferrand, France, for MS treated with first-line DMF since July 2017. Two months after treatment initiation, the patient presented with a range of migrating polyarthralgias of an inflammatory nature at the knees, ankles, wrists, and hips, followed by the shoulders, lasting 1–3 days with complete resolution between each flare-up. She was thus referred to rheumatology consultation for suspected rheumatoid arthritis. The patient had no history of arthritis, and there were no extra-joint symptoms. Her antinuclear antibody and rheumatoid factor tests were negative, there was no inflammatory syndrome (erythrocyte sedimentation rate [ESR] = 9 mm/h; C-reactive protein [CRP] < 2.9 mg/L), and the x-ray proved normal, so rheumatoid arthritis was dismissed as diagnosis. The patient did not manifest the criteria for ankylosing spondylitis and tested negative for HLA B27 (A01; B08 B52; DRB*10; DRB1*15; DQB1*05; DQB1*06). The negative antinuclear antibody tests, absence of Raynaud phenomenon, and skin rash all disproved the hypothesis of connectivitis. Lyme blood testing was likewise negative. Later, the patient presented with arthritis in the right ankle followed by interphalangian arthritis in her right thumb, both of which spontaneously resolved within 24 h. Given the absence of any other etiology, DMF treatment was suspected to have caused this range of symptoms, and was discontinued at the end of November, 2017. The patient's polyarthralgias progressively regressed within 2 weeks following DMF discontinuation, with no recurrence. The treatment was then reintroduced without any symptoms recurring.

To the best of our knowledge, there is only one previous study reporting migrating polyarthralgias associated with DMF treatment, including three patients [2] of them treated for MS. The first case was a 39-year-old woman suffering from severe migratory musculoskeletal pain 4 months after DMF was initiated as second-line treatment following beta-interferon failure. She exhibited no anomalies on physical examination, yet did exhibit an inflammatory syndrome (VS = 60 mm at 1 h), and her rheumatoid factor testing proved negative. Given her persistent symptoms despite discontinuing DMF, the patient was administered corticotherapy with methylprednisolone at 1 g/d for 2 days, resulting in complete clinical and biological resolution. The second patient was-years-49 years old receiving first-line DMF treatment. She developed moderately-intense migrating arthralgias 6 months after commencing DMF treatment with no anomalies on physical examination, although she did exhibit an inflammatory syndrome (CRP = 17 mg/L and ESR = 19 mm/h), yet was negative for rheumatoid factor. Her pain continued after treatment discontinuation despite also receiving nonsteroidal anti-inflammatory drugs (NSAIDs). The third patient, aged -years-72 years, developed infrapatellar pain that varied in intensity and grew in frequency, resistant to NSAIDs. He exhibited an inflammatory syndrome (CRP = 10 mg/L, ESR = 33 mm/h), and achieved complete remission 1 month following treatment discontinuation. As with our own patient, these patients reported no other undesirable effects in relation with DMF. The delay in symptom occurrence proves comparable, though we noted some differences. Firstly, we observed no inflammatory syndrome in our case, and secondly, our patient developed two authentic arthritis flare-ups despite the physical examination being strictly normal except for these two episodes.

According to the French imputability method [3], intrinsic imputability takes account of the temporal relationship (the chronological criterion [c]) and the drug's mechanism of action (the clinical criterion [s]). Our case may be rated as C1-S2 given the absence of relapse on re-initiation of the treatment and the unexpected nature of the symptoms. This equated to a score of I2 (out of 6, 6 being the highest imputability score). Extrinsic imputability was rated as B2 (out of 4, 4 being the highest imputability score). The main weakness of our observation is our lack of proof of imputability. We cannot state with certainty that the DMF treatment and rheumatological symptoms were related, since the symptoms did not recur when treatment was resumed, and since the few cases reported have been disparate in nature. To conclude, it remains important to remember that this effect may occur in patients being treated with DMF who have arthralgia or arthritis. Nevertheless, further observations are needed to confirm the relationship between DMF and this potential adverse effect.

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Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Ruggieri S, Tortorella C, Gasperini C. Pharmacology and clinical efficacy of dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. Ther Clin Risk Manag 2014;10:229–39.
[2] Bernardini LR, Zecca C, Clerici VT, et al. Severe articular and musculoskeletal pain: an unexpected side effect of dimethyl fumarate therapy for multiple sclerosis. J Neurol Sci 2016;369:139–40.
[3] Cercle de réflexion sur l'imputabilité (CRI)Arimone Y, Bidault I, et al. Updating the French method for the causality assessment of adverse drug reactions. Therapie 2013;68:69–76.

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