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CE - LETTER TO THE EDITOR

Interdisciplinary approach to opportunistic infections: staphylococcal meningitis in a patient with multiple sclerosis on treatment with dimethyl fumarate

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Dear Editor,

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) representing a relevant cause of disability in young adults. In the last 20 years, new and emerging disease-modifying drugs (DMD) have been introduced in clinical practice revolutionizing the natural history of the disease [1]. However, immunomodulatory and immunosuppressive treatments for MS are associated with an increased risk of severe infections, which ranges from 0.2% to 2.6% [2].

Dimethyl fumarate (DMF) is an oral drug approved for MS with more than 450,000 patients treated worldwide [3]. Since the phase III DEFINE and CONFIRM studies and in ENDORSE, DMF has shown good efficacy and an excellent safety profile [3].

We report a case of a patient who develops a severe infection of the CNS during the DMF treatment.

Our patient is a 58-year-old woman with a medical history of an early stage of chronic obstructive pulmonary disease, hypothyroidism, and hypercholesterolemia. She was diagnosed with RRMS in October 2003, at the age of 39, after 2 relevant clinical episodes (Fig. 1). In November 2003, she started the treatment with interferon beta-1a, 22 µg 3 times per week, which was increased to 44 µg three times per week due to radiological activity. After that, she did not present clinical and radiological disease activity for 12 years. The neurological examination remained stable with an Expanded Disability Status Scale (EDSS) of 3.0.

In 2016, she presented the first episode of trigeminal neuralgia with a new brainstem lesion, and she has been shifted to DMF 240 mg twice daily since she refused infusion treatment.

On 2nd July 2020, she developed fever and respiratory distress and she was admitted to the emergency room (ER) of another hospital. The nasopharyngeal swab for Sars-Cov-2 was negative, the blood count showed mild leucocytosis and the thyroid function test was normal. The chest computed tomography revealed lobar pneumonia characterized by a focal dense opacification of the right lower lobe with relative sparing of the large airways. Blood cultures were positive for staphylococcus aureus methicillin-sensitive. DMF was not discontinued, and antibiotic therapy was started. The patient was discharged, on 21st July, apyretic and with negative blood cultures, she exclusively complained of mild headache.

On 19th September, she presented fever (up to 39°), intense headache and altered mental status. She went to the ER of our hospital, the nasopharyngeal swab for Sars-Cov-2 was negative, the blood count revealed leucocytosis [12,210/uL, normal range (nr) 4500–11,000], with enhanced neutrophils 9523/µL (nr 1500–8000) and normal lymphocytes count. We promptly suspended the DMF therapy and no alternative DMD was started.

The lumbar puncture was performed, and the cerebral spinal fluid (CSF) analysis revealed 1445 cells/µL (80% polymorphonuclear cells, 20% mononuclear cells), elevated protein content of 113 mg/dL, a low glucose level of 10 mg/dL (serum glucose level 100 mg/dL). Blood and CSF cultures were positive for Staphylococcus aureus methicillin-sensitive. Brain magnetic resonance imaging (MRI) showed frontoparietal leptomeningeal enhancement. The patient

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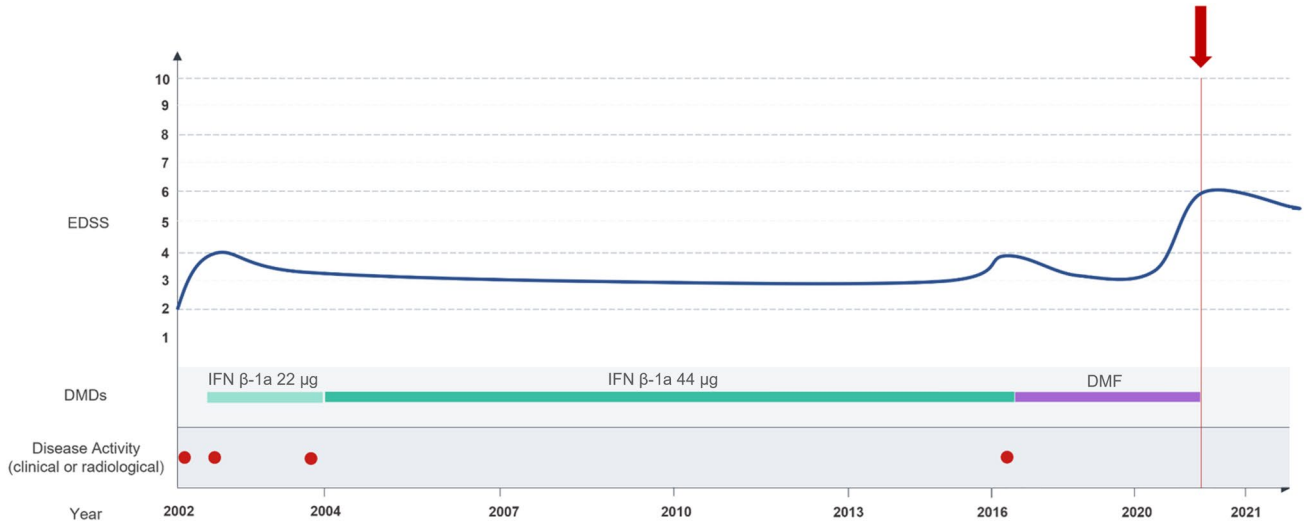

Fig. 1 MS course of the patient: the trend over time of the clinical and radiological activity of the disease, the DMDs and the disability levels expressed by the EDSS. *MS* multiple sclerosis, *DMDs* disease-modifying drugs, *EDSS* expanded disability status scale, *IFN* interferon, *DMF* dimethyl fumarate

started the antibiotic therapy with Ceftaroline 600 mg twice daily and Linezolid 600 mg twice daily. She had a good recovery from meningitis but since the infectious event, she complained of a restriction in gait (EDSS 6.0). At the last follow-up in November 2021, no other infectious adverse events (IAE) were reported, and the MS was clinically and radiologically stable. The patient rejected the proposal to start any DMD.

DMF is one of the most prescribed therapies in MS and it has shown good efficacy and an excellent safety profile whether in phase III or real-world studies.

In the placebo-controlled DEFINE study, the infections reported affected the upper respiratory tract or urinary tract or were influenza-like infections [3]. Severe infections were detected in 2% of the patients in all groups, but none of these was opportunistic[2]. In addition, IAEs seem to be not related to a lower lymphocyte count and they may occur in patients with normal leukocytes count as in our patient who never developed lymphopenia [3–5].

Several opportunistic infections during DMF treatment were submitted to the FDA Adverse Event Reporting System (FAERS), 11 affecting the CNS, but this is the first case of staphylococcal meningitis [5]. However, the opportunistic infections represent an extremely rare IAE during treatment with DMF.

We speculate that a careful evaluation of the risk/benefit profile would suggest temporary discontinuation of the DMF during severe infection, such as staphylococcal pneumonia. The continuous DMF exposure may have favoured the secondary infection of the central nervous system.

This clinical case highlights the importance of a close collaboration between neurologists experienced in the management of MS and other specialist figures, such as the internist, in the management of serious adverse events during immunotherapies.

We also suggest temporarily stopping DMF treatment in the course of serious infectious adverse events to avoid favouring the propagation and spread of the infectious agent.

Declarations

Conflict of interest MT has served on Scientific Advisory Boards for Biogen, Novartis, Roche, Merck, and Genzyme; has received speaker honoraria from Biogen Idec, Merck, Roche, Teva, Sanofi-Genzyme, and Novartis; and has received research grants for her Institution from Biogen Idec, Merck, Roche, and Novartis. PI has served on scientific advisory boards for Biogen Idec and has received funding for travel and/or speaker honoraria from Sanofi-Aventis, Biogen Idec, Teva, and Novartis. DP received advisory board membership, speaker's honoraria, travel support, research grants, consulting fees, or clinical trial support from Almirall, Bayer Schering, Biogen, Celgene, Excemed, Genzyme, Merck, Mylan, Novartis, Sanofi, Roche, and Teva. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The patient has consented to the submission of the case report to the journal and she signed an informed consent regarding publishing her clinical data. The adverse event was reported to the Italian Medicines Agency (AIFA).

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