

Desensitization for immediate hypersensitivity to oral dimethyl fumarate (Tecfidera)



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Clinical Implications

- Physicians should be aware that oral dimethyl fumarate might cause immediate hypersensitivity reactions. Desensitization can be carried out safely and effectively, preventing discontinuation of treatment.

TO THE EDITOR:

Dimethyl fumarate (DMF) is one of the new oral drugs available for the treatment of multiple sclerosis (MS).¹ The exact mechanism of action of DMF is still under investigation and seems to involve the modulation of the immune response, the interference with the intracellular redox balance, and, possibly, also an important effect on mitochondria.¹

Recent studies showed a significant clinical impact of DMF on disability progression in patients affected by relapsing-remitting MS, with an overall favorable safety profile.^{2,3} These encouraging results warranted its rapid regulatory approval, first by the US Food and Drug Administration, in 2013, and successively by the European Medicines Agency, in 2014.

However, DMF was associated with the appearance of adverse events, particularly gastrointestinal symptoms (nausea, vomiting, abdominal pain) and flushing, which occurred in 30% and 40% of patients, respectively.^{2,3} In the vast majority of cases, these symptoms subsided within the first 2 to 3 months. Thereafter, less than 5% of the patients treated with DMF still reported such complaints.^{2,3}

Also, DMF has been known as a skin irritant and delayed-type contact dermatitis sensitizer (used as a mold growth inhibitor in footwear, clothing, and furniture manufacturing).⁴⁻⁶ Moreover, a case of immediate-type contact urticaria was described in a woman wearing DMF-treated trousers.⁷

Although DMF has been used as an oral drug since 2013, to our knowledge, no immediate hypersensitivity reactions associated with its administration have been reported, so far. Here, we describe a case of a woman with MS, treated with oral DMF, who complained about immediate hypersensitivity symptoms and was successfully desensitized.

A 57-year-old woman, affected by relapsing-remitting MS, had been treated since 2010 with IFN- β -1a, which was discontinued because of unsustainable side effects. In May 2016, the patient commenced an oral treatment course with DMF (240 mg daily). One month after the beginning of treatment, the DMF dose was increased to 240 mg twice a day, as recommended. Two days later, the patient experienced an immediate drug-related hypersensitivity skin reaction, characterized by rapid

onset of urticaria with confluent wheels and itching within minutes from drug intake. The lesions were widespread, with prevalence on the lower limbs and the trunk, and disappeared within a few hours, after low-dose antihistamines. After a 7-day washout, the patient resumed taking DMF (240 mg daily). Also, in this case, an immediate generalized urticarial reaction occurred within a few minutes, suggesting a causative role for DMF. The immediate nature of the reaction was confirmed by a lymphocyte proliferation test (LPT), which proved negative. The LPT was carried out by exposing the patient's lymphocytes to 3 different DMF concentrations: 7 μ g/mL, the "therapeutic concentration," calculated on a distribution volume of 70 L (published distribution volume = 53-73 L),⁸ 0.70 μ g/mL, and 70 μ g/mL. Lymphocyte proliferation was assessed by bromodeoxyuridine incorporation. Moreover, skin prick tests were performed with a concentration of 7 μ g/mL DMF; the intradermal tests were also performed with 0.7 μ g/mL and 0.07 μ g/mL DMF. The results of both tests proved negative. Thus, the mechanisms underlying the pathogenesis of these immediate hypersensitivity reactions (ie, IgE-mediated/non-IgE-mediated) remain uncertain. Therefore, the diagnosis was based essentially on the clinical features of the case (time of onset, morphology of the lesions, rapid response to antihistamines).

Considering the good clinical response to DMF, we decided to desensitize the patient. To this purpose, we used and adapted a desensitization protocol published by Castells et al.⁹ The dose-escalating scheme is reported in Table I. On the first day, gradually increasing doses of DMF, given at 30-minute intervals, were tolerated up to dose 7, when the patient experienced a transient local urticarial reaction at the lower right limb. Therefore, we decided to continue the desensitization under prophylactic administration of antihistamines (ebastine, 10 mg twice a day). On the second day, the patient was able to receive all the escalating doses of DMF, with only dose 9 followed by local transient reaction after 30 minutes. The patient developed similar local urticarial reactions for the following 4 days, after dose 9. Afterward, no more reactions were observed. Therefore, the antihistamine prophylaxis was discontinued from day 7. At day 31, the dose of DMF was increased to 240 mg twice a day. Thus, the desensitization scheme was maintained doubling each individual dose (Table I). Also, in this case the drug was well tolerated, without need for antihistamines. From day 40 on, the schedule was further simplified (Table I).

Oral DMF was introduced in the clinical practice for the treatment of MS only recently. In spite of the abundant literature on delayed hypersensitivity to DMF,⁴⁻⁶ to our knowledge, this is the first hypersensitivity reaction case described for oral DMF, given therapeutically. In addition, a desensitization protocol has never been reported, so far. The number of reactions during the desensitization procedures that we propose was fairly low and their severity mild, comparable to what has previously been reported for other drug desensitization protocols.⁹ Notably, in our case, the mild reactions observed subsided with low-dose antihistamines. Neither oral steroids nor adrenalin was needed.

In conclusion, this case shows (1) that DMF can be responsible for immediate hypersensitivity drug reactions, even if taken orally. Given the increase in the use of this drug for MS,

TABLE I. Oral desensitization schedule for DMF

Dose number	Time (min) day 1-30	Dose (mg): day 1-30	Time (min) day 31-40	Dose (mg): day 31-40	Time (h) day 41 on	Dose (mg): day 41 on
1	0	1	0	2	0	120
2	30	3	30	6	1	120
3	60	6	60	12	12	120
4	90	10	90	20	13	120
5	120	20	120	40		
6	150	40	150	80		
7	180	50	180	100		
8	210	50	210	100		
9	240	60	240	120		
		Total dose: 240 mg			Total dose: 480 mg	Total dose: 480 mg

physicians should be aware of this potential effect of the drug. (2) Nonetheless, it is important to underline that desensitization can be carried out as a safe and effective method, to avoid discontinuation of treatment.

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REFERENCES

1. Linker RA, Haghikia A. Dimethyl fumarate in multiple sclerosis: latest developments, evidence and place in therapy. *Ther Adv Chronic Dis* 2016;7:198-207.
2. Gold R, Kappos L, Arnold D, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo controlled phase III study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;367:1098-107.
3. Fox R, Miller D, Phillips J, Hutchinson M, Havrdova E, Kita M, et al. Placebo controlled phase III study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012;367:1087-97.
4. Svecová D, Šimaljaková M, Doležalová A. Footwear contact dermatitis from dimethyl fumarate. *Int J Dermatol* 2013;52:803-7.
5. Foti C, Zamboni CG, Cassano N, Aresta A, Damascelli A, Ferrara F, et al. Occupational allergic contact dermatitis associated with dimethyl fumarate in clothing. *Contact Dermatitis* 2009;61:122-4.
6. Susitaival P, Winhoven SM, Williams J, Lammintausta K, Hasan T, Beck MH, et al. An outbreak of furniture related dermatitis ('sofa dermatitis') in Finland and the UK: history and clinical cases. *J Eur Acad Dermatol Venerol* 2010;24:486-9.
7. Stingeni L, Neve D, Tondi V, Bacci M, Lisi P. Immunological contact urticaria caused by dimethyl fumarate. *Contact Dermatitis* 2014;71:180-3.
8. U.S. National Library of Medicine. DAILYMED. TECFIDERA-dimethyl fumarate capsule. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=665d7e74-036c-5f68-5b67-ab84b9b49151>. Accessed August 9, 2016.
9. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80.

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