Dimethyl fumarate may still have a role in progressive multiple sclerosis

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Ther Adv Neurol Disord
2016, Vol. 9(4) 344–345
DOI: 10.1177/1756285616640396

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We read with great interest the paper by Strassburger-Krogias and colleagues showing a significant effect of dimethyl fumarate (DMF) on disability progression in progressive multiple sclerosis (MS) patients [Strassburger-Krogias *et al.* 2014]. They enrolled 26 patients, 12 affected by primary progressive MS and 14 with secondary progressive MS, of whom 18 were treated with Fumaderm (Biogen Idec GmbH, Ismaning, Germany) and eight on pharmacy-prepared DMF. During a total mean follow-up period of 13.2 ± 7.5 months, 57.7% of patients did not experience any disability progression and 19.2% of them showed an improvement of their disability measured with the Expanded Disability Status Scale (EDSS), with an overall favorable safety profile. There was no significant difference between the Fumaderm and DMF.

DMF is one of the new oral drugs available for the treatment of relapsing MS. The exact mechanism of action of DMF is still under research 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. The latter by inhibition of the mitochondrial respiratory complex II succinate dehydrogenase whose reaction product is precisely fumarate, and by activating the human mitochondrial NAD(P)+-dependent malic enzyme [Ruggieri *et al.* 2014; Scannevin *et al.* 2012].

Following the encouraging results on relapsing–remitting MS (RRMS) patients [Fox *et al.* 2012; Gold *et al.* 2012], and considering the multifaceted effects of DMF, a phase III study was planned and will commence and to be commenced in secondary progressive MS (SPMS) patients (Biogen INSPIRE study) [ClinicalTrials.gov identifier: NCT02430532]. However, despite the recent negative results from the natalizumab phase III study in SPMS, (ASCEND) [ClinicalTrials.gov identifier: NCT01416181], the decision made by Biogen to close the INSPIRE study seems at least disappointing, especially as the mechanisms of action of natalizumab and DMF are very different.

Although we agree that neurodegeneration, rather than inflammation, should be the primary therapeutic target in progressive MS, DMF has important effects on the immune response that may be relevant in progressive MS. Longbrake and colleagues [Longbrake *et al.* 2015] recently analyzed and characterized circulating blood leukocytes in 41 stable MS patients treated with DMF and found that circulating CD8+ and CD4+ T cells, CD56dim natural killer (NK) cells, CD19+ B cells and plasmacytoid dendritic cells were lower in the lymphopenic MS patients compared to either control, with no changes of CD56hi NK cells, monocytes or myeloid dendritic cells. Whether lymphopenic or not, within the CD4+ and CD8+ subsets, they found a reduction of memory cells and a relative expansion of naïve cells.

Relevant to DMF, there are two potential mechanisms pertinent to progressive MS. Firstly, the percentage of circulating CD56dim NK lymphocytes expressing perforin, a pore forming cytolytic protein found in the granules of cytotoxic cells, has been demonstrated to be increased in both primary progressive MS (PPMS) and SPMS [Plantone *et al.* 2013]. CD56dim cytotoxic NK cells have been hypothesized to have a role in the progression of the disease and, interestingly, also CD8+ T cells expressing perforin, representing another cytotoxic lymphocyte subset, have been proposed to play a role in disability progression both in Theiler's murine encephalomyelitis virus model of MS [Deb *et al.* 2010; Murray *et al.* 1998] and in human studies [Giovanni *et al.* 2011; Denic *et al.* 2013]. The reduction in CD56dim cytotoxic NK cells, along with CD4+ and CD8+ memory

T cells, crucial in MS pathophysiology [Bielekova *et al.* 2004; Crawford *et al.* 2004; Okuda *et al.* 2005] in patients on DMF [Longbrake *et al.* 2015] is therefore relevant.

Secondly, DMF may facilitate mitochondrial function, that pathological studies show to be altered in progressive MS [Su *et al.* 2009] with alterations of adenosine triphosphate (ATP) synthesis, permeability transition pore opening, release of proapoptotic factors, electron transport chain and ionic homeostasis dysfunction [Su *et al.* 2009].

For all of these reasons, we would support ongoing testing of DMF in SPMS.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Jeremy Chataway reports receiving support from the National Institute of Health Research (NIHR), University College London Hospitals/UCL Biomedical Research Centre, UK. No relevant conflict of interest or financial interest reported by the other authors.

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