Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

MMF Prodrugs

Evidence Summary

Offer no real advantages over dimethyl fumarate in either safety or efficacy as anti-inflammatory agents.

Neuroprotective Benefit: May be useful for reducing neuroinflammation associated with autoimmune diseases. Have not been studied in other patient populations.

Aging and related health concerns: Exert anti-inflammatory effects in the context of inflammatory autoimmune diseases, but more clinical studies are needed to determine if they have benefits in other populations.

Safety: No improved safety relative to dimethyl fumarate, and no is evidence available about long-term safety.

What is it? Monomethyl fumarate (MMF) prodrugs are drugs which are rapidly metabolized into MMF upon entering the body. MMF can enter cells and activate the Nrf2 antioxidant pathway. Dimethyl fumarate is the best studied MMF prodrug (see dimethyl fumarate report). Due to the side effect profile: flushing, gastrointestinal-related problems, and lymphopenia, which can limit the long-term use of dimethyl fumarate, there has been interest in developing other MMF prodrugs for clinical use. Thus far, two have been tested in clinical trials.

XP-23839 (tepilamide fumarate, PCC-06) was developed by Xenoport, which was later acquired by Arbor Pharmaceuticals/Dr. Reddy's Labs. It has been tested in Phase 1 and Phase 2 (NCT03421197) RCTs for use in treating chronic plaque psoriasis.

ALKS-8700 (diroximel fumarate, BIIB098) was originally developed by Alkermes but was bought by Biogen Idec (manufacturer of Rx dimethyl fumarate, Tecfidera®). It has been tested in Phase 1 (NCT02201849) and Phase 3 (NCT02634307RCT) trials for relapsing-remitting multiple sclerosis.

Neuroprotective Benefit: May be useful in reducing neuroinflammation. Have not been studied in other patient populations.

The only evidence for neuroprotection comes from the ability of ALKS-8700 to reduce inflammation associated disease activity in patients with relapsing-remitting multiple sclerosis in a Phase 3 RCT [1], suggesting it may be beneficial in reducing neuroinflammation.

Aging and related health concerns: Exert anti-inflammatory effects in the context of inflammatory autoimmune diseases, but more clinical studies are needed to determine if they have benefits in other populations.

The only established age-related benefit of XP-23839 [2] and ALKS-8700 [1] is their ability to reduce inflammation (pro-inflammatory lymphocytes), in the context of psoriasis, and multiple sclerosis, respectively.

Safety: No improved safety relative to dimethyl fumarate, and no is evidence available about long-term safety.

Types of evidence:

- 5 clinical trials (2 Phase 1 +1 Phase 3 RCT for ALKS-8700, 1 Phase 1 +1 Phase 2 for XP-23839)
- 1 observational study (lymphocyte counts monitoring for XP-23839)

Based on clinical trial evidence, there is no significant improvement in the side effect profile of XP-23839 [2; 3] or ALKS-8700 [1; 4; 5] relative to dimethyl fumarate. The most common adverse events were flushing and gastrointestinal-related events. Relative to dimethyl fumarate, XP-23839 has less flushing, but more gastrointestinal-events, while ALKS-8700 has less gastrointestinal-events and more flushing. Additionally, XP-23839 exhibits a higher risk of severe lymphopenia [6], which could increase the risk for opportunistic infections. There is no evidence on long-term safety.

Sources and dosing:

ALKS-8700: 462 mg 2x daily oral capsule is the bioequivalence for 240 mg 2x daily dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis

XP-23839: 400 mg 2x daily orally is the established therapeutic dose for the treatment of psoriasis.

References:

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3. Lissin D, Luo W, Tai E *et al.* (2014) Steady State Pharmacokinetics of Formulations of XP23829, a Novel Prodrug of Monomethyl Fumarate (MMF), in Healthy Subjects (P1.188). *Neurology* 82

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6. Steinman L, Fox R, Lissin D *et al.* (2014) Lymphocyte and Eosinophil Responses in Healthy Subjects Dosed with Tecfidera® and XP23829, a Novel Fumaric Acid Ester (FAE) (P1.201). *Neurology* 82

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.