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MILESTONE 4

Oral drugs expand therapeutic options

The treatment of relapsing–remitting multiple sclerosis (RRMS) made a leap forward in 2010 with the introduction of the first of three currently used oral therapies. Relative to the previous first-line treatments — inteferon-β (IFNβ) and glatiramer acetate (MILESTONE 1) — these therapies were similarly or more effective and expanded the options for the route of treatment administration.

Three oral therapies for RRMS were approved between 2010 and 2013: fingolimod, teriflunomide and dimethyl fumarate (DMF). These three molecules have distinct modes of action, but all three inhibit the immune activation in the brain that is characteristic of patients with RRMS and causes relapses. In 2016, these three drugs together accounted for nearly 40% of the market for MS therapies.

Fingolimod was discovered through chemical derivatization of myriocin, a fungal metabolite with immunosuppressant properties. Studies in animal models, particularly models of graft-versus-host disease, suggested that fingolimod acts differently from classical immunosuppressants. Subsequent work showed that it is an antagonist of the sphingosine 1-phosphate (S1P) receptor, which is highly expressed in numerous cell types including leukocytes. Fingolimod causes T cells to be sequestered in the lymph nodes, thereby reducing the number of circulating T cells and, consequently, the extent of T cell migration into the CNS.

Two phase III clinical trials published in 2010 demonstrated the efficacy of fingolimod. In the 24-month, double-blind FREEDOMS study, fingolimod reduced the annual relapse rate by ~60% compared with placebo, and in the 12-month, double-blind TRANSFORMS study, fingolimod reduced the annual relapse rate by ~50% compared with IFNβ. In both studies, fingolimod reduced the number of new or enlarged lesions visible on MRI scans. Importantly, in the FREEDOMS study, fingolimod also reduced the probability of disability progression. The reduced number of circulating lymphocytes was associated with a slightly increased risk of some viral infections in both studies.

The second oral therapeutic to be approved by the FDA, teriflunomide, is the active metabolite of leflunomide, a therapy for rheumatoid arthritis that has been in use since 1998. It inhibits the proliferation of rapidly dividing cells, such as T cells, by reducing their capacity to synthesize pyrimidine. In two key phase III, placebo-controlled trials in MS, known as TEMSO and TOWER, teriflunomide significantly reduced relapse rates, MRI evidence of disease activity and disability progression. Mean reductions in lymphocyte count with teriflunomide were small in these studies, and infection rates did not differ between patients treated with teriflunomide and those treated with placebo.

> “oral therapies have transformed the treatment of RRMS”

Within months of FDA approval of teriflunomide, a third oral therapy — DMF — was added to the list. DMF is a fumaric acid ester; similar molecules are known immunosuppressants and were being used in topical formulations for the treatment of psoriasis. DMF reduces the number of circulating T cells, particularly $CD8^+$ T cells, thereby suppressing immune responses. The phase III CONFIRM and DEFINE studies compared the effects of DMF with those of placebo over 2 years of treatment. In both studies, DMF treatment reduced the annual relapse rates and the number of new or enlarged lesions on MRI scans. In the DEFINE study, DMF also reduced the rate of disability progression. Lymphocyte counts were reduced in patients who were treated with DMF, but infection rates did not differ between the drug-treated and placebo-treated patients.

These three oral therapies have transformed the treatment of RRMS. The option to use oral, rather than injectable, therapies for equal or greater therapeutic benefit reduced the burden of treatment, thereby increasing both patient satisfaction and compliance.

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