SHOULD ALL MS PATIENTS BE TREATED WITH STATINS? NO

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Six disease modifying drugs (DMD) have been approved for the treatment of MS, including interferon-beta-(IFN-β)-1a (Avonex®, Rebif®), IFN-β-1b (Betaseron/Betaferon®), glatiramer-acetate (GA; Copaxone®), mitoxantrone (Novantrone®), and natalizumab (Tysabri®). The approval of two new oral drugs – fingolimod (Gilenia®) and cladribine (Leustatin®) and the introduction of several monoclonal antibodies and other DMD will soon increase the arsenal of treatment options for MS. Nevertheless, these therapies are only partially effective, and potential serious adverse events limit the use of some of them. More effective therapies are needed, using either new drugs and treatment strategies, or combination of drugs with complementary mechanisms of action that target several elements in the immunological and neurodegenerative cascades leading to inflammation, demyelination and axonal loss in MS.

Statins reduce cholesterol levels by inhibiting 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase. Their recently elucidated immunomodulatory, anti-inflammatory and neuroprotective properties, combined with their convenient once-daily oral administration, favorable safety profile and relatively low price make them attractive candidates for the treatment of MS either as monotherapy or in combination with other MS drugs. However, pro-inflammatory actions of statins have also been demonstrated that may be deleterious in MS and antagonize the effects of IFNβ; statins increase the production of interferon-gamma and interleukin (IL)-12, decrease the production of the anti-inflammatory cytokine IL-10 and enhance the activity of matrix metalloproteinase (MMP) 2 and 9. The combination of IFNβ-1b and atorvastatin increases the levels of IL12p70, the bioactive heterodimer form of IL-12. Moreover, in contrast to studies demonstrating neuroprotective and regenerative properties of statin, other studies showed inhibition and impairment of remyelination in the central nervous system induced by simvastatin.

Initial open-label clinical trials confirmed the safety and efficacy of statins as monotherapy on short-term clinical and magnetic resonance imaging (MRI) measures in MS. However, a recent double-blind placebo-controlled trial evaluating atorvastatin 80 mg/d for 12 months in 81 patients with clinically isolated syndromes (StayCIS) failed to demonstrate effect on progression to clinically-definite MS or prevention of the development of >3 new MRI T2 lesion, although significantly more patients in the atorvastatin group remained T2-lesion free compared with the placebo group.

Several in-vitro and animal studies demonstrated synergistic effects of statins combined with IFN-β, GA, rolipram or minocycline on immune responses, histological and clinical outcomes in experimental autoimmune encephalomyelitis (EAE). However, animal data cannot predict what will happen in human patients and should not be considered as having therapeutic implications. Although several small, mainly non-randomized open-label clinical studies in MS suggested that the combination of IFN-β and statins is safe and probably beneficial, other recent randomized studies failed to confirm these preliminary results, and one study even found increased MRI and clinical disease activity with the combination. In this small but well-designed randomized placebo-controlled study, Birnbaum et al. randomized 26 stable MS patients treated with subcutaneous IFNβ-1a to add-on treatment with 40 mg or 80 mg atorvastatin or placebo for 9 months. Ten of the 17 subjects on atorvastatin had either new or enhancing T2 lesions on MRI or clinical relapses, compared with one of the nine subjects on placebo (p=0.019). Some relapses occurred after years of stable disease, and baseline differences did not influence the risk of disease activity. Possible explanations for this antagonistic effect may include blocking of the STAT1 phosphorylation signaling pathway of interferon by statins and increased activity of MMP 2 and 9 that cleave IFNβ and increase inflammation. In a post-hoc analysis of the SENTINEL trial which determined the effects of natalizumab and intramuscular IFNβ-1a, 40 MS patients who received statins to treat their hyperlipidemia in addition to IFNβ-1a were compared to 542 patients who were treated with IFNβ-1a only. There were no differences between groups in annualized relapse rate, disease progression, number of MRI enhancing lesions or number of new or enlarging T2 hyperintense lesions after 2 years. Two other large randomized controlled combination clinical trials with statins yielded negative results: In the recently completed SIMCOMBIN trial, 380 treatment-naïve RRMS patients were randomized to intramuscular IFNβ-1a 30 mcg weekly plus either daily simvastatin 40 mg or placebo

for 12-24 months. Although the combination was safe and the bioactivity of IFNβ as measured by mRNA expression of its biomarkers MxA protein and TRAIL was not affected by simvastatin, the preliminary results did not show an additive effect. In another unpublished study, 150 active RRMS patients who started treatment with glatiramer acetate were randomized to daily simvastatin 40 mg, vitamin D as alfacalcidol 1 mcg or placebo. After one year, there were no differences between groups in the number of new enhancing lesions or other MRI and clinical outcomes.

Although statins are generally safe and well-tolerated, their adverse events are neither rare nor of trivial impact. Statins may cause rhabdomyolysis, myopathy and other muscle and tendon problems, liver toxicity, intracerebral hemorrhage, behavioral, cognitive and sleep disorders, peripheral neuropathy, dermatological and other disorders. Statin toxicity increases under combination therapies, and it is possible that myalgia and hepatotoxicity shared by both statins and interferons may synergize by their concomitant use.

There is no convincing indication or data at present to suggest that MS patients should be treated with statins. In order to be incorporated in to clinical practice, statins still need to be tested for efficacy in large controlled phase-III clinical trials, either as monotherapy or in combination with other MS treatments. Until class-I evidence is available, the use of statins as DMD in MS cannot be recommended and should be restricted to clinical trials and for the indication of hyperlipidemia. Several obstacles exist for the rationale development of statins as MS therapy, such as ethical and methodological problems of study design, financial barriers, increased availability of other established MS therapies, and loss of interest following several negative key clinical trials. Moreover, since the number of MS patients using statins for hyperlipidemia in addition to their MS treatment is expected to grow, caution should be taken regarding negative effects of their combination therapies and these patients should be closely observed for possible increased toxicity and antagonistic clinical effects