PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Do Statins Prevent Parkinson's Disease?

In this issue: Statins and Parkinson's disease; safety and tolerability of statins; apixaban and venous thromboembolism; and FDA actions.

Statins and Parkinson's disease

In 2012, the FDA expanded warnings on statins to include cognitive impairment, such as memory loss, forgetfulness, and confusion, based on adverse event reports from some statin users. There have been few data to confirm cognitive changes or other neurologic side effects associated with these drugs other than case reports. But still, many media outlets have reported that this warning is evidence of increased risk for Alzheimer's disease and other brain disorders. To the contrary, in last year's warning, the FDA specifically stated that memory changes are reversible when the medication is stopped. Other studies have suggested that highly lipophilic statins such as simvastatin, which crosses the blood-brain barrier easily, may in fact protect against dementia — although other studies refute this finding. Parkinson's disease (PD) has also been studied with regard to statin therapy, and those data may be a bit more compelling in favor of statins. A recent study from Taiwan took a unique approach to this problem. Reasearchers looked at the incidence of PD in patients who discontinued statin therapy compared to those who continued. Among the nearly 44,000 statin initiators, the incident rate for PD was 1.68 per 1.000,000 among lipophilic statin users and 3.52 among hydrophilic statin users. Continuation of lipophilic statins was associated with a marked decrease in the risk of PD compared to discontinuation (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.64]). This finding was not affected by comorbidities or other medications. Hydrophilic statins did not reduce the occurrence of PD. Among the lipophilic statins, simvastatin had the greatest effect (HR, 0.23; 95% CI, 0.07-0.73), while atorvastatin was also beneficial (HR, 0.33; 95% CI, 0.17-0.65). The effect among women was even more dramatic with a nearly 90% reduction in the incidence of PD for simvastatin and a 76% reduction for atorvastatin. Most of the benefit was seen in the elderly subgroup. The authors suggest that continuation of a lipophilic statin was associated with a decrease in the incidence of PD as compared to discontinuation, especially in women and the elderly (*Neurology* published online July 24, 2013. DOI: 10.1212/WNL.0b013e31829d873c). An accompanying editorial suggests that the lipophilic statins may reduce oxidative stress, and may have other direct actions in the brain that reduce the risk of PD, although more research is needed. The authors add, "For those who have to be on statins, it is a comforting thought that there is potential added advantage of having a lower risk of PD, and possibly other neurologic disorders as well." (*Neurology* DOI: 10.1212/WNL.0b013e31829d87bb). ■

Safety and tolerability of statins

Overall statin safety and tolerability was the focus of a recent (non-company sponsored) meta-analyses of more than 135 trials involving nearly 250,000 individuals. Statin therapy was no differ-

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ent from control with regard to myalgia, creatine kinase elevation, cancer, or discontinuation due to adverse events. There was a higher incidence of diabetes associated with statin use (odds ratio [OR], 1.09; 95% CI, 1.02-1.16). Transaminases were also elevated more commonly (OR, 1.51; 95% CI, 1.24-1.84). The safest statins appeared to be simvastatin and pravastatin. When similar doses were compared, there were higher discontinuation rates with atorvastatin and rosuvastatin. The highest dose (80 mg) of simvastatin was associated with a significantly increased risk of creatine kinase elevation (OR, 4.14; 95% CI, 1.08-16.24). The authors conclude that statins, as a class, are well tolerated, except for a higher risk of diabetes. Simvastatin and pravastatin seem to be more tolerable than other statins (*Circ Cardiovasc Qual Outcomes* published online July 9, 2013. DOI: 10.1161/CIRCOUTCOMES.111.000071). ■

AMPLIFY trial results

Currently, there are three novel oral anticoagulants on the market — dabigatran, rivaroxaban, and apixaban. All are approved for stroke prevention in patients with nonvalvular atrial fibrillation, but only rivaroxaban is approved for deep vein thrombosis/pulmonary embolism (PE) prevention and treatment. That may change with the publication of the AMPLIFY trial, which compared apixaban with conventional anticoagulant therapy in patients with acute venous thromboembolism (VTE). In a randomized, double-blind study, apixaban was compared with enoxaparin/warfarin (conventional therapy) in nearly 5400 patients with acute VTE. The primary outcome was recurrent symptomatic VTE or death related to VTE. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding. The primary outcome (recurrent VTE) occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the conventional therapy group (relative risk [RR] 0.84; 95% CI, 0.60-1.18). Major bleeding occurred in 0.6% of those in the apixaban group and 1.8% in the conventional therapy group (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and nonmajor bleeding occurred more than twice as often in the conventional therapy group. Rates of adverse events were similar. The authors conclude that a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with less bleeding. The findings were the same for patients with PE or extensive disease (*N Engl J Med* published online July 1, 2013. DOI: 10.1056/NEJMoa1302507). An accompanying editorial states that this is "an exciting time in thrombosis care," although more information is needed on reversal strategies and monitoring of these new agents (*N Engl J Med* July 1, 2013. DOI: 10.1056/NEJMe1307413). The option to safely treat VTE with fixed-dose oral options is very appealing. Both dabigatran and apixaban are expected to be reviewed for these indications in the near future. ■

FDA actions

The FDA has issued a Safety Communication regarding the oral antifungal ketoconazole that includes limiting the drug's use. The warning states that ketoconazole should never be used as a first-line agent due to the risk of liver toxicity, adrenal insufficiency, and drug interactions. The new guidance states that ketoconazole should only be used "when alternative antifungal therapies are not available or tolerated." In addition, the agency has revised the list of indications for the drug, removing dermatophyte and *Candida* infections.

The FDA has also issued a Safety Communication about the antimalarial drug mefloquine hydrochloride regarding neurologic and psychiatric side effects. The drug is used for treatment of malaria but more commonly for prevention of *Plasmodium falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. Neurologic side effects — which may be permanent — include dizziness, loss of balance, and tinnitus. Psychiatric side effects include anxiety, paranoia, depression, or hallucinations. The brand form of mefloquine (known as Lariam) is no longer marketed, but several generic forms of the drug are available. The new warnings are contained in a boxed warning — the FDA's most serious warning. The drug was recently in the news regarding a number of violent military incidents among soldiers taking the drug, including the murder of 16 Afghan civilians last year.

A nasal steroid spray may soon be available over the counter (OTC). The FDA's Nonprescription Drugs Advisory Committee has recommended the switch to OTC for Sanofi's triamcinolone acetonide (Nasacort AQ), the popular steroid nasal spray for the treatment of seasonal and perennial allergic rhinitis. The drug was originally approved in 1996 for use in adults and children ages 2 years and older, and has been widely used since. If approved by the full FDA later this year, it would be the first nasal steroid to be sold OTC. The drug has been available as a generic since 2008. ■