Drug Monitor

Atorvastatin for Older Patients with Diabetes

Few trials have assessed the efficacy of statins for the primary or secondary prevention of cardiovascular disease (CVD) in patients with type 2 diabetes—let alone older patients with the condition. And among the studies that have been conducted, results have been inconsistent. One problem, say researchers from the multicenter, randomized, double-blind, placebo-controlled Collaborative Atorvastatin Diabetes Study (CARDS), might be that diabetes subgroups in these trials were relatively small.

By contrast, CARDS enrolled 2,838 patients with type 2 diabetes and no history of CVD—1,129 patients aged 65 to 75 years and 1,709 patients aged 40 to 64 years. All patients also had baseline low-density lipoprotein (LDL) levels of 160 mg/dL or lower. The researchers conducted a post hoc analysis comparing the two age groups and found similar, significant reductions in the relative risk of a first major cardiovascular event with atorvastatin 10 mg/day (38% for the older patients and 37% for the younger patients).

The reduction in absolute risk of cardiovascular events was greater for the older patients than the younger patients (3.9% versus 2.7%), which reflects the older patients' higher absolute risk, the researchers say. As a result, the number of patients needed to treat to avoid one event over four years was lower for the older patients than the younger patients (21 versus 33). Both age groups tolerated the treatment well and had similarly high rates of adherence, despite the fact that many older patients were taking concomitant medications.

The researchers say their findings "extend the evidence base" for current recommendations that all patients aged 40 or older with diabetes receive statin therapy—regardless of their baseline LDL levels.

Source: *Diabetes Care.* 2006;29:2378–2384.

Imatinib Five Years Later

The latest findings from the International Randomized Study of Interferon and ST1571 (IRIS) are good news for patients with chronic myeloid leukemia (CML). A multicenter, open-label, phase III trial, IRIS was designed to compare standard therapy (interferon alfa plus cytarabine) with imatinib in 1,106 patients with CML. But early results with imatinib were so dramatic that the study evolved into a long-term evaluation focusing on the 553 patients originally assigned to receive imatinib. After a median follow-up of 60 months, an estimated 83% of these patients had not relapsed and 93% had not progressed to accelerated phase CML or blast crisis. The five-year estimated overall survival rate was 89%.

The risk of treatment failure was highest in the second year (7.5%) and lowest in the fifth year (0.9%). Similarly, the risk of progression to accelerated phase or blast crisis was highest in year two.

Imatinib inhibits the BCR-ABL tyrosine kinase. In this study, patients who had a complete cytogenetic response or a decrease of at least 3 log in levels of BCR-ABL transcripts were significantly less likely to experience disease progression. The researchers note that trends in their ongoing study indicate that the rate of disease progression is decreasing—though nonsignificantly thus far. If this trend persists, they say, it would support findings that BCR-ABL gene mutations are the major cause of relapse in patients with CML who receive imatinib therapy.

Source: *N Engl J Med.* 2006;355:2408–2417.

Substituting Sirolimus for Posttransplant Steroids

Steroids are a mainstay of posttransplantation immunosuppressive therapy, but long-term exposure to these agents is associated with a number of problems. Consequently, there is a push to find a safe way to withdraw the steroid component of the immunosuppressive regimen. Results from an exploratory study conducted by researchers from the University of Texas Medical School at Houston suggest that switching patients from prednisone to sirolimus can work.

The researchers enrolled 30 patients, aged 18 to 70, who had undergone renal transplantation at least six months earlier and had been receiving a stable regimen of cyclosporine and prednisone for at least one month. They then introduced sirolimus into the regimen and tapered off the prednisone. In order to minimize interactions with sirolimus, they also progressively reduced the cyclosporine dosage based on the average concentration and serum creatinine levels. The study group was monitored for 24 months, and the findings were compared retrospectively with data from a control group of 60 demographically matched transplant recipients who received ongoing immunosuppression with cyclosporine and prednisone.

Of the 30 study patients, 27 completed steroid withdrawal. Four of these patients subsequently needed to restart steroids, one due to chronic allograft nephropathy, one due to disease recurrence, and two due to

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chronic rejection. Overall patient and graft survival rates were similar between the study and control groups.

There were some changes from baseline among the patients switched to sirolimus—for good and for bad. At 24 months, the study group reported quality-of-life improvements in the areas of energy levels, health, and appearance satisfaction. They also reported better relief of cyclosporine-related adverse effects (such as hypertrichosis, weight gain, and gingival hypertrophy)—probably due to the reductions in cyclosporine dosages. On the other hand, fewer patients reported feeling calm and more of them said they experienced pain all the time. And laboratory monitoring showed significant increases in urine protein and serum triglyceride levels by study's end, as well as a significant drop in white blood cell counts.

The researchers contrast their results with an earlier study in which nearly all the participants failed the attempted medicatin conversion. They attribute their success to "previous experience dealing with the marked pharmacokinetic interactions between sirolimus and cyclosporine, which demand tight concentration control."

Source: *Transplant Proc.* 2006;38:2842–2846.

Oxycodone Plus Naltrexone

Preliminary research has suggested that, paradoxically, addition of an "ultralow" dose of an opioid antagonist actually can enhance opioids' analgesic effects—and suppress physical dependence. Researchers from Lifetree Clinical Research, Salt Lake City, UT, and Pain Therapeutics Inc., San Francisco, CA conducted a phase III clinical trial at 45 U.S. centers to find out whether this would hold true for a combination agent containing oxycodone and ultralow dose naltrexone.

The researchers randomly assigned 719 patients with chronic low back pain to receive placebo, oxycodone alone four times daily, or the oxycodone-naltrexone combination either four times daily or twice daily. Since each combination tablet contained 1 µg of naltrexone, the twice daily and four times daily regimens provided 2 and 4 µg/day of naltrexone, respectively. Following a washout period, patients receiving oxycodone—alone or in combination—started with a daily dosage of 10 mg and titrated up until they reached adequate relief, a tolerable level of adverse effects, or the maximum daily dose of 80 mg. That dose was maintained for 12 weeks, after which treatment was stopped abruptly in order to evaluate withdrawal symptoms. Patients rated the severity of 10 withdrawal symptoms using the Short Opiate Withdrawal Scale (SOWS) on their last day of treatment (baseline) and on each of the next four days.

All active treatments relieved pain significantly better than placebo, and there were no significant differences between the treatment groups in reduction of pain scores from baseline. The total average daily dose of oxycodone needed to achieve comparable analgesia, however, was significantly lower for patients taking the combination drug (34.5 and 34.7 mg/day, respectively, for patients taking four times daily and twice daily regimens) than for those taking oxycodone alone (39 mg/day).

For all groups, pain scores did not change once the optimal dose was achieved—suggesting that no analgesic tolerance developed over the 12 weeks of fixed-dose treatment. On the first day after drug discontinuation, mean SOWS scores were approximately 56% lower for patients who had been taking twice daily oxycodone-naltrexone than for those who had been taking oxycodone alone. Notably, this reduction was more pronounced for the subgroup of patients over 50 years of age. While the researchers acknowledge that the lower oxycodone dose may have contributed to the reduction in physical dependence, they say it's unlikely that the 4.3-mg difference would cause such a profound decrease in SOWS scores.

Overall, the incidence of adverse events did not differ between the active treatment groups. But there were significantly fewer moderate to severe events with oxycodone-naltrexone twice daily than with oxycodone alone: 44% less constipation, 33% less somnolence, and 51% less pruritus.

One major limitation to the study, the researchers say, was the large proportion of dropouts (more than 50%) in all treatment groups. They point out that the rate of dropouts due to adverse events during titration was somewhat higher in the twice daily combination therapy group than in the group taking oxycodone alone (14% versus 22%). The difference, they say, is most likely due to the higher individual doses of oxycodone in twice daily versus four time daily administration. As such, they advise slower titration for patients taking twice daily oxycodone-naltrexone, as well as a lower starting dose. ●

Source: *J Pain.* 2006;12:937–946.