Tips from Other Journals

Tips from Other Journals are written by the medical editors of *American Family Physician.*

The trade names of drugs listed in Tips from Other Journals are based on what is currently available and not necessarily the brand of drug that was used in the study being discussed.

Rifapentine Plus Isoniazid for the Treatment of Tuberculosis

Background: Although nine months of daily isoniazid therapy is routinely recommended to treat latent *Mycobacterium tuberculosis* infection, only 30 to 64 percent of patients complete the prolonged regimen. Rifapentine (Priftin) has shown promise for treating latent tuberculosis in animal studies. Sterling and colleagues investigated whether adding rifapentine to isoniazid therapy could eradicate tuberculosis with a shorter treatment duration.

The Study: Persons at high risk of developing active tuberculosis were randomized to receive nine months of daily isoniazid monotherapy (5 to 15 mg per kg per day; maximum daily dosage of 300 mg), or three months of once-weekly isoniazid (15 to 25 mg per kg; maximum weekly dosage of 900 mg) plus rifapentine (900 mg, with adjustments for persons weighing 50 kg [111 lb] or less). Participants were followed for a total of 33 months after treatment initiation. Eligible participants had a positive tuberculin skin test and had been in close contact with a patient with active tuberculosis, although patients with human immunodeficiency virus (HIV) could be enrolled with either of these criteria. Exclusion criteria included confirmed or suspected tuberculosis, pregnancy, breastfeeding, recent treatment with either study agent, HIV treatment within 90 days after enrollment, or an aspartate transaminase level five times the upper limit of normal. The primary end point was the development of active tuberculosis, with secondary end points including completion of study therapy or treatment discontinuation because of an adverse drug reaction.

Results: A total of 7,731 persons were randomized between the monotherapy and combination therapy groups, with 86 and 88 percent of patients completing 33 months of follow-up, respectively. Approximately twice as many patients in the isoniazid-only group developed tuberculosis compared with the combination therapy group (0.43 versus 0.19 percent of patients). Patients receiving combination therapy were significantly more likely to complete their treatment than those receiving monotherapy (82.1 versus 69.0 percent; $P < .001$). Although the combination therapy group experienced fewer adverse events than the monotherapy group (14.7 versus 17.6 percent; $P < .001$), they were more likely to stop treatment because of these events (4.9 versus 3.7 percent; $P = .009$). However, there were no differences between the groups in the likelihood of a severe adverse event. The proportion of participants with drug-related hepatotoxicity was significantly greater in the monotherapy group (2.7 versus 0.4 percent; $P < .001$).

Conclusion: Once-weekly rifapentine plus isoniazid for three months was as effective as daily isoniazid for nine months at preventing the development of active tuberculosis, with higher treatment completion rates and lower rates of adverse events and hepatotoxicity.

KENNETH T. MOON, MD

Source: Sterling TR, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med.* December 8, 2011;365(23):2155-2166.

Colchicine Is Effective for Recurrent Pericarditis

Background: A common complication of acute pericarditis is recurrent pericarditis. Approximately 10 to 30 percent of patients

with a first episode have a recurrent episode, and the recurrence rate increases to 50 percent after a first recurrence. Colchicine has shown promise for preventing recurrent pericarditis, but recommendations for its use have been based on observational studies. Imazio and colleagues evaluated colchicine as an adjunct to conventional therapy for the secondary prevention of recurrent pericarditis.

The Study: The Colchicine for Recurrent Pericarditis trial is a randomized, double-blind, placebo-controlled study that included 120 patients with a first recurrence of pericarditis. Participants were randomized to receive placebo or 2 mg of colchicine on the first day, followed by 1 mg per day for six months, divided into twice-daily doses. Patients who weighed less than 156 lb (70 kg) or who could not tolerate this dosage received a lower dosage (0.5 mg every 12 hours on the first day, followed by 0.5 mg daily). All participants also received conventional treatment with 800 to 1,000 mg of aspirin or 600 mg of ibuprofen every eight hours for seven to 10 days, with tapering over three to four weeks. Exclusion criteria included renal or hepatic disease, blood dyscrasias, myopathies, or pericarditis from a tuberculous, purulent, or neoplastic source. The primary end point was the recurrence rate of pericarditis at 18 months (12 months after treatment cessation).

Results: Remission rates were significantly higher in the colchicine group at 72 hours and at one week after starting treatment *(see accompanying table)*. The median time to first recurrence also was significantly prolonged in the colchicine group compared with placebo (2.5 versus 1 month, respectively; $P < .001$). At 18 months, the recurrence rate remained significantly lower in the colchicine group compared with placebo (absolute risk reduction = 0.31; relative risk reduction = 0.56; number needed to treat = 3).

Table. Colchicine for the Treatment of Recurrent Pericarditis

End point	*Placebo group (%)*	*Colchicine group (%)*	P *value*
Persistent symptoms at 72 hours	53	23	.001
Persistent symptoms at one week	52	18	< .001
Recurrence rate at 18 months	55	24	< .001

NOTE: *All patients also received conventional therapy with aspirin or ibuprofen.*

Similar rates of adverse effects and drug withdrawal occurred in both groups, with gastrointestinal intolerance being the main adverse effect (7 percent in the colchicine group versus 5 percent in the placebo group). One case of hepatotoxicity related to concomitant hepatobiliary tract disease was noted in the placebo group.

Conclusion: Colchicine is safe and effective as an adjunct to conventional therapy for recurrent pericarditis, with significant reductions in the recurrence rate, prolonged time to subsequent recurrence, and no severe adverse effects.

KENNETH T. MOON, MD

Source: Imazio M, et al. Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med.* October 4, 2011;155(7):409-414.

Intensive vs. Conventional Glycemic Control in Patients with Type 2 Diabetes

Background: Recent randomized clinical trials comparing intensive blood glucose control with conventional control have not shown a reduction in cardiovascular disease or mortality in patients with type 2 diabetes mellitus. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in 2008 was stopped early because of increased all-cause and cardiovascular mortality in the intensive control group. However, other studies have shown a reduction in microvascular complications with intensive control. Although overall glycemic control likely helps prevent morbidity and mortality, debate persists about the optimal glycemic target and the benefits and risks of achieving an intensively lowered glycemic goal. Hemmingsen and colleagues performed a systematic review and meta-analysis on the effects of intensive glycemic control compared with conventional control on all-cause mortality, cardiovascular mortality, cardiovascular disease, and microvascular disease in patients with type 2 diabetes.

The Study: The authors searched for randomized controlled trials published in any language in the Cochrane Library, Medline, Embase, Science Citation Index Expanded, LILACS, and CINAHL, and reviewed unpublished data. Trials that compared a strict glycemic target with a more relaxed one were eligible, although "strict" or "intensive" control was defined differently in each study. The primary outcomes included all-cause mortality, cardiovascular mortality, nonfatal myocardial infarction, composite microvascular complications, retinopathy, nephropathy, and severe hypoglycemia. The data on each outcome were statistically summarized as relative risks with 95% confidence intervals. To determine clinically relevant results, trial sequential analysis was used to identify information (sample) sizes that could reflect a

10 percent relative risk reduction for mortality (equivalent to a number needed to treat of 100). The meaningful increased relative risk of severe hypoglycemia was set at 30 percent, equivalent to a number needed to harm of 50.

Results: Fourteen trials met the inclusion criteria. These trials included data from 28,614 participants (15,269 randomized to intensive glycemic control and 13,345 to conventional control), and dealt exclusively with glycemic control in the usual care setting. Target A1C levels varied between trials; the lowest was less than 6 percent in the ACCORD and Veterans Affairs Diabetes Trial studies. Some trials used fasting glucose concentrations as a treatment target instead of a predefined A1C value. The conventional care targets varied from achieving an A1C level less than 7 to 8 percent, to avoiding hyperglycemia.

In the meta-analysis, all-cause mortality was not reduced with intensive glycemic control, and this finding was confirmed by trial sequential analysis. Cardiovascular mortality was not reduced in the meta-analysis, but trial sequential analysis showed too little evidence to conclude risk, benefit, or no difference. Although there seemed to be a small but statistically significant risk reduction for nonfatal myocardial infarction in the intensive control group, trial sequence analysis showed a lack of sufficient evidence to support it. Similarly, the small reductions in relative risk for composite microvascular complications with intensive control were not confirmed by trial sequential analysis. Conversely, the risk of severe hypoglycemia was significantly increased in the intensive glycemic control groups, a result confirmed by trial sequential analysis.

Conclusion: In this large meta-analysis, intensive glycemic control did not reduce mortality and was associated with a significantly increased risk of severe hypoglycemia.

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Source: Hemmingsen B, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ.* November 24, 2011;343:d6898.

Is Selenium a Beneficial Treatment for Graves Orbitopathy?

Background: Inflammation from oxygen free radical–production is believed to contribute to the development of Graves orbitopathy. Agents that reduce oxidation or the associated inflammation could improve symptoms of Graves orbitopathy. Selenium has antioxidant properties, and supplementation with an antioxidant has been shown to promote euthyroidism more quickly in patients with Graves disease taking methimazole (Tapazole). Preliminary evidence also has suggested that pentoxifylline (Trental) may benefit patients with Graves orbitopathy because of its anti-inflammatory and immunomodulatory effects. The European Group on Graves' Orbitopathy investigated whether selenium or pentoxifylline would benefit patients with mild Graves orbitopathy.

The Study: In this double-blind, placebo-controlled trial, patients were randomized to receive twice-daily doses of sodium selenite (100 mcg per dose), pentoxifylline (600 mg per dose), or placebo for six months. Patients were followed for a total of 12 months. Evaluations included periodic thyroid testing, as well as eye examinations performed by study-blinded ophthalmologists. A validated Graves orbitopathy–specific quality of life questionnaire also was administered. The two primary outcome measures were assessment of eye changes and quality of life based on responses to the questionnaire.

Results: A total of 152 patients (54 in the selenium group, 48 in the pentoxifylline group, and 50 in the placebo group) were included in the final analysis. Baseline traits, including thyroid status, quality of life, and severity of orbitopathy, were similar among groups. The selenium and pentoxifylline groups had significant reductions in thyroid peroxidase autoantibodies from baseline ($P = .001$ and .02, respectively), but the placebo group did not ($P = .4$).

Compared with those in the placebo group, significantly fewer patients in the selenium group reported decreased quality of life (17 versus 43 percent respectively; $P = .004$), and more patients showed improvements in eyelid aperture and soft-tissue involvement. These improvements persisted in the selenium group at 12 months (six months after treatment was stopped). In contrast, no benefit in quality of life or severity of orbitopathy occurred in the pentoxifylline group at any point. Seven patients in the pentoxifylline group had drug-related adverse effects (e.g., gastrointestinal symptoms, erythema, pruritus), whereas no adverse effects were noted in the selenium or placebo groups.

Conclusion: Selenium, but not pentoxifylline, resulted in significant improvements in quality of life and level of orbitopathy involvement in patients with mild Graves orbitopathy. The beneficial effects of selenium supplementation continued for at least six months after the treatment was discontinued.

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Source: Marcocci C, et al. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med.* May 19, 2011;364(20):1920-1931. ■