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Clindamycin, TMP-SMX Are Equally Effective for Skin Infections

Mary Ann Moon

VITALS

Key clinical point: Clindamycin and TMP-SMX had similar efficacy and adverse-effect profiles for treating uncomplicated skin infections, including both abscesses and cellulitis.

Major finding: At 7-10 days after therapy completion, the rates of cure in the evaluable population were 89.5% with clindamycin and 88.2% with TMP-SMX.

Data source: A prospective, multicenter, randomized, double-blind clinical trial involving 524 adults and children followed for 1 month after treatment.

Disclosures: This trial was supported by the National Institutes of Allergy and Infectious Diseases and the National Center for Advancing Translational Sciences (NCT00730028). Dr Miller reported receiving consulting fees from Cubist, Durata, and Pfizer; his associates reported ties to Cubist, Pfizer, EMMES, Theravance, AstraZeneca, Trius, Merck, and Cerexa.

Clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX) are similarly safe and effective for treating uncomplicated skin infections, including both cellulitis and abscesses, in ambulatory settings in regions where MRSA is endemic, according to a report published online March 19 in the *New England Journal of Medicine*.

The data comparing these two agents in an ambulatory setting are limited, though both are commonly recommended as empiric therapy for skin infections in patients who present to clinics and emergency departments and have only minor or no coexisting conditions, said Dr Loren G. Miller, of the Los Angeles Biomedical Research Institute and the Division of Infectious Diseases at Harbor-UCLA Medical Center, and his associates.

They performed a prospective double-blind randomized trial comparing clindamycin with TMP-SMX in 524 ethnically diverse adults and children who presented as outpatients with uncomplicated skin infections during a two-year period in Chicago, San Francisco, Los Angeles, and Nashville—areas in which community-associated MRSA is endemic. The mean patient age was 27, and approximately 30% were pediatric patients. All the participants had cellulitis without abscesses (including erysipelas), one or more abscesses larger than 5 cm in diameter, or both conditions. A total of 264 were randomized to clindamycin and 260 to TMP-SMX daily for 10 days.

Cure rates did not differ significantly between the two study groups. At seven to 10 days after therapy completion, cure rates in the intention-to-treat population were 80.3% for clindamycin and 77.7% for TMP-SMX, and in the evaluable population the rates were 89.5% and 88.2%, respectively.

At one month follow-up, the cure rates in the evaluable population were 83.9% for clindamycin and 78.2% for TMP-SMX, the investigators said (*N Engl J Med.* 2015;372:1093-103 [doi:10.1056/NEJMoa1403789]). Rates of adverse events were nearly identical between the two study groups (18.9% vs 18.6%), and most were mild and resolved without sequelae. There were no treatment-associated serious adverse events, and the rates of treatment discontinuation

VIEW ON THE NEWS

Reassuring findings for most patients

"Given the immense importance of MRSA infections during the past 20 years, prospective clinical trial data to inform the choice of outpatient treatment of skin infections are surprisingly sparse," according to Dr Michael R. Wessels. The findings of Miller et al reassure that outcomes are good for most such patients when they are treated with either of the two most popular agents, he noted in an accompanying editorial.

But carefully designed clinical trials like this one are still needed to determine which therapies are most effective and safe for cellulitis and skin abscesses in patients who are more severely ill, such as those who have high fever or lymphangitis, as well as for patients who have coexisting conditions such as diabetes, cancer, or obesity, Dr Wessels wrote.

Dr Michael R. Wessels is a member of the Division of Infectious Diseases at Boston Children's Hospital and in the Department of Pediatrics at Harvard Medical School, Boston. He reported having no financial disclosures. Dr Wessels made these remarks in an editorial accompanying Dr Miller's report (*N Engl J Med*. 2015;372:1164-65 [doi:10.1056/NEJMe1500331]).

were similar between patients receiving clindamycin (8.3%) and those receiving TMP-SMX (8.8%).

The study was supported by grants from the National Institutes of Allergy and Infectious Diseases. Dr Miller reported receiving consulting fees from Cubist, Durata, and Pfizer; his associates reported ties to Cubist, Pfizer, EMMES, Theravance, AstraZeneca, Trius, Merck, and Cerexa.

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Hormone Therapy 10 Years Postmenopause Increases Risks

Tara Haelle

VITALS

Key clinical point: Hormone therapy in postmenopausal women increases stroke risk.

Major finding: Stroke increased by 24%, venous thromboembolism by 92%, and pulmonary embolism by 81% in postmenopausal women receiving hormone therapy.

Data source: A review and meta-analysis of 19 randomized controlled trials involving 40,140 postmenopausal women who received orally administered hormone therapy, placebo, or no treatment for prevention of cardiovascular disease.

Disclosures: One study was funded by Wyeth-Ayerst. Two studies received partial funding from Novo-Nordisk Pharmaceutical, and one study was funded by the National Institutes of Health with support from Wyeth-Ayerst, Hoffman-La Roche, Pharmacia, and Upjohn. Eight other studies used medication provided by various pharmaceutical companies.

Hormone therapy in postmenopausal women does not prevent heart disease but does increase the risk for stroke and blood clots, according to a recently updated Cochrane review.

"Our review findings provide strong evidence that treatment with hormone therapy in postmenopausal women for either primary or secondary prevention of cardiovascular disease events has little if any benefit overall, and causes an increase in the risk of stroke, or venous thromboembolic events," reported Dr Henry Boardman, of the University of Oxford John Radcliffe Hospital, and his associates.

The researchers updated a review published in 2013 with data from an additional six randomized controlled trials. The total of 19 trials, involving 40,410 postmenopausal women, all compared orally administered estrogen, with or without progestogen, to a placebo or no treatment for a minimum of six months (*Cochrane Database Syst Rev*. 2015 March 10 [doi:10.1002/14651858.CD002229.pub4]).

The average age of the women in the studies, mostly from the United States, was older than 60, and the women received hormone therapy anywhere from seven months to 10 years across the studies. The overall quality of the studies was "good" with a low risk for bias.

The sharp rise in cardiovascular disease rates in women after menopause had been hypothesized to be related to a decline in hormone levels that causes a higher androgen-to-estradiol ratio, and observational studies starting in the 1980s showed lower mortality rates and cardiovascular events in women receiving hormone therapy—previously called *hormone replacement therapy*—compared to those not receiving hormone therapy.

Two subsequent randomized controlled trials contradicted these observational findings, though, leading to further study. In this review, hormone therapy showed no risk reduction for all-cause mortality, cardiovascular death, nonfatal MI, angina, or revascularization.

However, the overall risk for stroke for those receiving hormone therapy for both primary and secondary prevention was 24% higher than that of women receiving placebo treatment (relative risk [RR], 1.24), with an absolute risk of 6 additional strokes per 1,000 women.

Venous thromboembolic events occurred 92%

more and pulmonary emboli occurred 81% more in the hormone treatment groups (RR, 1.92 and 1.81, respectively), with increased absolute risks of 8 per 1,000 women and 4 per 1,000 women, respectively.

The researchers calculated the number needed to treat for an additional harm (NNTH) at 165 women for stroke, 118 for venous thromboembolism, and 242 for pulmonary embolism.

Further analysis revealed that the relative risks or protection hormone therapy conferred depended on how long after menopause women started treatment.

Mortality was reduced 30% and coronary heart disease was reduced 48% in women who began hormone therapy less than 10 years after menopause (RR, 0.70 and 0.52, respectively); these women still faced a 74% increased risk for venous thromboembolism, but no increased risk for stroke.

Meanwhile, women who started hormone therapy more than 10 years after menopause had a 21% increased risk for stroke and a 96% increased risk for venous thromboembolism, but no reduced risk for overall death or coronary heart disease.

"It is worth noting that the benefit seen in survival and coronary heart disease for the group starting treatment less than 10 years after the menopause is from combining five trials all performed in primary prevention populations and all with quite long follow-up, ranging from 3.4 to 10.1 years," the authors wrote.

These results may reflect the possibility of a time interaction, with coronary heart disease events occurring earlier in predisposed women, making it impossible to say whether short duration therapy is beneficial in this population or not, the researchers wrote.

Eighteen of the 19 trials included in the analysis reported the funding source. One study was exclusively funded by Wyeth-Ayerst. Two studies received partial funding from Novo-Nordisk Pharmaceutical, and one study was funded by the National Institutes of Health with support from Wyeth-Ayerst, Hoffman-La Roche, Pharmacia, and Upjohn. Eight other studies used medication provided by various pharmaceutical companies.

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"Perfect storm" of Depression, Stress Raises Risk for MI, Death

Sharon Worcester

VITALS

Key clinical point: Concurrent depression and stress in coronary heart disease patients may increase early risk for MI and death.

Major finding: CHD patients with high depressive symptoms and high stress at baseline had an increased risk for MI and death early during follow-up (adjusted HR, 1.48).

Data source: A prospective cohort study of 4,487 adults.

Disclosures: The National Institute of Neurological Disorders and Stroke and the National Heart, Lung, and Blood Institute supported the study. Dr Alcántara reported having no disclosures; two other authors received salary support from Amgen for research, and one served as a consultant for DiaDexus.

Patients with coronary heart disease (CHD) who have both depression and stress are at increased risk for MI and death, according to findings from a large, prospective cohort study.

Of 4,487 adults with CHD who were part of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, 1,337 experienced MI or death during a median of nearly six years of follow-up. Those with both high depressive symptoms and high stress at baseline—about 6% of the study population—were at significantly increased risk for such events (adjusted hazard ratio [HR], 1.48) during the first 2.5 years of follow-up, compared with those with low stress and low depressive symptoms. However, the association was not significant beyond the initial 2.5 years (HR, 0.89), Carmela Alcántara, PhD, of

Columbia University, New York, and her colleagues reported.

Those with low stress and high depressive symptoms, and those with high stress and low depressive symptoms, were not at increased risk (HR, 0.92 and 0.86, respectively) at any point during follow-up (*Circ Cardiovasc Qual Outcomes*. 2015 March 10 [doi:10.1161/IRCOUTCOMES.114.001180]).

The findings provide initial empiric evidence to support a "psychosocial perfect storm conceptual model" based on the idea that it takes an underlying chronic psychosocial vulnerability such as depression, along with a more transient state such as psychological stress, to precipitate a clinical event. The confluence of these factors may be particularly destructive in the short term, the investigators concluded, noting that the findings could have implications for the development of preventive treatments that focus on depression and stress during this vulnerable period in CHD patients.

The National Institute of Neurological Disorders and Stroke and the National Heart, Lung, and Blood Institute supported the study. Dr Alcántara reported having no disclosures, but two other authors received salary support from Amgen for research, and one served as a consultant for DiaDexus.

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Type 2 Diabetes Lower in Familial Hypercholesterolemia

Mary Ann Moon

VITALS

Key clinical point: The prevalence of type 2 diabetes appears to be significantly lower in patients with familial hypercholesterolemia than in their unaffected relatives.

Major finding: The prevalence of type 2 diabetes was 1.75% in 25,137 patients with familial hypercholesterolemia, compared with 2.93% in 38,183 of their unaffected relatives.

Data source: An observational cross-sectional analysis of data for 63,320 people in the Dutch national registry of familial hypercholesterolemia.

Disclosures: The study sponsor was not specified; the familial hypercholesterolemia registry is subsidized by the Dutch government. Dr Besseling reported having no financial disclosures; his associates reported ties to Aegerion, Amgen, AstraZeneca, Boehringer Ingelheim, Cerenis, Eli Lilly, Genzyme, JSiS, MSD, Novartis, Pfizer, Regeneron, Roche, and Sanofi.

The prevalence of type 2 diabetes appears to be significantly lower in patients with familial hypercholesterolemia than in their unaffected relatives, according to a report published online March 10 in *JAMA*.

In an observational cross-sectional analysis of data from a nationwide Dutch registry of familial hypercholesterolemia, the prevalence of type 2 diabetes was 1.75% in 25,137 patients with the disorder, compared with 2.93% in 38,183 of their unaffected relatives.

If this finding is confirmed in further research, it would support the hypothesis that cellular cholesterol metabolism plays a role in the development of type 2 diabetes, "perhaps because increased intracellular cholesterol levels are detrimental for pancreatic β-cell function," said Dr Joost Besseling, of the Department of Vascular Medicine, Academic Medical Centre, Amsterdam, and his associates.

Patients with familial hypercholesterolemia require strict clinical follow-up, and it has been noticed—but, until now, not substantiated—that they are less prone to developing type 2 diabetes.

In what they described as the first study to examine this relationship, Dr Besseling and his colleagues found that the strong inverse association (odds ratio, 0.62; 95% confidence interval, 0.55-0.69) between familial hypercholesterolemia and type 2 diabetes was consistent across every sub-

VIEW ON THE NEWS

Findings shouldn't alter current statin use

The findings by Besseling et al should allay any concerns clinicians may have about using statins in patients who have familial hypercholesterolemia. The drugs are now known to promote type 2 diabetes in the general population, but these patients appear to be at low risk for that metabolic disorder.

The study results do not, and should not, alter the use of these important medications in patients at elevated cardiovascular risk, who clearly benefit from statin therapy.

Dr David Preiss and **Dr Naveed Sattar** are at the BHF Glasgow Cardiovascular Research Centre at the University of Glasgow. Dr Preiss reported serving as a consultant for Sanofi-Aventis; Dr Sattar reported financial relationships with Amgen, Kowa Pharmaceuticals, and Sanofi-Aventis. They made these remarks in an editorial accompanying Dr Besseling's report (*JAMA*. 2015;313:1016-7).

group they evaluated, regardless of patient age, statin use, smoking status, and other possible confounding factors.

In addition, they found that the severity of the genetic mutation underlying the familial hypercholesterolemia also correlated, in an inverse dose-response manner, with the prevalence of type 2 diabetes (*JAMA*. 2015;313:1029-36).

If these findings are confirmed, "they might provide support for development of new approaches to the prevention and treatment of type 2 diabetes by improving function and survival of pancreatic β-cells," the investigators said.

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Mongersen Induces 55%-65% Remission Rates in Crohn's

Mary Ann Moon

VITALS

Key clinical point: Mongersen, an oral SMAD7 antisense oligonucleotide, induced remission rates as high as 55%-65% in a small 2-week phase II clinical trial.

Major finding: Rates of remission were 65% in the 43 participants who received 160 mg of mongersen, 55% in the 40 who received 40 mg, 12% in the 41 who received 10 mg, and 10% in the 42 who received placebo.

Data source: A randomized, placebo-controlled, double-blind phase II clinical trial involving 166 adults at 17 medical centers in Italy and Germany.

Disclosures: This study was sponsored by Giuliani, acting under contract to Nogra Pharma. Dr Monteleone reported ties to Giuliani, Novo Nordisk, Teva, Sirtris, Lycera, Sofar, and Zambon, and holds a patent related to the use of SMAD7 antisense oligonucleotides in Crohn's disease. His associates reported financial ties to numerous industry sources.

Mongersen, an oral SMAD7 antisense oligonucleotide formulated to deliver its active ingredient primarily into the lumen of the terminal ileum and right colon, induced remission rates as high as 55%-65% in a small, brief, manufacturer-sponsored, phase II clinical trial, according to a report published online March 19 in the *New England Journal of Medicine*.

In Crohn's disease, gut inflammation is characterized by abnormal reductions in a particular immunosuppressive cytokine caused by increased levels of SMAD7. Mongersen (formerly GED0301) downregulates SMAD7 using a classic antisense mechanism, which in turn restores the proper cytokine function and suppresses inflammation, said Dr Giovanni Monteleone, of the Department of Systems Medicine, University of Tor Vergata, Rome, and his associates.

They assessed a two-week course of mongersen in 166 adults with active, moderate to severe Crohn's disease who were treated and followed for approximately three months at 17 medical centers

VIEW ON THE NEWS

Clinical versus biologic remission

The clinical response reported by Monteleone et al is impressive, but it was not confirmed by endoscopic evidence of mucosal healing and it did not correlate with normalization of biomarkers such has fecal calprotectin or C-reactive protein. In short, there is a lack of congruence between clinical remission and biologic remission, an issue that must be addressed in future studies of this agent.

Also intriguing was the finding that clinical response was maintained for the duration of follow-up even though mongersen was only administered for two weeks and is thought not to linger in tissues. This is a stark contrast to the rapid recurrence of symptoms that characterizes withdrawal of existing anti-inflammatory drugs.

Severine Vermeire, MD, PhD, is in the Department of Gastroenterology at Leuven (Belgium) University Hospital. She reported receiving grant support and personal fees from AbbVie, Merck Sharp & Dohme, Pfizer, Genentech/Roche, Takeda, and Mundipharma. Dr Vermeire made these remarks in an editorial accompanying Dr Monteleone's report (*N Engl J Med.* 2015 March 19 [doi:10.1056/NEJMe1415053]).

in Italy and Germany. The study participants were randomly assigned to receive one of three doses of the agent or a matching placebo in a double-blind fashion. The study's primary endpoint was the percentage of patients in remission at day 15 who remained in remission for at least two more weeks. Remission was defined as a Crohn's Disease Activity Index (CDAI) score of < 150.

Rates of remission were 65% in the 43 participants who received 160 mg of mongersen, 55% in the 40 who received 40 mg, 12% in the 41 who received 10 mg, and 10% in the 42 who received placebo. Thus, remission rates at the two highest doses of mongersen exceeded those achieved in other phase II trials for Crohn's therapies, which ranged from 16% to 48%, the investigators said (*N Engl J Med.* 2015 March 19 [doi:10.1056/NEJMoa1407250]).

Rates of attaining the secondary endpoint of "clinical response," defined as a decrease of 100 or more points in the CDAI score at day 28, also were significantly higher at the two highest doses of mongersen—72% and 58%—than with the lowest dose (37%) or with placebo (17%).

No safety issues related to mongersen were identified in this study, but a two-week course of treatment in such a small group of patients likely is not adequate to determine safety. Adverse events occurred in 65% of the active-treatment groups and 64% of the placebo group and were mostly mild. The nine serious adverse events that occurred were unrelated to study treatment, Dr Monteleone and his associates said.

Further study is needed to assess longer durations of treatment and to judge the effectiveness of the drug on the basis of endoscopic analyses of mucosal healing, rather than on CDAI score. It also will be important to determine whether higher doses or longer treatment courses of mongersen raise the risk for fibrosis, given that the targeted cytokine plays a profibrogenic role in many organs, they added. **CR**

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