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The essential monthly primary care update

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HbA1c Following Successful Initial Metformin Therapy

Source: Nichols GA, et al. *Diabetes Care*. 2006;29:504-509.

Appropriate initial treatments for type 2 diabetes (DM2) include a diversity of oral agents and/or insulins. One of the most popular current initial treatments is metformin (MET), due to its efficacy, tolerability, and weight-neutrality. Because diabetes is typically a progressive disorder, most patients progress to require intensification of treatment. Nichols et al studied a large cohort of DM2 patients (n = 1,288) who had received MET as their initial treatment, and had achieved an A1c level of < 8%. Subjects were followed to evaluate which factors predicted loss of control of DM2, defined as the addition of other agents for glucose control, or finding an A1c > 8%.

MET failure occurred within 36 months in 50% of individuals who initially attained an A1c 7-7.9% on MET alone. In comparison, there was a steep linear relationship between degree of initial control and likelihood of secondary drug failure: those who initially attained better control on MET monotherapy (A1c 6-6.9%) did not experience drug failure until at least 60 months, and those with the best degree of control (A1c < 6%), maintained MET as successful monotherapy for greater than 84 months. Another critical factor discerned amongst this population was that weight gain had a major impact upon failure. As little as 1 kg increase in weight was associated with a 4-6% increased likelihood of treatment failure. Hence, vigilance in glucose control combined with maintenance of weight both factor significantly into long-term treatment success. ■

Triple Therapy in Type 2 Diabetes

Source: Rosenstock J, et al. *Diabetes Care*. 2006;29:554-559.

The most commonly used agents for the treatment of type 2 diabetes are metformin and a sulfonylurea. Despite adequate doses of both of these medications, many patients remain uncontrolled, or progress to inadequate control over time. The next best step after dual therapy fails is indeterminate. It is tempting to place patients on a third oral agent, usually a thiazolidinedione (TZD), but this enthusiasm must be tempered by two cold realities: 1) that usual A1c reductions rarely exceed 1.4-1.7% on triple therapy, hence patients with baseline above 8.7% are unlikely to achieve their goal, and 2) the expense of adding a TZD is not inconsiderable. On the other hand, there is a substantial resistance to utilization of insulin, or any other injectable medications (eg, exenatide) for that matter.

To compare the utility of adding a TZD (rosiglitazone) vs insulin (glargine) to the regimen of persons uncontrolled with dual oral therapy, Rosenstock et al randomized 217 patients. In the glargine group, dose was titrated to a fasting glucose less than 120 mg/dL; in the TZD group, rosiglitazone was increased up to 8 mg/d if fasting glucose was above 120 mg/dL.

The overall reduction in A1c was similar in both groups, averaging a 1.7% reduction from baseline. However, in the group further from goal (A1c > 9.5%), the reduction in A1c with insulin was far greater than with TZD: 3.6% vs 2.6%. Although hypoglycemic events were more frequent with insulin, weight gain and lipid changes were more favorable with insulin. When faced with a challenge of best next-step treatment, there is solid evidence to provide guidance, dependent upon the degree of baseline control, risk of hypoglycemia, weight control, and cost issues. ■

Calcium, Vitamin D, and Fractures

Source: Jackson RD, et al. *N Engl J Med*. 2006;354:669-683. Erratum in: *N Engl J Med*. 2006;354:1102.

Calcium (CAL) and vitamin D (VITD) are commonly considered a cornerstone of customary treatment for postmenopausal women to prevent osteoporosis and fractures. In placebo-controlled trials of other osteoporosis therapies such as bisphosphonates and selective estrogen receptor modulators, inclusion of CAL and VITD supplementation has been standard.

The Women's Health Initiative, the same trial from we learned the limitations of postmenopausal hormone replacement therapy, included a large cohort of postmenopausal women (n = 36,282) between the ages of 50-79 who were randomly assigned to CAL/VITD or placebo, and followed for 7 years.

Although bone density was favorably affected by CAL/VITD, fractures were not. Neither hip fracture, spine fracture, nor total fractures achieved statistical significance when CAL/VITD was compared with placebo. Discouragingly, the incidence of kidney stones was increased by 17%. This data would suggest that healthy women do not experience a clinically beneficial reduc-tion in fractures from CAL/VITD. Sen-sitivity analysis indicated that the subgroup of

women with the highest adherence to the treatment regimen did experience a fracture reduction, but the absolute benefit was small: 4 fewer hip fractures per 10,000 women. ■

What is the Relationship Between Gatifloxacin and Glucose Changes?

Source: Park-Wyllie LY, et al. *N Engl J Med*. 2006;354:1352-1361.

QUINOLONES HAVE BECOME SOME OF the most popularly prescribed antibiotics in the United States. They are characteristically well tolerated and functional in a diversity of tissue compartments, although we have lost a few quinolones due to specific toxicities (such as the hepatotoxicity exhibited by trovafloxacin).

Case reports of hyperglycemia associated with gatifloxacin (GAT) have prompted further evaluation. Physiologically, GAT has the potential to produce either hyper- or hypoglycemia: animal studies indicate a potential to enhance insulin release (hence hypoglycemia), and alterations in beta cell function have been associated with hyperglycemia.

The authors looked at two separate populations of persons with abnormal glucose excursions within 30 days of receiving a new antibiotic prescription: subjects with hypoglycemia (n = 788) and a separate population (n = 470) with hyperglycemia. Compared with macrolide antibiotics, GAT was associated with a statistically significant fourfold increased odds ratio for risk of hypoglycemia, and a 16 times increased odds ratio for hyperglycemia. Clinicians who prescribe GAT should be vigilant for variations in glucose, and advise patients to be similarly observant. In the event of untoward glucose impact from GAT, because other quinolones have similar efficacy profile (without attendant glucose changes), substitution may be appropriate. ■

Altering the Course of Chronic Hepatitis B

Source: Chang TT, et al. *N Engl J Med*. 2006;354:1001-1010.

THE PRESENCE OF HEPATITIS E ANTIGEN (HEA) for prolonged periods is characteristic of chronic hepatitis B. The consequences of chronic hepatitis B include an increased risk of hepatic carcinoma, as well as progressive liver disease. The currently available agents to treat chronic hepatitis B include interferon alfa, lamivudine, pegylated interferon alfa-2a, adefovir dipivoxil, and entecavir (EVR). Unfortunately, some of the existing agents have substantial limitations; for instance the efficacy of interferon alfa is 40% or less. Lamivudine (LAM) does result in histologic hepatic improvement in more than 50% of recipients, but less than 20% of patients enjoy suppressed viral replication, and lamivudine resistance has emerged in as many as 70% of cases.

Animal studies have indicated that EVR effectively inhibits production of Hepatitis B DNA. Indeed, in these animal models, the incidence of hepatic cancer and survival were both favorably impacted. Chang et al have compared EVR with LAM in more than 700 subjects with hepatitis C. End points included attaining an undetectable hepatitis B DNA level, changes in hepatic histology, and conversion from e antigen positive to negative.

For all 3 end points, EVR was found to be superior to LAM. Additionally, there was no evidence of emergence of EVR viral resistance, and there was no major difference in adverse effect profile between the two agents. EVR may be considered an appropriate primary therapy for e-antigen positive chronic hepatitis B patients. ■

Does Home Blood Pressure Monitoring Improve Adherence?

Source: Ogedegbe G, et al. *J Clin Hypertens (Greenwich)*. 2006;8:174-180.

THE LATEST REPORTS FROM THE National Health and Nutrition Surveys (NHANES) indicate that less than 40% of hypertensive patients are aware of their condition, they are treated, and controlled to BP < 140/90. Amongst the factors which affect compliance is the use of self-monitoring. Although individual reports of home blood pressure monitoring (HBPM) have generally been favorable, this is the first systematic review of randomized controlled trials that addressed HBPM and adherence.

Eleven trials satisfied all predefined inclusion criteria, comprising over 1500 subjects. Adherence was monitored with a variety of tools: self report, pill count, and electronic monitoring devices. Over half of the trials demonstrated statistically significant improvement in medication adherence that was attributed to HBPM, however 9 of the 11 trials reviewed employed what were termed complex interventions: in addition to HBPM, subjects met with case managers and patient counselors who provided them with personal support and behavioral tips to enhance lifestyle issues favorable in hypertension.

Only in studies utilizing electronic devices or pill counts to monitor adherence (as opposed to self report) was HBPM was found to enhance compliance. HBPM may enhance compliance when coupled with appropriate adherence monitoring. ■

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