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How Safe and Effective is Pramlintide in Improving Long-Term Glycemic Control and Weight Loss in Patients with Type 2 Diabetes Mellitus Receiving Insulin?

Sanjana Iyengar, Kaitlin Love, Brian Bauerband, and José Rodríguez

relapse than monotherapy (14 trials, N=1,323; risk ratio [RR] 0.62; 95% CI, 0.54–0.70). There was no significant difference in combined mortality and morbidity with either therapy (17 trials, N=1,523; Peto OR 0.13; 95% CI, 0.0–6.8). None of the adverse reactions had subgroup analyses for relapsers. However, anemia was the most common adverse effect reported with combination therapy (35 trials, N=7,402; RR 9.5; 95% CI, 7.4–12; NNH=7). Combination therapy was also associated with more leukopenia (3 trials, N=144; RR 3.4; 95% CI, 1.4–8.5), dermatitis (3 trials, N=1,002; RR 1.7; 95% CI, 1.2–2.3), pruritus (18 trials, N=3,908; RR 1.6; 95% CI, 1.3–2.0), and rash (12 trials, N=2,538; RR 1.7; 95% CI, 1.2–2.6).

A 2002 Cochrane review of 18 trials involving 1,170 patients with hepatitis C, in mixed samples of relapsers and nonresponders to initial interferon, examined follow-on interferon treatment duration.[2] Most studies lasted 24 to 48 weeks. There were 484 patients who initially responded to treatment but relapsed within 6 months. Three trials totaling 308 relapsing patients examined the effect of interferon dose on liver histology. More relapsing patients who received 3 million units interferon 3 times a week for 24 weeks showed improvement in fibrosis than relapsing patients who received 10 million units interferon 6 times a week for 2 weeks then 3 times a week for 12 weeks (32% vs 8%; *P*=.04).

Another 3 trials with 298 relapsing patients compared 24 with 48 weeks of interferon monotherapy. These 3 trials used 3 different types of interferon: lymphoblastoid interferon, consensus interferon, and interferon-alpha 2b. There were no significant differences in the responses to the individual type of interferon. However, patients receiving the shorter course were less likely to achieve a sustained normalization of alanine aminotransferase at 6 months (RR 0.73; 95% CI, 0.62–0.85) and were less likely to have a disappearance of hepatitis C RNA at 6 months (RR 0.74; 95% CI, 0.62–0.85).[2]

Brandon W. Cook, BS
José E. Rodríguez, MD
FSU College of Medicine
Tallahassee, FL

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How safe and effective is pramlintide in improving long-term glycemic control and weight loss in patients with type 2 diabetes mellitus receiving insulin?

Evidence-Based Answer

Addition of pramlintide to the treatment of patients with type 2 diabetes mellitus (DM2) already using basal insulin results in a modest reduction of glycosylated hemoglobin (HbA1c) levels and greater weight reduction compared with controls (SOR: **A**, meta-analysis of RCTs).

A meta-analysis of 8 RCTs with 1,616 participants (31–67 years old) studied the effect of pramlintide on glycemic control and weight in patients with DM2 and in obese patients without diabetes.[1] In the 4 DM2 studies, 930 randomized patients with poorly controlled DM2 for 9 to 12 years and who were receiving basal insulin were given subcutaneous pramlintide (120–150 mcg BID-TID) before major meals. As the control, 3 of the studies used meal-time placebo in a randomized, double-blind design and 1 study used rapid-acting insulin in a randomized, open-label design. Trials used a variety of follow-up periods (12–13, 24–26, and 39 and 52 weeks).

In the DM2 studies, there was a significant reduction in HbA1c in the pramlintide group at the trials' endpoints (4 trials; N=930; mean difference [MD] –0.33; 95% CI, –0.51 to –0.14) that persisted up to 52 weeks (2 trials; N=607; MD –0.40; 95% CI, –0.58 to –0.21). Pramlintide was associated with significantly more weight loss than control at 24 to 26 weeks (3 trials; N=719; MD –2.6 kg; 95% CI, –3.8 to –1.4) and at 52 weeks (2 trials; N=607; MD –2.1 kg; 95% CI, –2.9 to 1.3).

Combining data from patients with DM2 and obese patients without diabetes, patients randomized to pramlintide were more likely to report mild, moderate, or severe nausea versus control with both less than 6 months of treatment (3 trials; N=911; risk ratio [RR] 2.1; 95% CI, 1.1–4.1) and more than 6 months of treatment (2 trials; N=607; RR 1.7; 95% CI, 1.1–2.6).

The 2013 American Diabetes Association clinical practice guidelines recommend metformin, other oral agents, glucagon-like peptide-1 agonists (exenatide, liraglutide), and insulin for the pharmacologic treatment

of patients with DM2. Pramlintide is not mentioned as a therapy for DM2.[2]

Sanjana Iyengar, BS
Kaitlin Love, BS
Brian Bauerband, MD
José E. Rodríguez, MD
FSU College of Medicine
Tallahassee, FL

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How often should serum protein electrophoresis be done in someone with monoclonal gammopathy of undetermined significance (MGUS)?

Evidence-Based Answer

Patients with an initial diagnosis of MGUS should have a serum protein electrophoresis (SPEP) rechecked in 6 months. Risk stratification by free-light chain (FLC) ratio, immunoglobulin (Ig) type, and serum monoclonal (M) protein level is warranted. Low-risk patients should have SPEP every 2 to 3 years, while patients with higher-risk MGUS should have SPEP every year (SOR: **C**, expert opinion).

A cohort of 1,148 patients with MGUS, defined as a serum M protein <30 g/L, bone marrow plasma cells <10%, and the absence of end-organ damage attributable to the plasma cell proliferative disorder, were followed for a median of 15 years.[1] Risk of progression to malignancy correlated with 3 characteristics: kappa-to-lambda FLC ratio <0.26 or >1.65 (HR 2.6; 95% CI, 1.7–4.2), serum M protein level >15 g/dL (HR 2.4; 95% CI, 1.7–3.5), or non-IgG type MGUS (HR 2.6; 95% CI, 1.7–4.0). The 20-year risk of malignant progression in patients with 3 risk factors was 58%; in patients with 2 risk factors, the 20-year risk was 37%; in patients with 1 risk factor, the 20-year risk was 21%; and in patients with no risk factors it was 5%. A limitation of the study was the lack of detailed characterization of the 32% of patients who were not followed until death.

In a non–risk-stratified cohort of 241 patients with MGUS followed for a median of 13 years, the interval between diagnosis of MGUS and the diagnosis of multiple myeloma or a related disorder ranged from 1 to 32 years, with a rate of progression of 1.5% per year.[2]

Based on these 2 cohort studies, the International Myeloma Working Group recommended that patients with low-risk MGUS have a SPEP repeated at 6 months and then every 2 to 3 years and that patients with a kappa-to-lambda FLC ratio <0.26 or >1.65, serum M protein level >15 g/dL, or non-IgG type MGUS have SPEP repeated in 6 months and then annually for life.[3] EBP

Christine K. Jacobs MD
St. Louis University FMR
St. Louis, MO

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GLOSSARY

ARR=absolute risk reduction
CDC=Centers for Disease Control and Prevention
CI=confidence interval
CT=computed tomography
FDA=US Food and Drug Administration
HR=hazard ratio
LOE=level of evidence
MRI=magnetic resonance imaging
NNH=number needed to harm
NNT=number needed to treat
NSAID=nonsteroidal anti-inflammatory drug
OR=odds ratio
RCT=randomized controlled trial
RR=relative risk
SOR=strength of recommendation
SSRI=selective serotonin reuptake inhibitor