Relias Media
From Relias

Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

Vol. 43, Issue 8, April 30, 2021
ReliasMedia.com

ABSTRACT & COMMENTARY

Is Metformin a Wonder Drug?

By Joseph E. Scherger, MD, MPH

Core Faculty, Eisenhower Health Family Medicine Residency Program, Eisenhower Health Center, La Quinta, CA; Clinical Professor, Keck School of Medicine, University of Southern California, Los Angeles

SYNOPSIS: An analysis of patients taking metformin for diabetes showed they were less likely to report back, knee, neck/shoulder, or multisite musculoskeletal pain.

SOURCE: Carvalho-E-Silva AP, Harmer AR, Ferreira ML, Ferreira PH. The effect of the anti-diabetic drug metformin on musculoskeletal pain: A cross-sectional study with 21,889 individuals from the UK Biobank. *Eur J Pain* 2021; Feb 9. doi: 10.1002/ejp.1747. [Online ahead of print].

A team from Australia studied a database that included 21,889 patients with type 2 diabetes collected from 2006-2010 in England, Wales, and Scotland. Medications, symptoms, and lifestyle factors were recorded. Musculoskeletal (MS) pain was recorded for the back, knee, hip, and neck/shoulder. It was considered significant if the pain interfered with usual activities over three months.

Patients using metformin reported significantly lower rates of MS pain in all these sites vs. people with diabetes on other treatment. The associations were significant for both men and women, and generally stronger in women. This association with metformin alleviating MS pain has been shown in other studies.[1] Metformin may influence pain by triggering activated protein kinase (AMPK).[2] AMPK may reduce the excitability of peripheral nociceptors and mechanical allodynia in neuropathic pain.[3]

■ COMMENTARY

The many positive pleiotropic effects of the inexpensive and effective drug metformin for type 2 diabetes are fortuitous. I tell patients who may be hesitant to take this drug that it may improve their health in several ways, and help them live longer. There is strong biology to support these effects.[4]

Metformin has become a popular anti-aging drug in part because of the work of Harvard biologist David Sinclair, who uses metformin to lengthen lifespan.[5] A recent article in *Internal Medicine Alert* indicated hospitalized patients on metformin were at a lower risk of mortality.[6]

Financial Disclosure: Dr. Stephen Brunton, physician editor, reports he is on the speakers bureau for AstraZeneca, Bayer, Lilly, and Novo Nordisk; and is a retained consultant for Abbott, Acadia, AstraZeneca, Bayer, Novo Nordisk, Sanofi, and Xeris. The relevant financial relationships listed have been mitigated. None of the remaining planners or authors for this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Internal Medicine
Evidence-based summaries of the latest research in internal medicine [ALERT]

Internal Medicine Alert (ISSN 0195-315X) is published semimonthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Internal Medicine Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This Enduring Material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins 1/15/2021. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 2 AAFP Prescribed credits.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

Patients should take metformin with or after a meal to avoid the gastrointestinal side effects. The 500 mg dose is used in prediabetes and for anti-aging. Start with 500 mg in people with type 2 diabetes so they can adjust to the drug for about two weeks. Then, increase the dose to 1,000 mg, both twice daily. ■

REFERENCES

1. Smith B, Ang D. Metformin: Potential analgesic? *Pain Med* 2015;16:2256-2260.
2. Ouyang JY, Parakhia RA, Ochs RS. Metformin activates AMP Kinase through inhibition of AMP deaminase. *J Biol Chem* 2011;286:1-11.
3. Viollet B, Guigas B, Sanz Garcia N, et al. Cellular and molecular mechanisms of metformin: An overview. *Clin Sci* 2012;122:253-270.
4. Hattori Y, Hattori K, Hayashi T. Pleiotropic benefits of metformin: Macrophage targeting its anti-inflammatory mechanism. *Diabetes* 2015;64:1907-1909.
5. Sinclair DA, LaPlante MD. *Lifespan: Why We Age — and Why We Don't Have To*. Simon & Schuster; 2019.
6. Ulrich A. Prior metformin use in patients with diabetes hospitalized for COVID-19. *Internal Medicine Alert* 2021;43:25-26.

ABSTRACT & COMMENTARY

Accounting for Patient Preference, Cardiovascular Disease Risk in Statin Therapy

By Austin Ulrich, PharmD, BCACP

Clinical Pharmacist Practitioner, UpStream Pharmaceutical Care, Greensboro, NC

SYNOPSIS: Researchers weighed patient preferences and risks regarding statin therapy after reviewing 10-year atherosclerotic cardiovascular disease risk scores.

SOURCE: Brodney S, Valentine KD, Sepucha K, et al. Patient preference distribution for use of statin therapy. *JAMA Netw Open* 2021;4:e210661.

The American College of Cardiology/American Heart Association, U.S. Preventive Services Task Force, and the U.S. Department of Veterans Affairs/Department of Defense Health Care Systems clinical guidelines provide clear recommendations for statin therapy as primary atherosclerotic cardiovascular disease (ASCVD) prevention for certain groups.[1-3] Despite these recommendations favoring statin treatment for patients at risk for CVD, only about one-third of eligible patients take statins.[4] Although the guidelines all include similar stratification of risk thresholds, they differ in the exact thresholds established. Historically, one suggestion to improve clinical guideline recommendations has been to incorporate patient preference into guideline development, although this rarely is the case.[5]

To determine the feasibility of using patient preference for statin therapy in establishing ASCVD risk thresholds, Brodney et al conducted a "survey study" to determine preferences for statin therapy. Patients included in the study were not taking a statin or proprotein convertase subtilisin/kexin type 9 inhibitor for primary prevention. Participants entered their age, sex, cholesterol levels, blood pressure, hypertension treatment, diabetes status, and smoking status to determine their 10-year ASCVD risk scores. They also received a description of the benefits and possible adverse effects of statins.

There were 304 participants in the final survey sample, with an average age of 54.8 years. In total, 137 patients indicated they would choose to take a statin (26 answered "definitely take" and 111 answered "probably take"). The remaining 167 patients indicated they would not choose to take a statin (91 answered "probably not take" and 76 answered "definitely not take"). When participants were asked about taking a statin across various ASCVD risk levels, they were more likely to choose statin therapy as risk levels increased (54.7% at ≥ 5% risk to 81.1% at ≥ 25% risk). Statin preferences were partially dependent on whether a healthcare provider had talked to the participant about statin therapy. There was

a significant increase in patients who would choose to take a statin if they had engaged in a discussion. Interestingly, patients with better health literacy, higher subjective numeracy scores, and higher knowledge scores were significantly less likely to want statin therapy.

The authors concluded there is not a specific CV risk threshold for which shared decision-making should be applied to initiate statin therapy. Rather, shared decision-making could be applied to a wide range of CVD risk scores.

■ COMMENTARY

In this study, no ASCVD risk level reached the recommended 95%-99% threshold where patient preference could inform guideline recommendations.[5] However, this was a fairly small sample size, and many patients who are otherwise eligible for statin therapy already are taking a statin. This selection bias was a major limitation of this study and may underestimate the true proportion of patients who would take a statin, since patients already taking a statin likely would choose to stay on statin therapy in this survey study setting. Additionally, the way the risks (denominator of 1,000) and benefits (denominator of 100) were presented could have falsely skewed patients' perceptions to be less favorable toward statins. Internal medicine and other primary care practitioners frequently experience resistance from patients about taking statins. Although it is helpful to take patients' preferences into consideration and engage in shared decision-making, clinicians should present their patients with accurate information and evidence-based recommendations about statin use for optimal outcomes and to promote patient engagement. ■

REFERENCES

1. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596-e646.
2. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2016;316:1997-2007.
3. O'Malley PG, Arnold MJ, Kelley C, et al. Management of dyslipidemia for cardiovascular disease risk reduction: Synopsis of the 2020 updated U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. *Ann Intern Med* 2020;173:822-829.
4. Colantonio LD, Rosenson RS, Deng L, et al. Adherence to statin therapy among US adults between 2007 and 2014. *J Am Heart Assoc* 2019;8:e010376.
5. Eddy DM. Clinical decision making: From theory to practice. Designing a practice policy. Standards, guidelines, and options. *JAMA* 1990;263:3077, 3081, 3084.

ABSTRACT & COMMENTARY

Is Empagliflozin Safe in Combination with a Neprilysin Inhibitor for Heart Failure?

By Michael H. Crawford, MD

Professor of Medicine, Lucy Stern Chair in Cardiology, University of California, San Francisco

SYNOPSIS: A prespecified subgroup analysis of heart failure patients with reduced ejection fraction who were on neprilysin inhibitors before empagliflozin was administered (vs. those not on neprilysin inhibitors) showed the reduction in mortality and hospital admissions for heart failure was not attenuated by concurrent neprilysin use.

SOURCE: Packer M, Anker SD, Butler J, et al. Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: The EMPEROR-Reduced trial. *Eur Heart J* 2021;42:671-680.

There are little data on the effect of combining a neprilysin inhibitor with a sodium-glucose cotransporter-2 (SGLT2) inhibitor in patients with systolic heart failure. In the EMPEROR-Reduced trial of the SGLT2 empagliflozin vs. placebo in patients with heart failure and reduced ejection fraction, 20% of 3,730 randomized patients were on concomitant sacubitril/valsartan at baseline.[1] Packer et al conducted a prespecified subgroup analysis of this 20% (727 patients). These patients were New York Heart Association (NYHA) class II-IV heart failure with ejection fraction less than 40% and were on appropriate treatment for heart failure, including devices. They were randomized to empagliflozin 10 mg/day vs. placebo. The primary endpoint was the composite of adjudicated cardiovascular death or hospitalization for heart failure. The authors also assessed several secondary endpoints involving renal function, symptoms, and blood metabolic parameters.

Among baseline clinical characteristics, those treated with neprilysin inhibition recorded lower blood pressure readings, heart rate, and BNP levels, and were more likely to have a cardiac device and be from North America. Compared to placebo, empagliflozin reduced the primary endpoint by 23% in those not on neprilysin inhibition and by 36% in those on neprilysin inhibition (HR, 0.77; 95% CI, 0.66-0.90; P = 0.0008 and HR,

0.64; 95% CI, 0.45-0.88; *P* = 0.009, respectively). The heart failure hospitalization component of the primary endpoint also declined by 29% in subjects who were not on a neprilysin inhibitor and by 35% in those on a neprilysin inhibitor (HR, 0.71; 95% CI, 0.58-0.88; *P* = 0.002 and HR, 0.65; 95% CI, 0.42-1.00; *P* = 0.052, respectively). Also, empagliflozin slowed the rate of decline in estimated glomerular filtration rate (eGFR) by 1.7 mL/min/1.7m^2/year in those not on a neprilysin inhibitor (*P* < 0.0001) and by 1.92 mL/min/1.7m^2/year in those on a neprilysin inhibitor (*P* = 0.016). There were no significant differences in adverse events between those on or off neprilysin inhibition treated with empagliflozin.

The authors concluded the beneficial effects of empagliflozin in patients with symptomatic heart failure with reduced ejection fraction are not attenuated by concomitant neprilysin inhibition treatment, and such therapy is well tolerated.

■ COMMENTARY

The most recent heart failure guideline update now recommends NYHA class II-IV patients with heart failure caused by systolic dysfunction to start an angiotensin receptor/neprilysin inhibitor (ARNI) and a beta-blocker soon after stabilization of volume status and relief of congestion. Then, in those with an eGFR > 30 mL/min and a potassium < 5 mEq/L, start a mineralocorticoid antagonist and a SGLT2 inhibitor.[2] This recommendation was given on the strength of studies such as DAPA-HF, which showed robust reductions in mortality and hospitalizations when SGLT2 inhibitors were administered on top of ACEI or ARB, beta-blocker, and mineralocorticoid inhibition.[3] However, in DAPA-HF, only 11% of patients also were on an ARNI, so the efficacy and safety of this subgroup was underpowered for firm conclusions.

Since EMPEROR-Reduced included about twice as many patients on an ARNI at baseline, it made sense to evaluate the benefit of adding an SGLT2 inhibitor in this subgroup. Not only were the beneficial effects statistically similar in this subgroup, numerically, the effects were larger. This is somewhat surprising, since the ARNI group was exceptionally well treated at baseline: 95% on beta-blockers, 70% on mineralocorticoid antagonists, 27% with an implanted cardiac defibrillator, and 10% with a cardiac resynchronization device. In addition, this combination was well tolerated. There was minimal additional blood pressure-lowering and volume depletion in the ARNI group, and other adverse effects were unusual in both groups.

What was disturbing was the aggregate of all serious adverse effects occurred in about 50% of subjects in both groups with the addition of empagliflozin. Hence, it is difficult to rationalize how the authors could state that empagliflozin was "well tolerated." This observation raises the difficult issue of patient tolerance of the ever-growing list of must-have drugs to treat heart failure, especially since clinicians are supposed to titrate the drugs to the maximum doses used in trials. Of course, trial participants are not exactly equivalent to the patients seen in practice, such that most heart failure patients are not on the optimal doses of all these drugs because of intolerance, usually caused by low blood pressure or heart rate, or metabolic derangements, such as hyperkalemia. Once again, clinicians are challenged to bring patients on board with all these lifesaving drugs.

There were limitations to this study. For this type of trial, the number of patients was relatively small. The authors did not address the reverse issue of adding an ARNI to someone already on an SGLT2 inhibitor, such as a diabetic patient. Also, the authors did not explore the timing of initiation of the recommended drugs for systolic heart failure. The sequence and timing of the administration and titration of the recommended drugs in new heart failure patients are not well studied, but perhaps the SGLT2 inhibitors should be introduced before mineralocorticoid antagonists. ■

REFERENCES

1. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413-1424.
2. Maddox TM, Januzzi JL Jr, Allen LA, et al. 2021 update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 pivotal issues about heart failure with reduced ejection fraction: A report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2021;77:772-810.
3. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995-2008.

ABSTRACT & COMMENTARY

Antibiotics: Less Is Better, Sometimes

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN; Department of Pediatrics, Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates

SYNOPSIS: In England, and likely in many other areas of the world, antibiotics are given for longer than necessary. Excessively long durations of antibiotic use do not help patients and risk leading to more resistant infections.

SOURCE: Palin V, Welfare W, Ashcroft AM, van Staa TP. Shorter and longer courses of antibiotics for common infections and the association with reductions of infection-related complications including hospital admissions. *Clin Infect Dis* 2021; Feb 24. doi: 10.1093/cid/ciab159. [Online ahead of print].

Increasing resistance of bacteria to antimicrobials is a threat to global health, and growing resistance has been linked to overuse of antibiotics. In the United Kingdom, primary care providers issue more than 80% of antibiotic prescriptions, and there is variability in prescribing habits. Some focused research studies have revealed shorter courses of antibiotics are similar in effectiveness to longer courses. Palin et al used a national database to explore links between the duration of antibiotic treatment and complications of the inciting illness.

The authors of a population-based cohort study used a database from general practices in England that include diagnoses, medication prescriptions, and demographic information with longitudinal follow-up. The study population included patients who received a prescription for a systemic antibiotic from their general practitioner and who were diagnosed with urinary tract infection or a non-pneumonia respiratory tract infection. Attention was paid to infection-related complications prompting hospitalization within 30 days of the prescription.

More than 4 million consultations for acute infections were registered during the study period: 59% upper respiratory infections, 25% lower respiratory infections, and 16% urinary tract infections. Overall, 62% of antibiotic prescriptions were for six to seven days. Amoxicillin was the most commonly prescribed antibiotic for respiratory tract infections. However, for those receiving medication for eight- to 15-day courses, penicillin and doxycycline were used most commonly. Trimethoprim was the antibiotic most commonly used for urinary tract infections.

Most infection-related hospitalizations occurred during the first week following initiation of the prescribed antibiotic, and 0.15% of patients were hospitalized for infection-related reasons. Early hospitalizations during the treatment course, likely suggesting a more severe illness at the time of presentation, were most common for patients living with more comorbidities or who received longer-course prescriptions. Hospitalizations after the first week of treatment were independent of the length of antibiotic treatment, suggesting there was no increased risk with shorter-course treatment. The authors concluded longer courses of antibiotics did not improve outcomes and shorter courses of antibiotics did not add significant risk. They suggested reversing the current trend of prescribing relatively longer courses of antibiotics for respiratory and urinary infections.

■ COMMENTARY

There are historical precedents for using 10-day courses of penicillin for streptococcal pharyngitis, based on the initial studies conducted ("if it works, why change it?") and based on data suggesting a greater risk of rheumatic fever with shorter courses. In developed nations, routine 10-day courses of antibiotics became common for a variety of conditions. However, antibiotic course durations are decreasing.

Even a couple of decades ago, otitis media usually was treated with a 10-day course of antibiotics. Then, observation without antibiotic treatment (with antibiotics subsequently given only to those who did not improve during the initial days of self-recovery) was found to be safe and effective for children older than age 1 year.[1] Cephalosporins were found to be effective for streptococcal pharyngitis when administered for "just" five days. Urinary tract infection treatment courses shifted from 10 to five to three days and, for adults, to single doses.

Palin et al excluded patients with pneumonia from their study. However, although physicians in many developed nations continue to treat pneumonia for 10 days, the World Health Organization has demonstrated good practical and scientific success in treating childhood pneumonia for just three to five days. More data and recommendations from the United States also support shorter treatment courses for pneumonia.[2]

One of the beauties of the Palin et al study is they analyzed outcomes in two different periods: the first week after prescription of the antibiotic and the subsequent three weeks. As expected, early complications (i.e., hospital admissions) were more common in those who were sicker at presentation. However, a review of later complications showed abbreviated antibiotic courses

were not less effective than longer courses. Thus, this study reminds clinicians that shorter antibiotic courses can be both safe and effective. Judicious antibiotic use should include not only limiting initiation of unnecessary antibiotics but also limiting the duration of treatment with necessary antibiotics. Palin et al conducted other studies related to antibiotic overuse. They found simply reducing antibiotic prescriptions might be dangerous.3 Decreased antibiotic prescription rates were associated with subsequent increases in infection-related hospitalizations.[3] Appropriate antibiotics must be given, but not for too long. ■

REFERENCES

1. Homme JH. Acute otitis media and group A streptococcal pharyngitis: A review for the general pediatric practitioner. *Pediatr Ann* 2019;48:e343-e348.
2. Same RG, Amoah J, Hsu AJ, et al. The association of antibiotic duration with successful treatment of community-acquired pneumonia in children. *J Pediatr Infect Dis Soc* 2020;piaa0.55. doi: 10.1093/jpids/piaa055.
3. van Bodegraven B, Palin V, Mistry C, et al. Infection-related complications after common infection in association with new antibiotic prescribing in primary care: Retrospective cohort study using linked electronic health records. *BMJ Open* 2021;11:e041218.

ABSTRACT & COMMENTARY

Herpes Zoster Vaccine: Effective but Underused

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The adjuvanted recombinant herpes zoster vaccine is highly effective in practice, but it is vastly underused.

SOURCES: Sun Y, Kim E, Kong CL, et al. Effectiveness of the recombinant zoster vaccine in adults aged 50 and older in the United States: A claims-based cohort study. *Clin Infect Dis* 2021; Feb 13:ciab121. doi: 10.1093/cid/ciab121. [Online ahead of print].

Izurieta HS, Wu X, Forshee R, et al. Recombinant zoster vaccine (Shingrix) real-world effectiveness in the first two years post-licensure. *Clin Infect Dis* 2021; Feb 13:ciab125. doi: 10.1093/cid/ciab125. [Online ahead of print].

Sun et al used a large administrative claims database to examine the real-world protective efficacy of Shingrix, an adjuvanted recombinant vaccine that was approved in the United States in 2017 for prevention of herpes zoster. Of almost 5 million vaccine-eligible individuals, only 173,745 received two doses of the vaccine, with the second dose received 30-210 days after the first. The median duration of follow-up after the second dose was seven months. The incidence of herpes zoster in those who were vaccinated was 258.8 per 100,000 person-years, a significant reduction from the rate of 893.1 per 100,000 person-years in those who remained unvaccinated. The effectiveness was 86.8% in those age 50-79 years and 80.3% in those ≥ age 80 years. The overall effectiveness was 85.5% (95% CI, 84.6%-88.7%) and was 84.8% in those who had received the live vaccine in the five years prior to receipt of the recombinant material.

Using Medicare claims and enrollment databases, Izurieta et al examined a cohort whose mean age was 74 years, approximately 10 years older than those examined by Sun et al. Of those who received the recombinant vaccine, 78% completed the second dose by six months and 86% completed it by 12 months. A delay in second dosing did not significantly affect outcomes. The overall adjusted vaccine efficacy was 70.1%, with little difference between those age 65-79 years and those older. Those who received only a single vaccine dose were less protected: 56.9%. In those who had received the attenuated zoster vaccine (Zostavax), the efficacy was 63.0%, but this result presumably was artifactually diminished by residual effectiveness in the control group in this study. Receipt of both vaccine doses resulted in a protective efficacy of 76% against the development of post-herpetic neuralgia.

■ COMMENTARY

Shingrix was approved for the prevention of herpes zoster in 2017 in adults ≥ age 50 years. The vaccine requires two intramuscular doses given two to six months apart. After its FDA approval, Shingrix supplanted Zostavax, which proved to be a less effective vaccine and, furthermore, as a live attenuated viral vaccine, was not recommended for use in immunocompromised patients. Although it requires two doses, the absence of replicative virus in this recombinant vaccine makes it potentially safer. On the other hand, the not insignificant incidence of non-severe adverse reactions (possibly related to the presence of an adjuvant) after receipt of Shingrix raised concern about whether, outside the cloak of a clinical trial, many patients might not return for a second dose. In fact, although the effectiveness of the vaccine was high in these studies, including when compared to Zostavax, effectiveness was lower than in the two clinical trials leading to approval. The reasons for this

are discussed further in an excellent comprehensive commentary by Harpaz.[1] Perhaps the most startling result in these analyses was only 3.6% of potential vaccine candidates in the United States had received both doses. Considering the efficacy and cost savings associated with its use, this is shameful. This also is a reflection of the inadequate support of public health measures, including vaccination, in the United States, an issue discussed by Harpaz and one which, if seized on, could be affected favorably by lessons learned in the COVID-19 pandemic.[1] In this regard, once again we have much to learn from our Canadian compatriots. Martins et al reported the introduction of a publicly funded herpes zoster immunization program in 2019 was associated with significant reductions in medically attended visits, ED visits, and hospitalization related to zoster — and this was with the use of the less effective live virus vaccine.[2] ■

REFERENCES

1. Harpaz R. The effectiveness of recombinant zoster vaccine: Observations in the wild. *Clin Infect Dis* 2021; Feb 13:ciab130. doi: 10.1093/cid/ciab130. [Online ahead of print].
2. Martins D, McCormack D, Tadrous M, et al. Impact of a publicly funded herpes zoster immunization program on the burden of disease in Ontario, Canada: A population-based study. *Clin Infect Dis* 2021;72:279-284.

PHARMACOLOGY UPDATE

Dasiglucagon Injection (Zegalogue)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

The FDA has approved a glucagon analog to treat severe hypoglycemia. Seven of 29 amino acids of native glucagon peptide are substituted, providing improved stability of the peptide in solution. It is marketed as Zegalogue.

INDICATIONS

Dasiglucagon should be prescribed to treat severe hypoglycemia in pediatric and adult patients (≥ age 6 years).[1]

DOSAGE

The recommended dose is 0.6 mg given subcutaneously.[1] If there is no response after 15 minutes, an additional dose may be administered. Dasiglucagon is available as 0.6 mg/0.6 mL single-dose autoinjector or single-dose prefilled syringe.

POTENTIAL ADVANTAGES

Dasiglucagon is soluble and physiochemically stable at physiologic pH vs. native glucagon while still providing the biopotency of glucagon.[2] It features ready-to-use preparation and does not require reconstitution.

POTENTIAL DISADVANTAGES

There is a potential for immunogenicity with a modified, nonnative peptide. In clinical trials, four of 498 subjects developed treatment-emergent, antidrug antibodies.[1]

COMMENTS

The safety and efficacy of dasiglucagon were evaluated in three randomized, double-blind, placebo-controlled trials, two in adults and one in pediatric subjects with type 1 diabetes (age 6 to 17 years).[1] Subjects were randomized to dasiglucagon (0.6 mg) or placebo. In one adult trial and in the pediatric trial, glucagon 1 mg was included as an active comparator. Severe hypoglycemia was induced by IV administration of insulin to a target plasma level of glucose < 60 mg/dL in adults and < 80 mg/dL in pediatrics. The primary efficacy endpoint was time to plasma glucose recovery (i.e., increase of ≥ 20 mg/dL) from time of administration without additional intervention within 45 minutes. Plasma levels were assessed periodically at predose and from four to 90 minutes after treatment.

The median times to glucose recovery were 10 minutes for dasiglucagon, 12 minutes for glucagon, and 40 minutes for placebo in the first adult study and 10 minutes and 35 minutes for dasiglucagon and placebo, respectively, for the second adult study. In the pediatric study, median times were 10 minutes for dasiglucagon and glucagon and 30 minutes for placebo. The most frequently reported side effects were nausea, vomiting, and headache, which occurred more frequently in adults than in pediatric subjects.[1]

In a pharmacokinetic/pharmacodynamic study, dasiglucagon 0.6 mg showed similar time to reach plasma glucose levels ≥ 70 mg/dL and time to increase levels ≥ 20 mg/dL vs. glucagon.[3] However, dasiglucagon showed a higher and longer-lasting glucose response, potentially reducing the risk for recurrent hypoglycemia.

CLINICAL IMPLICATIONS

Severe hypoglycemia (< 55 mg/dL) is an acute, potentially life-threatening complication of diabetes. Children with type 1 diabetes on insulin are particularly

vulnerable.[4] Glucagon is the primary FDA-approved treatment for rescue of severe hypoglycemia.[5] Currently, there are two approved rescue glucagon lyophilized powder kits that require reconstitution (GlucaGen Hypokit and Glucagon Emergency Kit). A non-aqueous solution (formulated in an aprotic solvent with dimethylsulfoxide) is available (Gvoke Hypopen), but is associated with more injection site erythema, edema, and discomfort.[6] Glucagon also is available as an intranasal preparation (Baqsimi), but produces a slower glycemic response.[2]

Dasiglucagon provides a ready-to-use injection as an alternative to subcutaneous glucagon. Pricing has not been announced, but the company has stated it plans to offer "parity pricing" with similar products. ■

REFERENCES

1. Zealand Pharma A/S. Zegalogue prescribing information. March 2021. https://bit.ly/31UUYva
2. Li S, Hu Y, Tan X, et al. Evaluating dasiglucagon as a treatment option for hypoglycemia in diabetes. *Expert Opin Pharmacother* 2020;21:1311-1318.
3. Hövelmann U, Bysted BV, Mouritzen U, et al. Pharmacokinetic and pharmacodynamic characteristics of dasiglucagon, a novel soluble and stable glucagon analog. *Diabetes Care* 2018;41:531-537.
4. Saydah S, Imperatore G, Divers J, et al. Occurrence of severe hypoglycaemic events among US youth and young adults with type 1 or type 2 diabetes. *Endocrinol Diabetes Metab* 2019;2:e00057.
5. Centers for Disease Control and Prevention. How to treat low blood sugar (hypoglycemia). Last reviewed Jan. 20, 2021. https://bit.ly/3sZMoHs
6. Hawkes CP, De Leon DD, Rickels MR. Novel preparations of glucagon for the prevention and treatment of hypoglycemia. *Curr Diab Rep* 2019;19:97.

CME QUESTIONS

1. What is a benefit of taking metformin for type 2 diabetes?
a. Increased libido
b. Lower blood pressure
c. Lower cholesterol
d. Less musculoskeletal pain

2. In the statin preferences survey study by Brodney et al, which is true about the preferences for statin use in their sample population?
a. Individuals who had discussed statin use with a healthcare provider were more likely to want statin therapy.
b. Individuals with better health literacy and higher numeracy scores were more likely to want statin therapy.
c. As estimated cardiovascular risk increased, the proportion of participants who wanted statin therapy decreased.
d. The results of the survey indicated incorporating patient preferences into clinical guidelines is likely to result in worse outcomes affected by statin use.

3. Adding a sodium-glucose cotransporter-2 to optimal heart failure treatment, including a neprilysin inhibitor/angiotensin receptor blocker, resulted in:
a. significantly more hypotension.
b. worse renal function.
c. a lower mortality rate.
d. fewer heart failure hospitalizations.

4. According to the study by Palin et al, which is true regarding courses of oral antibiotics of fewer than 10 days for upper respiratory infections?
a. They are uniformly associated with worse outcomes.
b. They are associated with increased risk of invasive bacterial infection.
c. They are associated with outcomes similar to those with longer courses of treatment.
d. They are considered malpractice.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.