RELIAS MEDIA

Internal Medicine

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

Vol. 42, Issue 14, July 30, 2020
ReliasMedia.com

ABSTRACT & COMMENTARY

Androgen Deprivation Therapy and SARS-CoV-2

By Martin S. Lipsky, MD

Chancellor, South Jordan Campus, Roseman University of Health Sciences, South Jordan, UT

Dr. Lipsky reports no financial relationships relevant to this field of study.

SYNOPSIS: Cancer patients are at a higher risk of contracting SARS-CoV-2 vs. non-cancer patients. However, prostate cancer patients who received androgen deprivation therapy seem to be partially protected from such infections.

SOURCE: Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: A population-based study (N = 4532). *Ann Oncol* 2020; May 6;S0923-7534(20)39797-0. doi: 10.1016/j.annonc.2020.04.479. [Online ahead of print].

The full spectrum of COVID-19 ranges from mild to severe disease. In the United States alone, the virus has caused more than 134,000 deaths.[1] Research indicates SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface to gain entry. In addition to ACE2 receptors, TMPRSS2, a serine protease found on the cell surface, can act as a cofactor to facilitate viral entry. Epidemiologic data indicate COVID-19 affects men more severely; one explanation is TMPRSS2, an androgen-regulated gene, is more prevalent in men. TMPRSS2 also is highly expressed in both localized and metastatic prostate cancers.[2] First- or second-generation androgen deprivation therapies (ADTs) lower TMPRSS2 levels.

Based on this association, Montopoli et al hypothesized ADTs may protect patients afflicted with prostate cancer from SARS-CoV-2 infections. To test this hypothesis, the authors examined data from 9,280 patients (4,532 men) with laboratory-confirmed SARS-CoV-2 infections from 68 hospitals in an Italian region where the pandemic hit particularly hard. The parameters identified for each COVID-19-positive patient were gender, hospitalization, admission to intensive care unit (ICU), death, tumor diagnosis, prostate cancer diagnosis, and ADT. The authors found men developed more severe complications, were hospitalized more frequently, and experienced worse clinical outcomes than women. Among 4,532 men, 430 had cancer (118 with prostate cancer). Comparing

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott Diabetes, Acadia, AstraZeneca, and Boehringer Ingelheim; and he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Editor Jason Schneider; Editorial Group Manager Leslie Coplin; and Accreditations Director Amy M. Johnson, MSN, RN, CPN, report no financial relationships relevant to this field of study.

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.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

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

ACCREDITATION
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only 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 1/15/2020. 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.

the total number of SARS-CoV-2-positive cases, prostate cancer patients receiving ADT were at a significantly lower risk for contracting a SARS-CoV-2 infection vs. patients who did not receive ADT (odds ratio [OR], 4.05; 95% confidence interval [CI], 1.55-10.59). A greater difference was found comparing prostate cancer patients receiving ADT to patients with any other type of cancer (OR, 5.17; 95% CI, 2.02-13.40).

■ COMMENTARY

Current reports continue to emerge indicating COVID-19 affects older men with chronic illnesses more severely than women.[3] While not all U.S. states report COVID-19 cases by sex, those that do reflect epidemiological data from other countries that indicate men are disproportionately affected. One proposed explanation for sex-related disparities and COVID-19 outcomes is differences in sex hormones.

Sex hormones play a role in modulating the immune system and contribute to variations in the immunologic responses of men and women. They help balance the immune response between helpful responses that combat infection and those that trigger harmful inflammation. In general, the male sex hormone testosterone is immunosuppressive, while the female sex hormone estrogen tends to enhance the immune response.[4]

Testosterone also stimulates TMPRSS2 gene expression, which is a cofactor for SARS-CoV-2 cell entry and may increase the susceptibility of men for severe SARS-CoV-2 infections. Montopoli et al found prostate patients receiving ADT demonstrated better COVID-19 outcomes and speculated ADT might block or decrease the severity of SARS-CoV-2 infections.

In contrast, some theoretical evidence suggests low testosterone may be harmful. Inflammatory cytokines play a central role in the progression of COVID-19 infection. While a robust immune system is needed to fight an infection, unchecked, the response may be detrimental. Since hypogonadism is associated with more pro-inflammatory cytokines, low testosterone might lead to immune system dysregulation and trigger the cytokine storm that often characterizes severe COVID-19 infection.[5] Exactly how and if sex hormones positively or negatively affect outcomes in the milieu of COVID-19 remains uncertain.

The finding that ADT is associated with better outcomes provides a potential clue for developing effective treatments related to sex hormones. Trials evaluating therapies related to both testosterone and estrogen are in progress. Unraveling the exact role of the sex hormones offers the promise of developing beneficial therapeutic interventions using drugs that are already part of the primary care physician's toolbox. ■

REFERENCES

1. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19). Cases in the U.S. https://bit.ly/2Vbz7fS
2. Lucas JM, Heinlein C, Kim T, et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. *Cancer Discov* 2014;4:1310-1325.
3. Global Health 500. Sex, gender and COVID-19: Overview and resources. https://bit.ly/2VcoiKD
4. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. *Trans R Soc Trop Med Hyg* 2015;109: 9-15.
5. Mohamad NV, Wong SK, Wan Hasan WN, et al. The relationship between circulating testosterone and inflammatory cytokines in men. *Aging Male* 2019; 22:129-140.

ABSTRACT & COMMENTARY

Neurologic Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China

By Alexander E. Merkler, MD

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College, and Assistant Attending Neurologist, New York-Presbyterian Hospital

Dr. Merkler reports he receives grant/research support from the American Heart Association and is a consultant for Medicolegal.

SYNOPSIS: Neurological symptoms and impairments have been found in one-third of hospitalized patients with COVID-19 from countries that have reported these observations so far. This is a rapidly evolving consequence of SARS-CoV-2 infection.

SOURCE: Mao L, Jin H, Wang M, et al. Neurological manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; April 10. doi: 10.1001/jamaneurol.2020/1127. [Online ahead of print].

The world currently is under siege by coronavirus disease 2019 (COVID-19). Since December 2019, COVID-19 has affected more than 12 million people and caused more than 570,000 deaths worldwide. Although the most common manifestations of COVID-19 include fever, cough, and shortness of breath, this study by Mao et al is the first to report the frequency of neurological symptoms in hospitalized patients with COVID-19. In this retrospective, observational study performed at three centers in Wuhan, China, the authors studied the frequency and characteristics of neurological symptoms in hospitalized patients with COVID-19 infection between Jan. 16 and Feb. 19, 2020. For each subject, neurological symptoms were reviewed and confirmed by two trained neurologists, with a third resolving any disagreements.

The authors categorized neurological symptoms of COVID-19 into three categories: central nervous system (dizziness, headache, impaired consciousness, stroke, ataxia, seizures), peripheral nervous system (taste or olfactory impairment, vision impairment, and nerve pain), and skeletal muscular injury. Among 214 hospitalized patients, 78 had neurological symptoms; 53 originated from the central nervous system, 19 from the peripheral nervous system, and 23 were skeletal muscular injury. Dizziness (16.8%) and headache (13.1%) were the most common neurological symptoms. Taste and olfactory impairment occurred in 5.6% and 5.1%, respectively.

Most neurological symptoms occurred early in the illness (median time, one to two days). Neurological symptoms were more common in patients who had severe respiratory disease vs. non-severe respiratory disease (45.5% vs. 30.2%) and in those with lower lymphocyte and platelet counts. Six patients had a stroke. Stroke was the initial presenting complaint in two of the six patients with stroke. These patients did not show typical respiratory manifestations of COVID-19 (fever, cough, diarrhea), although they exhibited typical computed tomography chest findings of COVID-19.

■ COMMENTARY

Neurological symptoms appear to be common in patients with COVID-19, occurring in more than one-third of hospitalized patients. Taste and olfactory loss occurred in 5% of patients. Other reports suggest impairments in these modalities are common and often seen in milder cases of COVID-19 disease that do not require hospitalization.[1] Stroke occurred in 2.8% of hospitalized patients with COVID-19 and, interestingly, consistent with another report, often was the initial presenting symptom of COVID-19.[2] Stroke mainly occurred in patients with severe COVID-19 infection, which is consistent with another study that found evidence of stroke in 3 of 13 patients with severe COVID-19 infection.[3]

The mechanisms underpinning these neurological symptoms remain unclear. As with other viral infections (such as influenza) inflammation, hypercoagulability, and endothelial injury likely increase the risk of stroke. In addition, many patients hospitalized with severe COVID-19 infection are systemically ill, often requiring mechanical ventilation and developing other risk factors for stroke, such as atrial fibrillation. Loss of olfaction may suggest that the olfactory epithelium could serve as a nose-brain entrance path for the virus, but this remains to be confirmed. Most patients with worse sense of smell do not develop severe neurological consequences, such as stroke.[4]

Taken together, the neurological symptoms among hospitalized patients with COVID-19 not only are common but may be the sole presenting feature in the disease. The rate of neurological symptoms among people who do not require hospitalization with COVID-19 is uncertain, but clinicians should consider COVID-19 as an etiology of new neurological

symptoms, especially in patients with acute onset loss of taste or smell. ■

REFERENCES

1. Yan CH, Faraji F, Prajapati DP, et al. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. *Int Forum Allergy Rhinol* 2020; April 14. doi: 10.1002/alr.22592. [Online ahead of print].
2. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020;382:e60.
3. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020; April 15. doi: 10.1056/NEJMc2008597. [Online ahead of print].
4. Marinosci A, Landis BN, Calmy A. Possible link between anosmia and COVID-19: Sniffing out the truth. *Eur Arch Otorhinolaryngol* 2020; April 17. doi: 10.1007/s00405-020-05966-0. [Online ahead of print].

ABSTRACT & COMMENTARY

Eat Flavonoids for a Healthy Brain

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

Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: An investigation of the Framingham Offspring Study revealed a higher intake of dietary flavonoids found in plants is associated with modest slowing of age-related dementia.

SOURCE: Shishtar E, Rogers GT, Blumberg JB, et al. Long-term dietary flavonoid intake and change in cognitive function in the Framingham Offspring Cohort. *Public Health Nutr* 2020;23:1576-1588.

The Framingham Offspring Study, part of the original Framingham Heart Study, began in 1971 when researchers started following 5,124 men and women who were children of the original cohort and their partners. Shishtar et al used data from the Framingham Offspring Study to determine if there is any connection between long-term intake of dietary flavonoids and a decline in cognitive function over a follow-up period of up to 15 years.

A total of 1,779 subjects ≥ age 45 years and free of dementia had attended at least two of the last three Framingham Offspring Study exams. Subjects were well-educated, reported engaging in light physical activity, and were overweight (average body mass index, 27.8 kg/m^2). The authors controlled for other variables, such as smoking and comorbidities. Subjects completed at least four validated food frequency questionnaires, which researchers used to learn more about long-term flavonoid intake. This intake was separated into four groups: 15th, 30th, median, and 60th percentiles.

Over a median follow-up of 11.8 years, the authors observed "nominally significant trends" toward a slower decline in cognitive function among those who consumed more flavonoids. Despite these trends, the authors stopped short of concluding there was a clear, direct link between consuming more flavonoids and slowing cognitive decline.

■ COMMENTARY

Flavonoids are a group of foods found in certain plants. The food frequency questionnaires used in this study included a list of 126 foods. Flavonoids were divided into recognized groups, including berries, citrus fruits (including orange juice), apples, pears, strawberries, and red wine. These foods feature antioxidant properties and can scavenge cellular breakdown products. Recent evidence shows flavonoids exert favorable cognitive effects by protecting neurons from neurotoxins and combating neuroinflammation.[1,2]

The popular American diet, loaded with excess processed carbohydrates, leads to obesity, prediabetes, and type 2 diabetes — and it certainly does no one any favors when it comes to cognition. One-third of Americans ≥ age 85 years are afflicted with Alzheimer's disease; one in three seniors die with some form of dementia.[3] A growing collection of recent work suggests better nutrition and modified lifestyle factors could prevent and even reverse cognitive decline.[4,5] Nutrition science, such as the work carried out by Shishtar et al, may be life-saving for the brain. ■

REFERENCES

1. Spencer JPE. Flavonoids: Modulators of brain function? *Br J Nutr* 2008;99:ES60-ES77.
2. Vauzour D. Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. *Oxid Med Cell Longev* 2012;2012:914273.
3. Alzheimers.net. 2019 Alzheimer's statistics. https://bit.ly/2YoDUwu
4. Bredesen DE. Reversal of cognitive decline: A novel therapeutic program. *Aging* 2014;6:707-717.
5. Sherzai D, Sherzai A. *The Alzheimer's Solution: A Breakthrough Program to Prevent and Reverse the Symptoms of Cognitive Decline at Every Age*. HarperCollins; 2017.

ABSTRACT & COMMENTARY

Benefits of Exercise in Established Atrial Fibrillation

By Michael H. Crawford, MD

Professor of Medicine, Associate Chief for Education, Division of Cardiology, University of California, San Francisco

Dr. Crawford reports no financial relationships relevant to this field of study.

SYNOPSIS: A large, long-term, prospective, Norwegian population study of patients with established atrial fibrillation revealed physical activity at or above recommended levels reduces all-cause and cardiovascular mortality vs. atrial fibrillation patients who are inactive.

SOURCE: Garnvik LE, Malmo V, Janszky I, et al. Physical activity, cardiorespiratory fitness, and cardiovascular outcomes in individuals with atrial fibrillation: The HUNT study. *Eur Heart J* 2020;41:1467-1475.

Persistent atrial fibrillation (AF) is associated with higher rates of morbidity and mortality. When AF accompanies almost every other disease, the prognosis is much worse. Physical activity (PA) is known to reduce the incidence of AF, but little is known about its value in established AF.

Garnvik et al evaluated data from the third wave of the Nord-Trøndelag Health Study (HUNT 3) from the northern region of Norway. Their goal was to assess the effect of PA and cardiorespiratory fitness (CRF) on all-cause mortality as well as cardiovascular (CV) mortality and morbidity in patients with documented AF and those free of AF. Clinical data were obtained from hospital and physician office records using standard criteria. Information on PA was obtained using a validated questionnaire, with details about frequency, intensity, and duration of exercise. Patients were classified as inactive, below recommended exercise levels, or at/above recommended exercise levels. CRF was estimated using a validated non-exercise method based on sex, age, waist circumference, resting heart rate, and PA. Patients in HUNT 3 were enrolled between 2006 and 2008 and followed until death, their first CV event, or 2015. Data analysis was adjusted for multiple clinical variables that could influence the results.

From 50,802 participants in HUNT 3, 1,117 with AF not related to an acute stressful event and with complete data were included. Approximately two-thirds of the study population were men (average age about 70 years; about 60% had persistent or permanent AF). AF patients meeting recommended PA levels recorded a significantly lower all-cause mortality rate than inactive patients (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.81-0.95), as did those with highest CRF levels vs. the lowest quartile (HR, 0.64; 95% CI, 0.47-0.89). CV mortality also was significantly lower in patients meeting or exceeding recommendations vs. inactive patients (HR, 0.54; 95% CI, 0.34-0.86) and those in the highest vs. lowest CRF quartile (HR, 0.61; 95% CI, 0.38-0.98).

CV morbidity and stroke rates were lower in patients at or above the recommended PA level and in those with higher CRF. CV mortality also was lowest with patients on moderate-intensity exercise vs. inactive patients (HR, 0.50) and vigorous activity vs. inactivity (HR, 0.70). AF patients who met recommended PA experienced similar rates of all-cause mortality, CV mortality, and stroke as inactive, non-AF patients. Sensitivity analyses showed the benefits of PA were not significant in obese patients (body mass index > 30 kg/m^2). Men benefitted more from higher CRF than women. The authors concluded that higher PA and CRF reduced the long-term risk of all-cause and CV mortality in patients with AF.

■ COMMENTARY

The health benefits of PA and enhanced CRF has been shown in healthy populations and certain disease states (e.g., post-myocardial infarction). Also, recent studies have shown PA and CRF can prevent AF, but there are few data about their effects on established AF. Nevertheless, this is important because the symptoms of AF, medications used, and comorbidities often discourage patients from exercising. That is why this study is of interest. Norway would seem to be ideal for a study like the one Garnvik et al conducted. One might expect the prevalence of AF to be high since the genetic component of AF is most common in those of Northern European descent. Additionally, Norway's national health system mandates the reporting of patient outcomes. Finally, Norwegians seem to enjoy participating in such studies because > 50% of the entire population of Nord-Trøndelag County participated in the HUNT 3 investigation. Other strengths of the Garnvik et al study included the prospective design and the long-term follow-up of about eight years. Finally, the diagnosis of AF was well validated.

There were several limitations, most importantly the association between PA/CRF and lower all-cause and CV mortality rates does not confirm causality, nor does it elucidate the mechanism of any potential benefits observed. AF may just be a marker for CV disease. Also,

it is unclear whether the PA reported was occurring before or after the AF diagnosis. PA may just be a continuation of a patient's routine. Thus, prescribing exercise to a sedentary patient may not be effective. Other limitations included the fact that PA was self-reported and CRF was estimated rather than measured. The formula to estimate CRF includes resting heart rate, which could be problematic in AF. The authors did not report any data on medications or the progression of AF over time. The low rate in women, about one-third of the study population, is concerning since this would not be expected.

Despite these limitations, the results of this study support a role for regular PA and improved CRF in AF patients to help prevent the reported higher incidence of morbidity and mortality. Those AF patients who engaged in the most strenuous PA/CRF recorded event-free survival curves that approximated the inactive members of the non-AF general population. ■

ABSTRACT & COMMENTARY

Clostridioides difficile: Risk Factors for Disease

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Approximately one-tenth of asymptomatic patients with *Clostridioides difficile* colonization went on to develop disease. A wide range of antibiotic exposures represent a significant risk.

SOURCES: Poirier D, Gervais P, Fuchs M, et al. Predictors of *Clostridioides difficile* infection among asymptomatic, colonized patients: A retrospective cohort study. *Clin Infect Dis* 2020;70:2103-2210.

Webb BJ, Subramanian A, Lopansri B, et al. Antibiotic exposure and risk for hospital-associated *Clostridioides difficile* infection. *Antimicrob Agents Chemother* 2020;64(4). pii: e02169-19.

A retrospective examination by Webb et al of patients with *Clostridioides difficile* infection (CDI) in InterMountain Healthcare Hospitals from 2006 to 2012 identified multiple risk factors by multivariate analysis. These factors included prior exposure to each of a wide range of antibiotics (approximately 20). The antibiotics posing the greatest risk were cephalosporins (beyond first-generation), carbapenems, fluoroquinolones, and clindamycin. The odds ratios for daptomycin and doxycycline were < 1.0, suggesting a possibly protective effect. Perhaps the most interesting result in the study was the finding that antibiotics received in the 60 days before hospital admission (often during a prior hospitalization) posed a greater risk than antibiotics administered during the index hospitalization, with the risk increasing by 12.8% for every day of prior antibiotic exposure.

The recognition of asymptomatic colonization of new hospital admissions by *C. difficile* has raised important questions regarding the risk of disease development. Beginning in November 2013, the Quebec Heart and Lung Institute began screening all admissions for evidence of asymptomatic colonization with *C. difficile* by detection of the *tcdB* gene by polymerase chain reaction (PCR), with isolation of all who had a positive test. By January 2017, they identified colonization in 960 of 19,112 admissions. Sixty-three percent received at least one dose of a systemically administered antibiotic, with a median duration of receipt of seven days.

Of the 513 colonized individuals who met criteria for inclusion in their study, 39 developed hospital-onset CDI at a median of four days after admission, although in one-fifth the diagnosis was based on new diarrhea and a positive admission test without repeat testing. The attributable mortality was 15%. Another 17 patients were deemed to have developed CDI after discharge, bringing the total number of colonized individuals who developed disease to 56. Exposures to β-lactam/β-lactamase inhibitors (BL/BLI), second-generation cephalosporins, and carbapenems, as well as exposures to multiple antibiotic classes, were associated with an increased risk of CDI. Additional risk factors were cirrhosis, use of opioids, and longer length of stay. Notably, the use of proton pump inhibitors was not found to be a risk factor, nor was the administration of antibiotics aimed to prevent the development of CDI, although the number of patients in this group was small.

■ COMMENTARY

All studies of risk factors for CDI have several limitations, beginning with the variable means of diagnosis. That is true regarding the two papers reviewed here.

In the study by Poirier and colleagues, the range of intervals from admission testing to onset of CDI was apparently 1-27 days, meaning that some cases with "hospital-onset" disease likely were incubating the illness at the time of hospital entry. Poirier et al also did not provide information regarding antibiotic exposure prior to hospitalization.

In fact, antibiotic exposure in the 60 days before hospitalization under examination was identified as an important risk factor in unscreened admissions by Webb et al. As many others have, Poirier et al identified exposure to BL/BLI, cephalosporins, and carbapenems as risk factors, while Webb et al found almost any antibiotic (with the exceptions of daptomycin and doxycycline) potentially was implicated. The lesson is that a focus on reducing the use of individual antibiotics is an inadequate approach, and that all unnecessary antibiotic use must be targeted. In patients admitted to hospitals where screening for colonization is performed, special antibiotic stewardship attention could be directed at those whose tests are positive. ■

PHARMACOLOGY UPDATE

Insulin Lispro-aabc Injection (Lyumjev)

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.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The Food and Drug Administration (FDA) has approved a new rapid-acting human insulin analog. Insulin lispro-aabc (ILispro-a) is a novel formulation of insulin lispro that speeds absorption from the subcutaneous injection sites. It will compete with currently available rapid-acting insulin: insulin lispro (Humalog), insulin glulisine (Apidra), insulin aspart (NovoLog), and the "faster" version of insulin aspart (Fiasp). ILispro-a is marketed as Lyumjev.

INDICATIONS

ILispro-a is indicated to improve glycemic control in adults with diabetes mellitus.[1]

DOSAGE

ILispro-a is given subcutaneously at the start or within 20 minutes after starting a meal.[1] Injection sites include the abdomen, upper arm, thigh, or buttocks. The dosage is individualized based on the patient's metabolic needs, glucose monitoring results, and level of glycemic control.[1] ILispro-a is available as 100 units/mL (10 mL vials, 3 mL single-use pens and cartridges) and 200 units/mL (3 mL single-use pens).

POTENTIAL ADVANTAGES

ILispro-a is formulated to speed the absorption of insulin lispro from the injection site into the blood stream. The formulation uses a microdose of treprostinil, a prostacyclin analog vasodilator, and sodium citrate that may enhance vascular permeability.[2] ILispro-a absorbs faster vs. insulin lispro and insulin aspart, as well as "faster" insulin aspart.[3] This corresponded to significant postprandial glucose-lowering vs. insulin-lispro and insulin aspart, but not "faster" insulin aspart.

POTENTIAL DISADVANTAGES

ILispro-a is not FDA-approved for use in children and is not approved for use in insulin pumps.

COMMENTS

The efficacy of ILispro-a was evaluated in a randomized, active-controlled, non-inferiority, 26-week, treat-to-target trial in adult type 1 diabetics (T1D) as well as a study of type 2 diabetics (T2D).[1] In the T1D study, subjects were a mean age of 44 years, their mean duration of diabetes was 19 years, 56% were male, 77% were white, and mean body mass index (BMI) was 25.5 kg/m^2. Researchers randomized subjects to mealtime ILispro-a (451 subjects), mealtime insulin lispro (442 subjects), or open-label postmeal ILispro-a (329 subjects). Mealtime administration was zero to two minutes before the meal. Postmeal administration was 20 minutes after the start of the meal. All subjects were on basal insulin (either insulin glargine or degludec). The primary endpoint was change from baseline in hemoglobin A1c (HbA1c) at week 26. The inferiority margin was prespecified at 0.4%. At week 26, mealtime ILispro-a showed a mean reduction in HbA1c of 0.12% (baseline, 7.3%) compared to -0.04% for mealtime insulin lispro (baseline, 7.3%), and +0.1% for postmeal ILispro-a (baseline, 7.4%). Both ILispro-a arms met the criteria for noninferiority vs. insulin lispro. In the T2D study, subjects were a mean age of 61 years, 53% were male, 69% were white, their mean disease duration was 17 years, and their BMI was 32.3 kg/m^2. Subjects were randomized to mealtime ILispro-a (n = 336) or mealtime lispro (n = 337). At week 26, the mean reduction in HbA1c was -0.36% vs. -0.38%, respectively, from a mean baseline of 7.3%, similarly meeting noninferiority criteria vs. insulin lispro.

CLINICAL IMPLICATIONS

The goal for development of rapid-acting insulin analogs is to mimic mealtime endogenous insulin. Insulin lispro was first approved in 1996, followed by insulin aspart (2000), insulin glulisine (2004), and "faster" insulin aspart (2017). The three newer rapid-acting insulins, including ILispro-a, generally feature improved pharmacokinetics (faster onset) and improved pharmacodynamics (better postprandial glucose excursion) vs. the older two, and are significantly faster than subcutaneously human insulin analog.[3-5] However, the improved pharmacokinetic (PK) and pharmacodynamics (PD), in general, have not translated into significant improvements in glycemic control (i.e., HbA1c) among the rapid-acting insulins and compared to regular human insulin when these are used with basal insulin.[4] In T1D patients, rapid-acting insulin may reduce severe hypoglycemia vs. regular insulin, but less so in T2D patients in whom the incidence generally is much lower.[4] ILispro-a is the latest rapid-acting insulin with superior PK/PD characteristics vs. the slowest of the rapid-acting insulin (lispro). However, ILispro-a only showed noninferiority in terms of glycemic control. There is no clinical evidence showing ILispro-a will offer any advantage over the other rapid-acting insulins. The cost for ILispro-a is the same as for insulin lispro and priced at $274.70 for a 10 mL vial (U-100) vs. $284 for insulin glulisine and $289.30 for "faster" insulin aspart. ■

REFERENCES

1. Eli Lilly. Lyumjev prescribing information. June 2020. https://bit.ly/2NYDWFB
2. Eli Lilly. A study to evaluate the pharmacokinetics and glucodynamics of LY900014 compared to Humalog in children, adolescents, and adults with type 1 diabetes mellitus. July 18, 2018. https://bit.ly/2Ay9dvM
3. Heise T, Linnebjerg H, Coutant D, et al. Ultrarapid lispro lowers postprandial glucose and more closely matches normal physiological glucose response compared to other rapid insulin analogues: A phase 1 randomized, crossover study. *Diabetes Obes Metab* 2020; May 21. doi: 10.1111/dom.14094. [Online ahead of print].
4. Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabetes Obes Metab* 2012;14:780-788.
5. Haahr H, Heise T. Fast-acting insulin aspart: A review of its pharmacokinetic and pharmacodynamic properties and the clinical consequences. *Clin Pharmacokinet* 2020;59:155-172.

CME QUESTIONS

1. **A 65-year-old man presents with one to two days of anorexia and fatigue followed by acute sudden onset left hemiparesis. He denies cough, fever, or shortness of breath. His vital signs are normal. Which statement is most accurate?**
   a. Stroke can be an initial manifestation of COVID-19, and most patients with stroke will have non-severe respiratory disease.
   b. Stroke can be an initial manifestation of COVID-19, and most patients with stroke will have severe respiratory disease.
   c. Stroke can be an initial manifestation of COVID-19 without any other symptoms.
   d. Stroke occurs as a late manifestation of COVID-19.

2. **What food includes flavonoids, which may prevent dementia?**
   a. Berries
   b. Salmon
   c. Coconut
   d. Turkey

3. **Which receptor facilitates the entry of the SARS-CoV-2 virus into the cell?**
   a. Angiotensin-converting enzyme 1 receptors
   b. Testosterone receptors
   c. HER-2 receptors
   d. TMPRSS2 receptors

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.