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ABSTRACT & COMMENTARY

Calcitonin Gene-Related Peptide Targeting Therapies for Migraine

By Matthew S. Robbins, MD, FAAN, FAHS

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

SYNOPSIS: Two randomized clinical trials showed that calcitonin gene-related peptide targeting therapies are effective and safe for primary headache disorders.

SOURCES: Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med* 2019;381:132-141.

Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med* 2019;381:142-149.

Goadsby et al conducted a multicenter, randomized, controlled trial (RCT) of galcanezumab, a monoclonal antibody targeting calcitonin gene-related peptide (CGRP), for the prevention of episodic cluster headache (CH). Patients 18 to 65 years of age had to present with pre-existing CH with bouts lasting for at least six weeks. They were treated with either galcanezumab 300 mg subcutaneously or placebo. Patients could not use contemporaneous prophylaxis but could use common acute attack therapies, such as triptans and oxygen. After a screening interval and a prospective baseline period lasting 10-15 days, the eight-week treatment regimen began, featuring galcanezumab administration at treatment onset and at month one.

Trial enrollment was curtailed because of too few subjects in an active CH period. Ultimately, 57 subjects were treated with placebo and 49 subjects with galcanezumab, without major baseline differences between the two groups. For the primary endpoint, subjects who were treated with galcanezumab exhibited an 8.7 ± 1.4 reduction in weekly cluster headache attack frequency across weeks 1 through 3

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vs. 5.2 ± 1.3 in the placebo group (95% confidence interval, 0.2-6.7; $P = 0.04$). The 50% attack frequency reduction rate at week 3 was 71% for galcanezumab vs. 53% for placebo ($P = 0.046$). Efficacy rates in the second month converged across the groups. No serious adverse events were reported, with injection site reactions reported most commonly. Drug discontinuations were rare.

In another study, Lipton et al conducted a large, multicenter RCT of a single dose of rimegepant, an oral CGRP receptor antagonist, for the acute treatment of migraine. The study included more than 1,000 subjects 18 years of age and older with two to eight migraine attacks monthly, excluding patients who would satisfy criteria for chronic migraine. There were no differences in baseline characteristics between the subjects receiving rimegepant 75 mg (n = 537) and placebo (n = 535).

For the first primary endpoint, patients receiving rimegepant reported higher rates of two-hour pain freedom than those receiving placebo (19.6% vs. 12.0%; $P < 0.001$). For the second primary endpoint, patients receiving rimegepant showed higher rates of two-hour most bothersome symptom freedom (mostly photophobia) than those receiving placebo (37.6% vs. 25.2%; $P < 0.001$).

Serious adverse events were rare and included one patient with back pain in the rimegepant group, one patient with chest pain in the placebo group, and one patient with a urinary tract infection (UTI) in the placebo group. Overall, adverse events were uncommon (nausea and UTI were the most frequently reported adverse events).

■ COMMENTARY

These two landmark articles document safe and effective treatments for primary headache disorders. Both treatments target CGRP, either via monoclonal antibody to the ligand itself (galcanezumab) or small molecule receptor antagonist (rimegepant). It is clear that CGRP is pivotally involved in headache pathophysiology in both the peripheral and central nervous systems. Presumably, the site of action of galcanezumab is peripheral, based on limited ability to cross the blood brain barrier, although rimegepant may act both peripherally and centrally. This study led galcanezumab to become the first-ever FDA-approved preventive treatment for CH, although in a separate study it did not demonstrate efficacy for chronic CH. Further, fremanezumab, another monoclonal antibody to the CGRP ligand, did not demonstrate efficacy in trials for episodic and chronic CH. This distinguishes CH from migraine, where CGRP-based therapies have shown consistent efficacy across drugs and migraine spectrum severity (episodic and chronic).

[These two landmark articles document safe and effective treatments for primary headache disorders.]

Previous guidelines show a major gap in preventive treatment for CH, which has a 1/1,000 lifetime prevalence. Whether galcanezumab can supplant verapamil, the most commonly used CH treatment believed to be the most effective, is unclear; certainly, cost and access will be major factors. Its potentially short treatment latency may place it at an advantage, reducing the need for simultaneous short-term preventive treatment such as oral steroids or greater occipital nerve injection.

Rimegepant, and potentially other gepants, will prove to be an additional treatment option for patients to treat acute migraine attacks, although efficacy rates seem to be similar to triptans and other acute treatments. Still, tolerability, apparent lack of contraindications (particularly cardiovascular), and lack of evidence for an association with medication overuse may place gepants at a distinct advantage over triptans. Gepants also may be more tolerable than lasmiditan, another triptan alternative (a 5HT1F receptor agonist that likely will receive FDA approval soon).

Long-term safety, tactics for repeat dosing, cost, and access will be major factors influencing rimegepant's clinical practice niche, as may be safety with simultaneous CGRP targeting monoclonal antibodies. ■

ABSTRACT & COMMENTARY

Treating Infective Endocarditis in Moderate-Risk Patients

By Michael Crawford, MD

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

SYNOPSIS: There are patients with a moderate risk of infective endocarditis who may warrant consideration of antibiotic prophylaxis.

SOURCE: Østergaard L, Valeur N, Wang A, et al. Incidence of infective endocarditis in patients considered at moderate risk. *Eur Heart J* 2019;40:1355-1361.

U.S. guidelines recommend antibiotic prophylaxis for patients at high risk for infective endocarditis (IE). The authors of recent studies have identified patients at moderate risk, but the magnitude of this risk is unclear. Investigators analyzed Danish national patient registries to determine the incidence of IE in patients considered moderate risk.

Moderate-risk patients were defined as those with acyanotic congenital heart valve disease, acquired valve disease, hypertrophic cardiomyopathy (HCM), mitral valve prolapse or regurgitation, and implanted cardiac electrical devices. Each diagnostic category was compared to matched controls without any of these conditions. Researchers also examined patients with prosthetic heart valves as a high-risk comparator group. Patients were followed until another moderate- or high-risk condition developed or 10 years passed. The primary outcome was hospital admission for IE.

Østergaard et al identified 83,453 patients with a left-sided valve disorder, 50,828 with an implanted electrical device, and 3,620 with HCM for a total of 137,901 patients. The median follow-up was 3.7 years. There was a 0.9% incidence of IE in left heart valve disorders, 1.3% in electrical devices, and 0.5% in HCM. Compared to controls, these three conditions led to a higher risk of IE (hazard ratio [HR], 8.75, 6.63, and 6.57, respectively), but were lower than the risk in high-risk patients (HR, 0.27, 0.28, and 0.13, respectively). Further, the 10-year mortality rate was higher in these three groups vs. controls ($P < 0.0001$). Similar findings were present when those with acyanotic congenital heart valve defects were analyzed. The authors concluded that the cumulative risk of IE in moderate-risk patients at 10 years was about 1%, which was higher than controls but lower than the high-risk population (4.8%).

■ COMMENTARY

The authors of a recent paper from England[1] identified patient groups at moderate risk for IE, which Østergaard et al corroborated in this study. However, Østergaard et al quantitated the risk as compared to an age- and sex-matched control population and included considerably more clinical details, making comorbidity adjustments more robust. In addition, these authors compared the incidence rates to those of a high-risk subgroup with prosthetic valves. They identified the following moderate-risk groups: left heart valve disease, HCM, and implanted electrical devices. They provided robust data on the these conditions, which showed incidence rates of about 1% (one-fifth to one-quarter the rate in patients with prosthetic valves). Thus, these were truly moderate-risk groups.

Is a 1% risk of IE enough to give antibiotic prophylaxis to everyone in these groups? The authors of the current guidelines thought not, but perhaps there are subgroups who would benefit. For this question, Østergaard et al provided some granularity that could be helpful. For example, they found that implanted defibrillators led to higher rates of IE compared to pacemakers. However, those with any device with more than one lead were at higher risk than those with single-lead devices. Other studies have shown that bicuspid aortic valves and moderate or more regurgitation of a left-sided valve increases the risk of IE. Østergaard et al did not provide these data. Also, other studies have shown that HCM with obstruction is higher risk than without obstruction; again, these authors could not confirm this.

There were other limitations to the Østergaard et al study. The authors lacked autopsy data, which could have reduced IE incidence rates. They did not have data on whether IE was left- or right-sided, nor were there any bacteriologic data. Of course, since this was a retrospective database study, there could have been unmeasured confounders.

Does this study inform my decisions on antibiotic prophylaxis to prevent IE? Yes, it does. It reinforces the prior studies that showed there were moderate-risk patients at significant risk, such as those with left heart valve disease, HCM, and implanted electrical

devices. However, it probably is not reasonable to provide prophylaxis to all these patients. As other studies have shown, those with moderate or more regurgitation, bicuspid aortic valves, or obstructive HCM (who probably also have significant mitral regurgitation) certainly are worth considering for antibiotic prophylaxis. The electrical device situation is more complex, as few single-lead devices are placed in the United States now. Most pacemaker patients could be candidates for prophylaxis. Also, lead-related IE is difficult to diagnose, and the consequences of lead IE could be dire for the patient. Thus, I am inclined to recommend prophylaxis for multilead defibrillator and biventricular pacemaker patients, but perhaps not dual-chamber pacemaker patients who are uncomplicated. ■

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ABSTRACT & COMMENTARY

CRP and Reduction of Antibiotic Use in Acute Exacerbations of COPD

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: Point-of-care C-reactive protein testing can safely and effectively reduce antibiotic use in patients with acute exacerbations of COPD.

SOURCE: Butler CC, Gillespie D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med* 2019;381:111-120.

Butler et al examined the value of point-of-care C-reactive protein (CRP) testing to guide the need for antibiotic therapy in patients > 40 years of age with exacerbations of COPD. To this end, they performed a randomized, open-label, controlled trial at 86 general practices in the United Kingdom. An exacerbation was defined as the presence of at least one of the widely used Anthonisen criteria: increased breathlessness, increased sputum volume, or increased sputum purulence. Subjects were randomized to usual care alone or usual care guided by CRP testing.

Participating clinicians received guidance for the interpretation of CRP results, indicating that antibiotic therapy was unlikely to be beneficial and ordinarily should not be prescribed if the value was < 20 mg/L, that it was likely to be beneficial if CRP was > 40 mg/L, and that it may be beneficial for those with intermediate levels, particularly if purulent sputum is present. Clinicians also were told that general clinical factors should be considered in decisions about antibiotic use. The median CRP in the 317 patients randomized to the usual care plus CRP group and in whom the test was performed was 6 mg/L, with 241 < 20 mg/L, 38 were 20-40 mg/L, and 38 were > 40 mg/L. At the initial consultation, antibiotics were prescribed to 47.7% and 69.7% in the CRP-guided and usual care alone groups, respectively (adjusted odds ratio, 0.31; 95% confidence interval [CI], 0.21-0.45). Overall antibiotic use in the four weeks after randomization (a coprimary endpoint) was reported by 57% in the CRP group, while it was 77.4% in the usual care group (adjusted odds ratio, 0.31; 95% CI, 0.20-0.47). At two weeks, the adjusted mean difference in the Clinical COPD Questionnaire score was -0.19 points (two-sided 90% CI, -0.33 to -0.05) in favor of the group guided by CRP testing, demonstrating, at a minimum, a lack of harm from this approach.

■ COMMENTARY

Considering the frequency of COPD occurrence, it is somewhat disturbing that our knowledge of the role of antibiotics in the management of exacerbations seems so limited and confused. As stated in Murray and Nadel's *Textbook of Respiratory Medicine*, "The use of antibiotics for exacerbations of COPD is somewhat controversial." The authors of a recent Cochrane Review, while agreeing that antibiotics are beneficial in patients who require intensive care admission, concluded that the effects of antibiotic therapy on other inpatients and on outpatients are small and "inconsistent for some outcomes (treatment failure) and absent for other outcomes (mortality, length of hospital stay)."[1]

In previous studies, researchers have examined the use of procalcitonin measurements in these exacerbations. Thus, the authors of a meta-analysis concluded that although the quality of the available evidence was only low to moderate due to methodological limitations and small populations, the use of procalcitonin-based

protocols was associated with reduced antibiotic use.2 On the other hand, the authors of a retrospective study of 203,177 patients hospitalized for management of COPD exacerbations concluded that procalcitonin measurement had little effect on decisions to initiate antibiotic therapy.[3] Researchers also have studied the use of a comprehensive viral respiratory panel for which there is evidence of potential benefit.[4]

The study by Butler et al is welcome in shedding a light on this subject. Their work demonstrates that point-of-care CRP testing can be used effectively and safely to reduce antibiotic use in patients with acute exacerbations of COPD. Further exploration of predictors of antibiotic benefit and work aimed at improving prescribers' behavior must follow. The issue of the importance of altering prescriber behavior is evident in the study by Butler et al since almost half of patients with low CRP levels nonetheless received prescriptions for antibiotic therapy. ■

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ABSTRACT & COMMENTARY

No Antibiotic Prescription Required

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: Acquisition of antibiotics without a prescription can be easy in the United States.

SOURCE: Grigoryan L, Germanos G, Zoorob R, et al. Use of antibiotics without a prescription in the U.S. population: A scoping review. *Ann Intern Med* 2019; Jul 23. doi: 10.7326/M19-0505. [Epub ahead of print].

Grigoryan et al performed a scoping review to assess the prevalence and factors influencing the use of antibiotics without a prescription in the United States. The purpose of a scoping review is to identify and map the available evidence at a time while the latter remains in flux.[1] As the evidence matures, a systematic review becomes more appropriate.

Only 31 of 17,422 screened articles met inclusion criteria for review. Venues where antibiotics were acquired included flea markets, pet stores, botanical stores, health food stores, and online sources. Additional sources were family and friends, markets or stores, leftover prescribed antibiotics, and other countries. Four populations were studied: patients or parents outside healthcare systems, those within healthcare systems, Hispanics/Latinos, and injection drug users. The prevalence of nonprescribed antibiotic use was highly heterogeneous, ranging from 1% to 68%, as was the intent to store an antibiotic for future use, which varied from 14% to 48%. Among patients in a primary care practice, 25% intended to use antibiotics without a prescription. Factors that were reported to contribute to nonprescription antibiotic use were easy access to stores and markets that obtain antibiotics from outside the United States for under-the-counter sales, difficulties in accessing the healthcare system, costs and long wait times associated with visits to clinicians, and transportation difficulties.

■ COMMENTARY

In 2002, a reporter for *The New York Times* interviewed Marina Aguilera in her New York City West 135th Street apartment as she held a package of ampicillin tablets in her hand.[2] Aguilera, like many other Dominicans in her neighborhood, purchased them over-the-counter at her local bodega — no prescription needed. She said she took them for sore throats, earaches, chest pains, and bad colds, but she is doubtful that they are helpful in treating headaches.

This scoping review provided an estimate of the prevalence of the use of antibiotics absent a prescription and, more importantly, pointed to potential interventions to reduce nonprescription antibiotic use. Many of these undoubtedly apply in low- and middle-income countries in which evidence indicates that the high copays for drugs in the public sector, together with a requirement for prescriptions, may drive patients to settings where there is an incentive to provide such prescriptions.[3] The

likelihood of antibiotic overuse in that circumstance is consistent with the investigators' finding that high drug copays are associated with a significantly increased prevalence of antibiotic resistance. ■

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ABSTRACT & COMMENTARY

Carpal Tunnel Syndrome in the Extreme Elderly

By Michael Rubin, MD

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Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: Carpal tunnel syndrome (CTS), when seen in the very elderly, usually is severe and is not reliably diagnosed by ultrasound. Nerve conduction studies and electromyography are the most sensitive and specific tests to make accurate diagnosis of CTS.

SOURCE: Mulroy E, Pelosi L. Carpal tunnel syndrome in advanced age: A sonographic and electrodiagnostic study. *Muscle Nerve* 2019; Apr. 26. doi: 10.1002/mus.26496. [Epub ahead of print].

Affecting 1-5% of the population, with a 3:1 female:male ratio, carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, occurring most often in obese women, and least often in thin men. Diabetes, hypothyroidism, and rheumatoid arthritis, as well as pregnancy and aromatase inhibitors, are associated with CTS, but evidence that age plays a factor is controversial. Diagnosis usually is confirmed by electrodiagnostic studies, with ultrasonography showing a significantly increased cross-sectional area of the median nerve compared to controls, offering a painless way of making the diagnosis. However, ultrasound may not be reliable in the very elderly.

Data from all patients referred to the Department of Clinical Neurophysiology, Auckland, New Zealand, between May 2014 and May 2015, who had undergone both electrodiagnostic and ultrasonographic studies of the median nerve were reviewed retrospectively and divided selectively into two age groups: 40-65 years and 80-95 years. Electrodiagnostic studies conformed to recommendations of the American Association of Neuromuscular & Electrodiagnostic Medicine, and, to minimize operator bias, in all instances were preceded by ultrasound evaluation of the median nerve, performed by the same operator, consisting of evaluating the maximum median nerve cross-sectional area at the wrist as well as wrist-to-forearm ratio. Statistical analysis comprised Pearson's correlation coefficient and Shapiro-Wilk and Student t-tests. Among a total of 92 patients and 110 hands included in the study, 59 were 40-65 years of age and 33 were 80-95 years of age. CTS was more severe, both clinically and electrodiagnostically, in the very elderly, whereas, paradoxically, maximal median nerve cross-sectional area at the wrist was significantly larger in the younger group.

Additionally, as CTS severity worsened in the younger group, so too did maximal median nerve cross-sectional area increase at the wrist, whereas this correlation was not seen in the elderly group. Mid-forearm median nerve cross-sectional area was similar in both age groups. Sensitivity of nerve ultrasound was significantly lower in the elderly group, with 46% of clinically abnormal hands and 39% of electrodiagnostically abnormal hands exhibiting normal ultrasound median nerve cross-sectional area measurements.

No correlation was found in the elderly group between ultrasound and electrodiagnostic measurements. Electrodiagnostic testing was 100% sensitive in both groups with clinically moderate or severe CTS.

■ COMMENTARY

Despite a high prevalence, the etiology of CTS often remains uncertain. In 2002, a twin study in the United Kingdom suggested that the strongest risk factors for CTS in women were genetic.[1] Recently, the authors of a genome-wide association study, using 12,312 CTS cases and 389,344 controls from in the UK Biobank resource, identified 16 novel susceptibility loci for CTS, suggesting that genetic variants implicated in skeletal growth and extracellular matrix architecture alter the

environment through which the median nerve traverses, thus predisposing to CTS. Mendelian randomization analysis revealed a causal association between short stature and a higher risk for CTS, with CTS patients, on the average, 2 cm shorter than controls. Connective tissue abnormalities appear causally connected to carpal tunnel syndrome.[2] ■

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PHARMACOLOGY UPDATE

Darolutamide Tablets (Nubeqa)

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

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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 FDA has approved another androgen receptor inhibitor for nonmetastatic, castration-resistant prostate cancer. Darolutamide is the third to be approved, following apalutamide and enzalutamide, for this indication. Notably, darolutamide is chemically distinct from apalutamide and enzalutamide. The FDA granted fast-track designation and priority review. Darolutamide tablets will be distributed as Nubeqa.

INDICATION

Darolutamide should be prescribed to patients with nonmetastatic, castration-resistant prostate cancer.[1]

DOSAGE

The recommended dose is 600 mg (2 × 300 mg) taken orally twice daily with food.[1] Darolutamide is available as 300 mg tablets.

POTENTIAL ADVANTAGES

In vitro and mice studies suggest that darolutamide may be effective against enzalutamide-resistant prostate cancer and mutated forms of the androgen receptor.[2,4] Darolutamide produces minimal blood-brain barrier penetration and minimal effect on serum testosterone levels.[3,4] Also, darolutamide carries lower potential for overall drug-drug interactions involving CYP isoenzymes.[1,5,6] It does not carry the same class warning for seizures, falls, and fractures as enzalutamide and apalutamide.

POTENTIAL DISADVANTAGES

The most frequently reported adverse reactions (vs. placebo) include fatigue (16% vs. 11%), reduced neutrophil counts (20% vs. 9%), elevated AST (23% vs. 14%), and elevated bilirubin levels (16% vs. 7%).[1] In darolutamide-treated subjects, dosage interruption occurred in 13%, dosage reduction in 6%, and permanent discontinuation in 9%.[1] Darolutamide shares the class warning for embryo-fetal toxicity.[1] Men with female partners of reproductive potential should use effective contraception during treatment and for one week after the last dose. Concomitant use of combined P-glycoprotein and strong or moderate CYP3A4 inducers should be avoided.[1] Concomitant use with breast cancer-resistant protein substrates (e.g., rosuvastatin) increases their systemic exposure.[1]

COMMENTS

The safety and efficacy of darolutamide was evaluated in a double-blind, placebo-controlled trial that included subjects with nonmetastatic, castration-resistant prostate cancer with prostate-specific antigen doubling time (PSADT) of ≤ 10 months.[1,7] Subjects were randomized to darolutamide (600 mg twice daily; n = 955) or placebo (n = 554). The median PSADT was 4.5 months; 73% of subjects received prior antiandrogen treatment (bicalutamide or flutamide), 42% had undergone surgery or radiotherapy to the prostate, and 73% had a Gleason Score of ≥ 7 at diagnosis. The primary efficacy endpoint was metastatic-free survival (MFS; time from randomization to radiographic progression or as the time to death without radiographic progression). Secondary endpoints included overall survival and time to pain progression. Median MFS was 40.4 months for darolutamide subjects and 18.4 months for placebo subjects (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.34-0.50). Benefit was observed regardless of PSADT status (≤ 6 months or > 6 months). The first interim analysis suggested lower risk of death (HR, 0.71; 95% CI, 0.50-0.99). However, median survival has not been reached. Also, there was longer time to pain progression (40.3 months vs. 25.4 months; HR, 0.65; 95% CI, 0.53-0.79).

The primary outcomes (MFS) were similar to those outcomes reported for apalutamide (40.5 months vs. 16.2 months; HR, 0.28; 95% CI, 0.23-0.35) and enzalutamide (36.6 months vs. 14.7 months; HR, 0.29;

95% CI, 0.24-0.35).[8,9] Fracture and fall rates were similar to placebo (4.2% vs. 3.6% for fracture; 4.2% vs. 4.7% for falls).[7] In contrast, fracture and fall rates were numerically higher than placebo for apalutamide (6.3% vs. 4.6% for fracture; 7.4% vs. 7.0% for falls) and enzalutamide (combined nonpathologic fractures and falls 17% vs. 8%).[8,9]

CLINICAL IMPLICATIONS

Prostate cancer is the most commonly diagnosed solid tumor and is the second leading cause of cancer deaths among U.S. men.[10] Generally, androgen deprivation is standard treatment (medical or surgical castration). However, despite castrate levels of testosterone, most cancers eventually become castration-resistant. Nonmetastatic, castration-resistant prostate cancer represents a small portion of advanced prostate cancers.

Darolutamide is the third agent approved for this cancer; all three options are recommended by the National Comprehensive Cancer Network (version 4.2019) for those with PSADT of ≤ 10 months and no or minimal symptoms. Darolutamide may be better tolerated, but its role in enzalutamide- or apalutamide-resistant cancer remains to be confirmed through further clinical trials.

Darolutamide costs $11,550 for a 30-day supply, which is similar to enzalutamide ($11,549) and apalutamide ($11,673). ■

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CME QUESTIONS

1. Which statement regarding galcanezumab is correct?
a. Galcanezumab has shown efficacy in the treatment of chronic cluster headaches.
b. Galcanezumab showed no benefit in reducing the frequency of cluster attacks.
c. Galcanezumab is FDA-approved for prevention of episodic cluster headaches.
d. Galcanezumab is effective in treating all headache types.

2. The highest risk of infective endocarditis is in patients with:
a. a prosthetic heart valve.
b. left-sided valve disease.
c. hypertrophic cardiomyopathy.
d. an implanted electrical device.

3. Which is correct regarding point-of-care C-reactive protein (CRP) testing in patients with acute exacerbations of COPD?
a. Withholding antibiotics based on a low CRP level (< 20 mg/L) is associated with an increased risk of subsequent hospitalization.
b. Its measurement is associated with an increased use of antibiotics.
c. Its measurement is associated with reduced antibiotic use.
d. Withholding antibiotics based on a low CRP level is associated with a subsequent worse Clinical COPD Questionnaire score.