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ABSTRACT & COMMENTARY

THC-Related Neuropsychiatric Symptoms in Older Adults

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SYNOPSIS: Using cannabis-based medicine often exposes patients to delta-9-tetrahydrocannabinol (THC), which is associated with psychotic symptoms. THC also can cause lightheadedness, dizziness, and thinking or perception disorder in older adults.

SOURCE: Velayudhan L, McGoohan KL, Bhattacharyya S. Evaluation of THC-related neuropsychiatric symptoms among adults aged 50 years and older: A systematic review and metaregression analysis. *JAMA Netw Open* 2021;4:e2035913.

In recent years, the use of cannabis-based medicines (CBMs) has increased substantially, with a growing number of U.S. states allowing CBMs for medical conditions.[1] These conditions often affect older adults and include a variety of chronic diseases, such as Parkinson's disease, Alzheimer's disease, cancer pain, and chemotherapy-induced nausea and vomiting. Active ingredients in cannabis include delta-9-tetrahydrocannabinol (THC), which can induce psychotic symptoms, memory impairment, and anxiety, and cannabidiol (CBD), which is not addictive and can possibly ameliorate the psychotic effects of THC.[2] Although investigations of CBMs continue, these studies generally include small sample sizes and the authors use different formulations of CBMs (consisting of various combinations of THC and CBD), often preventing clear conclusions about efficacy of these treatments.[3]

While the occurrence of psychotic symptoms from THC-containing CBMs is well established in younger individuals, effects on older adults are less understood.[1,4]

In a recent systematic review and metaregression analysis, Velayudhan et al evaluated randomized studies (published from January 1990 to October 2020) of THC-containing CBM use in people age 50 years and older to determine any associations with neuropsychiatric effects. The authors identified 30 randomized, controlled trials (RCTs) using THC-only CBMs and 24 RCTs using CBD and THC combinations. There were 1,417 patients in intervention groups and 1,210 patients in control groups for the THC-only RCTs. There were 1,917 patients in intervention groups and 1,835 patients in control groups for the CBD and THC combination RCTs.

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Internal Medicine
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In the THC-only studies, higher THC doses were significantly associated with an increase in dizziness or lightheadedness (incident rate ratio estimate, 0.05; 95% CI, 0.02-0.08; $P = 0.001$) and an increase in thinking or perception disorder (incident rate ratio estimate, 0.07; 95% CI, 0.03-0.11; $P < 0.001$). There was no evidence of association with higher THC doses and other neuropsychiatric effects for either the THC-only or CBD and THC combination RCTs.

The authors concluded that in older adults, higher THC doses resulted in a more frequent occurrence of dizziness or lightheadedness and thinking or perception disorder. Additionally, THC use did not appear to increase the risk of other neuropsychiatric effects in this population.

■ COMMENTARY

These findings demonstrate the need for physicians and their patients to be aware of potential adverse effects of THC-containing CBMs. As is the case for many medications, adverse effects of CBMs in the older population may be different than for younger populations. Dizziness and lightheadedness can be especially dangerous for older adults because of a higher risk of falls and delirium, which often lead to poor outcomes, such as placement in long-term care facilities and death. Thus, THC-containing CBMs should be used with caution in patients age 50 years and older, and patients should be educated correctly on the potential risks and benefits of these treatments. Although Velayudhan et al employed sound methodology for identifying THC-containing CBM RCTs, the overall results are limited by individual study quality of the RCTs, each of which received very low to moderate Grading of Recommendations, Assessment, Development, and Evaluations scores. Many trial authors did not employ structured questionnaires to identify adverse effects, relying instead on patient self-reporting, possibly resulting in underreporting of neuropsychiatric effects. Notably, the authors reflected that a primary limitation of the research is few studies included patients age 65 years and older (n = 4), rendering a sensitivity analysis in this subgroup impractical. Since many of the conditions for which CBMs are studied involve this population, more evidence is needed to draw conclusions about adverse effects and correctly advise patients age 65 years and older of the risks and benefits of CBMs. ■

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ABSTRACT & COMMENTARY

Healthcare Workers with COVID-19 Antibodies: Strong Protection Against Reinfection

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: A study of healthcare workers demonstrated the presence of antibody to SARS-CoV-2 spike protein or to nucleocapsid provides strong protection against infection for up to six months.

SOURCE: Lumley SF, O'Donnell D, Stoesser NE, et al; Oxford University Hospitals Staff Testing Group. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med* 2020; Dec 23:NEJMoa2034545. doi: 10.1056/NEJMoa2034545. [Online ahead of print].

Lumley et al at the Oxford University Hospitals prospectively evaluated the incidence of the occurrence of SARS-CoV-2-positive polymerase chain reaction (PCR) tests in healthcare workers (HCWs) who, at baseline, either had or lacked antibody to the virus to assess the protection provided by the presence of antibody.

At baseline, 11,364 of 12,541 HCWs tested negative for the presence of immunoglobulin G (IgG) anti-spike antibody, while 1,177 were seropositive and another 88 seroconverted during the 31 weeks of the study. HCWs were followed for a median of 200 days after a negative test and 139 days after a positive test. Follow-up testing of the 11,364 HCWs who were seronegative for antibody to spike protein at baseline detected 223 who subsequently had a positive PCR, for an incidence of 1.09 per 10,000 days at risk. The positive PCR occurred in the presence and absence of symptoms in 123 and 100 subjects, respectively.

Among the 1,265 who were seropositive (including the 88 who first became seropositive after the baseline assessment), only two subsequently produced a positive PCR test, each at a time when they were asymptomatic, for an incidence of 0.13 per 10,000 days at risk. Comparing those who were seropositive to those who were seronegative, the risk ratio for a subsequent positive PCR test was 0.12 (95% CI, 0.03-0.47; $P = 0.002$). There were no symptomatic PCR-confirmed infections in the seropositive cohort, while among the seronegatives, the incidence was 0.60 per 10,000 days at risk. Similar risk ratio results were seen with analyses of anti-nucleocapsid IgG antibody. Confirming the protective role of antibodies, the incidence of occurrence of positive PCR tests was inversely correlated with the titers of antibody to the spike protein ($P < 0.001$). In fact, this protection extended to individuals who had detectable antibody but at levels too low to meet the threshold used to declare a test as positive.

■ COMMENTARY

This study confirms the presence of antibody to SARS-CoV-2 as the result of natural infection is protective against subsequent infection, especially against symptomatic infections. This effect lasts at least six months, a finding consistent with recent evidence of the persistence of immunological memory for at least eight months. These findings carry important implications for understanding protection associated with COVID-19 vaccines. It also provides information that is valuable to the safety of HCWs with naturally acquired immunity as well as to their patients. However, the rare occurrence of a positive PCR test indicates protection is not complete (something already known from the rare occurrence of reinfection in individuals who have recovered from the coronavirus, and there is a potential danger that they may transmit infection even when they are asymptomatic. ■

ABSTRACT & COMMENTARY

COVID-19 Patients Can Be Managed Safely with Noninvasive Respiratory Techniques

By Betty Tran, MD, MSc

Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago

SYNOPSIS: In adult patients hospitalized with COVID-19 for one month, using a noninvasive respiratory protocol that encouraged high-flow nasal cannula, noninvasive mechanical ventilation, and self-proning did not result in any significant increase in mortality.

SOURCE: Soares WE 3rd, Schoenfeld EM, Visintainer P, et al. Safety assessment of a noninvasive respiratory protocol for adults with COVID-19. *J Hosp Med* 2020;15:734-738.

This was a retrospective chart review of 469 consecutive adult patients admitted to any of four hospitals in the Baystate Health system with a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 between March 15, 2020, and April 15, 2020. A noninvasive COVID-19 respiratory protocol (NCRP) encouraging early use of high-flow nasal cannula (HFNC), noninvasive ventilation (NIV), and self-proning was developed and implemented on April 3, 2020. The primary outcome was mortality during the post-NCRP implementation period compared to the pre-implementation period. Rates of proning, HFNC, NIV, and intubation before and after protocol implementation were analyzed. Secondary outcomes included unexpected cardiac arrests, ICU transfers and consultations, and rapid response team (RRT) activations in the pre-implementation vs. postimplementation period.

After protocol implementation, there was an increase in HFNC use (5.5% to 24.7%) and self-proning (7.5% to 22.8%), while intubation rates decreased from 25.2% to 10.7% ($P < 0.01$). The median time to mechanical ventilation increased from 0.66 days

(interquartile range [IQR], 0.23-1.69 days) to 1.4 days (IQR, 0.21-2.9 days) in the pre-implementation vs. postimplementation period. Overall mortality was 26.2% during the study period. During the pre-implementation period, 61 of 254 patients died vs. 62 of 215 in the postimplementation period ($P = 0.14$). After excluding patients with established (prior to admission) do not resuscitate/do not intubate (DNR/DNI) orders, the mortality rate was comparable pre-implementation vs. postimplementation (21.8% vs. 21.9%). In terms of secondary outcomes, there was no increase in RRT activations or ICU consults in the postimplementation period. ICU transfers decreased in the postimplementation period. There was one unexpected cardiac arrest in the postimplementation period compared to none before the protocol.

■ COMMENTARY

Our management of COVID-19 patients has evolved rapidly. In the first months of the pandemic, COVID-19 patients were intubated and placed on mechanical ventilation early in their course, often after failing up to 6 L/min of nasal cannula. This strategy was based on perceptions and reports of rapid clinical decline, ineffectiveness of noninvasive methods, and incomplete knowledge of viral transmissibility with a focus on healthcare provider safety. In their review, Soares et al reported 24% of patients died in the pre-implementation period compared to 28.8% in the postimplementation period ($P = 0.14$), although this finding was not statistically significant. The comparison became more equal after excluding patients with an established DNR/DNI order before admission. Considering the study's retrospective nature, we cannot evaluate the effectiveness of the noninvasive respiratory protocol itself because of the potential for selection bias and unadjusted confounders. In other words, if more patients died while on an early noninvasive respiratory therapy, does it mean this approach was harmful (in terms of delaying the need for invasive mechanical ventilation), or just that sicker patients will require invasive mechanical ventilation and be more likely to die regardless of the interventions they received?

Overall, the findings suggest an early, noninvasive respiratory approach can reduce the rate of mechanical ventilation while not significantly affecting overall mortality, although the latter conclusion is limited by retrospective data. Soares et al noted the failure to find a reduced mortality after protocol implementation could be related to other factors, namely because of an increased proportion of established DNR/DNI patients, many coming from skilled nursing facilities and nursing homes, admitted after the protocol was implemented compared to prior. Considering the one-month period of this chart review, there were no novel medications, and it was unlikely providers changed their interventions or treatment plans significantly during this time, except for perhaps encouraging more patient self-proning.

Even if there is no significant reduction in mortality with an early, noninvasive approach, the reduction in rates of invasive mechanical ventilation may produce other benefits the authors did not explore here, such as shorter length of stay, fewer hospital-related comorbidities, decreased rates of PTSD and functional impairment, and lower healthcare costs, while freeing resources, such as ventilators and ICU beds. ■

ABSTRACT & COMMENTARY

Early Convalescent Plasma to Treat COVID-19 in Elderly Patients with Mild Symptoms

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Administering convalescent plasma obtained from survivors of COVID-19 within 72 hours of onset of mild symptoms in elderly patients with the virus was associated with a significant reduction in the risk of development of severe respiratory disease.

SOURCE: Libster R, Pérez Marc G, Wappner D, et al; Fundación INFANT–COVID-19 Group. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med* 2021; Jan 6. doi: 10.1056/NEJMoa2033700. [Online ahead of print].

In this clinical trial performed in Argentina, 160 patients with COVID-19 were randomized to a single infusion of convalescent plasma that had been obtained with high titers (> 1:1,000) of immunoglobulin G (IgG) antibody to SARS-CoV-2 spike protein from individuals who had recovered from COVID-19 or a normal saline placebo. Study entry required patients to be symptomatic for 72 hours or fewer and were either age 65-74 years with one of a series of specified comorbid conditions or were older than age 75 years with or without a comorbid condition.

There were several exclusion criteria, including severe respiratory disease, primary hypogammaglobulinemia, lymphoproliferative disorders, cancer with treatment in the previous six months, immunosuppressive therapy, solid organ transplant, chronic liver or lung disease, and receipt of anticoagulants.

The primary endpoint was the development of severe respiratory disease, defined as a respiratory rate 30 breaths or more per minute, an oxygen saturation < 93% while breathing ambient air, or both. A power analysis estimated a requirement to enroll 210 patients to achieve an 80% power to detect a difference between treatment groups at an $\alpha = 0.05$. The authors ended enrollment after only 76% of the target population joined the trial as the local epidemic waned. The mean age was 77.2 ± 8.6 years (55% were ≥ 75 years of age) and 60% were women; approximately four-fifths of the cohort presented with comorbidities. In an intent-to-treat analysis, severe respiratory disease occurred in 13 of 80 patients assigned convalescent plasma and 25 of 80 patients assigned placebo, resulting in a calculated relative risk of 0.52 (95% CI, 0.29-0.94; *P* = 0.03). This represented a 48% risk reduction and a number needed to treat of 7. In a modified intent-to-treat analysis that excluded six patients who reached the primary endpoint before receiving their designated infusion, relative risk favoring plasma was 0.40 (95% CI, 0.20-0.81). The response was greater in those who received plasma with the highest antibody titers. No adverse reactions were observed.

■ COMMENTARY

This study shows a highly selected group of patients with COVID-19 benefit from receipt of convalescent plasma. These include patients with mild symptoms of no more than 72 hours duration who were > 75 years of age and/or 65-74 years of age with limited specified comorbidities. It excluded patients with a long list of other comorbidities, a factor that significantly limits the applicability of the results.

The results also may be considered possibly surprising based on prior published experience. Thus, in a supplementary appendix, the authors listed five previous randomized, controlled trials that enrolled between 81 and 333 patients and that failed to demonstrate benefit from administration of convalescent plasma in the treatment of patients with COVID-19. However, Libster et al noted those studies enrolled adults as young as age 18 years and the median duration of symptoms before enrollment in these studies ranged from eight to 30 days. In addition, the evaluation of convalescent plasma in COVID-19 patients admitted to intensive care as part of the REMAP-CAP adaptive trial ended recently because of futility.

In contrast to these negative results, the apparent benefit of monoclonal antibodies, bamlanivimab as well as the combination of casirivimab and imdevimab, is more modest than seen with convalescent plasma in the study reviewed here. However, in their trials, they were administered to a population that was as young as age 18 years and could be affected by a variety of comorbidities. Further, the participants received their infusions after a median duration of symptoms of four days and three days, meaning more than half the subjects would not have been eligible for the convalescent plasma study, in which the plasma was administered within 72 hours of symptom onset. Of note is the emergency use authorizations for these monoclonals allow for infusion to patients with symptom durations as long as 10 days.

Thus, convalescent plasma with high IgG antibody titers should be considered for administration to patients who match the entry/exclusion criteria in the Libster et al study. Furthermore, their results may provide lessons for using monoclonals until there is more direct evidence related to the use of these products. Among these is the greater likelihood of benefit the earlier the infusion is administered. This knowledge would be especially useful in circumstances of shortage. It also is apparent from the study evaluating casirivimab/imdevimab that patients who lack antibody at the time of intervention are most likely to benefit, but this would require the availability of an antibody test with rapid turnaround time.

Another factor that has not been evaluated in this context relates to the usual disappearance of viable (replication competent) SARS-CoV-2 after approximately eight days, at least in patients without severe immunocompromise. Presumably, antibody administration would produce little or no benefit if the virus is no longer replicating, something that can be determined using a polymerase chain reaction test specific for negative-strand ribonucleic acid. ■

ABSTRACT & COMMENTARY

Prednisone vs. Placebo in Short-Term Prevention of Episodic Cluster Headaches

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Prednisone, given at 100 mg for five days and then tapering by 20 mg every three days, is a safe and effective short-term prevention for episodic cluster headaches while waiting for longer-acting preventive agents to be initiated.

SOURCE: Obermann M, Nägel S, Ose C, et al. Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: A multicentre, double-blind, randomised controlled trial. *Lancet Neurol* 2021;20:29-37.

Cluster headache is a primary headache disorder characterized by attacks of severe, unilateral facial and head pain accompanied by trigeminal autonomic symptoms, with attacks lasting 15-180 minutes and occurring from once every other day to up to eight times a day in clusters lasting between one week and several months. Treatments for acute attacks include high-flow oxygen, triptans, and intranasal lidocaine. Preventive medications, such as verapamil and lithium, reduce the number of attacks and potentially terminate the cluster episode. However, they need to be titrated gradually to avoid side effects and can take several weeks to achieve efficacy. Although headache guidelines recommend treatment with oral corticosteroids to break the initial cluster episode while waiting for preventive medications to take effect, this recommendation has not been rigorously assessed. The purpose of this trial was to assess the safety and efficacy of prednisone 100 mg for the short-term prevention of episodic cluster headaches.

The study was a multicenter, randomized, double-blind, placebo-controlled trial performed at 10 specialized pain and headache centers throughout Germany. Eligible patients were age 18-65 years and met criteria for episodic cluster headache as defined by the International Classification of Headache Disorders. To avoid confounding data caused by spontaneous remission, the authors included patients whose prior cluster episodes lasted at least 30 days. Patients could use triptans, high-flow oxygen, intranasal lidocaine, ergotamine, and oral analgesics as needed. Patients were randomized to receive oral prednisone or placebo. Prednisone was given at a dose of 100 mg for five days and then tapered by 20 mg every three days. Oral verapamil was initiated at a dose of 40 mg three times a day at the same time and increased every three days to a maximum daily dose of 360 mg. Patients also received 20 mg of pantoprazole daily to prevent gastrointestinal side effects from corticosteroids.

Patients used diaries to record the number and severity of cluster attacks, associated autonomic symptoms, and the use of acute rescue medication. The primary endpoint was the mean number of cluster attacks within the first week of treatment compared with placebo. Over five years, the authors prescreened 157 patients and randomized 116 to participate in the study, 57 to the prednisone group and 59 to the placebo group. The mean number of attacks within the first week of treatment was 25% less in the prednisone group (7.1; standard deviation [SD] 6.5 vs. 9.5; SD 6.0; $P = 0.002$) vs. placebo. In addition to improvement in the primary endpoint, the prednisone group also performed better in terms of the number of cluster attacks after 28 days (15.6 vs. 20.2), the number of cluster attacks after seven days (3.9 vs. 5.1), and the number of days with cluster attacks at 28 days (8.8 vs. 11.0). After seven days, cluster attacks had ceased in 35% of the prednisone group vs. 7% of the placebo group. At least a 50% reduction in attack frequency at day 7 was seen in nearly 50% of the prednisone group vs. only 15% in the placebo group. The need for acute medication also was higher in the placebo group.

There were no significant differences in the frequency or severity of adverse events between the two groups. The Clinical Global Impression scale showed significant differences between groups, with 15% of patients in the prednisone group (but none in the placebo group) rated as "normal" at seven days.

■ COMMENTARY

This study supports the clinical impression and prior societal recommendations that prednisone, starting with 100 mg and with gradual reduction over 17 days, is of value in the management of acute cluster attacks. Patients treated with prednisone reported significantly fewer cluster attacks, with more than one-third reporting complete cessation of attacks after seven days, nearly one-half reporting at least a 50% reduction in attacks, and marked reduction in the number of days with cluster attacks as well as the need for acute medication. Prednisone, given at 100 mg for five days and then tapering by 20 mg every three days, is a safe and effective short-term prevention for episodic cluster while waiting for longer-acting preventive agents to be initiated. The study was limited to small numbers in each group because of funding difficulties and the challenges of recruiting patients

who may have been exposed to the treatment medications previously. The results need to be interpreted with caution since many patients with cluster headache will experience spontaneous remissions; limiting the study to patients with prior cluster periods lasting more than 30 days offsets this concern. In future studies, oral prednisone could be compared with occipital nerve block and other long-term preventive agents. ■

PHARMACOLOGY UPDATE

Evinacumab-dgnb Injection (Evkeeza)

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 recombinant, fully human monoclonal antibody that binds angiopoietin-like protein 3 (ANGPT3) for the treatment of homozygous familial hypercholesterolemia (HoFH), an ultra-rare, severe form of familial hypercholesterolemia. ANGPT3 is involved in the regulation of lipid metabolism in the liver.[1] Evinacumab was designated as a breakthrough therapy, an orphan product, and received a priority review. It is distributed as Evkeeza.

INDICATIONS

Evinacumab should be prescribed as an adjunct to other low-density lipoprotein cholesterol (LDL-C)-lowering therapy to treat patients age 12 years and older with HoFH.[1]

DOSAGE

The recommended dose for evinacumab is 15 mg/kg, given by intravenous infusion (over 60 minutes) once every four weeks.[1] It is available as 345 mg/2.3 mL and 1,200 mg/8 mL single-dose vials.

POTENTIAL ADVANTAGES

Evinacumab reduces LDL-C levels independent of the activity of LDL receptors that normally act to remove LDL-C from the circulation.[1,2] It provides significant LDL-C reduction in HoFH patients on maximum doses of currently available lipid-lowering therapy.[1,3]

POTENTIAL DISADVANTAGES

Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported (1%), and the drug may cause embryo-fetal toxicity.[1] Evinacumab reduces HDL cholesterol by about 30%.[3] Dose administration requires monthly intravenous infusions. The effect of evinacumab on cardiovascular morbidity or mortality has not been determined.[1]

COMMENTS

HoFH is caused by mutations in genes regulating plasma levels of LDL-C, including LDL receptor (LDLR), apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes.[4] The most common is the impairment or loss-of-function variants in the LDLR, resulting in the inability to clear LDL-C from the circulation. Inhibition of ANGPT3 results in less production of LDL-C by the liver and is independent of LDLR function.[4]

The efficacy and safety of evinacumab were evaluated in a double-blind, randomized, placebo-controlled, 24-week trial that included 65 subjects with HoFH.[1,3] Subjects were randomized to evinacumab (n = 43) or placebo (n = 22). The primary endpoint was the percent change in the calculated LDL-C from baseline to week 24. At baseline, the mean age was 41.7 years ± 15.5 years, 54% of subjects were female, 74% were white, the mean LDL-C was 255.1 mg/dL ± 165.2 mg/dL, 32% showed a complete absence of LDLR expression, 94% were on a statin, 77% were on a PCSK9 inhibitor, and 34% were on extracorporeal LDL-C filtration (apheresis).

At week 24, there was a mean difference from placebo of -49%. Non-LDL-C, triglycerides, APOB, and total cholesterol were similarly reduced. Lipid-lowering with evinacumab in pediatric subjects (n = 13) generally was similar to those seen in adults.[1]

CLINICAL IMPLICATIONS

HoPH affects about one in 160,000 people worldwide.[4] These individuals often live with defective or loss of function of the LDLR gene.[5] The clinical spectrum of the disease is dependent on the severity of the LDLR mutation. It is characterized by high LDL-C (> 387 mg/dL), resulting in premature atherosclerotic cardiovascular disease and early mortality. Current therapies include high-intensity statins and PCSK9 inhibitors for those with LDLR gene-defective mutations (but residual function) and apheresis in those with loss-of-function mutations.[5] Evinacumab provides an alternative therapy for patients with severe HoFH and no LDLR function. The cost of a single dose for a 70 kg patient is $37,500 or $487,500 per year (every four weeks for one year). ■

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CME QUESTIONS

1. In patients admitted to the hospital with COVID-19 after implementation of a noninvasive respiratory protocol, which statement is true?
a. There was an increase in rapid response team activations.
b. There was an increase in ICU consultations.
c. There was no change in rates of intubation.
d. There was no change in mortality.

2. Which is correct regarding the trial of convalescent plasma treatment of patients with COVID-19?
a. It was most effective in patients receiving mechanical ventilation.
b. It was most effective in patients with symptoms lasting longer than five days.
c. Plasma with high antibody titer to SARS-CoV-2 spike protein were more effective than those with low titer.
d. It was most effective in patients age 35-65 years.

3. Which is true about using THC-containing cannabis-based medicines (CBMs) in older adults?
a. THC-containing CBMs have been extensively studied in the older adult population and can be used for a variety of indications.
b. THC-containing CBMs are proven to result in serious psychotic effects in older adults, regardless of whether CBD is used concurrently with THC.
c. THC-containing CBMs should be avoided in older adults because of an increased risk of developing psychosis.
d. THC-containing CBMs can increase the risk of dizziness and thinking or perception disorders in older adults and should be used with caution.

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.