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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Clinical Trials of IL-6 Inhibitors for the Treatment of Neuromyelitis Optica Spectrum Disorders

By Jai S. Perumal, MD

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

Dr. Perumal reports she is a consultant for Biogen and Genzyme.

SYNOPSIS: In a randomized, placebo-controlled trial of neuromyelitis optica spectrum disorder patients, satralizumab monotherapy demonstrated a decrease in relapse rate when compared to placebo. In a randomized, open-label, multicenter trial of tocilizumab vs. azathioprine, treatment with tocilizumab demonstrated a decreased risk of a relapse compared to azathioprine.

SOURCES: Zhang C, Zhang M, Qiu W, et al. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): An open-label, multicentre, randomised phase 2 trial. *Lancet Neurol* 2020;19:391-401.

Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: A randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol* 2020;19:402-412.

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Classic NMO, or Devic's disease, is characterized by concurrent episodes of optic neuritis (ON) and transverse myelitis (TM). NMO spectrum disorder (NMOSD) is diagnosed in patients with isolated ON or TM who have the NMO IgG (aquaporin-4) antibody, which is potentially pathogenic and has high specificity for this group of diseases.

Currently, the only disease-modifying therapy that is a Food and Drug Administration (FDA)-approved treatment for NMOSD is eculizumab, a humanized monoclonal antibody that is a complement-5 inhibitor. It was approved in 2019. However, other medications

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that traditionally have been used include pulse corticosteroids, intravenous immunoglobulin (IVIG), azathioprine, mycophenolate mofetil, and rituximab. More recently, several medications with diverse mechanisms of action are being explored for the treatment of NMOSD, either as combination therapy or as monotherapy. There is a need for such therapies because NMOSD can be a devastating illness resulting in severe disability from relapses. In this review, we report on recently published results from clinical trials of satralizumab and tocilizumab.

SATRALIZUMAB

Satralizumab is a humanized monoclonal antibody that is an interleukin-6 (IL-6) inhibitor. IL-6 is a pro-inflammatory cytokine that is believed to have multiple pathogenic effects in NMOSD. An earlier trial with satralizumab or placebo as an add-on therapy for patients already on immunosuppressive treatment for NMOSD showed that patients in the satralizumab arm had a decrease in risk of relapse. In the current study, researchers explored satralizumab monotherapy.

This was a phase 3, double-blind, placebo-controlled, multicenter study. The double-blind period was followed by an open-label extension. Both seropositive and seronegative NMOSD patients were included in the study. Ninety-five patients were randomized to either satralizumab (63) or placebo (32). Study medication was administered subcutaneously at weeks 0, 2, and 4, and then every four weeks for the duration of the study. The primary outcome was the time to first protocol-defined relapse. Secondary outcomes included visual analog scale (VAS) pain score, Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score, proportion of relapse-free patients, annualized relapse rate, and change in disability scores.

The median treatment duration in the double-blind phase was 92.3 weeks (range zero to 202 weeks). Thirty-five protocol-defined relapses were observed during the double-blind periods; 19/63 (30%) of patients in the satralizumab arm and 16/32 (50%) of patients in the placebo arm (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.23-89; $P = 0.018$). Patients in the placebo arm also had a shorter time to relapse. No significant change was observed between the groups on the VAS pain score or the FACIT fatigue score. During screening for the study, the number of aquaporin-4 immunoglobulin G (AQP4-IgG) seronegative patients was kept at 30% of the subjects. A subanalysis of the results by sero-status showed that satralizumab was effective in reducing the risk of relapse on AQP4-IgG seropositive patients. There was not enough evidence to demonstrate efficacy in the seronegative group. Regarding adverse events, the incidence was similar between the satralizumab and placebo groups. The most commonly reported adverse events were urinary tract and upper respiratory tract infections. No opportunistic infections were reported.

Although the patient numbers were small, satralizumab demonstrated efficacy in reducing the risk of relapse, predominantly in seropositive patients, and no unexpected serious adverse events were noted.

TOCILIZUMAB

Tocilizumab also is an IL-6 inhibitor that currently is FDA-approved for several autoimmune diseases, including severe rheumatoid arthritis and giant cell arteritis. Prior reported case series demonstrated efficacy of tocilizumab in decreasing the risk of relapse in NMOSD. In this open-label, multicenter, randomized, phase 2 trial, tocilizumab was compared to azathioprine, a medication that is used in an off-label manner for the treatment of NMOSD.

One hundred eighteen NMOSD patients were randomized in a 1:1 manner to either tocilizumab or azathioprine. Each arm had 59 patients. Azathioprine was titrated up until a target dose of 2 mg/kg to 3 mg/kg per day was reached. This dosage was maintained. Tocilizumab was administered intravenously at a dose of 8 mg/kg every four weeks. The planned total duration of follow-up was 60 weeks after randomization. The primary outcome was time to first relapse. Secondary outcomes included proportion of patients with confirmed disability progression and change in serum AQP4-IgG levels at the end of the trial.

At the end of 60 weeks, the risk of a relapse was lower in the tocilizumab group when compared to the azathioprine group (HR, 0.24; 95% CI, 0.123-0.607; $P = 0.0006$). In the tocilizumab group, 8/59 patients (14%) had a relapse when compared to 28/50 patients (47%) in the azathioprine group. The median time to first relapse was longer in the

tocilizumab group when compared to the azathioprine group (78.9 weeks vs. 56.7 weeks). The incidence of adverse events was similar between the two groups. Most were mild. The most common adverse events in both groups were elevated liver enzymes, upper respiratory tract infections, and urinary tract infections.

Two patients died, one in the azathioprine group and one in the tocilizumab group, but neither death was considered treatment-related. The patient who died in the azathioprine group had a relapse of thoracic myelitis, then developed a high fever and was diagnosed with meningoencephalitis caused by *Listeria monocytogenes*. The death in the tocilizumab group occurred in an individual with extensive transverse myelitis that ascended to the medulla oblongata and resulted in respiratory arrest and cardiopulmonary failure.

■ COMMENTARY

NMOSD is characterized by severe relapses with a significant risk of disability from the residual deficits from relapses that can be refractory to treatments used for acute relapses (i.e., steroids, IVIG, plasmapheresis). Hence, medications that decrease the risk of a relapse are vital in preventing disability. Although several medications have been used off-label for the treatment of this disease, there currently is just one medication that was FDA-approved in 2019 for NMOSD — eculizumab. There is an urgent need for further treatment options for those who fail existing medications or have tolerability issues. Based on these two studies, satralizumab and tocilizumab have demonstrated efficacy without any prohibitive adverse events and would expand the armamentarium of NMOSD treatment. They appear likely to be approved by the FDA in the near future. ■

ABSTRACT & COMMENTARY

Brachial Plexopathy Localization in Patients with Cancer

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Brachial plexopathy associated with cancer may involve any region of the brachial plexus and can be distinguished from radiation-induced brachial plexopathy only by the use of high-resolution magnetic resonance imaging.

SOURCE: McNeish BL, Zheutlin AR, Richardson JK, Smith SR. Primary cancer location predicts predominant level of brachial plexopathy. *Muscle Nerve* 2020; June 8. doi:10.1002/mus.26994. [Online ahead of print].

Shoulder and axillary pain are the most common presenting symptoms of neoplastic-induced brachial plexopathy (NIBP). Involvement of the inferior trunk is more common than that of the upper trunk, and breast and lung cancer are the most frequent neoplasms. Distinguishing cancer recurrence from radiation-induced brachial plexopathy (RIBP) can be challenging. Horner syndrome, pain at symptom onset, and lower plexus involvement traditionally are more likely in NIBP, whereas RIBP often is painless early on, is associated with more severe paresthesiae and weakness than NIBP, and tends to affect the upper trunk. In the era of computer-guided radiation dosing, targeting, and delivery, is this traditional approach to causation and localization still correct?

In this retrospective electronic medical record review, researchers analyzed all nerve conduction (NCS) and needle electromyography (EMG) studies performed at The Michigan Medicine Electrodiagnostic Laboratory in Ann Arbor from January 2008 through January 2019 and coded for brachial plexopathy. Collated information included age, gender, cancer type, clinical symptoms, radiation history, imaging information, and NCS/EMG findings. Inclusionary criteria required presenting symptoms consistent with brachial plexopathy in a patient with a history of cancer and radiation therapy. Patients with a history suggesting trauma or neuralgic amyotrophy (Parsonage-Turner syndrome) were excluded. NCS required the presence of decreased motor and sensory amplitudes, with abnormal spontaneous activity and high-amplitude, long-duration motor-unit potentials and reduced recruitment on needle EMG study. Spontaneous activity included positive sharp waves, fibrillation potentials, and myokymic discharges. Imaging results indicating the presence or absence of tumor invasion of the plexus and/or adjacent lymph nodes differentiated NIBP from RIBP, respectively. Statistical analysis comprised Student's t-test, chi-square test, logistic regression, and bivariate analyses, with 0.05 used as the threshold for statistical significance.

Among 912 cases of brachial plexopathy, 22 were diagnosed as NIBP and 34 as RIBP. NIBP more often presented with pain, but there was no difference between NIBP and RIBP in the distribution of predominant trunk involved. The primary cancer location (superior

or inferior to the clavicle) was significantly associated with plexopathy location (upper or lower trunk) in both NIBP (P = 0.047) and RIBP (P = 0.003), and multivariate analysis revealed that the primary cancer location superior or inferior to the clavicle was the strongest predictor of upper or lower trunk involvement, respectively. Infraclavicular tumors (e.g., lung and breast cancers) were highly predictive of predominantly lower trunk plexopathy, whereas supraclavicular tumors (e.g., head and neck cancers) were predictive of upper trunk plexopathy, regardless of whether the injury was related to radiation or neoplastic invasion. As the authors concluded, current high-resolution imaging contradicts the traditional teaching around localization of brachial plexus lesions.

■ COMMENTARY

Other studies report different findings. Among 44 patients with breast cancer seen at the Asian Medical Center in Seoul, South Korea, between 2000 and 2016, of whom 41 were evaluated by EMG, upper trunk involvement of the brachial plexus was most frequent, affecting 22%. Lower trunk involvement was seen in 9.9%. Among 19 patients who underwent magnetic resonance imaging, supraclavicular-region metastases were found in 57.9%. It would appear that metastases from either above or below the clavicle may affect either the upper or lower portions of the brachial plexus. Clinical observation and imaging indicate that any cancer can affect any part of the brachial plexus.[1] ■

REFERENCE

1. Kim J, Jeon JY, Choi YJ, et al. Characteristics of metastatic brachial plexopathy in patients with breast cancer. *Support Care Cancer* 2020;28:1913-1918.

Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Anticoagulation in Patients with Ischemic Stroke Related to Atrial Fibrillation, Following Reperfusion Therapy

SOURCE: Giustozzi M, Acciarresi M, Agnelli G, et al. Safety of anticoagulation in patients treated with urgent reperfusion for ischemic stroke related to atrial fibrillation. *Stroke* 2020; July 10. doi:10.1161/STROKEAHA.120.030143. [Online ahead of print].

Following ischemic stroke in patients with non-valvular atrial fibrillation, the timing to restart anticoagulation treatment is uncertain and controversial. In addition, there is little data available regarding timing to restart anticoagulation following reperfusion therapy with either systemic thrombolysis and/or mechanical thrombectomy. Guidelines state that no anticoagulation should be given within the first 24 hours following thrombolysis or mechanical thrombectomy, but there are no further recommendations that have reached a level of consensus. These investigators attempted to assess the incidence of early recurrence of stroke or major bleeding in patients with acute ischemic stroke and atrial fibrillation treated with reperfusion therapy who then received oral anticoagulants for secondary prevention.

The investigators analyzed data from two large studies of patients with ischemic stroke and atrial fibrillation, and compared the composite rates of recurrent stroke, transient ischemic attack, systemic embolism, intracerebral hemorrhage, and major extracerebral bleeding within 90 days from inclusion into the study. The study included 2,159 patients, with 26% receiving acute reperfusion therapy. Ninety percent of patients treated with acute reperfusion therapy were started on oral anticoagulation, compared to 81% of those who were untreated. The timing of starting oral anticoagulants was similar in both groups (median 7.5 days vs. 7.0 days, respectively).

At 90 days, the primary study outcome occurred in 7% of patients treated with acute reperfusion therapy, compared to 9% of patients who were treated conservatively without reperfusion. There was no statistically significant difference between the two groups. After matching the groups and further analysis, the risk of primary outcome was comparable between the two groups. The investigators concluded that acute reperfusion therapy did not influence the risk of early stroke recurrence or major bleeding in patients with ischemic stroke related to atrial fibrillation. ■

Treatment of Central Retinal Artery Occlusion with Intravenous Thrombolysis

SOURCE: MacGrory B, Nackenoff A, Poli S, et al. Intravenous fibrinolysis for central retinal artery occlusion. A cohort study and updated patient-level meta-analysis. *Stroke* 2020;51:2018-2025.

Central retinal artery occlusion (CRAO) is a serious threat to vision caused by interruption of the blood supply to the retina and leading to sudden, painless loss of vision in one eye. For 30 years there have been anecdotal reports and small case series suggesting that

intravenous thrombolysis might be beneficial in this disorder, but none of the stroke treatment guidelines have incorporated thrombolysis as definitive treatment for this disorder. At the present time, there is no effective treatment that has been proven to salvage vision in patients with CRAO.

The investigators in this study enrolled consecutive patients with acute CRAO within 48 hours of symptom onset who had a visual acuity < 20/200. This was an open-label trial, and there was no randomization. Patients were treated per the local treating physician. The primary outcomes were safety and functional visual recovery. Rates of recovery were compared for those treated with alteplase within 4.5 hours of symptom onset to those who did not receive alteplase, including a comparison with untreated patients who presented within the window for potential thrombolytic treatment, or 4.5 hours from onset of symptoms. Cases were collected from several different medical centers, and the protocols for treatment varied considerably from different centers.

The principal investigators enrolled 112 patients into the prospective cohort, of whom 25 (22.3%) were treated with intravenous alteplase. One patient had an asymptomatic brain hemorrhage after alteplase treatment. Forty-four percent of patients treated with alteplase had recovery of visual acuity if treated within 4.5 hours of symptom onset compared to 13.1% of those who were not treated with alteplase ($P = 0.003$) and 11.6% of those who arrived within four hours of symptom onset but did not receive alteplase. In a meta-analysis of 238 patients from multiple centers, including 67 patients treated with alteplase within 4.5 hours of symptom onset, the recovery rate for vision was 37.3%. Those who were not treated with intravenous alteplase had a 17.7% rate of recovery.

The authors concluded that administration of intravenous alteplase within 4.5 hours of onset of symptoms results in a much higher likelihood of a favorable visual outcome for patients who have acute CRAO. A randomized, prospective, placebo-controlled clinical trial is strongly recommended to determine definitively if this treatment is beneficial. ■

Widely Used in Asia, Cilostazol Appears Effective for Long-Term Secondary Stroke Prevention

SOURCE: McHutchison C, Blair GW, Appleton JP, et al. Cilostazol for secondary prevention of stroke and cognitive decline: Systematic review and meta-analysis. *Stroke* 2020; July 10. doi: 10.1161/STROKEAHA.120.029454. [Online ahead of print].

Cilostazol is a phosphodiesterase 3 inhibitor widely used in Asia for secondary stroke prevention but approved for use in North America only for symptomatic peripheral vascular disease. In animal studies, it has been demonstrated to have weak antiplatelet effects, but it stabilizes the endothelium and appears to aid myelin repair. It has been theorized that cilostazol might be beneficial in preventing the progression of small vessel disease in the brain and, therefore, may have a secondary effect in preventing vascular dementia.

The investigators undertook a systematic review and meta-analysis of randomized controlled trials of cilostazol to prevent stroke, cognitive decline, or small vessel disease progression in studies published from Jan. 1, 2019, until July 16, 2019, and they pooled the data for analysis. They calculated odds ratios (ORs) and 95% confidence intervals (CIs) for recurrent ischemic stroke, hemorrhagic stroke, death, and adverse symptoms.

They identified 20 randomized controlled trials, which included 10,505 patients, 18 studies in ischemic stroke and two in cognitive impairment. In a pooled analysis, researchers found that cilostazol decreased recurrent ischemic stroke (OR, 0.68; $P < 0.0001$), hemorrhagic stroke (OR, 0.43; $P = 0.0001$), deaths (OR, 0.64; $P < 0.0009$), and systemic bleeding (OR, 0.73; $P = 0.04$), but they noted an increased incidence of headache and palpitations when compared to placebo, aspirin, or clopidogrel. Cilostazol appeared to have greater benefit when given long term vs. short term (greater than six months) and did not increase hemorrhages. The data were insufficient to assess its effects on cognition, imaging, or functional outcomes.

The majority of these studies were performed in Asia-Pacific countries, and more trials in Western countries should be initiated to assess the effects of cilostazol treatment on cognitive decline and functional outcomes, as well as on the progression of small vessel disease in the brain. The studies from Asia suggest that it is a promising treatment, but it has not been studied sufficiently in clinical trials. ■

Should Patients with Ischemic Stroke and Large Vessel Occlusions Go Directly to Endovascular Thrombectomy?

SOURCE: Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981-1993.

Endovascular mechanical thrombectomy has become the standard treatment for patients with acute ischemic stroke caused by large vessel occlusion in both the anterior and posterior circulations. This is predicated on the ability to perform the procedure in a timely fashion or based on a mismatch between the size of infarction and brain perfusion.

Endovascular thrombectomy has better outcomes than intravenous thrombolysis alone for large vessel occlusion, and an ongoing debate exists regarding the need for administering intravenous alteplase initially, followed by thrombectomy, or moving immediately to thrombectomy alone.

In support of giving alteplase first is the observation that it may increase early reperfusion of the ischemic area and dissolve residual thrombi after endovascular thrombectomy. However, there is a risk that intravenous alteplase may delay mechanical thrombectomy and increase the risk of cerebral hemorrhage. These investigators undertook a strategy to determine whether endovascular thrombectomy alone would be noninferior to combined treatment with endovascular thrombectomy preceded by intravenous alteplase in patients with large vessel occlusion.

This study was performed in 41 academic tertiary care centers in China. Patients with acute ischemic stroke from large vessel occlusion in the anterior circulation were randomly assigned in 1:1 ratio to undergo endovascular thrombectomy alone or endovascular thrombectomy preceded by intravenous alteplase within 4.5 hours after symptom onset. The primary analysis for noninferiority assessed the differences between the groups in the distribution of the modified Rankin scale scores at 90 days on the basis of a lower boundary of the 95% confidence interval of the odds ratio (OR) ≤ 0.8. Secondary outcomes also were assessed, including death and reperfusion of the ischemic area.

Six hundred fifty-six patients were enrolled, with 327 assigned to the thrombectomy-alone group and 329 assigned to the combination therapy group. In regard to the primary outcome, endovascular thrombectomy alone was deemed noninferior to combined intravenous alteplase and endovascular thrombectomy (OR, 1.07; $P = 0.04$), but also was associated with a lower percentage of patients with successful reperfusion before thrombectomy (2.4% vs. 7.0%) as well as a lower overall successful reperfusion (79.4% vs. 84.5%). There was no difference in mortality at 90 days (17.7% vs. 18.8%).

In an accompanying editorial (published May 6, 2020, on NEJM.org), Dr. Greg Albers noted that the timing of endovascular thrombectomy overlapped with the administration of alteplase, which might have diminished the thrombolytic effect of the medication. Also, the successful perfusion rate in the thrombectomy-alone group was lower than in other large published studies. There was no difference in intracerebral hemorrhages, nor a difference in procedure-related ischemic stroke.

Thrombolysis may have been delayed because all patients were treated at a tertiary hospital, and the effects of earlier administration of alteplase, which is the standard in North America, could not be assessed.

Dr. Albers closed his editorial with the following statement: "Until more data are available, it is appropriate to follow current guidelines that recommend that all eligible patients receive alteplase before thrombectomy." ■

Mobile Stroke Units: What Is the Best Way to Use Them?

SOURCE: Holodinsky JK, Kamal N, Zerna C, et al. In what scenarios does a mobile stroke unit predict better patient outcomes? A modeling study. *Stroke* 2020;51:1805-1812.

It is well established that in the treatment of acute ischemic stroke, time and speed of diagnosis and treatment with thrombolysis or mechanical thrombectomy are critically important. A recent advance in ischemic stroke treatment is the mobile stroke unit, an ambulance outfitted with specialized equipment, computed tomography for brain imaging, and a specialized team with a stroke neurologist available either onboard or via telemedicine. Intravenous thrombolytics can be administered at the scene with the patient on the ambulance.

Multiple groups around the world have demonstrated that response to an acute stroke emergency by the mobile stroke unit results in more rapid treatment with intravenous thrombolysis. Several groups also have demonstrated better outcomes compared to standard ambulance transport. However, there is a controversy related to the triage of patients. Should an acute stroke patient suspected of having a large vessel occlusion be transported immediately to a thrombectomy-ready center and bypass treatment at a primary stroke center or on a mobile stroke unit?

The investigators developed eight separate scenarios for dispatch of the mobile stroke unit from an endovascular center to model which scenarios would result in the best outcomes. Overall, there is a very small relative difference in benefit between the deployment of the mobile stroke unit from the endovascular center compared to conventional ambulance transport. This depends predominantly on the difference in time it takes to reach a patient and administer thrombolysis. Each comprehensive stroke center needs to evaluate its own community and create a local model to determine if use of a mobile stroke unit will be of benefit to its local community. This will vary from urban to rural areas and will be very dependent on population density and traffic congestion. It is impossible to predict in advance in any particular geographic area if deployment of a mobile stroke unit will be helpful without detailed modeling of the community surrounding each endovascular center. ■

COVID-19 Infection Increases Stroke Risk by Almost Eight Times the Stroke Risk with Influenza

SOURCE: Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID–19) vs patients with influenza. *JAMA Neurol* 2020; July 2. doi:10.1001/jamaneurol.2020.2730. [Online ahead of print].

Early in the COVID-19 pandemic, reports emerged from China and France that there might be an increased risk of ischemic stroke. It was noted that many patients developed a hypercoagulable state with thrombotic complications in multiple organs, including the lungs, kidneys, heart, liver, and brain. During the recent surge in coronavirus infection cases in New York City, many neurologists observed an unusual frequency of ischemic stroke.

The investigators at Weill Cornell Medicine designed a retrospective cohort study of patients admitted with COVID-19 infection, confirmed by polymerase chain reaction testing by a nasal swab, from March 4, 2020, through May 2, 2020. They identified all acute strokes, and compared them with a matched group of patients hospitalized with influenza A and B from January 2016 through May 2018. It is well documented that influenza epidemics are associated with an increased risk of ischemic stroke and myocardial infarction, as are all systemic inflammatory disorders. These investigators wanted to determine if coronavirus infection induced a higher risk of ischemic stroke than other viral infections, such as influenza.

One thousand nine hundred sixteen patients with documented COVID-19 infection were admitted to the hospital, and 31 had an acute ischemic stroke during their hospitalization (1.6%; 95% confidence interval [CI], 1.1%-2.3%). The median age was 69 years, and 58% were men. Eight patients presented to the hospital with stroke as their chief complaint. Of 1,486 patients with influenza, only three had an acute ischemic stroke during hospitalization (0.2%; 95% CI, 0.0%-0.6%). After adjustment for demographic factors, age, sex, and race, the probability of stroke was higher with COVID-19 infection than with influenza infection (OR, 7.6; 95% CI, 2.3-25.2). This high rate of ischemic stroke is consistent with reports from other centers in New York City, as well as in cities around the world that have reported their findings. The thrombotic events that are being observed are likely the cause for the high rate of ischemic stroke in these patients and should be addressed aggressively as part of a comprehensive treatment plan. We do not know what the long-term consequences will be in this population, but there is likely to be a high rate of physical and neurological disabilities. ■

Ticagrelor Added to Aspirin Reduces Long-Term Risk of Recurrent Stroke or Death After Ischemic Stroke or TIAs

SOURCE: Johnston SC, Amarenco P, Denison H, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med* 2020;383:207-217.

Ticagrelor is a direct acting antiplatelet agent not dependent on metabolic activation that reversibly binds and inhibits the P2Y receptor on platelets. The Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES) study was designed to test the hypothesis that 30-day treatment with ticagrelor and aspirin would be superior to aspirin alone in reducing the risk of subsequent stroke or death in patients who had a non-cardioembolic ischemic stroke or transient ischemic attack (TIA).

This study was a randomized, placebo-controlled, double-blind trial with patients who had mild to moderate ischemic stroke (National Institutes of Health stroke scale score of 5 or less) or a TIA who were not undergoing thrombolysis or thrombectomy. The patients were assigned within 24 hours to receive a 30-day regimen of either ticagrelor plus aspirin or matching placebo plus aspirin. The primary outcome was a composite of recurrent stroke or death within 30 days. Secondary outcomes were the first subsequent ischemic stroke and the incidence of disability within 30 days. The primary safety outcome was severe bleeding.

Eleven thousand sixteen patients underwent randomization, and the primary outcome event occurred in 5.5% of the ticagrelor-aspirin group and in 6.6% in the aspirin-alone group (hazard ratio [HR], 0.83; $P = 0.02$). Ischemic stroke occurred in 5% of the ticagrelor-aspirin group and 6.3% in the aspirin-alone group (HR, 0.79; $P = 0.004$). Disability did not differ between the two groups. Severe bleeding occurred in 28 patients (0.5%) in the ticagrelor-aspirin group and in seven patients (0.1%) in the aspirin group.

The investigators concluded that the combination of ticagrelor and aspirin compared to aspirin alone was superior in reducing the risk of stroke or death within 30 days of an acute ischemic stroke or TIA, but disability did not differ between the groups. Severe bleeding was more common in the ticagrelor group. ■

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CME OBJECTIVES

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

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME QUESTIONS

1. **Regarding the treatment of neuromyelitis optica spectrum disorders, which of the following statements is true?**
   a. Corticosteroids are effective at preventing relapses.
   b. Azathioprine currently is the treatment of choice.
   c. Eculizumab is approved by the Food and Drug Administration for treatment of this disorder.
   d. Relapses are mild and of minimal concern regarding disability.
2. **Carcinomatous involvement of the brachial plexus:**
   a. primarily affects the upper trunk.
   b. primarily affects the middle trunk.
   c. primarily affects the lower trunk.
   d. may affect any portion of the brachial plexus.
3. **Patients with ischemic stroke related to atrial fibrillation, who undergo reperfusion therapy, should not have anticoagulation restarted because of a high risk of intracerebral hemorrhage.**
   a. True
   b. False
4. There is no proven, effective, or Food and Drug Administration-approved treatment for central retinal artery occlusion.
   a. True
   b. False
5. Cilostazol is an antiplatelet agent that appears to be at least as effective as aspirin for secondary stroke prevention.
   a. True
   b. False
6. Patients with acute ischemic stroke caused by large vessel occlusions in the anterior circulation should immediately undergo mechanical thrombectomy without administration of alteplase.
   a. True
   b. False
7. Mobile stroke unit treatment of acute ischemic stroke always results in better outcomes than acute hospital care.
   a. True
   b. False
8. COVID-19 is associated with multiple thrombotic complications, including a high rate of ischemic stroke.
   a. True
   b. False
9. After acute ischemic stroke, the combination of ticagrelor and aspirin is more effective and safer for secondary stroke prevention than taking aspirin alone.
   a. True
   b. False

[IN FUTURE ISSUES]

Stroke Alert