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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Treatment for Spinal Muscular Atrophy

By Renatta Knox, MD, PhD, and Devorah Segal, MD, PhD

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Dr. Knox and Dr. Segal report no financial relationships relevant to this field of study.

SYNOPSIS: In a randomized, double-blind, sham-controlled study of infants with spinal muscular atrophy (SMA) type 1, nusinersen treatment led to significant improvement in motor milestones and survival without significant adverse reactions. A safety trial of gene therapy for SMA type 1 demonstrated prolonged ventilator-free survival and improved motor milestones with minimal side effects.

SOURCES: Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med* 2017;377:1723-1732.

Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med* 2017;377:1713-1722.

In the Greek myth of the judgment of Paris, the prince Paris must choose among three goddesses, Aphrodite, Hera, and Athena, each with unique offerings, for the prize of the golden apple. We find ourselves in a similar circumstance, as several novel therapeutics are in the pipeline to treat spinal muscular atrophy (SMA), a debilitating neurologic disorder with an incidence of 1 in 10,000 live births. SMA type 1 is the most severe, presenting before age 6 months and usually resulting in death by age 2 years. SMA is caused by homozygous mutation or deletion of the SMN1 gene. However, there is a paralogue gene, SMN2, which normally produces low levels of functional SMN protein. Disease severity is correlated with the copies of SMN2, with more copies of SMN2 leading to a milder phenotype. Nusinersen, an antisense oligonucleotide drug, modulates SMN2 splicing to produce more functional SMN protein. In December 2016, the FDA made the decision to approve nusinersen for all types of SMA. The interim analysis of the Phase III sham-controlled study of nusinersen in patients with SMA type 1, which led to the landmark FDA decision, was published in the Nov. 2, 2017, issue of *The New England Journal of Medicine*. Additionally, this issue included the report of a Phase I safety study of a gene therapy approach that delivers a copy

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of SMN1, attractively packaged as a single-dose treatment for SMA type 1.

Finkel et al performed the first randomized, double-blind, sham-controlled Phase III study of nusinersen on 73 infants with SMA type 1 without significant respiratory disease (ENDEAR Trial). Subjects were assigned randomly to receive intrathecal nusinersen or sham treatments on days 1, 15, 29, and 64, with maintenance doses on days 183 and 302. They assessed motor function using two validated tools, the Hammersmith Infant Neurological Examination and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). The authors reported that in the final analysis, 51% of nusinersen-treated infants had a motor-milestone response compared to 0% of sham treated. The secondary outcome measure was event-free survival, defined as the proportion of infants who were alive without the use of permanent assisted ventilation, and, again, the authors noted a statistically significant difference between sham and treated patients. Adverse events were similar between both groups and included respiratory infections, pyrexia, and constipation, all of which likely were related to SMA and not the treatment. This study was terminated early for efficacy.

Mendel et al reported data on the first gene-replacement therapy for SMA using a single dose of intravenous adeno-associated virus 9 with functional SMN gene (scAAV9). Fifteen infants received low- or high-dose scAAV9 by 7 months of age and were subsequently assessed for adverse events, survival, need for permanent ventilator assistance, and motor milestones. All patients survived to at least 20 months without permanent ventilation compared to 8% of a historical control cohort not requiring permanent ventilation. Using CHOP-INTEND scores, patients in low- and high-dose cohorts had clinically significant improvement in motor milestones, with the high-dose cohort increasing scores by ~25 points. Of note, gene therapy was associated with an asymptomatic transaminitis, which was treated successfully with oral prednisolone.

■ COMMENTARY

These studies represent exciting advances in SMA therapeutics with two novel mechanistic approaches to increase functional SMN protein, leading to meaningful gains in motor milestones, improved functional status, and, most importantly, survival. Although nusinersen currently is FDA-approved for all types of SMA, clinicians soon will be faced with the difficult choice of which agent to use. Nusinersen currently is being delivered with multiple intrathecal doses for an unknown duration with a hefty price tag of $125,000 per dose, which is being negotiated in a dynamic insurance landscape. scAAV9 may be an attractive alternative, as it is given intravenously as a single dose and may prove efficacious with systemic SMA symptoms. However, this may come with a higher side effect profile, as seen with the transaminitis evident in the Phase I study. Oral agents are also in the pipeline, and include RO6885247 and RG7800, both SMN2-splicing modifiers, as well as small molecules targeting other pathways. The future likely holds trials with side-by-side comparisons of different agents as well as combinations of treatments targeting different molecular pathways all leading to exciting advances in this field and new hope for patients and their families. ■

ABSTRACT & COMMENTARY

Neurologic Consequences of Zika Virus Infection

By Joseph E. Safdieh, MD

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

SYNOPSIS: Neurologic sequelae of Zika virus infections include Guillain-Barré syndrome, encephalitis, transverse myelitis, and chronic inflammatory demyelinating polyneuropathy.

SOURCE: da Silva IRF, Frontera JA, Bispo de Filippis AM, et al. Neurologic complications associated with Zika virus in Brazilian adults. *JAMA Neurol* 2017;74:1190-1198.

Zika virus is a mosquito-born flavivirus that has emerged in Central and South America as well as the Caribbean and isolated parts of the United States. Transmission of infection can occur via a bite from an infected mosquito or via direct human-to-human sexual contact. Zika virus is known to cause microcephaly when pregnant women are exposed. However, other neurologic complications, mainly Guillain-Barré syndrome (GBS), have been described in association with Zika virus infections. Most of the reports of GBS and other neurologic complications of Zika in adults are based on retrospective case series.

Brazil encountered many cases of Zika virus infection in a 2015-2016 epidemic, with an estimated number of cases between 500,000-1.5 million nationwide. da Silva et al conducted a prospective, observational study in a single, large tertiary care academic hospital in Rio de Janeiro. The authors evaluated consecutive patients admitted between December 2015 and May 2016, and compared this cohort to a historical cohort in 2013-2014, before Zika virus existed in Brazil. Patients who were included in the analysis presented with a new-onset parainfectious or neuroinflammatory disease. Patients were considered to have recent exposure to Zika virus if rRT-PCR of serum or cerebrospinal fluid (CSF) was positive. If PCR was negative, the diagnosis also could be confirmed if serum or CSF Zika IgM was elevated in the presence of negative dengue serum IgM. If serum IgM for dengue was positive, further testing was needed to demonstrate that CSF IgM was negative, to exclude cross-reactivity.

Over the 5.2-month enrollment period, 40 patients were identified and included in this prospective analysis. These included 29 cases of GBS, seven cases of encephalitis, three cases with transverse myelitis, and one case of chronic inflammatory demyelinating polyneuropathy (CIDP). Median age of the patients was 44 years, and 38% were women. Eighty percent of the GBS/CIDP patients underwent electrodiagnostic studies. Compared to the reference period of 2013-2014, admissions for GBS, encephalitis, and transverse myelitis increased four-fold. Of the 40 patients included in the analysis, 35 (88%) had evidence of acute Zika virus infection. Three of the patients had positive Zika virus PCR and the remainder met diagnostic criteria by IgM testing. Positive testing for Zika infection was seen in 27 of 29 GBS patients, five of seven encephalitis patients, two of three transverse myelitis patients, and the single CIDP case. All patients were tested for HIV and other causes of these syndromes. Of the patients who tested negative for Zika virus, one had GBS following a yellow fever vaccine and two had encephalitis associated with chikungunya infection.

Of the patients who tested positive for Zika virus, 91% reported a viral prodrome, most commonly fever and rash. Median time from prodrome to development of neurologic symptoms was 10 days. Of the 35 patients who tested positive for Zika virus, 26% required admission to the ICU and 14% required mechanical ventilation. Three patients died: one with encephalitis who developed refractory brain edema and herniation, and two with GBS who developed hospital-associated pneumonia.

■ COMMENTARY

This is an important study because it collected patients prospectively, allowing for the evaluation of all patients who presented with a neuroinflammatory clinical syndrome. The study demonstrates that GBS is an important neurologic complication of Zika virus infection, which is consistent with all prior studies. Additionally, this study sheds new light on the neurologic complications of Zika virus infection, suggesting that encephalitis and transverse myelitis also may be associated with Zika virus infection. The study was limited by the authors pre-defining the syndromes that they suspected might be associated with Zika virus, possibly leaving out other syndromes that possibly could be associated if tested. However, overall, this study is valuable in that it demonstrates a significant increase in neuroinflammatory syndromes, presumably related to Zika infection, and expands the list of conditions that may be related to Zika infection. ■

ABSTRACT & COMMENTARY

MRI-guided FUS Thalamotomy for Medically Refractory Parkinson's Tremor

By Harini Sarva, MD

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

SYNOPSIS: This study comparing 20 individuals who received MRI-guided focused ultrasound thalamotomy with seven individuals who received sham treatment showed improvements in Parkinson's disease tremor. Side effects were similar to prior studies of this technology for essential tremor, with ataxia and limb/orofacial paresthesias being most common.

SOURCE: Bond AE, Shah BB, Huss DS, et al. Safety and efficacy of focused ultrasound thalamotomy for patients with medication-refractory, tremor-dominant Parkinson's disease: A randomized clinical trial. *JAMA Neurol* 2017; Oct. 30. doi:10.1001/jamaneurol.2017.3098.

This was a randomized, sham-controlled pilot study to assess the safety and efficacy of MRI-guided focused ultrasound (FUS) thalamotomy for the treatment of medically refractory tremor in tremor-predominant Parkinson's disease (PD). The patients were blinded for the first three months, after which those who received sham treatment were offered FUS. They were all followed unblinded for one year. All patients were prepared the same way. For the first three months, the patients and examiners were blinded. Those with tremor-predominant PD with severe, disabling, medication-refractory tremor were included. The FUS was planned and performed as in the previous essential tremor studies. The primary endpoint was a change in the Clinical Rating Scale for Tremor (CRST) Section A (assesses resting, postural, and action tremor) and Section B (assesses tremor while performing tasks such as handwriting) in the "on" medication state. Twenty-seven patients were enrolled, 20 in the treatment arm and seven in the sham procedure arm. The treated arm had a 62% reduction in the CRST scores from baseline whereas the sham arm had a 22% reduction from baseline. Secondary endpoints, such as improvements in the Unified Parkinson's Disease Rating Scale, were greater in the thalamotomy arm as opposed to the sham group. Thalamotomy and procedure-related adverse events were noted. In the thalamotomy group, ataxia and limb and orofacial paresthesias were the most common. At the one-year mark, 19% had persistent paresthesia and 4% had ataxia. Two had mild, transient hemiparesis. The common procedure-related adverse events were headache and vertigo. All patients were available for the three-month follow-up but after unblinding, six of the seven who received sham treatment received the FUS thalamotomy. Six of the original 20 treated subjects did not have follow-up at one year. Of the six who later received the treatment after unblinding, two had very good tremor control, one had marginal control, and three had inadequate tremor control. Of the 14 of the original 20 from the treatment cohort, 13 reported a positive outcome.

■ COMMENTARY

Deep brain stimulation (DBS) has been an effective surgical treatment for PD motor symptoms for more than a decade. However, implantable hardware, insufficient numbers of neurologists with DBS programming experience, and the invasiveness of the surgery make FUS lesioning a promising option to treat medically refractory PD symptoms. For those who have cognitive or medical contraindications to DBS, FUS offers a means of improving quality of life. The rationale for lesioning the ventral intermedius nucleus (VIM) thalamus is clear, as the tremor circuitry in PD likely involves the dentato-rubro-thalamic tracts. However, while tremor can be treated by lesioning this target, remaining PD symptoms would not respond to thalamic lesioning. Subthalamic nucleus (STN) and globus pallidus interna (GPi) would be the preferred targets, and studies of those targets are required in PD. An important consideration is that FUS is still a lesioning procedure, and in PD, both sides would need to be treated to obtain adequate symptom control. However, lesioning of bilateral targets, GPi, STN, or VIM would lead to unwanted side effects (dysarthria, ataxia, corticospinal tract involvement).

Thus, DBS remains a better option when bilateral surgical treatment is warranted. Another benefit of DBS over FUS is the use of electrophysiology in targeting the specific nuclei, but with the use of more advanced MRI technology such as tractography, visualization of the nuclei during FUS procedures is evolving. Despite the small sample size, this is still a promising study and opens the door for consideration of FUS in the treatment of PD, enabling better treatment of patients with medically refractory motor symptoms who cannot have DBS. ■

ABSTRACT & COMMENTARY

Optimizing Brain Oxygen in Severe Traumatic Brain Injury

By Alexander E. Merkler, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a Phase II, single-blind, randomized, multicenter trial, the use of intraparenchymal brain tissue oxygenation monitoring reduced brain tissue hypoxia in patients with severe traumatic brain injury.

SOURCE: Okonkwo DO, Shutter LA, Moore C, et al. Brain oxygen optimization in severe traumatic brain injury phase-II: A phase II randomized trial. *Crit Care Med* 2017;45:1907-1914. doi: 10.1097/CCM.0000000000002619.

Traumatic brain injury (TBI) remains a significant public health burden and accounts for 30% of all injury-related deaths in Americans.[1] In 2010, 25 million people sustained a TBI.[1] Persons with TBI and a Glasgow Coma Scale score of 3-8 are considered to have severe TBI. Patients with severe TBI are at a high risk for mortality and long-term cognitive, motor, and psychological disability. Furthermore, the societal and economic toll of TBI is massive, approximately $76 billion in 2010.[1] Therefore, further strategies are necessary to reduce secondary brain injury and improve long-term outcomes.

Prior studies in patients with severe TBI have focused on reduction of raised intracranial pressure (ICP) as a means to improve neurological outcomes. However, in a landmark randomized, controlled trial, Chesnut et al failed to show an improvement in mortality or neurological outcomes using targeted ICP reduction via ICP monitoring in patients with severe TBI.[2] Nonetheless, ICP monitoring in patients with severe TBI remains a level IIB recommendation from the Brain Trauma Foundation's: Guidelines for the Management of Severe TBI.[3] Advanced cerebral monitoring, including brain tissue oxygenation ($PbtO_2$), represents another physiological variable that may be targeted to reduce secondary brain injury and improve outcomes. Brain oxygenation is important to allow normal cellular metabolism; a decrease in brain oxygen delivery may lead to secondary brain injury and, as a consequence, poor neurological outcomes. Moreover, a decrease in $PbtO_2$ may herald elevated ICP and, therefore, may serve as a more valuable therapeutic target. Indeed, prior observational studies suggest that $PbtO_2$-guided therapy is associated with improved outcomes after severe TBI.[4] Thus, Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II (BOOST II) was created as a Phase II clinical trial to assess both the feasibility and safety of early $PbtO_2$-directed therapy in patients with severe TBI.

BOOST II was a two-arm, single-blind, prospective, randomized clinical trial performed at 10 Level 1 trauma centers. Patients with non-penetrating severe TBI were randomized to receive either ICP-only monitoring or ICP + $PbtO_2$ monitoring. Both groups received intraparenchymal monitors, which had both ICP and $PbtO_2$ monitoring capabilities. In the ICP-only group, a cover was placed over the $PbtO_2$ monitor so that the treating physicians were blinded to the $PbtO_2$ values. Treating physicians followed a stepwise treatment algorithm for elevated ICP (> 20 mmHg) in the ICP-only arm and elevated ICP or brain hypoxia ($PbtO_2$ < 20 mmHg) in the ICP + $PbtO_2$ monitoring arm. These algorithms used an explicit set of interventions that addressed isolated elevated ICP, isolated brain hypoxia, or simultaneous elevated ICP and brain hypoxia. Monitors were left in the brain until patients awoke from coma, when ICP and $PbtO_2$ values were normal for > 48 hours, or when the monitors had been in place for five days. The primary outcome was the physiologic efficacy of $PbtO_2$ monitoring, defined as the duration of time with brain hypoxia. Safety outcomes and six-month neurological outcomes also were recorded.

Of 119 patients, 62 were randomized to the ICP-only group and 57 to the ICP + $PbtO_2$ group. Overall, the duration of brain hypoxia was significantly less in the ICP + $PbtO_2$ group than the ICP-only group. Treatment of reduced $PbtO_2$ decreased the absolute duration of brain hypoxia by 29%. There was no difference in the proportion of time with an elevated ICP. Intraparenchymal monitors were placed on average nine hours after brain injury, and there was no difference in serious adverse events between the two groups. There was no difference in six-month neurological outcomes between the two groups, although there was a trend toward improved outcomes in the ICP + $PbtO_2$ intervention group.

■ COMMENTARY

This study showed that early $PbtO_2$-directed therapy in patients with severe TBI is feasible and associated with a reduction in the amount overall time with brain hypoxia. As brain hypoxia is associated with loss of normal cellular metabolism and resultant tissue death, these findings suggest a possible interventional target to avoid secondary brain injury and improve neurological outcomes. On the other hand, there was no difference in the duration of time with elevated ICP, and although safety outcomes were no different in the treatment groups, there was no control group (without an intraparenchymal monitor) of management via imaging and clinical parameters alone (found to be equally as good as ICP-monitoring in the Chesnut et al randomized, controlled trial).[2]

Overall, severe TBI represents a devastating neurological disease in which novel strategies for preventing secondary brain injury and improving neurological outcomes are imminently needed. Prior randomized clinical trials in patients with severe TBI have failed to show improvement in neurological outcomes after various interventions, including decompressive craniectomy,[5,6] induced hypothermia,[7] or targeted ICP monitoring therapy.[2] The promising results from BOOST-II suggest that $PbtO_2$-targeted therapy reduces the duration of brain hypoxia. Further study of whether reduction of brain hypoxia results in improved neurological outcomes is necessary. ■

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ABSTRACT & COMMENTARY

Systemic Immune Activation and the Course of Amyotrophic Lateral Sclerosis

By Norman Latov, MD, PhD

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Dr. Latov reports he is a consultant for Pfizer, receives grant/research support from Shire, and owns stock in Therapath LLC.

SYNOPSIS: Activation of the immune system has been recognized in patients with amyotrophic lateral sclerosis, and immune activation may influence the course of the disease and the speed of progression.

SOURCE: Murdock BJ, Zhou G, Kashian SR, et al. Correlation of peripheral immunity with rapid amyotrophic lateral sclerosis progression. *JAMA Neurol* 2017; Sept. 25.doi:10.1001/jamaneurol.2017.2255.

The number and types of circulating immune cells were assessed and tracked in 119 patients with amyotrophic lateral sclerosis (ALS) and 35 healthy controls to determine whether they are altered in and whether any alterations correlated with disease progression. Compared to controls, patients with ALS were found to have an increased numbers of total leukocytes, neutrophils, monocytes (CD16+ and CD16-), and natural killer cells, and an acute transient increase in CD11b+ myeloid cells expressing HLA-DR, CD11c, and CX3CR1. Changes in immune cell numbers, particularly neutrophils and CD4+ T cells, significantly correlated with disease progression as measured by the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale. The authors speculated that changes in the immune system contribute to the pathogenic features of ALS and may influence its time course and progression.

■ COMMENTARY

In ALS, there is evidence for systemic immune activation, as evidenced by increased levels of autoantibodies,[1] complement activation products,[2] and pro-inflammatory cytokines.[3] In this paper, the authors reported that patients with ALS also have increased numbers of circulating immune cells, and that the increase in neutrophils and CD4+ T cells correlated with disease severity and progression.

As with other disease associations, questions arise as to whether the association is a cause, contributory factor, consequence, or unrelated to the disease. The observation that the changes in cell numbers correlates with disease progression suggests that the two are related.

There is considerable evidence that neuroinflammation contributes to motor neuron degeneration. This process is thought to be mediated by microglia that secrete pro-inflammatory cytokines and neurotoxins. Studies of postmortem spinal cord samples from ALS cases reveal the presence of increased numbers of activated microglia and lymphocytes surrounding motor neurons, and the microglial activation occurs in the early stages of ALS.[4] Activation of microglia might occur secondarily to the neuronal degeneration, possibly in response to misfolded protein aggregates, or be induced by other factors, such as autoimmunity[5] or endogenous retroviruses.[6] In either case, they would contribute to motor nerve degeneration.

In preclinical studies, inhibition of complement C5a-C5a1 receptor signaling ameliorated disease pathology in an SOD1 mouse model of ALS.[7] Disruption of pathways involved in neuroinflammation offers potential therapeutic targets in patients with ALS. ■

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ABSTRACT & COMMENTARY

Neurologic Complications of Checkpoint Inhibitors

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Anti-programmed death 1 antibodies (checkpoint inhibitors) have become a mainstay in the treatment of many types of cancers, and now are known to cause frequent neuromuscular adverse effects that can cause severe disability or death if not recognized or treated promptly.

SOURCE: Kao JC, Liao B, Markovic SN, et al. Neurological complications associated with anti-programmed death 1 (PD-1) antibodies. *JAMA Neurol* 2017;74:1216-1222.

Anti-programmed death 1 (PD-1) antibodies, originally approved in the United States for the treatment of melanoma in 2014 and for non-small cell lung cancer in 2015, are used for the treatment of solid-organ tumors, including renal cell cancer, head and neck cancer, urothelial cancer, and Hodgkin's lymphoma. Phase III trials are underway for other tumors, including bladder, ovarian, and brain. Adverse events, as initially reported, were thought to be rare, occurring in < 1% of patients, and included thyroid dysfunction, pneumonitis, colitis, hepatitis, nephritis, hypophysitis, uveitis, type 1 diabetes, and myositis. However, reports of neurological complications associated with anti-PD-1 therapy are increasing, and most often are neuromuscular in nature, including myasthenia gravis, necrotizing myopathy, vasculitic neuropathy, and polyradiculoneuropathy, as well as focal seizures associated with inflammatory cerebral lesions on magnetic resonance imaging, limbic encephalitis, and retinopathy. What are the frequency, phenotype, and severity of neurological complications from PD-1 antibody use?

In a single-center, retrospective, cohort study, undertaken by the departments of Neurology, Oncology, and Pharmacy Services at the Mayo Clinic from September 2014 to May 2016, using the Mayo Cancer Pharmacy Database, patients who received anti-PD-1 monoclonal antibodies (pembrolizumab or nivolumab) for the treatment of malignant melanoma or other solid organ tumor and developed neurologic disorders within 12 months of anti-PD-1 antibody use were identified. Neurologic symptoms attributable to metastatic disease or other cancer treatment were excluded. Severity was measured using the modified Rankin Scale.

Among 347 patients who received anti-PD-1 antibody, 204 received pembrolizumab, 142 received nivolumab, and one received both. Neurologic complications occurred in 10 patients (2.9%), eight men and two women, after a median of 5.5 cycles of anti-PD-1 therapy, seven during pembrolizumab and three during nivolumab treatment. Myopathy (n = 2), one mild and one severe necrotizing, and neuropathy (n = 4), axonal, demyelinating, or mixed, were the most common adverse events, with individual cases of cerebellar ataxia, autoimmune retinopathy, bilateral internuclear ophthalmoplegia, and headache. Time to maximum symptom severity varied from one to 90+ days. One patient died, and nine improved, one spontaneously and eight with immunotherapy, including intravenous immunoglobulin, corticosteroid, and plasma exchange. Non-neurologic, immune-mediated, adverse events occurred in five of these patients as well, including hypothyroidism (n = 3), colitis (n = 2), and hepatitis (n = 1). Anti-PD-1 neurologic adverse events may be rapid and life threatening, necessitating prompt recognition and withdrawal of the inciting agent.

■ COMMENTARY

Cancer immunotherapy, initiated in 1891 when New York surgeon William Coley injected bacterial products into a sarcoma and watched it shrink, has today joined

surgery, radiation, and chemotherapy as a pillar of cancer treatment. Initially focused on accelerating T cell activity, today immunotherapy involves immune-checkpoint inhibitors, such as PD-1 monoclonal antibodies, which "release the immune system's brakes to unleash anti-tumor immune responses." Discovered in 1992, PD-1 is expressed on B cells and peripheral-activated CD4+ and CD8+ T cells, and suppresses T-cell activation, proliferation, and effector function. Thus, PD-1 blockade activates an antitumor immune system, preferentially recognizing tumor-derived antigens, rather than self-antigens. Immune-related adverse events may occur at any time but most occur during the first four months, with skin, gastrointestinal, and hepatic complications occurring early, within the first two months, and pulmonary, endocrine, and renal adverse events occurring beyond two months. Patients who fail to respond to immunotherapy may lack preexisting antitumor T-cell responses, and combination immune-checkpoint inhibitor therapy trials are underway to address this issue.[1] ■

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CME QUESTIONS

1. **Nusinersen is approved for which of the following?**
   a. Infants with SMA Type 1
   b. Infants with SMA Type 1 not on a ventilator
   c. Infants or children with any type of SMA
   d. All types of SMA, regardless of age
   e. All of the above
2. **Which of the following neurological illnesses may follow Zika virus infection?**
   a. Guillain-Barré syndrome
   b. Microcephaly
   c. Encephalitis
   d. Transverse myelitis
   e. All of the above
3. **Which of the following is *not* true regarding the results of this study?**
   a. FUS treatment had no adverse events.
   b. VIM thalamotomy was performed to treat medically refractory tremor.
   c. There was a 62% improvement in the CRST A in the treatment arm.
   d. Thirteen of the 14 in the treatment arm who were available for the one-year follow-up reported improvement in their tremor.
4. **Treatment of severe traumatic brain injury includes all of the following *except*:**
   a. decompressive craniectomy.
   b. hyperosmolar therapy (mannitol and/or hypertonic saline).
   c. induced hypertension.
   d. targeted ICP monitoring therapy.
   e. therapeutic hypothermia.
5. **Immune activation in amyotrophic lateral sclerosis includes all of the following elements *except*:**
   a. increased total leukocytes.
   b. increased total neutrophils.
   c. increased total monocytes.
   d. increased total plasma cells.
   e. increased total killer T cells.
6. **Neurologic adverse events with the use of anti-programmed death 1 (PD-1) antibodies (checkpoint inhibitors) include:**
   a. myopathy.
   b. neuropathy.
   c. cerebellar ataxia.
   d. headache.
   e. All of the above

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.

[IN FUTURE ISSUES]

Stroke ALERT Update