What’s New with RxPups?

This semester the Student Society of Pediatric Advocates (SSPA) at the University of Georgia College of Pharmacy added two new positions to the executive board, event coordinator co-chair and first-year pharmacy liaison.

Over the past fall semester, members attended four general body meetings which included a presentation about homeopathic medicine safety and a residency information presentation given by Children’s Healthcare of Atlanta pharmacy resident guest speaker Dr. Alessia Jankowski. During these meetings and presentations, members gained knowledge about the field of pediatric pharmacy. Also, members actively took part in multiple events such as presenting on the importance of immunization to students at Pharmtoberfest (UGA College of Pharmacy Health Fair) and on over-the-counter medication safety to the youth in the Athens community at Whatever It Takes (WIT) mentoring program. RxPups values giving back to the community. Members volunteered at the Food Bank of Northeast Georgia to pack nutrient rich bags of food for local food-insecure students and their families.

The executive board of RxPups is excited to see the events and community outreach projects come to fruition for the upcoming spring semester. RxPups has facilitated the College of Pharmacy’s involvement with UGA Miracle. A fundraising competition between different professional organizations at the College of Pharmacy benefitting UGA Miracle begins January 7th. UGA Miracle raises funds for Children’s Healthcare of Atlanta. Dance Marathon is UGA Miracle’s largest event of the year; RxPups members will be representing the College of Pharmacy at Dance Marathon on February 22nd.

As an organization, we feel that it is our duty as future pharmacists to not only educate ourselves on pediatric pharmacy but also the community around us. The purpose of this newsletter is to educate pharmacy students about pediatric pharmacy.

If you would like to contribute to PediaNews, please contact Nour Burjak at nourb@uga.edu
NEW DRUG UPDATE:

ONASEMNOGENE ABEPARVOVEC-XIOI (ZOLGENSMA®)

By: Nina Murphy, Pharm.D. Candidate 2021

FDA Approval Date: May 24, 2019

**Indication:** Recombinant adeno-associated virus vector-based gene therapy for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron-1 (SMN1) gene.

**Comparable drug(s):** Currently, nusinersen (Spinraza®), a survival motor neuron-2 (SMN2) antisense oligonucleotide, is the only other FDA approved drug available on the market for the treatment of SMA in pediatric and adult patients.

**Disease State/Drug Class Summary:** SMA is a progressive, monogenic motor neuron disease that affects the motor nerve cells in the spinal cord. It is caused by a mutation in the survival motor neuron gene 1 (SMN1), which in healthy individuals produces a protein critical to the functioning of motor neurons. In an individual with SMA, degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem occurs, leading to progressive muscle weakness and atrophy. Ultimately, this results in the inability to achieve motor milestones (such as walking, eating, or breathing), the need for permanent mechanical ventilation by the age of 2 years, and/or death. There are five types of SMA (0 through 4) which are based on the age of symptomatic onset and highest physical milestone achieved (Figure 1). SMA type 0 (prenatal onset) and SMA type 1 (infantile onset) are the most common and most severe types. SMA is the most common monogenic cause of infant mortality and affects approximately 1 in 11,000 births, and about 1 in every 50 Americans is a genetic carrier for SMA.

**Efficacy:** FDA approval of Zolgensma® was based on the STR1VE and START clinical trials. STR1VE, an ongoing, open-label, single-arm, single-dose, multi-center clinical trial evaluated Zolgensma® in 21 pediatric patients less than 2 years old (age range 0.5 to 5.9 months) with infantile-onset SMA (onset before 6 months old) and genetically confirmed bi-allelic SMN1 mutations. All patients had bi-allelic SMN1 gene deletions, two SMN2 gene copies, and an absence of the c.859G>C modification in exon 7 of the SMN2 gene (predicts a milder phenotype). The all patients received one dose of 1.1 x 10¹⁴ vector genomes/kg of Zolgensma®. Based on the natural progression of SMA, patients who met the inclusion criteria were not expected to attain the ability to sit without support and only ~25% of these patients were expected to survive beyond 14 months after treatment.

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**Clinical classification of spinal muscular atrophy (SMA)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of onset</th>
<th>Requires respiratory support at birth</th>
<th>Able to sit</th>
<th>Able to stand</th>
<th>Able to walk</th>
<th>Life expectancy</th>
<th>Predicted SMN2 copy number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Prenatal</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&lt;6 months</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>&lt;6 months</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&lt;2 years</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>6 to 18 months</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>10 to 40 years</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>&gt;18 months</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Assisted</td>
<td>Adult</td>
<td>3 to 4</td>
</tr>
<tr>
<td>4</td>
<td>&gt;5 years</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Adult</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>

**Figure 1:** [http://journal.frontiersin.org/article/10.3389/](http://journal.frontiersin.org/article/10.3389/)
As of March 2019, 19 patients were alive without permanent ventilation and were still continuing in the trial. Of these 19 patients, 13 reached 14 months of age without permanent ventilation, which was a co-primary efficacy endpoint. One patient died (age 7.8 months) due to disease progression, and one patient (age 11.9 months) withdrew from the study. 10 of the 21 patients achieved the ability to sit without support for > 30 seconds between 9.2 and 16.9 months of age.

START was a pivotal Phase 1, open-label, single-arm, ascending-dose clinical trial that showed that treatment with Zolgensma® was associated with an increased survival rate compared to the normal progression of SMA. START also demonstrated that Zolgensma® was associated with the achievement and maintenance of motor milestones that infants with SMA type 1 normally would not be expected to achieve. 15 patients (age range 0.9 to 7.9 months) with infantile-onset SMA meeting the inclusion criteria received a single dose of intravenous adeno-associated virus serotype 9 carrying SMN complementary DNA encoding the missing SMN protein, with 3 in a low-dose cohort and 12 in a high-dose cohort. The precise dosages received by patients were unclear due to a change in the method of measuring Zolgensma® concentration and to decreases in the concentration of stored Zolgensma® over time. As of August 2017, all 15 patients were alive and event-free at 20 months of age. One patient in the low-dose cohort met the endpoint of permanent ventilation and none of the patients in the low-dose cohort were able to sit without support, or to stand or walk.

In contrast, all 12 patients in the high-dose cohort were alive without permanent ventilation. Moreover, 9 of the 12 patients were able to sit without support for > 30 seconds and 2 patients were able to stand and walk without assistance (See Table 2). Comparison of the results between both the low- and high-dose cohorts showed a dose-response relationship that supported the effectiveness of Zolgensma®.

At the 2019 American Academy of Neurology (AAN) Annual Meeting, AveXis presented interim long-term follow-up data from the START trial showing the continued robustness of Zolgensma® in the original cohort nearly four years after the initiation of treatment. A long-term follow-up of the START trial included a total of 10 of the 12 patients in the original cohort that voluntarily enrolled. All 10 patients were alive and event-free, where an event is defined as either death or at least 16 hours per day of required ventilation support for 14 consecutive days. Moreover, all 10 patients maintained motor function and milestones gained and none of the patients had any additional requirements for nutritional or ventilatory support. Lastly, no new treatment-related adverse events emerged during this follow-up period11.
Warnings and precautions:

- **US BOXED WARNING: Acute serious liver injury.** Acute serious liver injury and elevated serum aminotransferases can occur with Zolgensma®. Patients with preexisting liver impairment may be at higher risk. Clinical examination and laboratory testing to assess liver function (hepatic aminotransferases, total bilirubin, and prothrombin time) should be performed in all patients prior to infusion. Administer systemic corticosteroid to all patients before and after Zolgensma® infusion to attenuate the risk of elevated serum aminotransferases. Continue to monitor liver function for at least 3 months after infusion.

- **Thrombocytopenia.** Transient decreases in platelet counts were observed at different time points after Zolgensma® infusion. Monitor platelet counts before infusion and regularly afterwards.

- **Elevated Troponin-1.** Transient increases in cardiac troponin-1 levels were observed following Zolgensma® infusion in clinical trials. The clinical importance of these findings is unknown; however, cardiotoxicity was observed in animal studies. Monitor troponin-1 levels before Zolgensma® infusion and on a regular basis for at least 3 months afterwards.

**Most common adverse events:** Elevated aminotransferases (>5%) and vomiting (>5%) are common adverse events.

**Usual dosage and administration:** In infants and children less than two years of age, the recommended dose is 1.1 x 10^{14} vector genomes/kg as a single dose. Zolgensma® should be administered as a slow IV infusion over 60 minutes; do not administer as IV push or bolus. Flush with saline before and after administration.

Note: Administer oral corticosteroids (e.g., prednisolone 1 mg/kg/dose once daily or equivalent) one day prior to infusion and continue for at least 30 days to help prevent hepatotoxicity through their anti-inflammatory and immunosuppressive properties. At the end of 30 days, clinically assess liver and hepatic function. If findings are unremarkable, taper prednisolone over 28 days. If evidence of hepatic impairment exists, continue oral prednisolone until AST/ALT <2 x ULN and all other assessments return to normal, then taper over 28 days. If unresponsive to corticosteroid therapy, consult a healthcare provider.

**Available products:** Zolgensma® is a suspension for intravenous infusion. Zolgensma® is shipped frozen in either 5.5 mL or 8.3 mL vials. Zolgensma® is provided as a customized kit to meet dosing requirements for each patient, with each kit containing: Two to nine vials of Zolgensma® and one alcohol wipe per vial.

**Advantages:** Zolgensma® is administered as a one-time single dose. In comparison, Spinraza® is administered by intrathecal injection starting with four loading doses (the first three loading doses are given at 14 day intervals, while the fourth loading dose is given 30 days after the third) and a maintenance dose that is given once every four months.

**Disadvantages:** Treatment for SMA has been mainly supportive, and the only current available treatments for SMA are Zolgensma® and Spinraza®. The development of further drugs for the treatment of SMA is warranted. Furthermore, the estimated cost of one dose of Zolgensma® is $2,125,000, making it the most expensive drug in the world. In comparison, the cost of each dose of Spinraza® is $125,000.

**Special note:** On June 28, 2019 AveXis Inc., the product’s manufacturer, reported a data manipulation issue to the FDA that impacted the accuracy of certain data pertaining to product testing that was performed in the animal studies submitted in the biologics license application (BLA). On August 6, 2019 the FDA issued a public statement on data manipulation/inaccuracy issues with Zolgensma®. According to the FDA, the manipulated data involved the production process for the product and did not affect the efficacy or safety results from the human clinical trials. The FDA is carefully assessing the situation and remains confident that Zolgensma® should remain on the market.

https://www.zolgensma.com/
TREATMENT AND PREVENTION OF RSV IN INFANTS AND CHILDREN

By: Gabrielle Bachner, Pharm.D. Candidate 2022

Respiratory syncytial virus (RSV) is a respiratory virus discovered in 1956 and is the most common cause of bronchiolitis and pneumonia in children under one year of age in the United States. Symptoms of RSV include runny nose, decreased appetite, fever, coughing, sneezing, and wheezing. Infants may present with irritability, decreased activity, and trouble breathing. RSV is a serious and potentially dangerous disease as it is responsible for about 33 million lower respiratory tract illnesses, 3 million hospitalizations, and almost 199,000 childhood deaths worldwide. Most children contract RSV by 2 years of age and it can reinfect older children and adults. In the majority of these cases, the child’s immune system will sufficiently fight off RSV in one to two weeks; however, some cases do require hospitalization, especially in children under the age of 6 months. Early detection of symptoms is a vital aspect of preventing the development of further complications such as pneumonia or bronchiolitis. The current mainstay in treatment of RSV is supportive care, but in specific pediatric populations, such as those with the risk factors presented in Table 1, there may be appropriate preventative and treatment options. In this article, these other treatment and prevention options will be discussed.

Risk Factors of RSV

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Premature infants (Born prior to 29 weeks gestation)</td>
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<tr>
<td>Infant under the age of 6 months</td>
</tr>
<tr>
<td>Child younger than 2 years with a chronic lung or heart disease</td>
</tr>
<tr>
<td>Child with a suppressed immune system</td>
</tr>
<tr>
<td>Child with a neuromuscular disorder</td>
</tr>
</tbody>
</table>

Table 1

References

There are several laboratory tests that can confirm the presence of RSV. In infants and children, the most common and effective methods for confirming RSV infection include a real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) or antigen detection tests. The sensitivity within these tests is typically 80-90% in children and infants. Once diagnosed with RSV, infants and children may be treated with ribavirin, which is the only FDA approved antiviral treatment for this specific patient population. Infants with a severe infection, requiring mechanical ventilation, benefit most from treatment with ribavirin. Ribavirin inhibits the replication of both RNA and DNA viruses, decreasing the amount of virus in the body, through interference of RNA capping, polymerase inhibition, lethal mutagenesis, inosine monophosphate dehydrogenase inhibition, and immunomodulatory effects. Each process is representative of direct and indirect mechanisms of action against viruses.

Palivizumab is indicated for the prevention of RSV infection. Palivizumab is a humanized monoclonal antibody which specifically targets the A antigenic site of the F protein in RSV. Palivizumab is limited to patients at a higher risk of an RSV infection. These specific risk factors used to prioritize candidates for palivizumab (Table 2) should be assessed for all patients that meet the criteria for increased risk of RSV infection. Palivizumab is active against both the A and B subtype of RSV.

Another option for prophylactic treatment of RSV is Medi-534, a live attenuated intranasal vaccine for use against RSV and parainfluenza. Medi-534 is currently in Phase 1 trials and has demonstrated safe usage in adults as well as children ranging from 1-9 years old. There is currently no information addressing the use of Medi-534 in the pediatric population less than 1 year old.

Other options are being studied in calf models, which look to be promising for the development of new prophylactic treatments. The disease seen in cattle, bRSV, is similar to the disease seen in humans; new treatments can be tested in the calves to see if it could be efficacious in humans.

Currently, there are different vaccinations and treatments being tested for the prevention of RSV. There are also some other options that can be given to patients as prophylactic treatment. This could lead to the prevention of RSV and in turn protect future children from this potentially deadly disease. As pharmacists, it is important to identify patients who are at risk of an RSV infection and ensure adequate prevention and treatment methods are provided. Pharmacists can also play a crucial role in providing proper education to parents about prevention, vaccinations, and treatment, allowing parents and caregivers to make well informed decisions for their children.

<table>
<thead>
<tr>
<th>Risk Factors for Prioritization of Palivizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (under 24 months) who are profoundly immunocompromised during RSV season</td>
</tr>
<tr>
<td>Preterm Infants (born before 29 weeks) without Chronic Lung Disease of Prematurity or Congenital Heart Disease</td>
</tr>
<tr>
<td>Preterm Infants (born before 32 weeks) with Chronic Lung Disease of Prematurity</td>
</tr>
<tr>
<td>Infants (under 12 months) with Hemodynamically Significant Congestive Heart Disease</td>
</tr>
<tr>
<td>Children in their First Year of Life with Pulmonary Abnormalities or Neuromuscular Disease that Impairs Ability to Clear Secretions from the Upper Airway</td>
</tr>
</tbody>
</table>

Table 2

References


AN UPDATE ON PEDIATRIC PEANUT ALLERGIES AND HOW TO OVERCOME THEM
By: Gelina Sani, Pharm.D. Candidate 2023

Peanuts and peanut products can be found in a wide variety of foods in the United States including peanuts, peanut butter, or peanut oil and can be traced in many prepared foods. Most people are familiar with more obvious examples like a peanut butter and jelly sandwich or candy with chocolate and peanut butter. However, prepared foods can be fried in peanut oil, and peanuts are often a flavoring ingredient in domestic and international cuisine. While many foods are comprised of peanuts or its associated products, up to 2.5% of pediatric patients are diagnosed with a peanut allergy with increasing rates since 19971. These statistics are alarming because peanut allergies are the leading cause of allergy-related death in the pediatric population. To overcome this challenge, scientists have begun manipulating the human immune system by introducing peanut antigens. With ongoing clinical trials targeting the peanut antigen-human immune system relationship, it may be possible to decrease the amount of allergy-related pediatric deaths as well as the severity of the allergy itself2.

A sensitization study used for peanut allergies involves patient exposure to peanut antigens and tracking the severity of their allergic reaction at different time points. The goal is to evaluate the relationship between early exposure to peanut antigens and severity of the allergy, and measure the immune system functionality to recognize peanut antigens. In 2008, one study looked at the prevalence of a peanut allergy in breastfed newborns and children, 4-18 years old. Investigators found there was a strong inverse relationship between peanut consumption during infancy and prevalence in childhood, indicating that it is possible to condition the immune system to become sensitized to peanuts3. This data supports the theory that introducing peanuts to children earlier may avoid severe allergy later in life.

Populations where sensitization may not be a valid option include children who cannot tolerate sensitization or are past infancy. In addition to the sensitization procedure, immunotherapies have been explored, targeting the immune response reactions that elicit peanut allergies. Immunotherapy involves exposing patients to isolated peanut antigens by mouth to investigate the relationship between the severity of the immune response and the dose of the peanut antigen4. In one study, AR101, a GMP peanut protein product resulted in desensitization in children and adolescents, less than 18 years of age who were highly allergic to peanuts5. Further research is needed to confirm the efficacy, safety, and cost-effectiveness of immunotherapies for peanut allergies6. However, if sensitization or desensitization is deemed inappropriate for patients, immunotherapy may play a role as an alternative therapy.

Reducing the severity of the peanut allergies would increase the quality of life of affected pediatric patients. Children would be able to experience the world without the constant worry of being exposed to peanut antigens, which may result in moderate to severe allergic reactions. The parents would also be more at ease without worrying about their child’s safety around peanut-containing foods. Overall, the ideal goal is limited impairment of daily activities associated with the constraints of having a moderate to severe peanut allergy. With newer technologies, such as desensitization and immunotherapy, children are more likely to assume normal lives.

References

OUR MISSION

The mission of RxPups is to bring awareness to the proper use of medication therapy in pediatric populations through various service and education-based initiatives. Service activities center around lending our medication-based knowledge to pediatric patients and their parents in our community. Overall, RxPups advocates for the safety and happiness of young patients while learning and having fun along the way. As an organization, we feel that it is our duty as future pharmacist to not only educate ourselves on pediatric pharmacy but also the community around us. The purpose of our newsletter is to educate pharmacy students about pediatric pharmacy.