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PEDIANEWS

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OUR MISSION

The Student Society of Pediatric Advocates is a student organization affiliated with the University of Georgia College of Pharmacy. We are a student group associated with the Pediatric Pharmacy Advocacy Group. The Mission of the SSPA 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. Educational activities are directed toward student members in an effort to safely and effectively extend pharmacy practice to pediatric populations by building relationships with mentors and professionals in the health care community, as well as supplementing didactic coursework with lectures by specialists and our peers. Overall, SSPA advocates for the safety and happiness of young patients while learning and having fun along the way. The purpose of our newsletter is to educate pharmacy students about pediatric pharmacy and advocate for pediatric patients within the University of Georgia College of Pharmacy.

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Gene Sequencing in Pediatric Cancer Treatment

Written by Emma Thomas, Pharm.D Candidate 2026

Pediatric patients at high risk for de novo cancer and pediatric patients with relapsed cancer have poor outcomes, with a survival rate of less than 20% after treatment.[1] Next generation sequencing (NGS) of pediatric cancer patients' genes has been studied to improve treatment efficacy and patient outcomes.[2] By using NGS techniques, physicians can analyze the genome of tumors and look for specific alterations such as single nucleotide variations, copy number variations, rearrangements, insertions, and deletions.[3] These findings aid medical teams in identifying targetable alterations and curating more personalized and effective treatment plans. Most studies researching the effects of gene sequencing treatment and outcomes for patients with tumors have been focused on adult patients, not pediatric patients.[1] Children's Healthcare of Atlanta (CHOA) recently performed a study in which gene sequencing effects were analyzed specifically in pediatric cancer patient treatments and outcomes.

In their study, CHOA took samples of germline and tumor tissue then subjected them to whole-transcriptome sequencing (RNA-seq) as well as whole-exome sequencing (WES). RNA-seq is a technique of gene observation that is a cheaper and simpler alternative to exome sequencing in turn allowing physicians to analyze the level of gene expression and splicing patterns in the tissue sample.[4] To avoid missing poorly expressed genes, RNA-seq was coupled with WES in the study. The complementary functions of the two techniques allowed the physicians to capture a wide range of genomic information with the WES technique, which were coupled with RNA-seq's ability to identify specific oncogenic gene fusions and alternative transcript variants.[5]

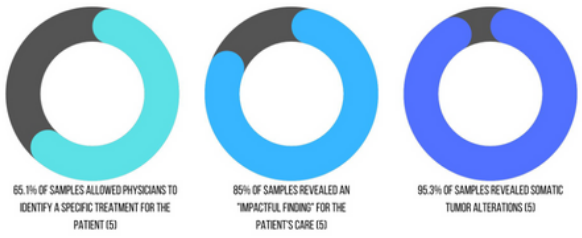
The depth of the collected data allowed physicians to make informed clinical decisions in identifying risk and determine therapy in the sampled patients.[5] The other method used in this study to analyze genes is the GEM ExTra assay, which sequences DNA and RNA to detect the frequencies of mutations, fusions, and variants within RNA in the tumor sample. [6]

The study included 129 patients less than 30 years old who had relapsed, refractory, or newly diagnosed leukemia, lymphoma, solid tumors, or brain tumors. The participants' tumors were sampled and sequenced by the GEM ExTra assay, which detected several alterations that were considered "therapeutically targetable".[5] After sequencing was completed, the study found that 85% of samples had at least one impactful finding, including a mutation that is drug-targetable or predisposed to become cancerous.[5] While similar testing has been performed previously by other researchers, the results are challenging to compare due to the variation in the definition of "impactful findings." To remedy this, the CHOA researchers developed a scoring tool that assigns weights to different components of alterations.[5]

In addition to providing evidence that supports the benefits of using gene sequencing to treat pediatric cancer patients, CHOA also developed a scoring system for future precision medicine experiments and treatments to compare efficacy. Previously, discoveries considered to be "impactful findings" were defined as several

different factors. One study described them as: targetable findings, findings that altered diagnosis or risk, and findings that identified cancer. Another study defined "impactful findings" as discoveries that could lead to a change in patient management and assessment when analyzed with the patient's history, symptoms, and other medical findings.[5] The inconsistent distinction between what makes a finding "impactful" or not has made it challenging to compare results between different precision therapy studies that use this term. Thus, it is difficult to make a compelling case for treatment. CHOA's scoring tool includes two tiers of weight: tier 1-2 and tier 3-5. Tier 1-2 deals with clinical treatment alterations, whereas tier 3-5 deals with recommendations and other findings not used to determine therapy, but are worth discussing with patients and their families.[5] It also includes a point system that assigns weight to findings. For example, findings that suggest the sample may be predisposed to developing cancer are assigned 1 point.[5]

Figure 1. Summary of Gene Sequencing's Role in Pediatric Cancer Treatment



CHOA's recent trial in next-generation gene sequencing provides evidence that supports using precision medicine to treat pediatric cancer patients. The evidence suggests that gene sequencing is beneficial in discovering "impactful findings" that can alter the course of treatment and improve outcomes for patients.

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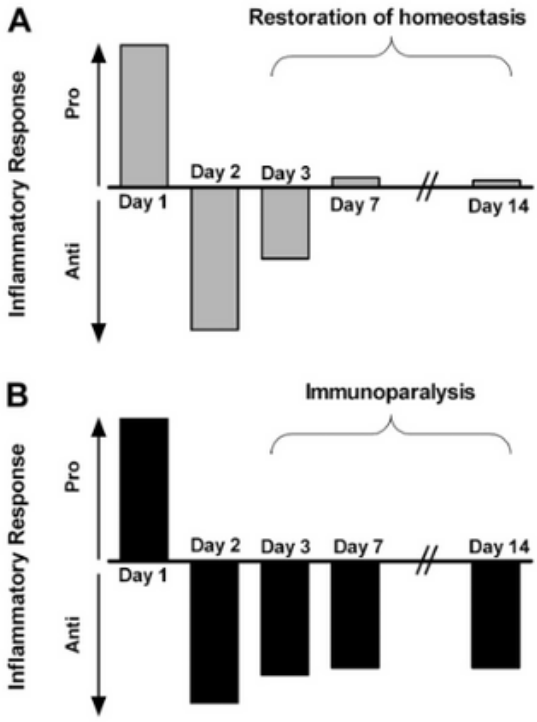
Reversibility of Immunoparalysis in Pediatric Critical Care Populations

Written by Emma Covington and Alex Ruehman, Pharm.D Candidates 2025

Upon insult to the immune system, proinflammatory mediators are released from innate immune cells conferring a hyperinflammatory state. Systemic Inflammatory Response Syndrome (SIRS) is a severe hyperinflammatory state characterized by tachycardia, tachypnea, abnormal temperature, and leukocytosis. Within 24 hours of SIRS onset, the immune system will compensate by producing anti-inflammatory cytokines to prevent further injury. This mechanism, termed Compensatory Anti-inflammatory Response Syndrome (CARS), can result in immunoparalysis which can lead to increased risk of nosocomial infections and death.[1]

Immunoparalysis has several clinical implications in trauma, sepsis, and cardiopulmonary bypass. Trauma induced innate immune suppression is common in severely injured children and can be associated with increased risks of developing nosocomial infections.[2] Depth and persistence of human leukocyte antigen-DR isotype (HLA-DR) expression are predictive of the development of secondary infection.[3] HLA-DR is expressed on the surface of monocytes which release the proinflammatory modulator tumor necrosis factor alpha (TNFa) once exposed to an immunostimulant. Studies have shown children who developed nosocomial infections had lower TNFa levels over the first week following injury than children who recovered without infection.[2] Reduction in TNFa responses were associated with higher severity of illness and longer stays in the Pediatric Intensive Care Unit (PICU).[4] Prolonged reduction of HLA-DR was associated with the development of SIRS and sepsis after utilizing cardiopulmonary bypass.[3] In an adult randomized controlled trial,

Figure 1. Comparison of Inflammatory Responses



researchers determined that an immunostimulating cytokine, Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), increased in neutrophil and monocyte numbers along with a rapid increase in depressed HLA-DR levels.[5] As HLA-DR levels returned to normal, a corresponding increase in proinflammatory cytokines, such as interleukin 6 (IL-6), and a decrease in specific anti-inflammatory cytokines were observed[5] as seen in Figure 1. Because GM-CSF administration produced favorable results in adult patients, it was hypothesized that similar outcomes would be seen in pediatric patients.

A small, fourteen patient randomized controlled trial in children was conducted using GM-CSF in half the subjects versus standard of care in the remaining seven.

The children receiving standard of care took over one week to achieve reversal of immunoparalysis and all acquired nosocomial infections. One patient acquired two separate nosocomial infections during their PICU stay and two children died. The children receiving GM-CSF achieved reversal of immunoparalysis in less than seven days, with zero nosocomial infections or deaths.[6] Although no observable increase in IL-6 was found in the pediatric trial, this could be due to the small sample size.

Overall, the use of GM-CSF in reversing immunoparalysis and preventing nosocomial infections is highly promising. More studies are needed to further determine further potential benefits of this therapy in adults and children. Currently, there is one trial focused on using GM-CSF as an immune modulator after trauma in pediatric patients (NCT01495637). Due to the high-risk of contracting nosocomial infections, utilizing GM-CSF therapy to stimulate the immune system may be critical in preventing infection and death in pediatric patients.

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[5] [5]

Pediatric Approval of Adalimumab for Ulcerative Colitis

Written by Molly Duckett, Pharm.D Candidate 2024

Ulcerative colitis is an inflammatory bowel disease that affects the colon. In ulcerative colitis, the body's immune system attacks the inner lining of the colon, or small intestine causing inflammation and leading to the formation of ulcers within the colon. According to the Crohn's and Colitis Foundation, as many as 900,000 Americans have from ulcerative colitis.[1] Although commonly diagnosed in adults in their mid-30s, children can also be affected by ulcerative colitis. Children diagnosed with ulcerative colitis may experience symptoms such as: diarrhea (with or without bloody stools), abdominal discomfort, urgency, tiredness, nausea, fever, loss of appetite, and anemia.[2]

Currently there is not a cure for ulcerative colitis; however, there are treatments that allow for disease remission. Several classes of medications are available to treat ulcerative colitis and research is ongoing in new treatment option development. An important area of research for ulcerative colitis treatment is blocking tumor necrosis factor alpha (TNF-α). The characteristic inflammation occurring with ulcerative colitis is believed to be partially due to an excess of the protein TNF-α.[2] Several drugs on the market block this protein, such as infliximab, etanercept, and adalimumab. It has been shown that TNF-α blockers help treat patients with ulcerative colitis, many of whom achieve remission. While there are several Food and Drug Administration (FDA)-approved TNF-α blockers for adults, only one TNF- α blocker has been approved in children.[2] Adalimumab (Humira) was recently approved in February 2021 to treat pediatric ulcerative colitis in patients five years of age and older.[3]

Initially approved by the FDA in 2002 to treat rheumatoid arthritis, Adalimumab was approved to induce and sustain remission of ulcerative colitis for adult patients in 2012.[3] Adalimumab works by binding to TNF-α and blocking the interaction with cell surface receptors, which helps to lower the inflammation that can cause many symptoms of ulcerative colitis. There is standard dosing for adults, but dosing for children is dependent on weight. In Figure 1, days 1 through 15 are considered to be the induction phase, while the maintenance phase begins on day 29.[4]

Table 1. Adalimumab Dosage Recommendations

- *Pediatric Patients 5 Years of Age and Older:*

Pediatric Weight	Recommended Dosage	
	Days 1 through 15	Starting on Day 29*
20 kg (44 lbs) to less than 40 kg (88 lbs)	Day 1: 80 mg Day 8: 40 mg Day 15: 40 mg	40 mg every other week or 20 mg every week
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 8: 80 mg Day 15: 80 mg	80 mg every other week or 40 mg every week

* Continue the recommended pediatric dosage in patients who turn 18 years of age and who are well-controlled on their HUMIRA regimen.

The phase 3 clinical trial that led to the FDA approval of adalimumab for pediatric ulcerative colitis was known as the ENVISION trial.[5] This study aimed to demonstrate efficacy and safety as well as assess the pharmacokinetic parameters of adalimumab administered subcutaneously in pediatric patients with moderate to severe ulcerative colitis. The primary endpoints measured in this trial were the percentage of participants who achieved clinical remission at Week 8 (designated as the induction period) and of the "Week 8 Responders," the percentage of participants with clinical remission at Week 52. Clinical remission was measured objectively in this study using the Partial or

Full Mayo Score. The ENVISION trial found that many participants treated with adalimumab achieved and maintained remission. The results were statistically and clinically significant, showing that 53% of the participants achieved clinical remission at week 8, while 37% achieved and maintained clinical remission at week 52. Throughout the trial, no new safety signals were seen, suggesting that adalimumab is both effective and safe for pediatric patients in treating moderate to severe ulcerative colitis.[6]

Although the FDA has approved adalimumab as safe and effective for ulcerative colitis in pediatric patients, there are still risks associated with chronic immunosuppressive therapy. Adalimumab should not be initiated in patients with active infections, as suppressing the immune system would impair the body's ability to clear the infection. Since TNF-α blockers suppress the immune system, patients on adalimumab should not receive live vaccines.[7] This precaution is particularly critical in children, as several vaccines in the Advisory Committee on Vaccine Recommendations for children include administration of live vaccines . Because TNF-α blockers such as adalimumab can cause pancytopenia in addition to immunosuppression, parents require education in monitoring their child for symptoms indicating pancytopenia (such as persistent fever, bruising, bleeding, or pallor changes).[4]

Adalimumab is a monoclonal antibody, so hypersensitivity reactions can occur when the medication is initiated.[4] The first dose may be given in a healthcare setting to monitor the patient, and to train the parents and caregivers on administering the drug to their child. Parents and children are also informed of the risk of adverse reactions when initiating adalimumab, the most common of which are upper respiratory tract infections and sinusitis, headache, rash, and injection site reactions.[4]

Adalimumab approval for pediatric ulcerative colitis is a significant advancement in treatment for pediatric patients. Although there are risks associated with beginning adalimumab therapy, many of the side effects can be mitigated, and ulcerative colitis treatment ultimately improves quality of life for patients that live with this condition. Adalimumab is the first TNF-α inhibitor approved for outpatient administration to pediatric patients,[8] drastically simplifying TNF-α treatment for pediatric patients and their families. Outpatient treatment of a TNF-α inhibitor allows for more[4] effective treatment regimens without the need to travel for scheduled infusions. Although risks are associated with beginning adalimumab therapy, by mitigating many side effects, the quality of life is improved for patients with ulcerative colitis.

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Butyrylcholinesterase: A Potential Biomarker for Sudden Infant Death Syndrome

Written by Tara Kennell, Pharm.D Candidate 2025

Sudden infant death syndrome (SIDS) is the leading cause of death in babies aged 1 month to 1 year in the United States. SIDS, is the sudden death of an infant under the age of 1 in which a cause cannot be identified through autopsy, investigations, and review of the clinical history.[1] According to the Centers for Disease Control (CDC), it is estimated that approximately 3,400 babies die each year in the United States from SIDS with 90% of these occurring within the first 6 months of a child's life.[1]

Many factors contribute to categorizing a baby as high-risk for SIDS occurrence, both modifiable and non-modifiable. The most common factors can be seen in the table below.[3]

Table 1. Factors Contributing to SIDS

Type of Factor	Examples
Physical Factors	Brain defects, low birth weight, respiratory infection
Sleep Environmental Factors	Sleeping on stomach or side, sleeping on a soft surface, sharing a bed, overheating
Risk Factors	Sex (more common in boys than girls), age (2-4 months old), race (non-white), family history, secondhand smoke exposure, premature birth
Maternal Risk Factors	Mother is younger than 20 y.o., smokes cigarettes, uses drugs or alcohol, inadequate prenatal care

While there are many factors contributing to the likelihood of SIDS occurrence, the "triple-risk model" is used to describe the three essential factors always present for a child who passes away from SIDS. The three factors are "(1) a vulnerable infant, (2) a critical development period in homeostatic control, and (3) an exogenous stressor(s)".[4] When all three of these are present, the infant's chances of SIDS increase and make them more vulnerable to sudden death when exposed to a stressful event while sleeping.

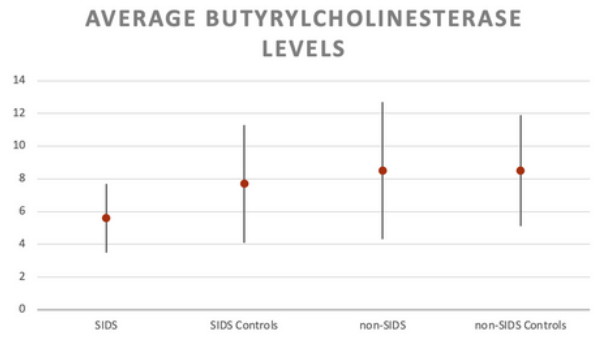
During stressful situations, the body's fight-or-flight response becomes activated and releases neurotransmitters. These neurotransmitters can be epinephrine, norepinephrine, or even acetylcholine. The increase in acetylcholine is caused by the inhibition of acetylcholinesterase (AChE).[5] There are two enzymes that break down and hydrolyze acetylcholine, acetylcholinesterase and butyrylcholinesterase (BChE).[6]

In a study conducted by the SIDS and Sleep Apnea Research Group in Australia, samples of dried blood spots were collected from newborns on postnatal days (PND) 2-4 and analyzed for BChE activity levels. The initial intent of the study was to measure both AChE and BChE levels, however the dried blood samples did not allow AChE to be measured. The study then compared BChE activity levels of SIDS infants against non-SIDS infants and date-of-birth and gender-matched control samples of surviving children whose blood spot was taken on the same PND. The overall goal of the study was to determine if there was a difference in the level of BChE activity in infants who died of sudden infant death syndrome or sudden unexpected death. For each sudden unexpected death in infancy (SUDI) case analyzed, ten date-of-birth and gender-matched samples of surviving children were identified, analyzed, and compared.[6]

To prepare the dried blood samples (DBS), two punches were taken out of the DBS cards, equivalent to 10 µL of blood and washed with 90 µL of water. The samples were then placed into a deep well plate and placed on a shaker for 30 minutes, spun for 10 minutes in a centrifuge, then transferred

to a new shallow well plate and sealed with heat-sealing foil. To analyze the samples, the researchers used the DetectX Butyrylcholinesterase Fluorescent Activity Kit and followed the manufacturer's instructions. The study also analyzed the total protein in each sample using the Bicinchoninic acid (BCA) Dual Range Protein Detection Kit. This total protein was used to calculate the specific activity of BChE by dividing the BChE activity by the total protein content.[6]

Figure 1. Average Butyrylcholinesterase Levels



From all the samples collected, the final analysis included 26 SIDS cases vs 254 matched controls, and 30 non-SIDS cases vs 291 matched controls. Mean values for BChE activity can be seen above. For SIDS cases and their controls the values were 5.6 ± 2.1 versus 7.7 ± 3.6 respectively, and for non-SIDS and their controls the mean values were 8.5 ± 4.2 vs 8.5 ± 3.4 respectively. A statistical analysis of the data showed strong evidence that lower BChE activity was associated with a SIDS death (P=0.0014) and showed no evidence of any linear association between BChE activity and a non-SIDS death (P=0.99).[6] Based on these results, it is believed that a lower level of BChE in a sample from post-natal days 2-4 can be a potential biomarker for the occurrence of SIDS in an infant. While this study is the first to identify such a biomarker, it paves the way for future researchers in coming up with a means to be able to identify and possibly prevent such tragic and sudden deaths of infants.

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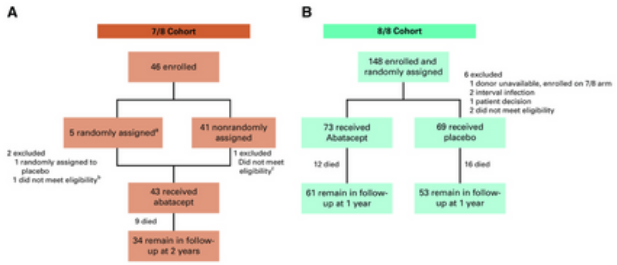
Approval of Abatacept in Children for the Prophylaxis of Acute Graft Versus Host Disease

Written by Elizabeth Spitzer, Pharm.D Candidate 2026

In 2021, the Food and Drug Administration (FDA) approved the use of abatacept with a calcium inhibitor and methotrexate for the prophylactic treatment of acute graft versus host disease in adults and children greater than 2 years of age undergoing hematopoietic stem cell transplant. Allogeneic hematopoietic stem cell transplant is an effective treatment and the only potential cure for patients with hematologic malignancies. Often, patients are unable to find a donor that is a complete human leukocyte antigen (HLA) match which results in many patients having to use an unrelated donor. The primary concern for unrelated donors is an increased risk for non-relapse mortality caused by acute graft versus host disease, or chronic graft versus host disease. Based on a trial conducted by Benjamin Watkins, MD, Muna Qayed, MD, MS, and Hematologists/Oncologists at the Aflac Cancer and Blood Disorders Center, abatacept reduced the risk of acute graft versus host disease and survival of adults and children when added to standard acute graft versus host disease. Patients with 7/8 HLA matched and 8/8 HLA matched were assigned control groups. The trial design for patients receiving 8/8 HLA matched grafts was, “a randomized double-blind placebo controlled” [1]These patients were randomly assigned 1:1 to abatacept or placebo, with varying patient ages greater and less than 21 years. The patients receiving 7/8 HLA matched graft were assigned to, “a single-arm open-label design, with comparison to a prespecified control group cohort from the Center of International Blood and Marrow Transplant Research”.[1] The 7/8 HLA matched graft patients initially compared to a double-blind placebo-controlled cohort. Because the risk of severe acute graft versus host disease, physicians were reluctant to randomly assign 7/8 HLA matched and 8/8 HLA matched were assigned control groups. The trial design for patients receiving 8/8 HLA matched grafts was, “a randomized double-blind placebo controlled”.[1] These patients were randomly assigned 1:1 to abatacept or placebo, with varying patient ages greater and less than 21 years. The patients receiving 7/8 HLA matched graft were assigned to, “a single-arm open-label design, with comparison to a prespecified control group cohort from the Center of International Blood and Marrow Transplant Research”.[1] The 7/8 HLA matched graft patients initially compared to a double-blind placebo-controlled cohort. Because the risk of severe acute graft versus host disease, physicians were reluctant to randomly assign 7/8 matched patients to placebo cohort, slowing recruitment and resulting in the change to an open-label single-arm design.

Findings from the study indicate improved acute graft versus host disease in 8/8 matched graft patients who received abatacept compared to those who received a placebo with 61 patients remaining in follow-up one year later. Patients with a 7/8 matched graft showed significant improvement of acute graft versus host disease resulting with 34 patients remaining in follow-up two years later.[1]

Figure 1. Phase II Trial of Costimulation Blockade with Abatacept for the Prevention of Acute GVHD



In conclusion, the survival outcomes of patients who received abatacept prophylaxis with a calcium inhibitor and methotrexate were favorable. Abatacept showed to be safe for patients and notably does not appear to increase the risk of the disease relapsing in either 7/8 and 8/8 matched patients. The results from this trial demonstrated the effectiveness of abatacept in preventing acute graft versus host disease and has led to the FDA approval which has a significant impact on patients with hematologic malignancies and their treatment options.[2]

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Olipudase Alfa: The First FDA-Approved Treatment for Acid Sphingomyelinase Deficiency

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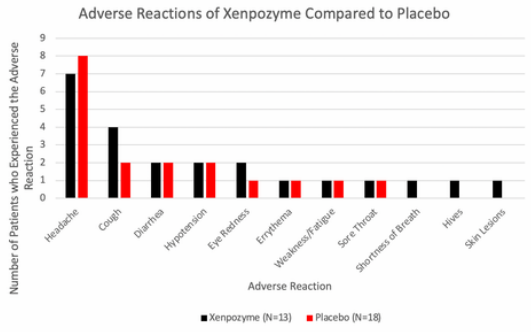
Acid Sphingomyelinase Deficiency (ASMD), also known as Niemann-Pick disease, is a rare lysosomal storage disorder caused by an autosomal recessive genetic abnormality resulting in a reduction in the enzyme acid sphingomyelinase (ASM). This enzyme is responsible for catabolizing the fatty substance sphingomyelin. When this metabolism does not occur, the sphingomyelin accumulates within cells throughout the body.[1] This abnormal accumulation ultimately results in the damage or death of cells, in turn exerting its effects on the brain, lungs, liver, and spleen leading to premature death in children and adolescents.[2] The estimated prevalence of ASMD is 1 in 250,000 newborns. Identifying all cases has been challenging due to a high frequency of the progressive genetic disorder being misdiagnosed or even undiagnosed.[3]

Characterized by a symptom continuum that increases based on severity, ASMD has two forms, Niemann-Pick disease Type A (NPD-A) and Niemann-Pick disease Type B (NPD-B). NPD-A and NPD-B differ based on their side effect profiles and onsets of action. Early detection and treatment are imperative in creating a positive health outcome.[4] Newborn screenings for ASMD are performed using a blood sample to measure ASM activity levels. If levels are outside of the normal range, a follow-up confirmatory genetic test should be performed. NPD-A has a fast onset of action and is the more severe form of the disease. Early signs and symptoms may arise within the first couple months of an infant's life, including vomiting, lack of motor skills, delayed growth, frequent pulmonary infections, and abdominal swelling due to the accumulation of sphingomyelin enlarging the

Administration (FDA) approved the first treatment for ASMD for pediatric and adult patients. Olipudase alfa (Xenpozyme) is administered through intravenous infusion and acts as a replacement therapy for the deficient enzyme ASM. Replenishing this enzyme allows for the breakdown of sphingomyelin into ceramide and phosphocholine resulting in the decreased buildup of acid sphingomyelinase within the cells. Side effects of this medication include fever, joint pain, hypotension, and cough. Olipudase alfa has a black-boxed warning for hypersensitivity reactions, and premedicating with an antihistamine is recommended. Olipudase alfa does not cross the blood-brain barrier, so it is able to treat the symptoms outside of the central nervous system.[1]

Genzyme, a biotechnology company, conducted a randomized, double-blind, placebo-controlled study where 31 participants with a previous confirmatory diagnosis of ASMD were treated with either olipudase alfa or a placebo formulation. The ASM blood levels were measured for each patient before and after treatment. The clinical trial's structure and design allowed researchers to definitively conclude that the drug is effective in treating this disease.[1]

Figure 1. Adverse Reactions of Olipudase Alfa Compared to Placebo



When compared to placebo (N=18), the patients who received olipudase alfa (N=13) reported comparable adverse effects with the most common (>10%) being headache, cough, diarrhea, hypotension, and eye redness[6] as seen in Figure 1.

Genzyme also conducted a clinical trial in 8 children (7=2-<12 years old and 1=<2 years old) that measured their overall outcomes after 1 year of treatment.[1] Olipudase alfa was able to improve these major side effects of ASMD that, without treatment, would lead to the debilitating heath disparities and ultimate mortality. Lung function was improved by almost 50%, spleen and liver volumes were reduced by 47% and 37%

Table 1. Improvements Seen with Olipudase Alfa Treatment

Improvement in Lung Function	**46%**
Reduction in Spleen Volume	**47%**
Reduction in Liver Volume	**38%**
Increase in Platelet Count	**38%**

respectively, and blood platelet counts were increased by 38% as summarized in Table 1. Overall, this drug is able to reduce the symptoms of ASMD and is a huge step in the right direction towards a cure for this disease.[6]

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