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NYS-ACCP Insider

University at Buffalo School of Pharmacy and Pharmaceutical Sciences

Special Points of Interest:

UBSPPS-ACCP Student Chapter Updates

40th ACCP Annual Meeting in Midtown, New York

You may have heard it before, but it's true; we live in an exciting and ever-expanding time for clinical pharmacy.

Just recently, state legislators in NYS have passed laws allowing student pharmacists to immunize. This legislation will allow students to gain experience immunizing patients well before they begin practice as a pharmacist. Collaborative Drug Therapy Management has continuously shown a positive benefit in both economic and clinical outcomes, which has helped to shed a positive light on our profession.

Our scope, as a profession, is expanding like never before. More pharmacists are moving away from the traditional dispensing role and moving to multiple different avenues, including clinics, hospitals and research centers.

At our UB SCCP chapter, we are dedicated to helping our students become the best clinical pharmacists they can be to better the overall wellbeing of our patients. Throughout each year, we hold events, such as journal clubs, where students learn how to read and interpret studies which is a crucial skill to learn in clinical practice. We also hold dinner and discussions, where guest speakers speak on topics that are typically not covered thoroughly in the classroom in order to help students gain insight on real world issues. In addition to these two great events, we have many more opportunities for students to grow as future health care practitioners.

The Clinical Research Challenge evaluates pharmacy students' ability to analyze a piece of literature pertaining to current research in the pharmaceutical field. Each year, a local exam is given, and the top three performing students are chosen to represent UB for the national competition. Out of almost 20 students who participated in the local event, Paul Stage, Katherine Coli, and Marissa Saber were the highest achieving of the group.

In October of 2019, multiple UB SCCP students travelled to NYC in order to attend the ACCP's national conference. At that meeting, we attended and participated in a plethora of seminars, including one called "Emerge from the Crowd". At this event, students learned how to make themselves standout residency candidates through honing application and letter of intent skills. Students were also exposed to the clinical pharmacy live challenge rounds, where schools across the nation competed in pharmacy trivia competitions. The ACCP meeting was a great opportunity for students to network and become exposed to current pharmacists and future colleagues across the nation.

The Dinner and Discussions are one of the essential core pillars of our local UB SCCP club. In November of 2019, our local chapter held a Dinner and Discussion which was led by our guest lecturer Dr. Laura Bielecki. Dr. Bielecki is a UB graduate who is a pharmacist employed at General Physician, an ambulatory care clinic located in Buffalo, NY. At the dinner and discussion, Dr. Bielecki discussed and educated our UB students on the use of clozapine in patients with a history of seizures over delicious Wegmans subs. These Dinner and Discussions help expose students to different topics that may not be fully covered in the pharmacy curriculum.

In addition to the Dinner and Discussions, our Journal Clubs are another crucial pillar in our local UB SCCP chapter. This past December, we held a journal club that discussed different antihypertensives (Benazepril plus Amlodipine or Hydrochlorothiazide) for hypertension in high-risk patients. More recently, we held our second journal club of the year this month, discussing a trial that studied the potential benefit of cinnamon in diabetics. The journal club is a great opportunity to expose students to literature and help them to develop critical thinking and interpretation skills, which are beneficial in everyday pharmacy practice.

Upcoming events for our SCCP chapter include Professionalism 101, where students will learn about ways to improve their CVs and interviewing skills. Special opportunities for UBSPPS students, including the scholars and clinical research program, will also be discussed. Future journal clubs will cover the association of hypertension and dyslipidemia with increasing obesity in patients with Type 2 Diabetes Mellitus.

The UB SCCP chapter is also continuing the “Clinical Topic Discussion” event that was implemented last year, where students create a presentation on a clinical topic of their choosing. Students will then receive feedback from other students and faculty. This event allows students to gain experience and confidence in presenting various clinical topics and will prepare them for postgraduate training programs including fellowships and residencies.

We at UB SCCP are proud of the work we are doing in order to prepare the next generation of pharmacists, through multiple opportunities from journal clubs to Dinner and Discussions. We hope you enjoy the newsletter and learn a thing or two along the way.

- Matthew Butler, PharmD Candidate, UBSPPS Class of 2021
- Melissa Stein, PharmD Candidate, UBSPPS Class of 2023

Dinner and Discussion with Dr. Laura Bielecki, PharmD, MBA, PGY-1

New Drug Review: Palforzia/ Peanut (Arachis hypogaea) Allergen Powder-dnfp

In 2018, about 2.2% (1.25 million) of children and adolescence have peanut allergies, and about 40% of the allergies are severe and require epinephrine.[1 2] The prevalence of peanut allergies have tripled in the past 20 years and schools have had to figure out ways to manage the large student population with this allergy.[3] Today, schools have placed precautions to prevent severe allergic reactions by creating peanut free lunch tables, peanut free classrooms, and even peanut free schools.[4] In January 2020, the FDA approved Palforzia, manufactured by Aimmune Therapeutics to reduce the rates of severe allergy.

Palforzia is a biologic oral immunotherapy that is FDA approved to mitigate severe allergic reactions by peanuts due to accidental exposure in children between the ages of 4 and 17 years old.[5] This is the first treatment for the reduction of severity in food allergy exposure. The mechanism of action is not yet known, but data from clinical trials show that this is efficacious. In a double-blind, placebo-controlled, Food challenge (peanut protein) 5.1% of subjects on Palforzia experienced severe symptoms while 10.5% of subjects in the placebo group experienced severe symptoms.[5] Although data shows efficacy, this medication can have life-threatening side effects; thus, there is a boxed warning stating the risk of anaphylaxis.

The dosing occurs in 3 stages. The initial dose escalation must occur at a REMS approved healthcare facility where each dose is separated by 20-30 minutes until reaching at least 3 mg or 6 mg. The initial dose escalation cannot be modified; all dose levels must be completed. The up-dosing can be modified in the event that adverse reactions, including anaphylaxis. All dose levels must be completed before moving on to the maintenance phase. The maintenance phase can be continued at 300 mg every day. The dosage forms are available in capsules and sachets, and neither dosage forms can be taken whole. They must be opened and sprinkled onto semi-solid, NOT liquid foods. The medication should be refrigerated and protected from moisture. Palforzia should not be taken right after strenuous exercise as this places the body at a hypermetabolic state. Also, it should not be taken within 30 minutes before or 3 hours after a hot shower or bath.

The Phase 3 ARTEMIS Trial was pivotal in demonstrating safety and efficacy in AR101 (Palforzia). The proportion of subjects that tolerated 1,000 mg of peanut protein (about 4 peanut kernels) in the treatment group was 58%, compared to 2% of subjects in the control group.[6] The inclusion criteria included 4 to 17 years old with clinical history of peanut allergy, and dose limiting symptoms at or below 444 mg of cumulative peanut protein dose. The exclusion criteria included severe or life-threatening episode of anaphylactic shock within 60 days of screening.

Palforzia is only available through the REMS program. Prescribers of this drug must be certified by enrolling into the program. Healthcare settings must be equipped with staff and equipment to monitor at the initial dose escalation and at the 1st dose of each up-dosing level. Pharmacies can only dispense

the medication if they are enrolled in the REMS program. They can only dispense Palforzia to healthcare facilities and patients enrolled in the program.

Palforzia is contraindicated in patients with uncontrolled asthma, eosinophilic esophagitis, and other eosinophilic gastric diseases. It has not been studied in subjects with uncontrolled asthma. 12 subjects in the treatment group developed eosinophilic gastric disease, whereas 0 subjects in the placebo group developed these symptoms.[5] All subjects had symptomatic improvement upon discontinuation and 6 subjects with eosinophilic gastrointestinal disease was resolved.[5] Patients that develop eosinophilic gastric diseases must discontinue the medication. Other adverse events include abdominal pain, nausea, vomiting, pruritis, throat tightness, and anaphylaxis. Since this drug contains 3 proteins that cause peanut allergies (ARA 1, 2, and 6), there is a high risk of experiencing an allergic reaction while taking this medication. Patients must have an epinephrine auto-injector in the event a severe reaction occurs.

The direct and indirect costs of the medication will prevent many patients from obtaining therapy. Since it is a biologic, most insurances will place its coverage in the 3rd tier if they choose to cover it. The average wholesale price (AWP) ranges from $5.93 per one-6mg dose to $35.60 for 300mg maintenance and titration dose. Since the first dose of each stage of up-dosing therapy should be taken at the prescriber's office, an appointment must be made roughly every 2 weeks. If parents of patients work, they must figure out how to take the child to their appointment and stay at the office for at least 60 minutes after giving the dose. Conversely, without the medication, the emergency department costs, specialists' costs, medication costs, as well as opportunity costs due to job dismissal, change, or restriction cost billions of dollars annually in the United States.[3] Families and providers will have to take insurance and quality of life of the family into account before making this decision. If a patient on Palforzia suffers from an allergic reaction, they may incur a combination of these costs and take more time to achieving the maintenance dose.

Clinically, this medication shows to be efficacious in reducing the number and severity of life-threatening events, which is seen through clinical trials. Families of patients and patients with peanut allergies that can afford the direct and indirect costs of the medication may benefit from taking this medication.

– Anant Shah, PharmD Candidate, UBSPPS Class of 2022

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A Novel Serotonin Agonist: Lasmiditan (Reyvow™) for Acute Migraine Attacks

What is it:

Reyvow™ (Lasmiditan) is the first and only 5-hydroxytryptamine $(5\text{-HT})_{1F}$ selective agonist for treatment of acute migraine with or without aura in adults. Lasmiditan is a schedule V controlled substance. Lasmiditan was developed by Eli Lilly and Company as an acute treatment of severe pain relief during migraine attacks, but not for the preventive treatment of migraine.[1]

What does it treat:

The prevalence of migraines is so widespread that it is the leading cause of disability in people under 50 years old. The complete pathophysiologic mechanism for migraines are not entirely understood. Earlier theories believed that they were caused by intracerebral arterial vasoconstriction followed by extracranial vasodilation. Now they believe that it could be related to dysfunction in neuronal and broad sensory processing. Activation of sensory nerves causes the release of vasoactive neuropeptides that interact with the dural blood vessels to promote vasodilation. This results in neurogenic inflammation. Central pain transmission can activate other brainstem nuclei, causing more symptoms like nausea and photophobia.[2]

There are multiple drug classes that are used for both preventative measures and to treat attacks.[2] Preventative drugs include anti-epileptics, beta-blockers and antidepressants, which are not as efficacious as the other two but still can be beneficial. Even though patients may take preventative medication, this typically doesn't stop all migraine attacks. In the case of a migraine attack, NSAIDs and triptans are the most commonly prescribed for relief but patients don't always respond to the medication.[3]

Mechanism of Action:

Lasmiditan is a serotonin agonist that binds to 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptors with high affinity. Its therapeutic effects are presumably mediated by agonist effects at this receptor; however, the precise mechanism is unknown.[4]

Dose:

Lasmiditan is an oral medicine taken as tablets, with or without food, in doses of 50 mg, 100 mg, and 200 mg as needed. Lasmiditan tablets are only available in 50 mg or 100 mg strengths. No more than one dose should be taken in 24 hours, and the second dose has not been shown to be effective for the same migraine attack. There are no dosage adjustments for patients with renal or hepatic impairment,

but lasmiditan is not recommended use in patients with severe hepatic impairment (Child-Pugh C) since it has not been studied yet. Patients who are taking lasmiditan should avoid any potentially hazardous activities requiring complete mental alertness, such as driving or operating machinery, for at least 8 hours after each dose.[1] Dose selection for patients 65 years and older should start at lowest since dizziness occurred more frequently in this population (19% for lasmiditan, 2% for placebo). The higher occurrence of dizziness predisposes them to a high fall risk. This medication should be stored securely at 20°C to 25°C as in room temperature (68°F to 77°F).[4]

Adverse Events:

The most common side effects include dizziness, fatigue, paresthesia (tingling or numbing sensation on the skin), sedation, nausea and vomiting and muscle weakness, which occurred 5% of the time compared to 0% with placebo in clinical studies. It should be used with caution if taken with alcohol or other CNS depressants. The clinically significant adverse events include driving impairment, central nervous system depression, serotonin syndrome (rare), and medication overuse headache.[1] Patients should seek immediate medical attention if they experience any serious hypersensitivity reaction, which occurs in 0.2% of patients treated with lasmiditan.[4]

Studies involved in approval:

Two Phase 3 clinical studies, SAMURAI and SPARTAN, showed benefit over placebo in patients with mild or moderate neurologic treatment-emergent adverse events, leading to its approval in October. The drug became available at the end of January after it was reviewed by the DEA for its recommended controlled substance classification. Sponsored by Eli Lilly and Company, the manufacturer of Reyvow™ (Lasmiditan), studies examined the efficacy and safety of lasmiditan for the acute treatment of migraines versus placebo for patients 18 years or older with 3 to 8 migraine attacks per month.[5] Both were randomized, double-blind placebo controlled trials, with a total of 3,981 participants. Patients were evenly randomized to receive 50mg (SPARTAN only),100mg, 200mg or placebo and asked to treat within at least 4 hours of pain onset as long as the headache was not improving and at least moderate severity.

Inclusion criteria for both studies included age 18 years or older, ICHD-II diagnosis of migraine with or without aura, history of 3-8 migraines per month (greater than 15 headache days), and MIDAS score > 11 and patients with cardiovascular risk factors in addition to migraine. Exclusion criteria included patients with a history of chronic migraine or other forms of primary or secondary chronic headache disorder, patients taking >3 doses/month of opiates or barbiturates, patients who had initiated or changed preventative migraine medication in the past 3 months and the SAMURAI trial also excluded patients with known coronary artery disease, clinically significant arrhythmia or uncontrolled hypertension.[5] The primary endpoint for both studies was to assess the efficacy of lasmiditan versus placebo for patients who were pain-free at 2 hours post-dose. The key secondary efficacy endpoint assessed the difference between lasmiditan and placebo to determine the proportion of patients who were free of their most bothersome symptom at 2 hours post-dose.

A modified intent-to-treat was performed to assess the population. The efficacy response was broken down into two main subgroups, triptan-experienced and triptan naive. In the triptan-experienced group, the lasmiditan 100mg and 200mg showed statistical benefit compared to placebo.[5] Lasmiditan 100mg showed benefit over placebo in patients who reported headache pain freedom (p=0.435). The

200mg dose showed benefit over placebo in patients who reported headache pain freedom (p=0.210) and headache pain relief (p=0.200).

Patients who were triptan-naive showed enormous benefits of lasmiditan compared to placebo. Again, the 50mg dose didn't show huge results compared to the 100mg and 200mg doses. In this case, it only showed statistical significance in treating headache pain freedom ($p<0.05$). With the 100mg and 200mg doses, they showed benefit over placebo in headache pain freedom, most bothersome symptom freedom, and headache pain relief ($p<0.001$).[5]

Overall, lasmiditan showed efficacy in patients with mild to moderate neurologic treatment-emergent adverse events. Lasmiditan may be a useful treatment option for patients with migraines.

– Marissa Saber, PharmD Candidate, UBSPPS Class of 2022
– Qinyu Zuo, PharmD Candidate, UBSPPS Class of 2023

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Journal Club discussion on benefits of Cinnamon in Diabetic patients

New Combination Indication: Tecentriq (atezolizumab) and Abraxane (nab-paclitaxel)

FDA updated indication:

Atezolizumab was first approved in May 2016 for the treatment of urothelial carcinoma. In 2019, the FDA approved atezolizumab for the treatment of three more types of cancer including the PD-L1-positive, metastatic triple-negative breast cancer. Atezolizumab is the first FDA approved immunotherapy agent for triple-negative breast cancer, and it is to be used in combination with nab-paclitaxel.[1]

What these agents treat:

The three common receptors that can fuel the growth of most breast cancers are hormone epidermal growth factor receptor 2 (HER-2), estrogen receptors (ER), and progesterone receptors (PR). Triple negative breast cancer (TNBC), as the name implies, is test negative for PR, ER, and excess HER-2 protein. TNBC is more aggressive than other types of breast cancer mainly because it lacks necessary receptors for most targeted therapies, which means fewer treatment options. TNBC also grows and spreads quicker than other types of cancer and has a worse prognosis.[2]

TNBC occurs in about 10-20% of diagnosed breast cancers and is more likely to affect younger people, African-American and Hispanic women, and people with a BRCA1 gene mutation.[3] The symptoms of TNBC are similar to other breast cancer types, which can include a lump or thickening in an area of the breast and/or armpit, irregular size and shape or feel of the breast and/or nipple, a blood stained discharged from the nipple, dimpling of the skin, etc.

Mechanism of action:

Cancer cells can evade the attack of immune cells by stepping on an immune cell brake called a checkpoint. Programmed cell death protein 1 (PD-1) is a checkpoint protein found on T-lymphocyte cells. When PD-1 is bound to the programmed death ligand 1 (PD-L1) expressed on the cancer cells, the immune response will be suppressed, thus preventing T cells from attacking the cancer cells. Atezolizumab is an immune checkpoint inhibitor that blocks PD-L1 from binding to PD-1 and B7-1 (a costimulatory cell-surface protein), allowing the T cell to maintain its activity. Paclitaxel, on the other hand, binds to the β-tubulin subunit of microtubules, stabilize microtubules and prevent dynamic assembly-disassembly required for mitosis of the cancer cells. Paclitaxel is a chemotherapeutic agent that has been widely used to treat breast cancer. Combined with immunotherapy, it may additionally active toll-like receptor activity and promote dendritic-cell activity. Nab-paclitaxel is a form of paclitaxel that formulated without the use of a solvent and does not require glucocorticoid premedication to prevent hypersensitivity reactions. Nab-paclitaxel was selected to be used in combination with atezolizumab instead of conventional paclitaxel because the steroid premedication required for paclitaxel had been hypothesized to affect immunotherapy activity.[4]

Dosing and adverse reactions:

For each 28-day cycle, administer atezolizumab at a dose of 840 mg intravenously on days 1 and 15 and administer nab-paclitaxel at a dose of 100 mg per square meter of body-surface area intravenously on days 1, 8 and 15. Repeat cycle every 28 days until disease progression or unacceptable toxicity.[4] The most common adverse reactions (reported in ≥ 20% of patients) associated with this combination regimen were alopecia, nausea, cough, peripheral neuropathy, and neutropenia.[4]

Study involved in approval:

The study that gained atezolizumab its new indication is referred to as the IMpassion130 trial. It was a phase III trial funded by F. Hoffmann–La Roche/Genentech, the marketer of Tecentriq (atezolizumab). Impassion130 was designed as a randomized, double-blinded, placebo-controlled trial, and the agents of interest were a combination of atezolizumab and nab-paclitaxel in treatment of advanced or metastatic triple-negative breast cancer. The two primary endpoints that were assessed included progression-free survival time (PFS) in the PD-L1-positive subgroup and intention-to-treat population, as well as overall survival time (OS) in only the intention-to-treat population initially, but if significant would then be assessed in the PD-L1-positive subgroup.

The inclusion criteria required patients to be 18 years or older with a histologically documented history of metastatic or unresectable locally advanced triple-negative breast cancer. Patients were allowed to have received taxane monotherapy in the past, and also were allowed to have received radiation and previous chemotherapy if the treatment was completed greater than or equal to 12 months prior to randomization. The study also required patients to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), and Eastern Cooperative Oncology Group performance-status score of 0 or 1 (higher numbers mean greater disability), and stable hematologic and organ function.[4] Exclusion criteria included untreated symptomatic central nervous system disease, a history of autoimmune disorder, use of immune checkpoint-targeting therapies in the past, recent treatment with a systemic immunostimulatory agent within 4 weeks prior to trial, and the use of immunosuppressive drugs.[4]

The researchers randomly assigned untreated metastatic triple-negative breast cancer patients in a 1:1 ratio to receive either atezolizumab plus nab-paclitaxel, or placebo plus nab-paclitaxel. The dose of atezolizumab was 840 mg IV on days 1 and 15, and the dose of nab-paclitaxel was 100 mg/m^2 IV on days 1, 8, and 15, with both agents being repeated every 28-day cycle. Both interventions were continued until either disease progressed, or until the toxicities of the medications were no longer tolerable. Tumor imaging was performed at baseline and then every 8 weeks for 1 year, then followed by every 12 weeks for the remainder of the trial. Follow-up for survival was performed every 3 months following discontinuation in either intervention group. Further stratification was based on receival or non-receival of neoadjuvant or adjuvant taxane therapy, presence or absence of liver metastases at baseline, and presence or absence of programmed death ligand 1 (PD-L1) expression at baseline.

Each treatment group included an equal 451 patients, with the median follow-up time being 12.9 months. In the intention-to-treat population, the PFS was greater at 7.2 months with atezolizumab + nab-paclitaxel than when compared to the 5.5 months seen with placebo + nab-paclitaxel (HR for progression or death: 0.80; 95% CI 0.69-0.92; p=0.002).[4] In patients with PD-L1-positivity, the comparative median PFS was 7.5 month to 5 months, respectively (HR 0.62; 95% CI 0.49-0.78; p<0.001).[4] The median OS in the intention-to-treat population was 21.3 months with atezolizumab +nab-paclitaxel compared to 17.6 months with placebo + nab-paclitaxel (HR for death only: 0.84; 95% CI 0.69-1.02; p=0.08).[4] In patients with PD-L1-positivity, the comparative median OS was 25 months to 15.5 months, respectively (HR 0.62; 95% CI 0.45-0.86).[4] The drop-out rate due to adverse events was relatively low at 15.9% for atezolizumab + nab-paclitaxel patients and 8.2% for placebo + nab-paclitaxel patients.

Looking at the results of the Impassion130 trial, it is important to note the significant improvement of PFS (7.5 month to 5 months; HR 0.62) as well OS (25 months to 15.5 months; HR 0.62) for PD-L1-positive patients who were on atezolizumab + nab-paclitaxel.[4] The results in this study are in accordance with previous studies, and support the notion that there is a benefit to utilizing an immunotherapy + chemotherapy combination in PD-L1-positive patients.[4] The mechanism of action of atezolizumab allows the patient's own immune system to continue to function like it is supposed to, and supports the chemotherapy in attacking the foreign tumor. No new adverse reactions were discovered during this trial, which reassures that it is a relatively predictable regimen to initiate in triple-negative breast cancer patients. The strengths of this study are plentiful; its results were well powered and the primary endpoints were met, the treatment groups were well balanced with an equal number of participants and with similar baseline characteristics, and the results support what has been studied in the past with respect to checkpoint inhibitors' benefits in PD-L1-positive patients. Overall, the study yielded quality evidence to support the usage of atezolizumab + nab-paclitaxel as a first-line combination regimen in patients with locally advanced or metastatic triple-negative breast cancer.

-Jin Hong, PharmD candidate, UBSPPS Class of 2023
-Jonathan Wang, PharmD candidate, UBSPPS Class of 2021

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Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant *Pseudomonas aeruginosa*

Background

Antibiotic resistance is becoming more of a complicated issue, as rates of multi-drug resistant pathogens increase and last line therapies start to lose susceptibility[1]. While antimicrobial stewardship is an equally effective strategy aimed at reducing progression of drug-resistant organisms, novel antibiotics are a rare and much needed commodity in our age of ESBL-producing organisms such as Vancomycin-resistant *Enterococcus*, Multi-drug resistant *Pseudomonas Aeruginosa*, and many more drug-resistant organisms. One novel antibiotic that has started to gain some ground is ceftolozane/tazobactam. Ceftolozane/Tazobactam is a novel cephalosporin/beta-lactam beta-lactamase inhibitor combination with activity against multi-drug resistant (MDR) Gram-negatives, including *P. aeruginosa*, and is FDA approved for complicated urinary tract infections and complicated intra-abdominal infections[2].

Another antibiotic well handled to fight against MDR Gram-negatives, including *Pseudomonas aeruginosa*, is polymyxin. Polymyxin was first introduced as a rapidly bactericidal agent against Gram-negatives, but lost favor as its toxicity profile warranted better alternatives[3]. The surge of MDR Gram-negatives recently led to its revival and use as a last line agent, alone or in combination with other antibiotics. Finally, aminoglycosides are a class of antibiotics that generally are effective against Gram-negatives, including *P. aeruginosa*[4]. In this study, they were able to compare these treatments and assess which provided a safer and more effective treatment course against MDR and extensively drug resistant (XDR) *P. aeruginosa* for the patient.

Pharmacology

The basic structure of polymyxin includes a cyclic heptapeptide with a tripeptide side chain, and a fatty acid tail[6]. Polymyxin mainly targets and binds to LPS within the gram negative cell membrane- leading to the destabilization of lipid A and bacterial cell lysis. Administered intramuscularly, intravenously, or intrathecally, polymyxin has a half-life of 12 hours and undergoes extensive renal tubular reabsorption. Due to increased use of polymyxin, some strains of *Pseudomonas aeruginosa* exhibit polymyxin resistance through of the OM OprH membrane stabilizing protein in the bacteria[6].

Ceftolozane/tazobactam, on the other hand, inhibits PBPs with a higher affinity than most antibiotics and destabilizes cell-wall synthesis to cause cell death[7]. It is parenterally administered and primarily found to be eliminated renally with a half-life of 3 hours[8]. Compared to polymyxin, ceftolozane/tazobactam has been studied to have less toxicity. Known adverse effects include infusion-site reactions, diarrhea, cough, chest pain, and viral respiratory tract infection. Ceftolozane/tazobactam is active against wild-type Enterobacteriaceae, other ESBL-producing organisms, and is more potent against *P. aeruginosa* than similar cephalosporins like ceftazidime and cefepime.

Study design

A retrospective, observational cohort study was carried out to determine patient outcomes from those who received ceftolozane/ tazobactam versus those who received a polymyxin or aminoglycoside regimen. Overall, 200 patients were included in the study- evenly split between each treatment

regimen. Outcomes were studied for each regimen- specifically for the ceftolozane/ tazobactam regimen which focused on its contribution towards a clinical cure for the patient along with potential adverse side effects of acute kidney injury and long term hospitalization[9].

Statistical Analysis

Baseline characteristics, infection related variables, and outcomes between each treatment group were analyzed using bivariate comparisons. Categorical data was processed by Chi-squared or Fisher's test, and continuous variables with student T-test or Wilcoxon rank sum test depending on normality. Each outcome of interest (AKI, in-hospital mortality, and clinical cure) was modeled using multivariate analyses to sense any independent impact from each treatment group, and any covariates from ceftolozane/tazobactam therapy that had a P-value ≤0.20 in bivariate comparisons could also be included in the analysis. From there, adjusted odds ratios (aOR) for each included outcome were calculated for ceftolozane/tazobactam treatment.

Results

Most patients were admitted to the ICU (69%), mechanically ventilated (63%), and had severe sepsis/septic shock (42%) at the onset of infection. Patients were well matched for most covariates, except those on ceftolozane/tazobactam were generally older and more likely to have chronic kidney disease, resulting in higher mean serum creatinine levels (ceftolozane/tazobactam | polymyxin or aminoglycoside) (0.92 (0.67-1.31) | 0.79 (0.5-1.17); p=0.02) and lower mean creatinine clearances (65.9 (36-109) | 84.5 (56.7-166.5); p=0.003). No statistical significance was reached in terms of time to active therapy and time to study drug, but statistical significance was reached in utilization of combination therapy (15% ceftolozane/tazobactam versus 72% polymyxin or aminoglycoside; p<0.001). Combination therapy in the ceftolozane/tazobactam group were mostly inhaled polymyxin or aminoglycoside (12/15), while the polymyxin or aminoglycoside group were mostly systemic beta-lactams (57/72), of which 31 cases had in-vitro resistance, 17 cases of intermediate susceptibility, and 24 cases of in-vitro susceptibility). In the polymyxin or aminoglycoside arm, 56 patients received polymyxin therapy while 44 received aminoglycoside therapy. The ceftolozane/tazobactam arm had an independently associated and statistically significant effect on clinical cure rates compared to polymyxin or aminoglycosides (81% versus 61%; aOR 2.63 [1.31-5.30]) with no significant differences between polymyxins and aminoglycosides. Patients who had pneumonia and those in the ICU reached similar numbers in terms of clinical cure (80% versus 56%, p=0.02 | 83% versus 63%, p=0.008). Combination therapy did not significantly change the rate of clinical cure for any group, even in those with different in-vitro activity. AKI rates were significantly lower in ceftolozane/tazobactam therapy (6% versus 34%; aOR 0.08 [0.03-0.22]), and had no patients on RRT, compared to 7 patients in the polymyxin or aminoglycoside arm. To note, polymyxins had more AKI than aminoglycosides (43% versus 23%, p=0.0549). All other outcomes were statistically insignificant; in-hospital mortality (20% versus 25%; aOR

0.62 (0.30-1.28)), length of stay, seizures, *C. diff* infections, hypersensitivity reactions, new-onset neuropathy, and 30-day readmissions. A NNT of 5 was calculated for clinical cure using ceftolozane/tazobactam, and a NNH of 4 for AKI using polymyxin or aminoglycosides.

Critiques

In combination with previous studies (Gallagher et al. 2018, Bassetti et al. 2019), data produced from this study support utilization of novel beta-lactam/beta-lactamase inhibitors as preferred agents in MDR or extensively drug resistant (XDR) gram-negative infections[5]. In addition to superior clinical cure rates, tolerability of ceftolozane/tazobactam was proven with decreased incidence of AKI, no cases of hypersensitivity reaction, neuropathy, or seizure, and similar cases of *C. diff* compared to polymyxins or aminoglycosides. While this studies main objective wasn't to compare combination versus monotherapy, the statistical insignificance in clinical cure rates of the polymyxin or aminoglycoside arms raise interest in future research for rationally designed regimens in the critically ill. Limitations discussed in this study were mortality benefit and dosing of study agent(s). A lack of mortality benefit came from the study being underpowered, with an additional 150 patients in each arm needed to detect any difference provided alpha=0.05 and beta=0.2, and the characteristics of the study population as most patients were critically ill with various comorbidities and infection sites. The other limitation was the exclusion of dosing for polymyxins or aminoglycosides due to the disparate dosing practices of polymyxins and aminoglycosides combined with inconsistent serum concentration collection/adjustment at various sites. Future studies, such as ASCEPT-NP, could further implicate ceftolozane/tazobactam's effectiveness in nosocomial pneumonia[10].

Conclusion

In this retrospective, multicenter, cohort study ceftolozane/tazobactam was found to have statistically higher clinical cure rates and lower AKI rates compared to polymyxin or aminoglycoside therapy in treating MDR/XDR *P. aeruginosa*. A higher powered trial or better control of covariates might provide more information on the potential mortality benefit of ceftolozane/tazobactam. As it stands, ceftolozane/tazobactam has proven itself to be a reliable agent in the treatment of MDR/XDR *P. aeruginosa*, and should be appropriately utilized to preserve its efficacy.

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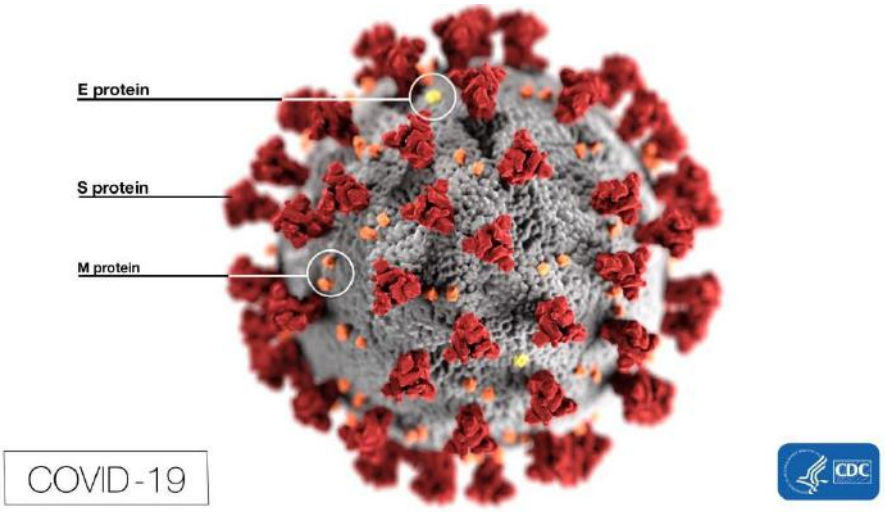
Pharmacologic Treatment for COVID-19 Associated COPD Exacerbations

Since the emergence of the novel coronavirus, COVID-19, in Wuhan, China, tens of thousands of people have been infected. As of March 11th, 2020, 118 326 confirmed cases and 4292 deaths have been reported worldwide by the World Health Organization (WHO) and COVID-19 was officially declared a pandemic.[1]

Coronaviruses are a type of enveloped, positive-stranded RNA virus that infects both humans and animals. Novel viruses such as COVID-19 develop due to genetic recombination that takes place between either the same or different types of coronavirus groups.[2] Due to the typically self-limiting nature of respiratory viral infections in healthy individuals, COVID-19 may present asymptomatically.[2,3] However, in patients who are more susceptible, such as those with comorbid conditions or who are immunocompromised, COVID-19 infections may present as acute respiratory disease.[2] Specifically, patients with Chronic Obstructive Pulmonary Disease (COPD) are at risk of acute exacerbations if they are infected by COVID-19.

COPD exacerbations are marked by an increase in respiratory symptoms, accelerated loss of lung function, and an overall decrease in quality of life. Exacerbations of COPD are critical in the progression of the disease because an association exists between their occurrence and patient mortality.[4]

Hospitalized patients infected with COVID-19 most often present with pneumonia. According to the Centre for Disease Control (CDC), patients presenting with a mild infection may not need to be hospitalized at first, however, their status should be monitored as symptoms may worsen. While a vaccine and therapeutic agents are currently being developed, there is no pharmacological treatment for COVID-19. Infection prevention and supportive care form the basis of clinical management when it comes to COVID-19 infections.[3] The WHO recommends considering COVID-19 as a potential etiology for all patients presenting with severe acute respiratory infections and suggests prompt initiation of supplemental oxygen therapy. When patients do not present with shock, cautious fluid management can be used in tandem as oxygenation may decline with vigorous fluid resuscitation. Specimens from the upper and lower respiratory tract should be collected for testing for COVID-19. In patients who are confirmed to have COVID-19, these collections should be repeated every two to four days to validate viral clearance.[5]



In regard to the treatment of COPD exacerbations, patients presenting to the emergency department must be assessed for pneumonia and viral respiratory infections.[6] A chest x-ray should be taken, and if the patient's presentation raises concern for acute respiratory academia, arterial blood gas measurements should be obtained.[6,7] Patients will be classified as either having no respiratory failure, non-life-threatening acute respiratory failure, or life-threatening acute respiratory failure. However, regardless of classification, patients with hypoxia should be given supplemental oxygen, either via nasal cannula or venturi mask. Their target O_2 saturation should be between 88-92% to avoid worsening any existing acidosis.[7] In terms of pharmacotherapeutics, we can administer albuterol with ipratropium bromide every four to six hours.[6,7] Oral corticosteroids should also be considered because they can improve lung function (FEV_1), oxygenation, and shorten hospitalization time.[2,7] Due to the potential of extending viral replication, the use of corticosteroids is not routinely recommended in COVID-19 infections without comorbidities such as COPD.[3]

While there is no treatment for COVID-19, a potential treatment against the virus is remdesivir.[2] Remdesivir is a nucleoside analog that integrates into the viral RNA leading to premature chain termination.[8] In the United States, remdesivir was used in a patient with confirmed COVID-19 and favorable results were achieved. With that being said, further studies are required before this drug can be recommended as treatment.[2]

Overall, although there is no current treatment for COVID-19, measures can be taken to limit the extent of decline in patients who present with an acute COPD exacerbation due to the virus. Infection prevention and supportive care are integral in treating these patients. While corticosteroids are not recommended in treating patients with COVID-19 who are otherwise healthy, they are recommended in patients with COPD. Finally, remdesivir may be used in the future against COVID-19, however, further studies are required which prevents their use for current cases.

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Relationship Between Treating *Helicobacter pylori* vs Family History of Gastric Cancer

Background

Helicobacter pylori is a bacterial infection in the stomach that affects around half of the world's population [7]. It causes various complications like superficial gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma [1]. People with *H. pylori* infection and a family history of gastric cancer have a higher chance of developing gastric cancer. A meta-analysis from the Leeds Gastroenterology Institute, St James's University Hospital shows that there is a 34% risk reduction of developing gastric cancer in patients being treated for *H.pylori* compared to people with untreated *H.pylori*[2]. However, a randomized controlled trial from the Department of Medicine, University of Hong Kong shows that gastric cancer occurrence was similar between the treatment and placebo group despite a large sample size of 1600 participants, with a mean follow up of 7.5 years [3].

Introduction

The main goal for this study was to determine if treating *H.pylori* infection would reduce the propensity of patients, with first-degree relatives with gastric cancer, developing gastric cancer themselves. The primary outcome was the occurrence of gastric cancer. This study was carried out in the National Cancer Center in South Korea. This was a single center, double blinded, placebo controlled and randomized trial. The study included 1838 subjects with current *H.pylori* infection, age 40-65 and a family history of a first degree relative with gastric cancer. Some of the main exclusion criteria were if the subjects have any history of cancerous organs, peptic ulcer or previous *H.pylori* treatments.

Methods

After subjects gave consent they were screened for presence of *H. pylori* and absence of other health conditions. Then the subjects were randomized into either placebo or treatment groups. The treatment group was given amoxicillin 1g, clarithromycin 500mg and lansoprazole 30mg twice a day for 7 days. This treatment of two antibiotics allows for efficient killing of the bacteria. A proton pump inhibitor is added so that the mucosal cells can recover without trauma from the stomach acid. The placebo group receives the same number of pills with identical taste and look as the treatment group pills.

Surveillance endoscopy was performed every 2 years. National Screening Program in South Korea claims that 2 years is enough to detect gastric cancer within stage 2, before the cancer proceeds to more advanced stages. Therefore, a biennial check was done in order to test for gastric cancer. At each checkup, suspicious lesions were retrieved for testing. The World Health Organization classification system was used for cancer histologic classification. The gastric tissue was classified as adenoma or carcinoma according to the Vienna classification. The trial also tests if people were still infected with *H. pylori* through the use of rapid urease test. This test is sensitive to *H. pylori* presence because the bacteria releases urease enzymes for the bacteria's survival in the acidic environment [4].

Statistics

The statistical test they used is log-rank test. The log-rank test is a non-parametric test used to test the null hypothesis that there is no difference between the populations in the probability of an event at any time point [5]. A nonparametric test is used when the data doesn't fit a normal distribution curve. Thus, using a nonparametric test is more accurate in describing the data than a T-test because the T-test assumes the data is normally distributed

The study uses a two sided test with a significance level of 0.05. Since the trial is testing if there is a difference between the treatment and placebo group, a two-sided test makes sense. Furthermore, the significance level of 0.05 means that the type 1 error is 5%. Type 1 error is the probability of rejecting a true null hypothesis. In this case, there is a 5% chance of finding a conclusion that states the treatment group is different from the placebo group, when in reality there isn't a difference. The expected power for this study is designed to be 80%. This means that the study has an 80% chance of truly finding a difference between the treatment and placebo group if there is truly a difference. Both the power and alpha follow standard acceptable values in a typical study.

Results

The study result for the primary outcome was that gastric cancer occurred in 10 of the 832 subjects in the treatment group (1.2%). On the contrary, there were 23 occurrences of gastric cancer out of 844 subjects in the control group (2. 7%). Of the 33 occurrences of gastric cancer, 28 occurred in 979 (2.86%) subjects that were still infected with *H. pylori*. The other 5 occurrences were in the 608 (0.8%) subjects that were successfully cured from H.*pylori*. The hazard ratio for development of gastric cancer in the treatment group versus the placebo group was 0.45 (95% Confidence interval, 35.1 to 503.8). Hazard ratio is a comparison of hazard rates between the experimental group and the control group over the entire study duration. A hazard ratio less than 1 means that at any point of time during the trial, the treatment group is experiencing less gastric cancer occurrence than the control group. The study also recorded any deaths during the study. Overall, there was no significant difference between the treatment group and the placebo group in terms of overall survival rates. In the treatment group, 16 people died out of 917 participants and 18 people died out of 921 participants in the control group. None of the deaths were due to gastric cancer.

Critique

The study was well designed ethically and procedurally. The participants were given informed consent regarding this research. At the end of the trial, participants that were still infected received quadruple therapy [a Proton Pump Inhibitor, bismuth, metronidazole and tetracycline] for 10 days. The study was also procedurally well done because it followed the standard acceptable values of power of 80% and alpha value of 5%. The assessment of gastric cancer followed a standard according to the World Health Organization classification system.

Furthermore, the results of the study were statistically valid because the P value was less than alpha of 0.05. However, there might be some concerns even though it was statistically significant. For instance, the number needed to treat to prevent one case was 65.7[95% Confidence Interval, 35.1 to 503.8]. Although the number is within the confidence interval, the range of the confidence interval goes all the way up to 503 subjects. The data would be more impactful if it was within the range of a narrower

confidence interval. Another important thing to note is that of the 10 people that got gastric cancer in the treatment group, 5 of them were successful in eliminating the bacterial infection. Yet, they still got gastric cancer. This shows that there are other factors that contribute to gastric cancer even though *H.pylori* is the main risk factor.

Although this was a well done study, some might argue the clinical significance of this study. Since this study took place in Korea, the subjects were all Korean. One benefit of this was that the variability should be low. However, the external validity of this study isn't that great because the study took place in Korea and the subjects were all Koreans. One might argue that the Koreans have slightly different genomes that made them more prone to gastric cancer due to *H.pylori*.

Currently the American College of Gastroenterology clinical guideline made no recommendations for routine testing for people with the bacteria infection and a first degree relative with gastric cancer because of lack of evidence [8]. Although this study did show that treating the bacteria infection lowered the rates of gastric cancer in the treatment group compared to the placebo group, more studies should be done because of the low external validity and half of the gastric cancer occurrences in the treatment group did occur even when successfully treated.

Conclusion

Treating people with *H. pylori* infection with history of first relatives with gastric cancer will reduce the risk of developing gastric cancer.

– Fei Li, PharmD Candidate, UBSPPS Class of 2022

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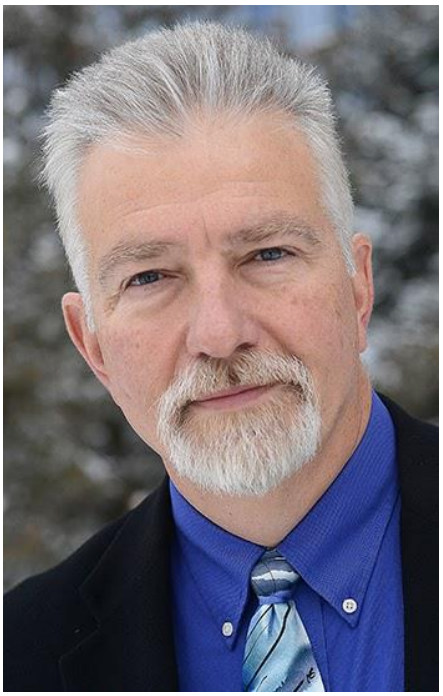
ACCP interview with Edward M. Bednarczyk, PharmD, FACCP, FAPhA, Clinical Associate Professor of Pharmacy Practice; University at Buffalo; School of Pharmacy and Pharmaceutical Sciences

1. You were given fellowship in the American College of Clinical Pharmacy (FCCP) in 2002. Can you speak about what this means and how ACCP has impacted your career as a Clinical Pharmacist?

ACCP was the first organization I felt a connection with. I joined in 1987 and went to my first national meeting in Chicago. The entire trip was funded by the chair of pharmacy practice at the Medical University of South Carolina. It was a great way for PharmD students to get involved with and present their research.



Dr. Edward M. Bednarczyk, PharmD, FACCP, FAPhA

2. You are the current director of the Center for Health Outcomes, Pharmacoinformatics, and Epidemiology (cHOPE). Can you share a little about what your role encompasses?

This program started several years ago as an idea by Dr. Jack Brown. The goal was combine these different areas of health outcomes, pharmacoinformatics, and epidemiology. Although there was no money to start, the NYS Department of Health got involved and it has been a success for the last decade with over $3million/year in renewable funding. This funding goes towards gaining insight into drug utilization in millions of Medicaid patients.

3. You're considered an expert on the field of Medical Marijuana. Can you comment on its current status and how restrictions on research may be slowing down the drug development process?

My stance on medical marijuana has always been the same. We should be using science to determine the role of cannabinoids in the management of disease. Medical and recreational are not interchangeable and one should not be used as a platform to push the other.

4. Do you have any advice for current students who are interested in Clinical Pharmacy?

Keep an open mind about your options and try things out even if you aren't sure of them. I found that in Pharmacy if you want to do the things you enjoy, you will have to pursue further credentials. When I was a student, clinical pharmacy was this new thing and I realized that I would have to obtain more training in order to pursue it. After obtaining my BS in Pharmacy, I went on to get a PharmD, got involved with research and completed a fellowship. I found myself in formal training much longer than I ever expected. I can look back and say I enjoyed every aspect of it...research the most. If I hadn't taken

these scary steps, I would not be in the position I am today. Those are what changed me as a pharmacist and a professional.

– Ali Zahid, PharmD Candidate, UBSPPS Class of 2022

General Body Meeting for Spring Semester

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Questions? Please contact: Amanda Engle, PharmD NYS-ACCP Secretary/Treasurer
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