Urinary incontinence is a prevalent condition affecting a disproportionate number of older women in the United States. Anticholinergic medications are the preferred treatment; however, a single anticholinergic agent has not emerged as the best treatment option. OnabotulinumtoxinA appears effective in the treatment of urgency urinary incontinence; however, it has led to incomplete voiding and the need for self catheterization in previous trials utilizing higher doses. A double-blind, double-dummy, controlled trial compared the efficacy and safety of onabotulinumtoxinA and anticholinergic medications for urgency urinary incontinence.

A total of 249 women were enrolled. Patients in the anticholinergic group initially received solifenacin 5 mg daily, with possible titration to 10 mg daily after two months and possible change to trospium XR 60 mg daily after four months if symptoms were inadequately controlled. They also received a placebo injection of saline. Patients assigned to onabotulinumtoxinA received a 100 unit injection of into the detrusor muscle and placebo tablets according to a titration schedule matching that of the anticholinergic group. Patients whose symptoms were well controlled at six months (PGSC score ≥4) were monitored for an extended follow-up period. During the extended follow-up, symptom control was assessed monthly for up to six months or until symptoms were no longer adequately controlled.

The primary endpoint was the change in mean number of daily urgency incontinence episodes over 6 months. Secondary outcomes included the number of women with complete resolution of incontinence, the proportion with a reduction of incontinence of ≥75%, and changes in quality of life scores. Safety endpoints included adverse events and the proportion of patients who required catheterization during the study period.

The mean reduction in daily episodes of urgency incontinence did not differ between anticholinergic and onabotulinumtoxinA during the six month active treatment phase (-3.4 vs. -3.3; p=0.81). Women who received onabotulinumtoxinA were more likely to experience complete resolution of urgency incontinence (27% vs. 13%; p=0.003). The rate of response after one month was rapid in both the anticholinergic (87%) and onabotulinumtoxinA (91%) groups. Both groups also experienced improvements in quality of life. More women in the onabotulinumtoxinA group retained symptom control one month after discontinuation of study medication (62% vs. 50%; p=0.006), but this difference was no longer significant after six months. Serious adverse effects did not differ between groups. More patients assigned to anticholinergics experienced dry mouth, while more patients assigned to onabotulinumtoxinA developed a UTI. More women from the onabotulinumtoxinA group required catheterization. The authors concluded that, while both treatments were equally effective, side effects differed between groups. The difference in adverse effects, and the different routes of administration can help practitioners decide which treatment option to use. This study was limited it allowed participants to change medications during active treatment. Researchers did not provide details on how patients progressed through the titration schedule, which may have altered the outcomes.

CONCLUSION: OnabotulinumtoxinA is as effective as anticholinergics for the treatment of urgency urinary incontinence. While dry mouth is less likely, the risk of urinary tract infection and the need for catheterization is increased due to urinary retention.


By Christina Buchman, Pharm.D. Candidate
Flublok®: Next-Generation Flu Vaccine

Currently, all influenza vaccines used in the United States are produced in egg embryos. This method of production raises some potential problems: people with egg allergies may adversely react to the vaccine, and in the event of a pandemic, long lead times are necessary for the production of egg-based vaccines. The novel Flublok® vaccine is produced using recombinant hemagglutinin (rHA) technology and baculovirus expression vector system to infect insect cells for protein production. The rHA proteins are purified and made into vaccine against each of the three influenza strains (H1N1, H3N2, and B) recommended by the World Health Organization for that season.

The novel manufacturing process of Flublok® provides several advantages over the current influenza vaccine which is produced in egg embryos. The new technology offers the potential for faster start-up of the vaccine manufacturing process in the event of a pandemic because it is not dependent on egg supplies or availability of the influenza virus. Flublok® also allows for a good genetic match between the vaccine and actual influenza strains because of the recombinant technology. Flublok® is highly purified and does not contain antigenic proteins present in eggs or require thimerosal for preservation. The higher HA content offers the potential to provide drift variant protection and the possibility for longer lasting and improved immunogenicity.

To establish the effective dose of Flublok®, a randomized, double-blind, placebo-controlled trial evaluated the vaccine formulated with either 15 mcg or 45 mcg of each antigen during the 2004-2005 influenza season. Four hundred sixty healthy adults, 18-49 years old, were randomly assigned to receive either placebo (n = 154); rHA vaccine containing 15 mcg of H1 and B and 45 mcg of H3 (n = 153); or rHA vaccine containing 45 mcg each of all three components (n = 153). Protective efficacy against culture-confirmed CDC influenza-like illness (CDC-ILI) was evaluated. Seroconversion rates were highest in the 135 mcg group, thus establishing the dose for Flublok®. The rates of CDC-ILI were seven in the placebo group (4.6%), two in the 75 mcg (1.4%), and zero in the 135 mcg vaccine group. The vaccine was formulated with a different H3 component than the one circulating in the community for the 2004-2005 influenza seasons so the investigators determined that Flublok®, formulated at 135 mcg, protected patients against drift variants.

Four additional trials assessed the safety and protective efficacy of Flublok® against CDC-ILI and immunogenicity in adults aged 18-92 years old. Patients aged 50 and older received either Flublok® or conventional egg-derived vaccine (TIV; Fluzone®), whereas patients aged 18-49 years received either Flublok® or placebo. The rates of injection site pain and headache were similar between Flublok® and TIV in 50-92 year olds. In those aged 18-49 years, injection site pain occurred in more patients vaccinated with Flublok®, but the rates of headache were similar between Flublok® and placebo. The overall protective efficacy for Flublok® was 44.6% (95% CI 18.8%, 62.6%) against drift variants in the 18-49 year old age group. In the other age groups, the CDC-ILI was too low to draw conclusions about protective efficacy between the two vaccines.

Flublok® was well tolerated and immunogenic in adults 18 years and older and protective against drift variants. Flublok® meets all the requirements for licensure except for B/Malaysia seroconversion in patients older than 50 years of age. It should be noted that the B strains formulated in each vaccine for the ≥65 years of age group were different, and the results should be interpreted cautiously due to lack of direct antigen comparison.

Another randomized, double-blind, multicenter study compared the safety, reactogenicity, and immunogenicity of Flublok® to TIV administered to children ages 6–59 months. Flublok® was safe but less immunogenic than similar volumes of TIV, particularly in the youngest children.

Flublok® trivalent rHA vaccine has similar efficacy as the trivalent inactivated licensed influenza vaccine in inducing HAI antibodies to prevent influenza infection. Flublok® has three times the amount of HA than conventional TIV and, consequently, induces higher antibody titers. Flublok® is only FDA approved in 18-49 year-olds and may be a good option in a crisis of a pandemic because of the novel production of the vaccine. Patients with egg allergies may also benefit from Flublok®. Otherwise, Flublok® had similar results to the already approved Fluzone®.

By Logan Tinsen, PharmD Candidate

REFERENCES:

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Sirturo™: a New Treatment Option for Multidrug-Resistant Tuberculosis

Sirturo™ (bedaquiline) was approved by the FDA on December 28, 2012 and is the first new tuberculosis treatment in 40 years. It works by targeting the ATP synthase enzyme in mycobacterium, thus interfering with energy metabolism and production of ATP. It is approved for the treatment of multiple drug resistant tuberculosis (MDR-TB) when used in combination with other agents. Bedaquiline was approved as part of the accelerated approval program and was also given fast track designation, priority review, and orphan-product registration. The approval was based off promising evidence from phase II clinical trials.

The first trial was an eight-week, randomized, multicenter, phase II trial conducted in South Africa that found bedaquiline treatment resulted in quicker conversions from positive to negative cultures when compared to placebo. Adult patients were included if they had newly diagnosed pulmonary tuberculosis that was resistant to both isoniazid and rifampin. Patients were excluded if their tuberculosis was resistant to aminoglycosides or fluoroquinolones. Patients assigned to bedaquiline received 400 mg daily for two weeks followed by 200 mg three times weekly for six weeks. Additionally, all patients received a background regimen of five typical tuberculosis medications for the full eight weeks. After eight weeks, the active treatment was discontinued, but patients continued to receive the background regimen for an additional 96 weeks. A total of 47 patients were randomly assigned to treatment with bedaquiline (n=23) or placebo (n=24).

The primary endpoint was the time to conversion of sputum cultures from positive to negative. The secondary endpoint was the change in log_{10} count of colony-forming units (CFUs) from baseline. Baseline characteristics were similar between treatment groups. After eight weeks of treatment, bedaquiline use resulted in sputum culture conversion in 48% of patients, compared to only 8% of placebo treated patients. The sputum culture conversion was significantly quicker in the bedaquiline treatment group (hazard ratio 11.8; CI 2.3 to 61.3). Median log_{10} CFU counts also declined more rapidly in the bedaquiline group across all time points. Most adverse effects were mild in nature and did not lead to any study discontinuations. Most commonly reported adverse effects included nausea, unilateral deafness, joint pain, hemoptysis, extremity pain, and chest pain. Nausea was significantly more common in the bedaquiline group (26% vs. 4%; p=0.04). This trial was limited by a small sample size and short duration.

To assess long-term efficacy and safety, patients from the first trial were followed for an additional 96 weeks as part of an extended, two-year follow up. Only 24 patients completed the entire trial, and 23 discontinued early (bedaquiline=10, placebo=13). Of the 23 patients who discontinued, twelve did so within the first 24 weeks. If the patients who discontinued during the first 24 weeks were considered treatment failures in the primary analysis, bedaquiline was significantly more effective than placebo (HR 2.253, CI 1.08-4.71). The time to 50% conversion was 78 days and 129 days in the bedaquiline and placebo groups, respectively. If patients who discontinued in the first 24 weeks were classified based on their culture status at the time they discontinued, bedaquiline was still significantly better than placebo (HR 3.135, CI 1.51-6.53). Side effects were similar between groups; only nausea was significantly more common in the bedaquiline group (26.1% vs. 0%). QTc elevations were observed in both groups but were more pronounced in patients receiving bedaquiline.

While not yet published, the interim results from a second placebo-controlled study evaluating bedaquiline support the evidence of efficacy from previous trials. Patients were recruited according to the same inclusion and exclusion criteria of the first study. Patients assigned to receive bedaquiline were given 400 mg daily for two weeks followed by 200 mg three times weekly for 22 weeks as well as the previously described background regimen. The primary endpoint was time to sputum culture conversion, and the secondary endpoint was the sputum culture conversion rate at 24 weeks. Patient characteristics were similar between groups. Efficacy was based on a modified intent-to-treat population which excluded patients with non-MDR tuberculosis, extremely drug-resistant tuberculosis, or results which were not evaluable. Bedaquiline treatment resulted in more rapid sputum culture conversion (median 12 weeks vs. 18 weeks; p=0.003) and higher conversion rates by week 24 (79% vs. 58%; p=0.008). While bedaquiline treatment resulted in significant efficacy, the rate of death among bedaquiline patients was significantly greater than the rate observed in placebo patients (11.4% vs. 2.5%). Mild to moderate side effects were similar between groups, and included nausea, arthralgia, hyperuricemia, headache, and vomiting.

Bedaquiline is supplied in 100 mg tablets with dosing recommendations of 400 mg daily for two weeks followed by 200 mg three days weekly for 22 weeks. It must be accompanied by a background regimen containing at least 3-4 other effective medications. There is a black box warning for increased risk of death and QT prolongation. Treatment should be reserved for adult patients with MDR-TB in whom an effective alternative treatment option is not available. Bedaquiline will be distributed by a single supplier with educational materials to help guide proper use. The manufacturer will continue to conduct studies on the long-term safety and efficacy of bedaquiline.

By Justin Perlich, PharmD Candidate

REFERENCES:

(Continued on page 4)
Literature Highlight:
Tedizolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections

Complicated acute bacterial skin and skin structure infections (ABSSSIs) are becoming increasingly difficult to treat due to resistant strains emerging to normally effective treatments. For ABSSSIs caused by methicillin-resistant Staphylococcus aureus (MRSA), the only orally approved antibiotic treatment is linezolid. Development of new antimicrobials to treat these difficult infections is necessary, especially in light of linezolid-resistant strains of MRSA.

Tedizolid, a new oxazolidinone, has been shown in previous trials to have efficacy against gram-positive bacteria, including strains resistant to linezolid. This randomized, double-blind, double-dummy, multicenter, phase three trial was done to determine noninferiority of tedizolid compared to linezolid in the treatment of ABSSSIs.

Six hundred and sixty-seven patients were randomized to receive 200 mg of tedizolid once daily (n=332) or 600 mg of linezolid twice daily (n=335). Patients included in the study either had confirmed or suspected gram-positive ABSSSIs. Blinding was maintained by dispensing medication in blister packs that contained active treatment and placebo, two tablets taken in the morning and one tablet taken 12 hours later. After day six, patients in the tedizolid group received all placebo tablets until treatment was complete. Treatment was completed after 10 days of therapy in both groups. The primary endpoint was clinical response at the 48-72 hour patient assessment. Clinical response was defined as patients with no fever, no growth of ABSSSI lesion, no unapproved antibiotic use, and no death of any cause. There was no statistically significant difference between the two groups. Response was seen in 79.5% of patients receiving tedizolid (95% CI: 74.8 – 83.7%) and 79.4% of patients receiving linezolid (95% CI: 74.7 – 83.6%). Adverse events of the study were comparable between tedizolid and linezolid (40.8% vs. 43.7%, respectively). More patients in the linezolid group experienced gastrointestinal disorders, but there were no other differences in adverse events. The most common adverse events were nausea, headache, and diarrhea.

The authors of this study concluded that a once daily regimen of tedizolid for six days was statistically noninferior to standard treatment of linezolid when treating ABSSSIs. This study was limited due to the lack of well-defined clinical endpoints for ABSSSIs, the possibility for variation on measurements of lesions, and the authors’ affiliations with the manufacturer, Trius Therapeutics Inc.

CONCLUSION: Tedizolid demonstrated noninferiority for the treatment of complicated ABSSSIs. Additional studies regarding superiority or treatment of linezolid-resistant infections should conducted for more information.


By Alexis Anderson, Pharm.D. Candidate

FluBlok® References (cont.)


Sirturo™ References (cont.)

Literature Highlight:
Sumatriptan Iontophoretic Transdermal System for the Acute Treatment of Migraine

Gastrointestinal (GI) complications associated with migraines, such as nausea and vomiting, interfere with the effective management of migraines and the ability to take oral medications. A randomized, parallel-group, double-blind, placebo-controlled trial evaluated the efficacy and tolerability of an iontophoretic transdermal system for the acute treatment of migraine. Iontophoresis is a novel technology in which low-level electrical energy transports drug across the skin, bypassing the GI tract.

Eligible patients were healthy adult individuals with migraines. Patients typically experienced ≥1 moderate-to-severe headache/month and had a ≥1-year history of migraines. Patients were randomly assigned either the sumatriptan iontophoretic patch or a placebo patch (identical to the treatment patch in appearance and operation but delivered sodium chloride instead) until one migraine occurred or two months had passed following randomization. The sumatriptan iontophoretic transdermal system delivered 6.5 mg sumatriptan over a four-hour period with an electrical current of 4 mA for one hour and 2 mA for the subsequent three hours of operation. The primary endpoint was the proportion of patients who were headache-pain-free two hours after patch activation.

Patients rated their baseline headache pain on a four-point scale (0-3, 3=severe) upon migraine onset. The patch was to be applied if their score was ≥2. Four hundred sixty-nine patients who applied the patch were included in the safety population, even if they did not activate the patch (sumatriptan n=234; placebo n=235). Four hundred fifty-four patients who applied and activated their patch and had ≥1 post-baseline assessment for headache pain were included in the intent-to-treat population (sumatriptan n=226; placebo n=228). Patients in the sumatriptan treatment arm were headache-pain-free two hours after patch activation compared with placebo (18% vs 9%, respectively; p = .0092). Adverse events were mild application site reactions and tended to be higher with the sumatriptan iontophoretic transdermal system compared with placebo (50% vs 44%, respectively). This study was limited because only a single headache was treated in each patient, so the consistency of efficacy across multiple headaches in each patient was not measured. Additionally, this study lacked an active comparator control group, and subjective endpoints were used. The authors concluded that the sumatriptan iontophoretic transdermal system produced improvements over placebo for rapid, sustained relief of acute migraine headache and associated symptoms.

CONCLUSION: Although oral administration is generally preferred by patients, non-oral routes of drug administration are recommended in patients experiencing prominent nausea or vomiting. Patients who received the sumatriptan patch compared to those patients who received placebo experienced headache pain relief and freedom from nausea at 30 minutes following patch activation. Within two hours following patch activation, patients who received the sumatriptan patch were free of headache pain, photophobia, and phonophobia. The sumatriptan iontophoretic patch offers patients an alternative method to deliver migraine medication while overcoming challenges associated with gastrointestinal symptoms of migraine.


By Logan Tinsen, Pharm.D. Candidate