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Formulary Information

Pneumococcal Vaccination: Two Shots Are Better Than One

By: Sydney Smith, Pharm.D.

Introduction: In September 2014, the Advisory Committee on Immunization Practices (ACIP) recommended that adults ≥65 years of age receive one dose of PCV13 (pneumococcal 13-valent conjugate vaccine [Prevnar 13®]) in series with PPSV23 (pneumococcal vaccine polyvalent [Pneumovax 23®]) for increased protection from pneumococcal infections (A-II recommendation).[1] The previous recommendation only included PPSV23 for patients ≥65 years, with those who were pneumococcal vaccine-naïve receiving only one dose, or those who had received any pneumococcal vaccine up to age 64 receiving one additional dose of PPSV23 after a minimum of 5 years.[2] This new recommendation was in response to concerns with the duration of protection of PPSV23 which may only be efficacious for 3 to 5 years, as well as, diminished immune responses to booster doses of PPSV23.[3]

Increased Immunogenicity with PCV13: The PCV13 vaccine contains a carrier protein conjugated to 13 pneumococcal polysaccharides or serotypes, while the PPSV23 vaccine contains 23 purified capsular pneumococcal polysaccharides.[4,5] The PCV13 and PPSV23 vaccines share coverage of 12 common pneumococcal serotypes; these serotypes are responsible for a majority of invasive pneumococcal disease (IPD) cases in adults worldwide as well as higher rates of morbidity and mortality.[3] Due to the conjugated polysaccharides, PCV13 has the potential to elicit a stronger, longer-lasting immune response and memory because the polysaccharides are converted from T-cell independent to T-cell dependent antigens.[6] This increased immunogenicity provided by PCV13 for the overlapping serotypes gives greater benefit to receiving both vaccines. Two immunogenicity studies by Jackson and colleagues

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New Safety Warning for Omalizumab

By: Meghan Wilson, Pharm.D. Candidate

Background: Omalizumab (Xolair®) is a humanized, monoclonal antibody that prevents IgE from binding receptors on mast cells and basophils, thereby hindering the IgE-mediated response seen in allergic asthma.[1] It is approved by the Food and Drug Administration (FDA) for patients 12 years or older for the following two indications: 1) patients who have moderate-to-severe asthma with either a positive skin test or *in vitro* activity to a perennial aeroallergen, whose symptoms are uncontrolled with an inhaled corticosteroid, or 2) patients with chronic idiopathic urticaria who are still symptomatic with H_1 antihistamine use.[2,3]

The Concern with Omalizumab: The FDA released an early communication in 2009 after manufacturers of omalizumab reported interim results from An **E**pidemiologic Study of **X**olair (omalizumab): Evaluating **C**linical **E**ffectiveness and **L**ong-Term **S**afety in patients with Moderate to Severe Asthma (EXCELS), a 5-year prospective, observational study which included asthmatic patients age 12 years or older.[4]

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evaluated the effects of PCV13 in PPSV23-naïve adults between the ages of 60 to 64 years and adults over the age of 70 years previously vaccinated with PPSV23.[3,6] The results in pneumococcal vaccine-naïve adults showed that titers were comparable or higher for the shared serotypes in those vaccinated with PCV13 compared to PPSV23.[6] Of adults over the age of 70 years who were vaccinated with PPSV23 five or more years prior to study enrollment, those who received PCV13 had significantly higher titers for a majority of the overlapping serotypes compared to those who received PPSV23.[3] However, those who received a dose of PCV13 one year after PPSV23 were found to have lower titers, an indication that PPSV23 may diminish the effect of PCV13 when administered first. Thus, PCV13 and PPSV23 should NOT be administered concomitantly.

Pneumococcal Vaccine Administration: Table 1 details the new administration schedules for PCV13 and PPSV23 for adults ≥65 years of age recommended by ACIP. According to ACIP, either pneumococcal vaccine may be administered at the same time as an inactivated or live-attenuated influenza vaccine.[7] The ACIP currently recommends concomitant administration of PPSV23 and zoster vaccine (Zostavax®) even though current product labeling still suggests that these vaccines be given 4 weeks apart.[5,8] This ACIP recommendation is based on results of a retrospective cohort study which did not find an increased risk of herpes zoster infections among patients who received concomitant administration of these vaccines.[8,9]

The Bottom Line: Adult patients ≥65 years should receive pneumococcal vaccination.[1] Due to increased immunogenicity and longer-lasting effects provided by PCV13, vaccination first with PCV13 and then with PPSV23, at least 8 weeks apart, may provide better protection against IPD. Consideration of appropriate administration intervals with pneumococcal vaccines is important in order to achieve maximal immunogenic effect. It would be advisable to check if Medicare or other health insurance plans will cover PCV13 and PPSV23 given in the recommended sequence.

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Table 1: Recommended Administration Schedules for PCV13 and PPSV13 in Adults ≥65 Years of Age [1]

Vaccine Status	Recommended Schedule
Pneumococcal vaccine-naïve or those with unknown vaccination history	One dose of PCV13 followed by one dose of PPSV23 given 6 to 12 months after PCV13*‡
Previously received PPSV23 at age ≥65 years	One dose of PCV13 ≥1 year after PPSV23
Previously received PPSV23 before age 65 years	One dose of PCV13 ≥1 year after PPSV23 Second dose of PPSV23 given 6 to 12 months after PCV13 and NO sooner than 5 years after the most recent dose of PPSV23

PCV13=pneumococcal 13-valent conjugate vaccine (Prevnar 13®) PPSV23=pneumococcal vaccine polyvalent (Pneumovax 23®)
*If PPV23 cannot be given within 6 to 12 months, it may be administered during the next office visit
‡PCV13 and PPSV23 should NOT be coadministered; minimum time interval between vaccines is 8 weeks

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The results showed increased cardiovascular and cerebrovascular events in patients treated with omalizumab. On September 26, 2014, after the final results of EXCELS were reported to the FDA, a label change for omalizumab was approved to include a warning about this increased risk.[5] For overall cerebrovascular and cardiovascular events in the EXCELS trial, an incidence rate of 13.4 per 1,000 patient years in patients treated with omalizumab relative to 8.1 per 1,000 patient years for those not treated with omalizumab was reported. In particular, increased incidence rates with omalizumab were noted for myocardial infarction (MI), unstable angina, pulmonary embolism/venous thrombosis, pulmonary hypertension, and transient ischemic attack. For ischemic stroke and cardiovascular death, there were no differences in incidence rates.[6]

Asthma, Cardiovascular Disease, and Stroke: Several studies have been conducted to explore cardiovascular disease and stroke in patients with asthma as it is proposed that the chronic inflammation associated with asthma as well as decline in pulmonary function can increase a patient's risk for cardiovascular disease.[7] A population-based longitudinal study found that there is an increasing risk of cardiovascular mortality and hospitalization as a patient's FEV_1 decreases.[8] The potential association between asthma, cardiovascular disease, and stroke is important to consider in the context of EXCELS. Patients in the omalizumab arm relative to the non-omalizumab arm were considered to have more severe asthma at baseline suggesting these patients were more likely to have a lower FEV_1.[6] Therefore, it is important to note that the patients in the omalizumab arm may have had a higher risk for cardiovascular events at baseline due to their asthma severity.

What About the Risk of Malignancy? Evaluating the long-term risk of malignancy with omalizumab was a component of EXCELS.[5] Prior to EXCELS, the manufacturer had reported to the FDA that in its analysis of data from clinical trials, most of which were less than 1 year in length, malignancies were noted in 0.5% of patients treated with omalizumab and 0.2% of patients who were not treated with omalizumab.[5,6] Corren and colleagues conducted a pooled analysis of 35 Phase I-III clinical trials for all omalizumab indications and noted similar results with a 0.5% incidence of malignancies reported in omalizumab-treated patients relative to a 0.18% incidence in patients not treated with omalizumab.[9] However data derived from EXCELS produced a hazard ratio for malignancy of 1.09 (95% CI:0.87-1.38) which was not considered statistically significant.[10]

Bottom Line: The FDA believes that the increased rates of cardiovascular and cerebrovascular events are of notable importance to warrant a labeling change for the product. In addition, despite the results from EXCELS, the FDA is maintaining a warning for malignancy on the labeling. For patients with a history of cancer, cardiovascular or cerebrovascular disease who are prescribed omalizumab, the risks and benefits should be discussed with their provider. Omalizumab is currently on the CCHS Formulary restricted to specific Staff Physicians from the Departments of Allergy and Immunology and Pulmonary, Allergy, and Critical Care Medicine for outpatient use only.

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Afrezza®: An Inhaled Insulin

By: John Hill, Pharm.D.

Introduction: In June 2014, the Food and Drug Administration (FDA) approved a new, rapid-acting inhaled insulin product, Afrezza® (insulin human) inhalation powder.[1] Afrezza® is indicated to improve glycemic control in adult patients with diabetes mellitus, types 1 and 2. The product will be jointly marketed by the MannKind Corporation and Sanofi and is expected to be on the U.S. market in early 2015.[2]

Pharmacokinetics of Inhaled Insulin: The insulin contained within Afrezza® is regular human insulin. Upon pulmonary absorption into the systemic circulation, the metabolism and elimination follow the profile of regular human insulin. Maximum serum insulin concentrations are reached within 12 to 15 minutes and return to baseline by approximately 180 minutes. The median time to maximum effect is approximately 53 minutes. Although Afrezza® displayed faster absorption when compared to subcutaneous insulin lispro, a more rapid onset of action is not observed.

Monitoring and Adverse Events: Prior to initiation of Afrezza® therapy, a physical examination and detailed patient medical history should be conducted.[1] Spirometry including forced expiratory volume in one second (FEV_1) should be performed at baseline before initiation, after 6 months, and annually, even in the absence of pulmonary symptoms. Afrezza® has been associated with a decline in lung function, over a 2 year observation period, as measured by FEV_1. Discontinuation of Afrezza® should be considered in patients who have a decline of ≥20% in FEV_1 from baseline. Insufficient data exist to determine causality, however, the manufacturer does recommend weighing the benefits versus the risks of Afrezza® therapy in patients with active lung cancer, a history of lung cancer, or patients at risk for lung cancer. More frequent monitoring may be warranted in symptomatic patients. Commonly observed adverse events (>5%) include: cough and throat pain or irritation. Other reported adverse reactions include: headache, diarrhea, fatigue, nausea, bronchitis, and urinary tract infection. As with all insulin therapies, mild weight gain was observed with Afrezza® therapy. Increased anti-insulin antibody concentrations were observed in Afrezza®-treated patients, however, their presence did not correlate with a reduction in efficacy. As with all insulin products, hypokalemia is a concern and in combination with thiazolidinediones (e.g., rosiglitazone, pioglitazone) patients with heart failure should be closely monitored for fluid retention.

Limitations and Contraindications: Limitations of Afrezza® therapy include that it is not recommended for the treatment of diabetic ketoacidosis or in patients who smoke.[1] In patients who have type 1 diabetes, it must be used concomitantly with a long-acting insulin. Afrezza® is contraindicated during episodes of hypoglycemia and in patients with hypersensitivity to regular human insulin or the excipients of Afrezza®. Afrezza® is contraindicated in patients with chronic lung disease, such as asthma, or chronic obstructive pulmonary disease (COPD). Afrezza® is classified as a pregnancy risk-category C.

Dosing Recommendations: Afrezza® is a rapid-acting insulin which is to be administered at the beginning of a meal.[1] The product is available as single-use cartridges in two strengths, 4 units (blue cartridge) and 8 units (green cartridge). The manufacturer-recommended dosing for insulin-naïve patients is 4 units at each meal. For patients already using subcutaneous prandial insulin, the dose conversion is outlined in Table 1. In patients using subcutaneous pre-mixed insulin, the recommendation is to divide half of the total daily injected insulin dose between the three meals of the day and dose Afrezza® according to instructions listed in Table 1. The other half of the previous daily dose is then administered as the injected basal insulin dose.

Risk Evaluation and Mitigation Strategy (REMS): Due to pulmonary concerns associated with its use, Afrezza® was approved with a REMS program requiring a communication plan. The goals of the Afrezza® communication plan include[3]:

- Informing healthcare providers that there is a risk of acute bronchospasm associated with Afrezza® in patients with chronic lung disease
- Informing healthcare providers that acute bronchospasm has been observed with Afrezza® in patients with asthma and COPD
- Informing healthcare providers that Afrezza® is contraindicated in patients with chronic lung disease
- Informing healthcare providers of the need to evaluate patients for lung disease before starting on Afrezza®

The FDA has also requested four post-marketing studies be conducted including: a pediatric population study, a 5-year long-term pulmonary malignancy trial, and two pharmacokinetic-pharmacodynamic trials aimed at identifying interpatient variability and optimal dose-ranging.[4]

Cost and Formulary Considerations: Exact pricing information is not yet available from the manufacturer. However, preliminary communications indicate that Afrezza® will be similar in price to existing pre-filled insulin syringes currently on the market.[5] Afrezza® has not been reviewed for addition to the Cleveland Clinic Health-System Formulary.

Conclusion: Afrezza® is a new, rapid-acting inhaled insulin product with the potential to provide a needle-free therapeutic option for diabetic patients. The manufacturer is currently positioning this product as a viable treatment option for newly diagnosed type 2 diabetic patients who are opposed to insulin treatment due to needle-phobia. The manufacturer also states it can be utilized as add-on therapy in type 1 diabetic patients already injecting basal insulin that would prefer the inhalation route instead of three additional daily mealtime injections. However, the current Guidelines published by the American Diabetes Association make no recommendation on the role of Afrezza® for the management of diabetic patients.[6] Afrezza® may serve a role in a niche market of diabetics who are opposed to self-administering injections, but careful consideration of the risks and benefits should be made with particular importance placed on pulmonary issues associated with its use.

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Table 1: Afrezza® Dosing Recommendations[1]

Injected Mealtime Insulin Dose	Afrezza® Dose	# of 4 unit (blue) Cartridges Needed	# of 8 unit (green) Cartridges Needed
Up to 4 units	**4 units**	**One blue**	--
5 – 8 units	**8 units**	--	**One green**
9 –12 units	**12 units**	**One blue** and **one green**	
13 – 16 units	**16 units**	--	**Two green**
17 – 20 units	**20 units**	**One blue** and **two green**	
21 – 24 units	**24 units**	--	**Three green**

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Arformoterol (Brovana®)	Long-acting beta-agonist	Long-term management of COPD	Comments: Arformoterol and formoterol are similar in efficacy and safety but arformoterol is less expensive. In order to standardize the Formulary, only arformoterol was added.
Eslicarbazepine (Aptiom®)	Anticonvulsant	Adjunct therapy for treatment of partial-onset seizures	Comments: Serious adverse effects include skin reactions, DRESS syndrome, and hyponatremia. Dosage adjustments are recommended for select drug interactions.
Pembrolizumab (Keytruda®)	Monoclonal Antibody	Treatment of advanced melanoma	Restriction: Restricted to the Department of Hematology and Medical Oncology for outpatient use only
Ramucirumab (Cyramza®)	VEGFR-2 antagonist	Treatment of advanced gastric or gastroesophageal junction adenocarcinoma in patients who have disease progression after first-line platinum-containing or 5-FU-containing therapy	Restriction: Restricted to the Department of Hematology and Medical Oncology for outpatient use only and it must be used on-label with paclitaxel (i.e., it cannot be used as a single agent)
Sublingual Allergen Extract (Grastek®)	Allergen extract	Treatment of grass pollen-induced allergic rhinitis, with or without conjuctivitis	Restriction: Restricted to Adult Immunology and Otorhinolaryngology for initiation of therapy in the outpatient setting
Sublingual Allergen Extract (Oralair®)	Allergen extract	Treatment of grass pollen-induced allergic rhinitis with or without conjuctivitis	Restriction: Restricted to Adult Immunology and Otorhinolaryngology for initiation of therapy in the outpatient setting

COPD=Chronic Obstructive Pulmonary Disease DRESS=Drug Reaction with Eosinophilia and Systemic Symptoms
5-FU=5-Fluorouracil VEGFR-2=Vascular Endothelial Growth Factor Receptor-2

Formulary Update

Medications Removed from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
All Intranasal Steroids	Corticosteroids	Treatment of Allergic Rhinitis	Patients may use their own supply of intranasal steroids from home; please follow the Patient's Own Medication Policy.
Nystatin Topical Powder	Antifungal agent	Treatment of skin and mucous membrane fungal infections	Miconazole 2% powder will be the therapeutic alternative.
Topical Acyclovir	Antiviral agent	Management of cold sores	Therapeutic alternatives are: oral acyclovir or docosanol 10% topical (Abreva®)

Addition to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Liposomal cytarabine (DepoCyt®)	Antineoplastic agent	Intrathecal treatment of lymphomatous meningitis*	Restriction: Restricted to the Department of Pediatric Hematology and Oncology for outpatient use only

*May also be used for off-label indications