Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria

Chronic idiopathic urticaria (CIU) is defined as itchy hives which persists longer than six weeks with no apparent trigger. Urticaria is caused by histamine release from mast cells, but basophils and IgE also play a role in CIU. The mainstay initial treatment for urticaria is non-sedating H1-antihistamines; however, many patients do not respond to H1-antihistamines. Omalizumab is a recombinant monoclonal antibody that reduces the levels of free IgE which plays a role in mast cell and basophil activation. Omalizumab was more effective than placebo in CIU patients who were unresponsive to H1-antihistamines.

A phase 3, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of omalizumab in patients with moderate-to-severe CIU who were unresponsive to H1-antihistamines. The study evaluated 323 patients between the ages of 12 and 75 years over a 12-week treatment period followed by a 16-week follow-up. Patients received subcutaneous omalizumab 75 mg (n=82), 150 mg (n=83), or 300 mg (n=79) or placebo (n=79) at four-week intervals. The primary endpoint was a change in baseline to week 12 in weekly itch-severity scores. Secondary endpoints included changes from baseline to week 12 in urticarial activity score (UAS7), the number of patients with a weekly itch-severity score >8 (scale of 0 to 21), and changes in weekly number of hives and overall dermatology life quality index (DLQI).

A significant reduction in weekly itch-severity scores at 12 weeks were observed in the groups receiving 150 mg (-8.1±6.4, p=0.001) and 300 mg (-9.8±6, p<0.001) versus placebo (-5.1±5.6, p<0.001). After discontinuation of omalizumab, patients were observed to slowly return close to baseline symptoms at the end of the 16-week follow-up. All secondary endpoints were significantly improved when taking 150 mg or 300 mg of omalizumab when compared to placebo (p<0.01). The onset of effects was observed within the first week of starting treatment. Overall, adverse reactions were similar across treatment groups and placebo with more severe side effects associated with the omalizumab 300 mg group. Omalizumab dosed at 150 mg or 300 mg administered at four-week intervals significantly reduced urticaria symptoms when compared with placebo.

One limitation of the study was that patients continued their pre-randomization dose of H1-antihistamine throughout the study period and used rescue doses of diphenhydramine 25 mg for itch relief. Reporting bias is one other limitation that may have affected the results.

CONCLUSION: Omalizumab, at doses of 150 mg and 300 mg, was an effective treatment in patients with CIU who are unresponsive to H1-antihistamine. Cost is a limitation that should be considered when adding omalizumab to a patient’s therapy. Additional, long-term studies are warranted to validate the placement of omalizumab in the treatment of CIU.


By Heather Trusty, PharmD Candidate
Canagliflozin (Invokana®), a novel treatment for type 2 diabetes

Current oral antihyperglycemic agents (AHA) are associated with high failure rates due to the progressive nature of type 2 diabetes and their high adverse effect profiles. Therefore, combination therapy with agents that have complementary mechanisms of action and minimal adverse effects is important in maintaining glycemic control in patients with diabetes. Canagliflozin (Invokana®), a new oral AHA with a novel mechanism of action, was approved in April 2013 for the treatment of type 2 diabetes. In early trials, canagliflozin was effective as monotherapy or adjunctive therapy with minimal adverse effects.

Canagliflozin is the first sodium-glucose cotransporter 2 (SGLT2) inhibitor. By inhibiting SGLT2, canagliflozin blocks glucose reabsorption and enhances glucose excretion by the kidneys. Increasing urinary glucose excretion reduces plasma glucose levels and may contribute to weight loss due to caloric loss from increased glucose excretion. Canagliflozin is also associated with modest osmotic diuresis. At doses ≥200 mg, canagliflozin is thought to weakly inhibit SGLT1 as well. SGLT1 is found primarily in the small intestine and is responsible for glucose absorption in the gastrointestinal tract. Therefore, the efficacy of canagliflozin at higher doses is partly due to delayed glucose absorption through SGLT1 inhibition.

A randomized, double-blind, placebo-controlled, phase 3 trial assessed the effect of canagliflozin monotherapy on HbA1c in patients with type 2 diabetes. Included in the study were 584 patients with an HbA1c 7-10.0% and an eGFR > 50 mL/min. Patients on an oral AHA had to discontinue the AHA 2 weeks before the study began. The patients received canagliflozin 100 or 300 mg or placebo once daily for 26 weeks. The primary endpoint was the change of HbA1c from baseline. Secondary endpoints included the change from baseline in body weight, HDL cholesterol, LDL cholesterol, and triglycerides.

Both canagliflozin doses significantly reduced HbA1c from baseline compared to placebo (p<0.001). The 300 mg, 100 mg, and placebo groups had mean Hb1Ac baseline changes of -1.03%, -0.77%, and 0.14%, respectively. Moderate reductions in body weight were observed in the canagliflozin 100 mg (-2.5 kg), and 300 mg (-3.4 kg) groups compared to placebo (-0.5 kg). Canagliflozin did not significantly change triglyceride levels compared to placebo. A modest, insignificant increase in HDL and LDL cholesterol was observed in both canagliflozin groups compared with placebo.

The canagliflozin groups had a slightly higher incidence of adverse effects than the placebo group. Genital mycotic infections were more common in canagliflozin-treated patients than in patients on placebo (6.2% and 6.6% vs. 2.1%). The incidence of urinary tract infections was similar in the canagliflozin groups compared to the placebo group (7.2% and 4.2% vs. 5.1%). The hypoglycemia incidence was similar in the 3 groups (3.6, 3.0, and 2.6%), with no reports of severe hypoglycemia.

The authors concluded that canagliflozin improved glycemic control in patients with type 2 diabetes. However, this study did not assess the safety and efficacy of canagliflozin in patients with renal impairment. Additionally, the efficacy of canagliflozin was not compared to the current standard oral therapies.

Another study compared canagliflozin with sitagliptin in patients with type 2 diabetes who were inadequately controlled with metformin plus a sulfonylurea. A total of 755 patients received canagliflozin 300 mg or sitagliptin 100 mg daily and continued their stable metformin plus sulfonylurea therapy for 52 weeks. The primary endpoint was the change in HbA1c at 52 weeks. Secondary endpoints included change in body weight and fasting plasma glucose.

Canagliflozin significantly reduced HbA1c compared to sitagliptin (mean reduction 1.03% vs. 0.66%, respectively). Canagliflozin also reduced fasting plasma glucose and body weight more than sitagliptin (p<0.001). Overall adverse event and hypoglycemia rates were similar between the drugs. However, canagliflozin patients had higher incidences of genital mycotic infections and adverse events related to osmotic diuresis.

The authors concluded that canagliflozin provided better improvement in glycemic control and body weight reduction than sitagliptin but increased genital infections in patients with type 2 diabetes. The evaluation of this study is limited because only the abstract was available for interpretation.

Since urine glucose excretion is proportional to the glomerular filtration rate, the efficacy of canagliflozin may be affected in patients with chronic renal disease. Canagliflozin was evaluated in subjects with type 2 diabetes and stage 3 chronic kidney disease (eGFR ≥30 and <50 mL/min/1.73m²). A total of 269 patients were randomized to receive canagliflozin 100 or 300 mg or placebo daily in addition to their stable AHA regimens (monotherapy or combination therapy with approved agents) for 26 weeks. The primary endpoint was change in HbA1c at week 26. Secondary endpoints included change in fasting blood glucose, adverse event reports, and renal safety parameters.

Canagliflozin doses significantly lowered HbA1c compared to placebo at week 26 (-0.33%, -0.44%, and -0.03%; p<0.05). Canagliflozin improved fasting blood glucose levels compared to placebo. The canagliflozin groups had increased incidences of genital mycotic infections, urinary tract infections, and adverse events related to osmotic diuresis compared to the placebo group, although at lower rates than in other studies. Hypoglycemia occurred more often in canagliflozin-treated patients who were also on insulin or a sulfonylurea. Canagliflozin patients had mild worsening of eGFR and increased serum creatinine early in the study, but

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Nicotine Conjugate Vaccine for Smoking Cessation

Intramuscular nicotine conjugate vaccine is a novel approach for promoting smoking cessation.\(^1\)\(^4\) Nicotine crosses the blood-brain barrier and causes a release of dopamine, which reinforces the addictive behaviors of smoking cigarettes. The vaccine elicits production of nicotine-specific antibodies after inhalation of tobacco products. The formed antibody-antigen molecule is too large to cross the blood-brain barrier, which prevents nicotine from reaching the receptors and causing dopamine release. Several trials have evaluated the abstinence rates, immunogenicity, and safety of nicotine vaccines.\(^2\)\(^3\)

Currently, at least four vaccine formulations are under investigation; however, only phase 2 studies with NicVAX\(^®\) and Nicotine-Qb have been published.\(^4\) Nicotine-Qb is nicotine coupled to virus-like particles formed by the coat protein of bacteriophage Qb.\(^2\) NicVAX\(^®\) is 3-amino-methyl-nicotine linked to Pseudomonas aeruginosa exoprotein A.\(^3\)

A randomized, double-blind, placebo-controlled trial evaluated Nicotine-Qb vaccine in adult patients who smoked at least 10 cigarettes daily.\(^2\) A total of 340 patients received 5 monthly doses of 100 mcg vaccine (n=229) or placebo (n=111) over a 6-month treatment period followed by a 6-month follow-up. The primary endpoint was smoking abstinence from month 3 to 12 months. Secondary endpoints were the immunogenicity, safety, and tolerability of the vaccine.\(^2\)

No significant increase in continuous abstinence rates were observed.\(^7\) However, patients who achieved high antibody (Ab) levels and received all 5 injections had significantly higher abstinence rates between 2 and 6 months compared to placebo (56.6% vs. 31.3%, p=0.004). The 12-month abstinence rates were also higher among patients with high Ab levels compared to placebo (41.5% vs. 21.3%, p=0.012). Overall, adverse events were mild and included flu-like symptoms, headache, myalgia, and pain at the injection site. The authors concluded that patients who achieved high Ab levels were more likely to be abstinent at 12 months. One limitation of the study was the small sample size. Also, patients received numerous counseling sessions that may have increased their motivation to quit smoking, which increases the potential for biased results.\(^2\)

Another randomized, double-blind, placebo-controlled trial evaluated the association between abstinence rates and antibody (Ab) concentrations, dosage, and frequency of NicVAX\(^®\) vaccine in 301 subjects who smoked >18 cigarettes/day.\(^3\) Patients were assigned to 6 groups split into 2 arms with different frequency schedules. Schedule 1 was four injections at weeks 0, 6, 12, and 26. Schedule 2 was five injections at weeks 0, 4, 8, 16, and 26. Patients on both schedules received 200 mcg or 400 mcg of vaccine or placebo. The primary endpoint was continuous smoking abstinence for 8 weeks starting at week 19. Secondary endpoints included continuous abstinence rates (CAR) for 52 weeks and the immunogenicity of the vaccine.\(^3\)

Significantly more patients who received the 400 mcg dose for 5 injections had prolonged abstinence for up to 6 months (17.6% vs. 6%, p=0.015 vs. placebo), as well as prolonged abstinence up to 12 months (15.7% vs. 6%, p=0.038).\(^3\) Patients with higher Ab levels (45 mcg/mL, n=18) had significantly higher CAR than placebo (19.7% vs. 10%, p=0.044). Overall, adverse effects were mild and included tenderness, myalgia, malaise, headache, burning at injection site, and nausea. The authors concluded that smokers with high Ab concentrations after vaccination were more likely to quit and remain abstinent from smoking. Limitations of the study included the small number of patients in each group. The majority of patients were Caucasian; therefore, extrapolation of results to other populations is limited.\(^3\)

No head-to-head studies comparing the different formulations of nicotine vaccine have been published. The results of a phase 2b, randomized, double-blind, placebo-controlled trial evaluating NicVAX\(^®\) in conjunction with varenicline have not been published yet; however, this will be the first head-to-head study evaluating an approved therapy with a nicotine vaccine to promote smoking cessation.\(^1\)

Nicotine vaccination is a novel concept for approaching smoking cessation. The vaccine can help patients who desire smoking cessation but may need an alternative approach, such as those who have relapsed or have failed traditional therapies. One major challenge with a nicotine vaccine is the variable immunogenicity among patients. Another challenge is that the vaccine requires multiple doses and frequent dosing to obtain high antibody levels and compliance can be a limitation. Nicotine vaccines are still in phase 2/3 trials and have not been FDA approved. Further, long-term studies are needed to determine the role of nicotine vaccine in smoking cessation.

By Heather Trusty, PharmD Candidate

References:
Mipomersen for Homozygous Familial Hypercholesterolemia

Kynamro® (mipomersen) was approved in January 2013 for the treatment of homozygous familial hypercholesterolemia (HoFH), a rare genetic disorder that prevents the clearing of low-density lipoproteins (LDL) from the blood. People with HoFH have a reduced life expectancy due to coronary artery disease (CAD). HoFH is resistant to traditional lipid-lowering therapies, and other treatment options at this time are invasive and expensive. Mipomersen, by contrast, is a once weekly 200 mg subcutaneous injection, which can be administered by the patient.

Mipomersen inhibits the synthesis of apolipoprotein B100, a necessary structural component of LDL. Inhibition of apolipoprotein B100 can result in fat accumulation in the liver, and hepatic steatosis is a potential serious adverse effect of mipomersen. Due to the potentially severe adverse liver effects, mipomersen is only available through a restricted program and is not approved for heterozygous familial hypercholesterolemia (HeFH), a more common genetic disorder that also results in cardiovascular morbidity and mortality.

In a phase 3, randomized, placebo-controlled, double-blind trial, 51 patients over 12 years of age with genetic confirmation or clinical diagnosis of HoFH received 200 mg mipomersen or placebo weekly for 26 weeks. Participants had to weigh >40 kg, have a low-fat diet and maximal doses of lipid lowering therapy, and have LDL >3.4 mmol/L (130 mg/dL) with triglycerides <4 mmol/L (350 mg/dL). Patients were excluded if they had a recent cardiovascular event, a history of liver or kidney disease, or other diseases that would predispose them to hyperlipidemia. Patients were also excluded if their creatine phosphokinase was 3 times the upper limit of normal. Participants who weighed <50 kg received 160 mg instead of 200 mg. The primary endpoint was the change in LDL from baseline. Secondary endpoints included changes in apolipoprotein B and total cholesterol from baseline.

Mipomersen was more effective than placebo, reducing LDL by 21.3% more than placebo (95% CI, -32.9 to -9.8%, p=0.0003). The average decrease in LDL was 24.3% with mipomersen versus 3.3% with placebo. Maximum LDL reduction was achieved in the treatment group by week 17. Increases in hepatic enzymes >3 times normal occurred in 4 mipomersen-treated patients, but no cases of hepatic injury occurred. The authors concluded that mipomersen could be valuable as add-on medication for patients with HoFH who are resistant to traditional lipid-lowering therapy. Limitations to this study were that hepatic fat was not routinely measured for hepatic steatosis and only one strength of mipomersen was used. Other small studies have used doses up to 300 mg weekly without adverse events.

A second phase 3 trial was designed to test the efficacy of mipomersen in adults with HeFH and stable CAD. One hundred twenty-four patients were randomized to 200 mg weekly mipomersen or placebo for 28 weeks. Patients had LDL >100 mg/dL and triglycerides <200 mg/dL and were on maximum-dose statin therapy. Exclusion criteria were similar to the previously mentioned study. The primary endpoint was the change in LDL from baseline to week 28. Secondary endpoints included changes in lipids, lipoproteins, and C-reactive protein (CRP).

Mipomersen treatment reduced LDL and apolipoprotein B levels by an average of 28% (95% CI, -34 to -22.1%, p<0.001) and 26.3% (95% CI, -31.2 to -21.4%, p<0.001), respectively. Mipomersen was associated with an increased in hepatic fat (4.9%, 95% CI, 1.4 to 13.2%, p<0.001) compared to placebo (0.4%, 95% CI, -0.7 to 1.3%). The treatment group had a higher incidence of elevated liver enzymes without an observed increase in bilirubin. Patients with the greatest elevation in liver enzymes had the greatest reductions in apolipoprotein B. LDL reduction in females was more pronounced than in males. There were no significant differences in CRP and HDL between the groups. The authors concluded that mipomersen provided additional reductions in apolipoprotein B in patients who were resistant to traditional therapy. Limitations to this study include the small study population and inability to extrapolate results to broader populations. Another limitation was that MRI for hepatic steatosis was only performed 70% of the time.

The third phase 3 trial had a similar design to the previously mentioned studies but included patients with severe hypercholesterolemia (LDL >5.1 mmol/L) and coronary heart disease (CHD) or LDL >7.8 mmol/L without CHD. Patients were excluded if they had poorly-controlled diabetes, hypertension, or significant hepatic or renal disease. One hundred four patients were randomized to mipomersen 200 mg or placebo once a week for 26 weeks. The primary endpoint was the change in LDL from baseline to week 28, and secondary endpoints were changes in other lipoproteins.

LDL reduction was associated with increased hepatic fat. Five patients (12.8%) in the mipomersen group had hepatic steatosis at 26 weeks compared to zero in the placebo group. Twelve participants withdrew from the mipomersen group due to an adverse event (n=8), non-compliance (n=1), or other reasons (n=3). One patient withdrew from the placebo group due to fatigue and headache. LDL decreased by 36% (95% CI, -51.3 to -15.3%, p<0.001) in the mipomersen group compared to a 12.5% decrease in the placebo group (95% CI, -10.8 to 35.8%). The authors concluded that mipomersen significantly lowered LDL and other lipoproteins. One limitation to the study was the small study size.

The most common side effects of mipomersen are injection site reactions (84% incidence). Nausea and flu-like symptoms are also common (13-66%). Development of antibodies (38-72%) is associated with a higher incidence of flu-like symptoms and discontinuation of mipomersen. Liver enzyme eleva-

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Canagliflozin (from page 2)

Canagliflozin is effective for improving glycermic control either as monotherapy or in combination with other hypoglycemic agents or with insulin for adults with type 2 diabetes. Patients on canagliflozin are at an increased risk for genital mycotic and urinary tract infections. Due to its osmotic diuretic effect, canagliflozin can cause increased urination and a decrease in blood pressure. The risk of hypoglycemia is increased in patients taking canagliflozin with insulin or a sulfonylurea. Serum cholesterol, potassium, and renal function should be monitored while on canagliflozin therapy. Studies evaluating the risk of cardiovascular events and osteoporosis with canagliflozin are currently ongoing. Further studies of the long-term safety and efficacy of canagliflozin are still needed.

By Megan Meis, PharmD Candidate

References:

Mipomersen (from page 4)

Mipomersen caused dramatic decreases in LDL in patients with HoFH. Unlike lomitapide, a microsomal triglyceride transfer protein inhibitor, mipomersen does not decrease HDL cholesterol. Mipomersen may be a valuable option for patients with hypercholesterolemia that is resistant to traditional statin therapy, although long-term efficacy in reducing cardiovascular morbidity and mortality has not been elucidated.

By Betsy DeMarcois, PharmD Candidate

References:
Literature Highlight:
Investigational Vaccine to Prevent *S. aureus* Infections

*Staphylococcus aureus* infections can cause serious complications after cardiothoracic surgery and lead to a substantial increase in morbidity and mortality. The novel vaccine, V710, was designed to contain a surface antigen of *S. aureus* to initiate an IgG mediated humoral immune response. However, the V710 vaccine was not effective in reducing the incidence of *S. aureus* infections in postoperative cardiothoracic surgery patients in a phase 3 study.

A randomized, double-blind, placebo-controlled, multicenter clinical trial enrolled 8031 patients to evaluate the safety and efficacy of the V710 vaccine. Included in this study were adult patients scheduled for a cardiothoracic surgery involving a full median sternotomy. The participants received a 0.5 mL intramuscular injection of either the V710 vaccine (60 mcg) or normal saline within 14 to 60 days before their scheduled cardiothoracic surgery. In addition, all participants received preoperative antibiotic prophylaxis and other perioperative treatments according to each site’s standard of care.

The primary endpoint was the incidence of *S. aureus* bacteremia and/or deep sternal wound infection within 90 days after surgery. Secondary endpoints included any *S. aureus* infection within 90 days after surgery and immunogenicity and safety of the vaccine. Efficacy was determined by at least a 20% reduction of *S. aureus* infections in the V710-treated group compared to the placebo group.

The study was terminated early due to a higher rate of mortality and multiorgan failure in recipients of the V710 vaccine. The V710 vaccine was not more effective than placebo in preventing *S. aureus* infections. The primary endpoint event rate in the V710-treated group and placebo group was 2.6 (95% CI 1.6-4.0) and 3.2 (95% CI 2.1-4.7) per 100 person-years, respectively. The vaccine resulted in an overall 25.3% (95% CI -3.4% to 46.2%) reduction of *S. aureus* infections when compared to placebo, but this was not significant. IgG antibody titers were significantly higher in the vaccinated group than the placebo group, which indicated the vaccine was immunogenic. However, despite achieving adequate humoral responses, vaccine-treated patients still contracted *S. aureus* infections. Therefore, the failure of the vaccine was not due its lack of immunogenicity.

Significantly more patients with *S. aureus* infection died in the vaccine group than the placebo group with respective mortality rates of 23.0 (95% CI 12.9-37.9) and 4.2 (95% CI 1.2-10.8) deaths per 100 person-years. Also, postoperative multiorgan failure was more common in the vaccine group versus placebo (0.9, 95% CI 0.6-1.2 vs. 0.5, 95% CI 0.3-0.8 events per 100 person-years, respectively). Despite early study termination, a limitation to this study was that the perioperative protocols were not standardized among the various sites. Therefore, differences in aseptic techniques and infection control at the various sites may have contributed to an increased risk for infection.

**CONCLUSION:** The V710 vaccine did not reduce the incidence of *S. aureus* infections compared to placebo after cardiothoracic surgery. Furthermore, the vaccine was associated with increased mortality and multiorgan failure in patients who developed *S. aureus* infections.


*By Megan Meis, PharmD Candidate*