Patients are at risk of developing postoperative atrial fibrillation following cardiac surgery. Omega-3 fatty acids may decrease this risk because they have the potential to positively affect pathways common to atrial fibrillation, including blood pressure, heart rate, and systemic vascular response.

A double-blind, placebo-controlled, randomized trial examined whether omega-3 fatty acids reduced postoperative atrial fibrillation more than placebo in patients undergoing cardiac surgery. A total of 1516 patients (≥18 years old) scheduled for cardiac surgery and with stable ECGs were included in the study. Patients who had unstable baseline ECGs, were using fish oil regularly, had a planned or an existing heart transplant, or were using a ventricular assist device were excluded. Patients received capsules of either olive oil (placebo) or eicosapentaenoic acid 465 mg/docosahexaenoic acid 375 mg. Patients were given preoperative loading doses of either 10 g over two to five days or 8 g over two days. They then received 2 g every day after surgery until post-op day 10 or until discharged. The primary endpoint was the incidence of atrial fibrillation lasting longer than 30 seconds. Secondary endpoints included sustained, symptomatic, or treated atrial fibrillation; the number of atrial fibrillation episodes per patient; arterial thromboembolism; and the need for blood transfusions.

The incidence of atrial fibrillation did not differ between the control and treatment groups (30.0% vs. 30.7%; p=0.74). The occurrence of sustained, symptomatic, or treated atrial fibrillation was also similar between the placebo and treatment groups (29.0% vs. 28.6%; p=0.70), and the numbers of atrial fibrillation episodes per patient did not differ between the placebo and treatment groups (1 episode: 20.6% vs. 20.7%; 2 episodes: 7.8% vs. 6.5%; 3 episodes: 2.4% vs. 2.8%, respectively; p=0.73). There were significantly fewer cases of arterial thromboembolism in the treatment group (1.7% vs. 0.7%; p=0.047), which also had less need for red blood cell transfusions (1.6 vs. 1.9; p<0.001). Omega-3 fatty acids significantly increased GI upset (5.8% vs. 3.6%; p=0.04) and burping (4.4% vs. 2.5%; p=0.05). The authors concluded that omega-3 fatty acids did not reduce the short-term incidence of postoperative atrial fibrillation. The study had a relatively short duration, so any long-term benefits or harmful effects of omega-3 fatty acids could not be determined. Another limitation of this study was the dose of the omega-3 fatty acids, which may have been too low to produce a benefit.

CONCLUSION: The use of omega-3 fatty acids did not reduce the short-term incidence of postoperative atrial fibrillation in cardiac surgery patients.


By Anthony Peterson, Pharm.D. Candidate
Xeljanz® (tofacitinib) was approved on November 6, 2012, to treat rheumatoid arthritis (RA) in patients who have had an insufficient response to standard methotrexate therapy. Its mechanism of action and oral dosage form make tofacitinib a unique second-line RA drug. Tofacitinib inhibits the autoimmune destruction from RA by preventing hematopoiesis and immune functioning within cells.

Tofacitinib monotherapy reduced signs and symptoms of RA in patients who received no benefit or developed adverse effects from at least one other biologic or non-biologic disease modifying drug. A phase 3, placebo-controlled trial enrolled 611 patients with moderate RA and an inadequate response to prior therapy to determine the safety and efficacy of tofacitinib. Patients were randomized to receive either tofacitinib 5 mg twice daily for six months, tofacitinib 10 mg twice daily for six months, placebo for three months followed by tofacitinib 5 mg twice daily for three months, or placebo for three months followed by tofacitinib 10 mg twice daily for three months. The primary endpoint was the number of patients achieving an American College of Rheumatology (ACR) 20 response, defined as a 20% reduction in the baseline number of tender or swollen joints and a 20% improvement of three or more of the five remaining ACR core measures (pain, disability level, C-reactive protein level, and global assessment of disease by patient and provider). The health assessment questionnaire-disability index (HAQ-DI) score was another endpoint. HAQ-DI scores range from 0 to 3, 3 being the highest level of disability. Tofacitinib therapy led to an ACR20 response in 59.8% of patients receiving 5 mg twice daily, 65.7% of patients receiving 10 mg twice daily, and 26.7% in the combined placebo groups (p<0.001 for both comparisons to placebo). The HAQ-DI score decreased by 0.5 points in the 5 mg group, by 0.57 points in the 10 mg treatment group, and by 0.19 in the combined placebo groups (p<0.001). An increase in serious infections as well as increases in LDL cholesterol, liver aminotransferases, serum creatinine, and decreases in neutrophil counts were adverse effects associated with tofacitinib. The authors concluded that tofacitinib improved physical function and decreased the signs and symptoms of RA. The primary study limitation was the small population size. Longer studies with larger populations are necessary to delineate the long-term safety of tofacitinib therapy.

Tofacitinib exhibited similar efficacy to adalimumab, an injectable second-line RA medication. In order to determine the safety and efficacy of tofacitinib, a randomized, phase 3 trial enrolled 717 patients with moderate RA who were taking concomitant methotrexate. Patients were randomized to receive either tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every two weeks, or placebo for three or six months followed by either tofacitinib 5 mg or 10 mg twice daily. The primary endpoints were the number of ACR20 responses at six months, changes in the HAQ-DI scores, and the number of Disease Activity Scores (DAS) less than 2.6 (indicative of low disease activity). There was a significantly greater ACR 20 response in the tofacitinib 5 mg (51.5%), tofacitinib 10 mg (52.6%), and adalimumab 40 mg (47.2%) groups compared to placebo (28.3%; p<0.001 for all comparisons). The HAQ-DI score significantly decreased in the tofacitinib 5 mg (-0.55), tofacitinib 10 mg (-0.61) and adalimumab 40 mg (-0.49) groups compared to placebo (-0.24; p<0.05 for all comparisons). Significantly more patients in the tofacitinib 5 mg and 10 mg groups and the adalimumab group had a DAS less than 2.6 (6.2%, 12.5%, and 6.7%, respectively) than in the placebo group (1.1%; p<0.05 for all comparisons). Adverse events in the tofacitinib groups included decreased neutrophil count, increased LDL cholesterol, and infections. The authors concluded that tofacitinib was more effective than placebo and similar in efficacy to adalimumab in patients with RA who had an inadequate response to methotrexate therapy. This study was not designed to compare tofacitinib directly to adalimumab; therefore, further trials are necessary to determine the place of tofacitinib in the current RA treatment algorithm.

The recommended tofacitinib dose is 5 mg twice daily. The dose should be reduced to 5 mg daily in patients with moderate to severe renal dysfunction, moderate hepatic dysfunction, and patients who are receiving moderate to strong CYP3A4 inhibitors or 2C19 inhibitors. Tofacitinib should not be given to patients with severe hepatic dysfunction, lymphocyte counts less than 500 cells/mm³, absolute neutrophil counts less than 1000 cells/mm³, or hemoglobin levels less than 9 g/dL. Tofacitinib should not be given with biologic disease modifying drugs or strong immunosuppressants.

Tofacitinib is a novel oral medication that reduces signs and symptoms of RA compared to placebo in patients for whom methotrexate is not effective. Important side effects of tofacitinib include infections, increased LDL cholesterol levels, and decreased neutrophil counts. Studies are ongoing to determine the long-term safety of the drug as well as its place in therapy.

By Kathryn Norton, Pharm.D. Candidate

REFERENCES:
Some triglyceride-lowering medications (e.g., fish oil) can increase low-density lipoprotein (LDL) cholesterol levels in patients with hypertriglyceridemia.\(^1\) The docosahexaenoic acid (DHA) in fish oil is thought to be one cause for the increase in LDL levels.\(^2\) Vascepa™ (icosapent ethyl; approved July 26, 2012) is an omega-3 fatty acid containing ≥96% eicosapentaenoic acid ethyl ester (EPA) and no DHA.\(^1,2\) Icosapent ethyl decreases triglyceride (TG) levels significantly without raising LDL cholesterol levels. A two-part study examined the efficacy and safety of icosapent ethyl.\(^1,3\)

Part I evaluated patients with TG levels between 500 mg/dL and 2000 mg/dL.\(^1\) This phase III, multi-center, placebo-controlled, randomized, double-blind, 12-week trial included 229 patients >18 years of age. Eligible participants were randomized to receive either icosapent ethyl 4 g/day (n=77), icosapent ethyl 2 g/day (n=76), or placebo (n=76). The primary endpoint was the percentage change in placebo-corrected median TG levels. Secondary endpoints included the percentage changes in LDL and HDL cholesterol levels.\(^3\)

Baseline TG levels were 680, 657, and 703 mg/dL for the 4 g/day, 2 g/day, and the placebo groups, respectively.\(^1\) TG levels were reduced by 33.1% in 4 g/day group (p<0.0001) and by 19.7% in 2 g/day group (p<0.0051). Placebo-corrected TG levels for patients with baseline TG levels ≥750 mg/dL were reduced by 45.4% in the 4 g/day group (n=28; p<0.0001) and 32.9% in the 2 g/day group (n=28; p=0.0016). Neither of the icosapent ethyl groups had significantly increased placebo-corrected median LDL cholesterol levels. Icosapent ethyl had no impact on HDL cholesterol levels. Occurrence of treatment-emergent adverse events, such as diarrhea, nausea, and eructation (belching), was >3% in all three groups and occurred most commonly in the placebo group. One person discontinued the study drug in the 2 g/day group due to diarrhea, and three patients discontinued placebo due to arthralgia, gout, and nausea.\(^1\)

Part II of the trial evaluated patients (n=702) with TG levels between 200 mg/dL and 500 mg/dL who were also on statin therapy.\(^1,4\) The study design, eligibility, and endpoints were the same as in part I, with the exception of a forty-week, open-label extension.\(^4\)

The placebo-corrected TG levels decreased by -21.5% (p=0.0001), and -10.1% (p<0.0005) in the 4 g/day and 2 g/day, respectively.\(^3\) Neither of the icosapent ethyl groups had a significantly increased placebo-corrected median LDL cholesterol level. In addition, the 4 g/day group had a significant reduction in LDL levels (-6.2%; p=0.0067). Icosapent ethyl was well tolerated and had a similar safety profile as the placebo. Adverse events were similar to those in part I of the trial, with the exception of nasopharyngitis, which occurred mostly in the placebo group. Discontinuation of the study drug occurred in five patients in the 4 g/day group, eight patients in the 2 g/day group, and twelve patients in the placebo group due to treatment-emergent adverse events. None of the patients experienced serious side effects.\(^3\)

The authors concluded that patients who were also receiving statin therapy had a greater TG-lowering effect compared to patients without statin treatment.\(^3\) The authors indicated that there could be a synergistic effect between icosapent ethyl and statins.\(^3\) There are limitations to this clinical trial. The study did not evaluate the coronary heart disease benefit of lowering TG levels. Patients who had a high risk for pancreatitis, had cardiovascular morbidity, or had TG levels ≥500 mg/dL were not included in the trial, so the effect of this icosapent ethyl formulation could not have been determined in these subgroups.\(^1,3\)

From the studies, the most common adverse effect of icosapent ethyl was joint pain.\(^1\) Significant adverse events include nausea, diarrhea, and urination. Icosapent ethyl is available in 1 gram capsules and is dosed as two capsules twice daily. The maximum daily dose is 4 g/day.\(^4\)

In many cases, diet, exercise, and lipid-lowering therapy are insignificantly implemented in patients with hypertriglyceridemia. Icosapent ethyl can help reduce TG levels in patients with TG levels ≥500 mg/dL without negatively influencing the LDL levels. Icosapent ethyl could be an alternative for patients who have been on statin therapy but who have not had a significant reduction in TG levels.

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Long-term complications of type 2 diabetes (T2DM) are difficult to control due to a lack of self-care adherence. Active involvement in self-care monitoring with continued psychological support from trained peers could improve the quality of care and reduce diabetes related complications. Trained peers tend to give successful diabetic self-care behavior advice based on their own personal experiences.

A randomized, controlled trial was done to compare the clinical, metabolic, and psychological outcomes in patients with T2DM after attending structured diabetes education programs run by either diabetes educators or trained peers with T2DM.

Patients (25-75 years old) who were diagnosed with T2DM and were followed by their physicians for at least two years, with more than two diabetes encounters, were selected from a clinic in Argentina. Patients with ESRD, class III or IV heart failure, cancer, blindness, drug or alcohol addiction, or an inability to provide self-care were excluded. A total of 198 patients were enrolled (control, n=105, diabetes duration=6±6 years; peer, n=93, diabetes duration=6±7 years). Patients were randomly assigned to attend a four-week structured diabetes education training (weekly sessions of 90-120 minutes each), followed by a reinforcement session at six months, led by either professional educators (control group) or trained peers (peer group). The peer group received additional continued psychological support and practical application of diabetes knowledge weekly via phone calls for the first six months, twice weekly for the following three months, and monthly till the end of the study, and face-to-face interviews in a group of ten participants twice a month for a year. A structured questionnaire regarding clinical, metabolic, and psychological progress was used to assess the interventions. The primary endpoint was the change in A1C. The secondary endpoints included the change in blood pressure (BP), classical diabetes symptoms (polydipsia, polyuria, polyphagia), fasting blood glucose (FBG), and psychosocial burden.

Baseline A1C values were close to 7% in both groups. The A1C values were similar between the peer and control groups (6.8±1.3 vs 7.0±1.1, respectively) at month 12. Systolic blood pressure (SBP) in the peer group significantly decreased from baseline (137±28 mmHg to 128±18 mmHg; p<0.016). The classical diabetes symptoms decreased significantly in both groups (p=0.01), whereas BMI and diastolic blood pressure did not significantly change in either group. During the follow-up period, baseline FBG values decreased significantly in the peer and control groups (136±51 to 121±38 mg/dL vs. 141±43 to 129±38 mg/dL, respectively; p<0.01). Diabetes distress (emotional burden, physician-related distress, and regimen-related distress) improved significantly in the peer group.

The authors concluded that trained peer education in a structured environment was non-inferior to education from a professional diabetes educator in improving outcomes in patients with T2DM. A major limitation of this study was the absence of blinding. The results of the study might not be applicable to patients in the United States because of differences in relationships of trust between American patients and healthcare professionals. Some patients in the United States may tend to confide more in doctors than trained peers.

CONCLUSION: Clinical, metabolic, and psychological outcomes in patients with T2DM participating in structured diabetes programs delivered by trained peers were similar to those produced by diabetes programs led by professional educators. Continued education about self-management of diabetes from trained peers significantly improved A1C, SBP, FBG, and psychological stress.


By Wai Wai Tun, Pharm.D. Candidate
Literature Highlight:
The Effect of Trastuzumab on Survival in Patients with HER2-Positive Advanced Breast Cancer

Approximately 20% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2) and are therefore treated with a HER2-targeted drug, specifically trastuzumab, in addition to chemotherapy. When breast cancer progresses after therapy with trastuzumab and standard combination chemotherapy with an anthracycline and a taxane, patients are treated with other chemotherapy regimens, such as lapatinib plus capecitabine. A new therapy (T-DM1) has been developed which conjugates trastuzumab with a derivative of maytansine, a microtubule-inhibiting agent. This new therapy may be useful in patients progressing after therapy with trastuzumab and a taxane.

The EMILIA study was a randomized, open-label trial which found T-DM1 to be effective for treatment of HER2-positive advanced breast cancer. This study compared oral lapatinib 1250 mg once daily plus oral capecitabine 1000 mg every 12 hours (LC group; n=496) to T-DM1 3.6 mg/kg IV every 21 days (n=495) in patients with HER2-positive advanced breast cancer who previously received treatment with trastuzumab and a taxane. The doses were reduced as necessary due to adverse events. This trial was initially designed to assess progression-free survival by independent review as the primary outcome; however, the investigators later decided to include overall survival as a co-primary endpoint. Secondary outcomes included progression-free survival, as determined by investigator assessment; objective response rate; and median duration of response.

Overall survival was significantly longer with T-DM1 (30.9 months) compared to LC therapy (25.1 months; HR for death from any cause, 0.68, 95% CI 0.55 to 0.85; p<0.001). Progression-free survival, as determined by investigator assessment, was 9.4 months in the T-DM1 group compared to 5.8 months in the LC group (HR for progression or death from any cause, 0.66, 95% CI 0.56 to 0.77; p<0.001). Progression-free survival, as determined by independent review, was significantly greater in the T-DM1 group (9.6 months) compared to LC group (6.4 months; HR for progression or death from any cause, 0.65, 95% CI 0.55 to 0.77; p<0.001). Objective response rate was 43.6% with T-DM1 and 30.8% with LC (p<0.001), and median duration of response was 12.6 months with T-DM1 therapy and 6.5 months with LC therapy.

Serious adverse events were seen in 15.5% of patients given T-DM1 and 18% of patients in the LC group. Diarrhea and palmar-plantar erythrodysesthesia were the most common serious events in the LC group, and thrombocytopenia and elevated aspartate aminotransferase and alanine aminotransferase were the most common events reported in the T-DM1 group. Bleeding events were higher in the T-DM1 group, and hyperbilirubinemia was more common in the LC group.

The authors concluded that trastuzumab emtansine therapy improved progression-free survival and overall survival in patients with HER2-positive advanced breast cancer who had previously been treated with trastuzumab and taxane therapy. Estimates of survival and recurrence may have been biased because of the relatively short follow-up period of this trial (13 to 19 months). Generalizing these results to patients with different demographics or genetic backgrounds is difficult because the majority of patients were ethnically homogeneous (Caucasian).

CONCLUSION: Trastuzumab emtansine increased progression-free survival and overall survival in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane.


By Kathryn Norton, Pharm.D. Candidate