Pentoxifylline Treatment in Acute Pancreatitis: A Double-Blind Placebo-Controlled Randomized Trial

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TITLE AND SUMMARY PAGE

Project Title: Pentoxifylline Treatment in Acute Pancreatitis; A Double-Blind Placebo-Controlled Randomized Trial

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Project Summary:
Background. Acute pancreatitis (AP) is a cause of significant morbidity and mortality and effective therapeutic regimens to treat this condition are lacking. Extensive experimental evidence indicates that tumor necrosis factor alpha (TNF-α) contributes to the pathogenesis of multiple organ failure (main cause of morbidity and mortality) in AP, suggesting a possible role for inhibition of TNF-α in the treatment of AP. There is no effective drug therapy for AP and hardly any human experience about the role of pentoxifylline in AP Methods: Randomized, double-blind, placebo-controlled study comparing three times daily dosing with Pentoxifylline from the time of admission until 72 hours of hospitalization in patients presenting with AP. Seventy-five patients will be enrolled in both the "treatment" and "placebo" groups (150 patients total). This study will be performed at Mayo Clinic, Rochester. Primary outcomes: Determine changes in CRP, TNF-α, IL-6, and IL-8 levels from admission baseline at one week. Significance: If our hypothesis is confirmed this trial will be a landmark development in the treatment of AP. A simple, safe, and inexpensive drug that can be given to all patients with AP, in all settings, will be available to decrease the significant morbidity and mortality due to this disease.

PROJECT DESCRIPTION

Specific Aims:

Aim1: Determine if oral pentoxifylline will improve clinical outcomes in AP. Persistent SIRS and organ failure, pancreatic and/or peripancreatic necrosis and infection (determinants) will be primary endpoints, while death (infrequent), length of stay, and the need for ICU and intervention will be secondary endpoints. These are all identified in the revised Atlanta classification as outcomes of interest. Hypothesis: Pentoxifylline will decrease the occurrence of any one of the following adverse outcomes in AP: pancreatic and/or peripancreatic necrosis and infection, persistent organ failure, prolonged hospital stay, need for ICU, and intervention and death in patients with AP.

Aim2: Determine if oral pentoxifylline will decrease serum levels of inflammatory markers. Hypothesis: Pentoxifylline will reduce levels of CRP, TNF-α, IL-6, and IL-8, and this reduction will correlate with clinical outcomes in patients with AP.

Background and Significance:

Acute pancreatitis, an inflammation of the pancreas gland, is the most common gastrointestinal hospital discharge diagnosis and averages $2.6 billion in costs per year. Yet, as common as it is, there is no specific drug to treat this disease. There has been no drug trial in AP since the beginning of this century. Based on previous animal studies and a pilot study in humans at our institution, pentoxifylline has shown to block the inflammation in this disease. A larger study must be performed before the efficacy of this drug can be confirmed. A successful study would provide a breakthrough in AP therapy, paving the way for a simple, safe, and inexpensive drug to be available world-wide to treat this disease. This novel approach would be a major advancement in the treatment of this disease.

Acute pancreatitis (AP) is a common inflammatory condition of the pancreas leading to the hospitalization of millions of patients annually worldwide. While the majority of patients (~80%) have mild, self-limiting disease with low mortality, severe acute pancreatitis (SAP) is associated with high morbidity and mortality (20-40%) and prolonged hospital stays. Specific pharmacological therapies, such as aprotinin, glucagon, gabexate, somatostatin and lexipafant, have not been shown to have any advantage in randomized controlled trials. As a result, treatment for AP is mainly supportive involving bowel rest, aggressive intravenous fluid resuscitation and pain control -a targeted therapy for AP is therefore urgently needed.

Significance

The morbidity, mortality, and increased costs in acute pancreatitis (AP) are mainly due to the more serious forms, moderate and severe, described in the latest revised Atlanta classification(4). The accepted important clinical outcomes of AP include systemic inflammatory response syndrome (SIRS), pancreatic and/or peripancreatic necrosis and infection, persistent organ failure, length of hospital stay, admittance to the intensive care unit (ICU) or intensive care intervention, and death. In our prospective study, 31% of 137 consecutively admitted patients with AP had moderate or severe AP,10 while in another study half of the 619 patients with AP, who had a computed tomography (CT) scan at our institution had such serious disease (unpublished data). Two important reasons for the significant morbidity and mortality seen in AP are the inability to accurately predict these serious forms in the early stages and the absence of an effective drug that could prevent the progression to such serious forms. It is for this reason current guidelines for the treatment of AP, recommend “supportive care” as the main treatment.(2) The many available predictors of severity in AP have reached a plateau for their efficacy(5) and thus there is no reliable way at admission to predict those who will require a drug to prevent the adverse outcomes. Hence, all patients need to be targeted. If all are to be given a drug, it has to
be inexpensive, easy to administer, and safe. Pentoxifylline meets all these criteria and can be administered in both academic and community settings. Complicated interventions like intravenous and intra-arterial therapies are not the ideal therapies for this purpose. With this background, it can be clearly appreciated that a simple, safe, and inexpensive drug that could be

administered to all patients diagnosed with AP in academic, as well as in community settings, is urgently needed. Clinical drug intervention trials in AP are conspicuously absent since the negative lexipafant study in 2001.(11) This is due to the inherent difficulties in conducting such trials and the lack of drugs with good efficacy in experimental animals. Extensive animal studies suggest that TNF-α is an important inflammatory mediator in AP.(12-15) TNF-α is the prototypic member of a cytokine family that regulates essential biologic functions such as cell differentiation, proliferation and apoptosis.(9,16) By up-regulating several different genes, such as cytokines, chemokines, NF-kB, cell adhesion molecules, and inducible nitric oxide synthase, TNF-α promotes a proinflammatory action.(17) In AP, TNF-α, IL-6 and IL-8 have been demonstrated to be substantially up-regulated in the pancreatic acinar cells.(17-21) C-reactive protein (CRP) is another inflammatory marker that has been found to be elevated in greater proportion of patients with more serious forms of the disease. Since TNF-α appears to play a central role in the pathogenesis of severe AP, it is possible that inhibition of TNF-α would ameliorate the course of AP.(22,23) Mortality of experimental pancreatitis is dramatically reduced in TNF-α and IL-6 knockout laboratory animals.(24)AP-related complications were ameliorated in rats given anti-TNF antibody.(8,25) Polyclonal blockade of TNF-α significantly reduced the biochemical manifestations of AP and a soluble TNF-receptor antagonist yielded a reduction in the severity and mortality of experimental AP.(26) Pentoxifylline has been used for years in peripheral vascular disease with high degree of safety and is also a TNF-α blocker. It is rapidly and extensively absorbed from the GI tract, peak plasma levels of the drug and active metabolites reach between 2 to 4 hours after a single oral dose of 400 mg extended release form and remain active for extended periods. Hence dosing every 8 hours has been effective for many years for disorders like claudication. Its use in alcoholic hepatitis, another TNF-α mediated inflammatory condition, has been well-established.(27) Human studies in cirrhosis,(28) cardiac surgery,(29) and hemodialysis(30) not only demonstrated its safety with regards to infection, hemorrhagic complications and renal complications but its beneficial effect all with the oral 8 hourly dosing (intravenous form not easily available in the US). We have already demonstrated the capability to successfully complete a clinical trial in AP at our institution due to the factors elaborated in the specific aims section, and the results were encouraging with regards to the safety of pentoxifylline (investigational drug#: 104240) and possible efficacy. We propose this study would validate the efficacy and safety of oral pentoxifylline to decrease the morbidity and mortality and reduce the levels of inflammatory markers in all patients presenting with AP.

Preliminary Results:

We have already successfully conducted a pilot double-blinded, placebo-controlled, allocation-blinded RCT of oral pentoxifylline in patients with AP with any one of several reported predictors of severe disease. By selecting many reported predictors of severity, we attempted to avoid as many patients with a mild form of the disease as possible. Both groups had 14 patients, evenly matched for age and sex; APACHE II and SIRS scores at admission; and pancreatic and/or peri-pancreatic necrosis. Compared to the placebo group, the pentoxifylline group experienced a 29% reduction in length of hospital stay, a 29% reduction in the need for an ICU stay, a 21% reduction in persistent organ failure, and a 7% reduction in pancreatic necrosis or fluid collection. The reductions translated to having no patients with: hospital stays over 10 days, an ICU need, persistent organ failure, interventions, or death in the pentoxifylline group . However, with the small sample size of this pilot study, these clinically significant differences failed to achieve statistical significance except for ICU need. There was no difference in the

inflammatory markers between the two groups over a short period of three days. We concluded that it is feasible to conduct a drug intervention study in a single institution, and pentoxifylline appeared safe and decreased the length of stay and the need for ICU intervention. With larger numbers, besides validating the above findings, we expect to see a beneficial

Experimental Design or Project Summary:

Acute pancreatitis (AP) is an inflammation of the pancreas gland and the most common gastrointestinal discharge diagnosis (approximately 280,000 admissions in 2009). It has resulted in $2.6 billion, annually, in health care costs, mainly due to the more serious forms of the disease. Lack of any specific drug to treat the condition and predictors to identify patients who will develop more serious forms of the disease contribute to this. Long-term objectives of the study are to find a drug to treat this disease, improve patient outcomes, and reduce the costs of health care. Based on our experience with animals and a small, human subjects pilot study, our hypothesis and specific aims are:

1. Pentoxifylline, administered within 72 hours of diagnosis, improves the clinical outcomes and decreases the occurrence of more serious forms of AP.

2. Pentoxifylline reduces the blood levels of inflammatory markers, which correlates with improvement in clinical outcomes. This study is a novel, exploratory clinical study of the effect of a drug that has a proven role in animal studies in blocking the inflammatory response in AP. It is also a high reward study that will lead to a breakthrough in the treatment of AP and challenge the age old recommendation of supportive treatment alone.

The study will have 2 groups of 75 patients each, all with AP, randomly assigned to either the drug or a placebo, which looks like the drug, for a period of 3 days or until the time they are discharged, if hospital discharge is within 7 days of admission. The levels of markers of inflammation (CRP, IL-6, IL-8 and TNF-α) will be measured at baseline and on 5 successive days or until the time of discharge, whichever occurs earlier. Determination of group size was based on the previous pilot study to decrease any of the important adverse outcomes, providing for a dropout rate of 10% during the study. During 2012, 263 patients with AP were admitted to this institution, which possesses the needed infrastructure for successful completion of clinical drug intervention trials. In the stipulated period of 2 years by the NIH, the required number of patients for the study could be recruited.

This project represents a single center study at Mayo Clinic Rochester. The trial is a randomized, double-blind, placebo-controlled study design.

Subjects: Subjects will be adult patients 18 years of age and greater which will be recruited from Mayo Clinic and admitted to the hospital with acute pancreatitis as defined by at least two of the following:

- amylase and/or lipase greater than 3 times the upper limit of normal values,
- characteristic cross-sectional imaging,
- characteristic pain syndrome.

If patients give consent to be in the study the PI may contact those patients before formally enrolling them in the study. By overseeing that one of the team (a study coordinator, PI, and co-investigator) is present during the weekends, we anticipate that those eligible patients during the weekend period are not going to be excluded.

Patients admitted within 24 hours with AP diagnosis will be included, with the exception of those meeting the exclusion criteria. Those patients that have been identified with AP diagnosis within 72 hours will be approached by the study coordinator and also by the principal investigator (PI) (whenever feasible) to explain the study and obtain written consent.

Inclusion criteria

- Enrollment within 72 hours of diagnosis of AP
- Ability to give informed consent or a legal adult representative LAR able to give informed consent for subject when needed as defined but LAR use guidelines.
- Adult subjects of age ≥18 years.

Exclusion Criteria:

- Moderate or severe congestive heart failure,
- History of seizure disorders or demyelinating disease,
- Nursing mothers,
- Pregnancy,
- History of prior tuberculosis or risk factors for tuberculosis
- Evidence of non- corticosteroid immunosuppression (such as malignancy, chronic renal failure, chemotherapy within 60 days, and HIV)
- Evidence of active hemorrhage,
- Paralytic ileus with severe nausea and vomiting.

Laboratory test and assessments:

Test / Procedure	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
TNF-a*	X	X	X	X	X	X
IL-6*	X	X	X	X	X	X
IL-8*	X	X	X	X	X	X
Pregnancy Test	X					
CRP	X*	X *	X*	X *	X*	X*

* Note: The C-RP, TNF-a, IL-6, IL-8 tests are charged to the research study. All other tests listed are clinical standard care for acute pancreatitis.
The pregnancy test may be done as standard of care and will be closely monitored by study staff to assure completion before subject receives study medication.
Follow up process may be done by telephone contact or review of medical records dependant on subjects follow-up information availability. Some subjects may do their follow up visits at a

local facility not return to Mayo Clinic Rochester for follow up visit within the 4 month time frame (plus or minus 15 days). Thus their medical record may not be available in the Mayo Network system. Then a telephone contact may be done to acquire the follow up information.

Randomization:
Randomization will be performed by the pharmacy under the direction of the study statistician, using randomized blocks, to ensure all clinical study personnel are blinded to patient allocation throughout the study. Subjects will be randomized into two groups. The "treatment group" will receive Pentoxifylline 400 mg one to three times daily by mouth from the time of enrollment until 72 hours from enrollment. Subjects will receive up to maximum of 9 doses of this medication. The "control" group will receive placebo dosing at similar intervals. Randomization will occur in a block fashion. Study medication will be administered at 1x/day if creatinine clearance < or =30ml/min. per the manufacture prescribing information. All other treatment for AP (fluid resuscitation, antibiotics, surgical intervention, pain control, etc.) will be at the discretion of the primary care team. However, the study investigators will ask primary teams to follow standardized treatment guidelines for acute pancreatitis (to control for intravenous hydration and enteral nutrition, which may influence IL levels).

Blinding: Both subjects and investigators will be blinded to the randomization.

Sample Size:
We propose testing 75 patients in each study arm. Our primary outcome will be whether the patient develops any of the following outcomes of moderate or severe AP: hospital stay longer than 10 days, admittance to the ICU, persistent organ failure, pancreatic and/or peripancreatic necrosis and infection, SIRS, need for intervention, or death. In our pilot study, 7.1% of the patients on pentoxifylline experienced at least one of these outcomes, compared to 28.6% of those on the placebo. If extrapolated to the larger RCT, this reduction in events of these critical outcomes (7.1% vs. 28.6%) would represent a significant and meaningful difference for patients. Using a 5% 2-sided type I error, 58 patients in each group would be needed to achieve 80% power to detect the anticipated difference. In order to account for the unlikely event of up to 10% study dropout, we plan to enroll 64 patients in each group. We will use a randomized block design stratifying for predicted disease severity (mild, moderate, or severe).

Adverse event management: Most of the side effects observed with long clinical use of pentoxifylline are mild and uncommon. Any unexplained hemorrhage of any magnitude will result in stopping the drug. Any of the serious events listed in the drug package insert and informed consent form will result in stopping of the drug if alternative explanation is not found. Adverse events experienced by subject during the study will be evaluated by the investigator Adverse events will be documented and reported in the IRB annual continuing review. Serious adverse events will be evaluated by both the investigator and found to be related to study then DSMB will be contacted. Serious adverse events will reported according to the FDA and IRB policies and guidelines.

DSMB

For this safety analysis, the study statistician will prepare a blinded assessment of adverse events and severe adverse events by study group. The DSMB, consisting of clinical experts in GI and AP who are not involved in the study will review the blinded report to assess whether they feel either study group is experiencing more adverse events or severe adverse events or more-severe adverse events or severe adverse events. If the DSMB concludes that one group has greater risk, the study statistician will determine whether that group was randomized to pentoxifylline or placebo; if the pentoxifylline group is at risk, the study team will stop enrolling patients and administering the study drug, but will continue to monitor follow-up in previously enrolled patients. DSMB will be constituted by clinicians having experience in TNF-α blockade therapy.

DSMB will receive general updates as well as having contact meeting not less than once a year (per FDA regulation) with either face-to-face, or telephone conference call or e-mail contact. Face-to-face meetings will be conducted as all member schedules allow. If unable to do face-to-face then telephone conferencing or e-mail will be utilized.

Data Collection and Handling: TNF-α, Il-6, and Il-8 will be handled by the research blood draw division of Mayo Clinic per usual practice. The C-RP testing on days1, 3, 4 and 5 will be handled by the research blood draw division of Mayo Clinic per usual practice. The clinical and research laboratory data will be recorded every day until discharge. Early discharges before completion of 3 days of drug or 5 days of study of markers after drug administration is not considered as protocol violation and data until the time of discharge will be recorded for the purpose of analysis. Data Safety Monitoring Board (DSMB) will be constituted by clinicians having experience in TNF-α blockade therapy.

Data Analysis: All access to data will be password protected. Analysis will be on an-intent-to treat basis. Outcomes will primarily be descriptive statistics such as means and percents. Continuous secondary end points will be analyzed with the t-test if the data are normally distributed and the Wilcoxon Rank Sum test if non-normal. Analyses of dichotomous secondary end points will use either the Chi-squared test or Fisher's Exact Test comparing proportions. Kaplan-Meier will be used to estimate survival. An interim analysis of data for preliminary review of less than target accrual may be done.

Feasibility: Nearly 250 patients with acute pancreatitis are seen at Mayo Clinic hospitals every year. Assuming ~60% of them are directly admitted to Mayo Clinic (not transferred from outside), and 50% agree to participate in the study it would take 24 months at Mayo to recruit 150 patients. If recruitment goals are not reached at Mayo Clinic after ~24months, the study may have to be extended for 6 months more. **Deliverables:**

We expect to publish at least one manuscript in a major academic journal as a result of this work. Our hope is that any reduction of morbidity or mortality from the novel therapy will have a profound effect on the treatment of acute pancreatitis and lead to future expanded clinical trials.

TAILED MILESTONES SCHEDULE

Endpoints:

May 2015 Mayo Institutional Review Boards (IRB) approval.

June 2015 Approximate NIH will release funds when IRB approved protocol is provided.

July 2015 - Approximate Patient enrollment begins at Mayo

April 2016 Approximate Data Safety Monitoring Board (DSMB) contact via teleconference or E-mail meeting to meet biannually and/or not less-than once a year.

June 2017 - Approximate Data analysis complete and manuscript submitted for publication

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