DETAILED PROTOCOL

Title:	Tocilizumab Augmentation in Treatment-Refractory Major Depressive Disorder: An Open-Label Trial
Principle Investigator:	Jessica Harder, MD
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I. Background and Significance:

Affecting an estimated 151.2 million people worldwide, depression remains the leading cause of years lived in disability.[1] Unfortunately, first-line treatments for major depression, primarily agents that inhibit reuptake of monoamines (serotonin, dopamine, and epinephrine) achieve symptomatic remission in only one to two thirds of patients, depending on the number of medication trials.[2] Standard antidepressant medications, primarily selective serotonin reuptake inhibitors (SSRIs) also take six to eight weeks to work, [3] and with the majority of patients requiring multiple trials of medications, patients can remain symptomatic for several months.[4] During this time, depressed individuals not only experience the disability associated with social withdrawal, low energy, decreased concentration, sleep problems, and appetite disturbance, but also potentially acute risks arising from suicidal thoughts and behaviors.[5] As a consequence, there is a great need for novel antidepressant agents that are more effective and that work more quickly.

In order to develop more effective treatments for depression, research has begun to focus on different neurobiological pathways which may be implicated in this psychiatric condition. Specifically, recent attention has focused on the role that inflammatory cytokines play in the pathogenesis of major depression,[6, 7] as these have been associated with depression in humans as well as in animal models.

Increased serum concentrations of pro-inflammatory cytokines in patients with major depression have been repeatedly documented[8], including increased levels of the cytokine interleukin-6 (IL-6).[9, 10] One study which assessed IL-6 levels over the course of standard antidepressant medication treatment in depressed patients found that after 8 weeks, initially elevated levels had decreased to a level on par with healthy controls.[11] Of note, not all research has consistently found that depressed patients have higher cytokine concentrations than their healthy counterparts,[12]suggesting immunological activation may be responsible for the pathogenesis of a specific subtype of depression.[13]

Animal studies have contributed to our knowledge of the complex relationship between depression and pro-inflammatory cytokines, specifically IL-6. In one study, IL-6 knockout mice demonstrated reduced depression like behavior, evident through reduced despair in a forced-swim task, enhanced hedonic behaviour, and increased sensitivity to reinforcing properties of sucrose.[14] Additionally, wild mice subjected to a learned helplessness paradigm showed a significant increase of IL-6 RNA in the hippocampus, a key structure implicated in rodent depression-like behaviors.[15]

Thus far, there is limited published research assessing the role that specific cytokine-targeting medications may play in alleviating the symptoms of depression. In a double-blind, randomized controlled trial assessing the effect of intravenous infliximab (a tumor necrosis factor-alpha antagonist), no significant difference between the treatment and control group was found in Hamilton Depression Rating Scale (HDRS) scores among all participants.[16] Post hoc analyses, however, revealed that for subjects with baseline levels of the inflammatory marker C-Reactive Protein (CRP) greater than 5 mg/L, treatment with infliximab led to a 3.1 point greater reduction in HRDS scores compared to placebo. A similar double-blind randomized controlled trial augmenting celecoxib (a COX-2 inhibitor) treatment in patients with an acute depressive episode yielded a significant reduction in HDRS scores, with a mean decrease of 14 points (55%) in the celecoxib condition within 6 weeks. [17] To our knowledge, no therapeutic trials have been published studying Il-6 antagonists and their impact on depression symptoms.

Tocilizumab (Actemra, Genentech), a humanized monoclonal antibody against the IL-6 receptor, is currently approved by the United States Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA) and systemic juvenile idiopathic arthritis (SJIA). In several phase III clinical trials conducted worldwide, tocilizumab, when combined with disease-modifying antirheumatic drugs (DMARDs), has shown consistent efficacy with regard to preventing joint destruction and improving quality of life in adult patients with moderate to severe active RA.[18] In vitro, tocilizumab binds to the soluble IL-6 receptor and membrane-bound IL-6 receptor, therefore inhibiting the binding of IL-6 to the IL-6 receptor and, in turn, reducing circulating serum levels of the cytokine.

Recent clinical research investigating tocilizumab in the rheumatoid arthritis (RA) patient population has yielded promising results with regard to depression and anxiety. Prospective studies assessing the impact of tocilizumab on fatigue have seen improvements in anxiety and depression within 4 months of treatment initiation.[19, 20] One study found depression symptoms significantly decreased from the moderate to mild range within 12 weeks of tocilizumab initiation.[20] While these studies did not establish causation between the tocilizumab and improved mood, the findings warrant further research, specifically in the depressed patient population who do not suffer from RA.

As our understanding of the complex relationship between pro-inflammatory cytokines (specifically IL-6) and depression symptoms becomes clearer, clinical trials to evaluate effective and novel treatments are needed. This proposed study sets out to examine the antidepressant effects of tocilizumab among patients with treatment refractory depression. As there have been no published tocilizumab trials among patients with major depression, this pilot study will adopt

a single-arm, open-label design. Due to the notion that inflammatory cytokines may play a role in a subtype of depression, this study will recruit patients with treatment refractory major depressive disorder, for whom established depression treatments have not been effective. In conducting this trial, we seek to examine the potential role of tocilizumab as an augmentation agent, with the hypothesis that it could reduce depression symptomatology in patients with major depression, who have not experienced symptom reduction through more traditional antidepressant therapies.

II. Specific Aims:

The primary aims of this study are:

1) To examine the effect of tocilizumab on depression symptoms (as measured by the Hamilton Depression Rating Scale) in patients with treatment-refractory major depression.

2) To evaluate the tolerability of tocilizumab in patients with treatment refractory depression and the feasibility of administering this drug in this population.

3) To assess any beneficial changes in co-morbid anxiety (as measured by the Hamilton Anxiety Rating Scale).

III. Subject Selection:

This study will enroll 45 adult subjects with treatment-refractory major depressive disorder, in hopes of administering the study drug to 15. Given the number of exclusion criteria, we anticipate needing to consent 45 subjects to gain 15 who are fully eligible.

Inclusion criteria:
- Aged 30-60
- Current diagnosis of major depressive disorder
- Hamilton Depression Rating Scale score of $\geq$20
- In treatment for depression for a minimum of 8 weeks
- Score of >2 on the MGH Staging Method of treatment resistance

Exclusion criteria:
- Active drug or alcohol disorder in the last three months
- History of psychosis, mania or hypomania
- Acute suicide or homicide risk
- History of liver disease, including HCV and HBV.
- HIV
- History of heart disease or a heart attack
- Active or latent tuberculosis, a history of a positive tuberculosis test, or having received the Bacillus Calmette–Guérin (BCG) vaccine

- Epilepsy or a history of seizures
- Abnormal thyroid-stimulating hormone (TSH <0.4 or >5.0mlU/L)
- Abnormal liver function tests on screening (ALT>50 U/L or AST>50 U/L)
- Low absolute neutrophil count (ANC) on screening (<4000/mm^3)
- Low platelet count on screening (<150,000/mm^3)
- Abnormal white blood cell count (<4,500 or > 10,000mcL)
- Patients with an active or recent infection, for example cellulitis, bacteremia, pneumonia, and pyelonephritis.
- Recent exposure to uncommon infections (e.g. histoplasmosis, blastomycosis, coccidioidmycosis) through recent travel to the Ohio and Mississippi River Valleys and the Southwest.
- Pregnant women, breastfeeding women or women of child-bearing age not using contraception
- History of or current autoimmune disease, including multiple sclerosis and inflammatory bowel disease.
- Diagnosis of chronic fatigue syndrome
- Temperature greater than 100.3F at the screening visit or any subsequent visits
- Dyslipidemia
- Currently taking oral steroids
- Currently taking statins
- Chronic aspirin or NSAID takers
- Currently taking any immunomodulating medications
- Inability to consent due to cognitive impairment

Source of Subjects and Recruitment Methods:
Subjects will be recruited through outpatient psychiatric clinics affiliated with Brigham and Women's Hospital, through physician referral, print advertisements, and flyers. Subjects will also be recruited from the general public through flyers in the community, newspaper advertisements (Boston Metro newspaper, etc.), and on internet posting websites such as Craigslist. Subjects will be under no obligation to enroll in the study; for individuals already receiving psychiatric care at Brigham and Women's Hospital, they will have the choice to continue their care as usual or to seek further screening to participate in the study. All subjects participating in the study will be instructed to continue their current outpatient psychiatric treatment as usual. Assuming a non-completion rate of approximately 20%, as is customary in clinical trials of antidepressants, we will enroll a total of 15 subjects, anticipating 12 study completers.

IV. Subject Enrollment:

Subjects will be recruited through outpatient psychiatric clinics affiliated with Brigham and Women's Hospital, through physician referral, print advertisements, and flyers. Demographics of the subjects are expected to largely reflect the referral patterns of these participating centers. Subjects will also be recruited from the general public through flyers in the community and on internet posting websites such as Craigslist. Both males and females will be enrolled, however given the gender distribution in the prevalence of depression, it is expected that approximately

2/3 of the sample size will be female and 1/3 will be male. Contact information for the study coordinator will be provided by the physician in the case of a referral, and it will also be listed on the flyer and advertisement.

When potential subjects contact the study coordinator, they will first be asked a set of screening questions as outlined in the screening phone script. These questions will confirm that the subject meets basic inclusion criteria. Subjects who are eligible at this time will be scheduled to attend the first baseline visit, where written informed consent will be obtained.

Details about the study, including objectives, procedures, and potential risks and discomforts will be discussed with the subject by the principal investigator (Dr. Jessica Harder) or a physician co-investigator. Subjects will be given the opportunity to ask any questions and will be given ample time to consider whether they wish to participate. They will be informed that refusal to participate will not interfere with their subsequent medical care.

During the first study visit, it will also be confirmed that the subject meets all other eligibility criteria, based on the clinical interviews and their laboratory results.

V. Study Procedures:

The study design represents an 8-week single-arm, open-label trial. The study procedures, as divided by study visits, are described below.

Study Visit 1 (screening):

At the first study visit, the principal investigator or co-investigator study physician will obtain informed consent and answer any questions from the subject. The clinical study staff will then administer the Hamilton Depression Rating Scale (HDRS) and the Mini International Neuropsychiatric Interview (MINI) to confirm the subject has an active diagnosis of major depressive disorder (as defined by DSM V criteria) and rule out diagnoses of exclusion (namely mania, psychosis or hypomania). Subjects with active suicidal ideation, represented by a score of >2 on HDRS item 3, will be ineligible for the study and referred for urgent or emergent clinical assessment as indicated in the safety plan. If there are no clinical exclusions at that point, the study staff will administer the Hamilton Anxiety Rating Scale (HARS) and the Clinical Global Impressions (CGI) scale. The subject will complete the Perceived Stress Scale (PSS), Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR), MGH Antidepressant Treatment Response Questionnaire (ATRQ) and the Systematic Assessment for Treatment Emergent Events (SAFTEE). These measures are all customary for clinical trials of antidepressant medication. Female subjects will also be asked to report whether they have regular monthly menstrual cycles, the date of their last menstrual period, and whether they are taking hormonal contraceptives (including which one) or not. Once all measures have been completed, subject's heart rate, blood pressure, temperature, height and weight will be taken. The latter are taken to allow the study team to calculate BMI. Waist:hip ratio will also be measured, as well as a blood draw to measure the following parameters: liver and thyroid function, lipid panel, complete blood count, and interleukin-1 (IL1), interleukin-6 (IL6), C-reactive protein (CRP), and tumor necrosis factor (TNF-alpha) levels. TB, HIV, HCV, and HBV will be screened

for serologically. For females subjects, estradiol levels, progesterone levels, and FSH levels will also be measured.

Subjects will also provide a urine sample for a urine toxicology screen. The 11-drug toxicology screen will be done by LabCorp and tests for: amphetamines, barbiturates, benzodiazepines, buprenorphine, cannabinoid (THC), cocaine, methadone, opiates, oxycodone/oxymorphone, phencyclidine (PCP), and propoxyphene. Women of child-bearing age will also receive a qualitative urine pregnancy test. All blood draws and urine collection will occur at Brigham and Women's Hospital Center for Clinical Investigation. Subjects determined eligible based on the results of the screening labs this time will be scheduled for study visit two.

Study Visit 2 (week 0):

Before study visit 2, the subject's labs will all be checked to confirm their eligibility. If the labs are within the identified ranges, the subject will receive the first subcutaneous injection of 162 mg of tocilizumab (the dose consistent with established clinical practice and provided as an Actemra prefilled syringe). The Investigational Drug Service (IDS) at Brigham and Women's Hospital will be responsible for storing 162 mg syringes of the study drug. The patient will be instructed to continue all of their current psychiatric medications (and any other treatments) as prescribed; the study does not request or require any changes to the subject's routine care.

If the tuberculosis screening test is positive, or if the subject tests positive for HIV, HCV or HBV, they will not be eligible to participate in the study but will be referred to their PCP for follow up, with the subject's permission.

Study Visit 3, 4, 5 and 6 (weeks 2 through 8):

The subsequent four study visits, conducted at two-week intervals, will follow the same study template. At these visits, study staff will administer the HDRS, HARS and CGI. The subject will complete the self-report PSS, QIDS-SR and SAFTEE. All subjects will be asked about any changes to their medications, for psychiatric or medical indications. Any interim changes in the subject's psychiatric treatment (e.g., beginning or ending psychotherapy) will be noted. Female subjects will also be asked if there have been any changes to the date of their last menstrual period or hormonal contraceptives since their last visit. Subject's temperature will also be taken. On completion of all measures, subjects will receive tocilizumab 162 mg subcutaneous (Actemra prefilled syringe) at visits 3, 4, and 5.

Following currently-recommended clinical guidelines for tocilizumab, at visit 4 (4 weeks following treatment initiation) and at visit 6 (at the end of the study), subjects will have repeat blood draws to assess the same parameters as the baseline test: liver and thyroid function, cholesterol, neutrophil count, platelet count, and IL6, CRP, and TNF-alpha levels. IL-1 levels will be measured at visit 6. For female subjects, estradiol levels, progesterone levels, and FSH levels are also measured. The bloods at V4 will be sent STAT to the BWH labs prior to the subcutaneous injection. The tocilizumab will be administered if all labs are in the outlined ranges to ensure there are no counter-indications to the injections.

For visits including a blood draw, (V1, 4, & 6) patients will be instructed not to consume anything (water, black coffee, and taking medications as usual are allowed) 12 hours prior. All efforts will be made to schedule these visits in the morning.
At the last study visit (number 6, at week 8), subjects will not receive any medication, though all clinical measures will be obtained. Study staff will advise any subject leaving the study that any beneficial effects from tocilizumab may theoretically subside in subsequent weeks or months. Subjects will be advised to follow up with their current outpatient psychiatric providers within two weeks of ending participation in the study.

Subjects who complete the study will receive a total of $225, divided into multiple increments and sent via postal mail after each study visit attended.

Subjects will be asked to refrain from consuming alcohol for the duration of the study to minimize the potential risks associated with worsening depression and with the study medication.

At each study visit, the study staff will enter the data into case report forms in paper binders, as well as on REDCap. All laboratory values will be reviewed by the principle investigator or another physician co-investigator. Paper files matching the case report forms in REDCap, and including the consent form, screening materials, and any additional correspondence will be stored in a locked filing cabinet in the office of the study staff at Brigham and Women's Hospital. All electronic study data will be stored securely on REDCap and de-identified prior to data analysis. Only group data will be reported.

If a subject decided to leave the study early, the study staff will ask the patient to come in for a final study visit. The final study visit will take about 60 minutes. At this visit, we will ask the subject about any side effects or health problems since last visit, complete interview scales of depression and anxiety symptoms, complete self-report questionnaires, draw a blood sample (if the subject ends participation before Visit 4).

VI. Biostatical Analyses:

Power and sample calculation: with 15 eligible subjects, we have 80% power to detect an effect size of 0.778 with a one-sample paired t-test at alpha =0.05 level.

The baseline data to be collected and analyzed are: subject age at enrollment, gender, age of onset, number of previous depressive episodes, CGI, HARS, HDRS, QIDS, ATRQ, and PSS. Subsequent, repeated measures for analysis will be CGI, HARS, HDRS, QIDS, and PSS. Cytokine and hormone levels will also be analyzed at each stage blood is drawn. The planned study end-point is at eight weeks after the first injection of tocilizumab and is not based on any pre-determined treatment response.

For the study outcomes, paired t-test will be used to check whether the change in HDRS, HARS, and CGI is statistically significant, while the proportion and confidence interval of subjects achieving remission (HDRS < 7) and response (HDRS >50% reduced from baseline) of their depression will be estimated. Linear and logistic regression models will also be used to see

whether age, gender, and number of previous depressive episodes are potential covariates for the outcomes.

Assuming a non-completion rate of approximately 20%, customary in clinical trials of antidepressants, we will enroll 15 subjects, anticipating 12 completers. For subjects who discontinue the trial prematurely, the missing HDRS, HARS, and CGI values will be treated using the last observation carried forward method.

VII. Risks and Discomforts:

Tocilizumab is currently approved by the U.S. Food and Drug Administration (FDA) to treat RA, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. The most common adverse events (=5%) that occurred in the rheumatoid arthritis trials in patients treated bi-weekly with subcutaneous tocilizumab vs placebo were: injection site reactions including erythema, pruritis, pain and hematoma (7.1% vs 4.1%, respectively), elevations in total cholesterol (19.6% vs 10.2%), elevations in ALT and AST $\geq$3 the upper limit of normal (3.4% and 0.7% respectively), decrease in neutrophil count (3.7% in tocilizumab group). It has been noted that subcutaneous and intravenous administration of tocilizumab share a comparable safety profile. In controlled trials of IV tocilizumab (8 mg/kg) versus placebo, administered to rheumatoid arthritis patients, common side adverse events (=5%) included: upper respiratory tract infections (8% vs 6% respectively), common cold (6% vs 4%), headache (5% vs 3%), and hypertension (4% vs 3%). Less common side effects included: dizziness, bronchitis, rash, mouth ulcers, abdominal pain, and gastritis. Uncommon side effects (<2%) included: oral herpes infection, gastric ulcer, stomatitis, weight gain, increase in total bilirubin, edema, shortness of breath, cough, conjunctivitis, hypothyroidism, and kidney stones. Of note, all patients in these trials received background non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

The effect of tocilizumab on an embryo, fetus, or a breastfeeding infant, is not well established and may be harmful. Because of these unknown risks, women cannot take part in this study if they are pregnant, trying to become pregnant, or nursing.

With the blood draws, there are risks of pain and bruising at the phlebotomy site, as well as lightheadedness.

With the subcutaneous injection, there are risks of pain and bruising at the injection site. As with any injection procedure, a minor risk includes infection at the injection site. Utilization of appropriate sterile techniques will help prevent infection and irritation.

The assessment of psychiatric history, including depression and substance abuse, can make some people feel uncomfortable as the information is sensitive to some subjects. Some may also be especially concerned about the confidentiality of mental health information. The study staff are trained in mental health assessments, and make every effort to make the subjects comfortable during study visits. All subjects will be assured that their history and responses will be kept confidential within the study, except as required by law, in the case of acute safety concerns, and in any instances as described in the informed consent form.

VIII. Potential Benefits:

No benefits can be guaranteed from participation in the study. However, since all enrolled participants will be receiving tocilizumab, it is expected that at least some subjects will experience a decrease in the severity of their self-reported depression symptoms. The results of this study also have potential to benefit larger clinical populations if it is identified that tocilizumab is an effective treatment for depression. Further, the data collected during the study will expand our knowledge of the role of immune biomarkers in depression and treatment response.

IX. Monitoring and Quality Assurance:

The principal investigator, Dr. Jessica Harder, will be responsible for monitoring the safety of all subjects. In the event that Dr. Harder is unavailable, physician co-investigators will be available to monitor the safety of all subjects.

All study staff are primarily located at Brigham and Women's Hospital. Study safety meetings, including the principal investigator, study coordinators, and study physicians will meet regularly to review the progress of currently-enrolled subjects and any reported side effects.

The Principal Investigator will assess all patients with regard to stopping criteria. In general terms, a subject will be discontinued from the study for the following reasons:

1) The subject has experienced an adverse event that, in the opinion of the principal investigator requires early termination
2) The subject's thoughts or behaviors become a safety risk at any time during the trial
3) The subject withdraws consent

Specific to this study, subjects will be closely monitored for adverse events and suicidal thoughts at every visit. Subjects who develop active suicidal ideation, represented by a score of >2 on HDRS item 3, will be referred for urgent or emergent clinical assessment. A patient who develops active suicidal thoughts will be urgently evaluated by a study physician. In any case where there are acute safety concerns arising from suicidality (such as a plan or actual intent), the patient will be sent to the BWH Emergency Department for further evaluation under Section 12a, and in compliance with hospital policies. If there are no acute safety concerns based on the urgent evaluation, the patient will be monitored according to study protocol and instructed to contact study staff immediately with any worsening in their mood or thinking. The study physician will review the urgent or emergent safety assessment and determine if the subject can continue in the study. Any subject who requires a level of care exceeding customary outpatient services (i.e., psychiatric hospitalization or participation in a partial hospital program) will be removed from the study. If a subject must be transferred from the study into clinical care, the study physicians will continue to follow the subjects until they are accepted into appropriate, longer-term care, if clinically indicated.

Following the currently-recommended clinical guidelines for tocilizumab, subjects' laboratory results will be monitored for changes in liver function, cholesterol, and neutrophil and platelet count 4 and 8 weeks after treatment initiation. Subjects will not receive subsequent tocilizumab doses if their ALT or AST levels is >2 times the upper limit of normal. Subjects will also have to discontinue the study drug if their platelet count is less than 50,000/mm^3, neutrophil count is less than 500/mm^3, or if a serious infection develops. At each visit, subject's temperature will be taken to monitor the possible development of injections. If their temperature is greater than 100.3F at any time point, the study drug will not be administered. If any of the events occur that require patients to not receive the study drug, they will be withdrawn from the study. All subjects will undergo a tuberculosis screening test before treatment initiation. Any subject who must discontinue the tocilizumab due to laboratory abnormalities arising during the study will be advised to follow up with their primary care physician. If an adverse event occurs, or there is an abnormal finding during laboratory testing, that information will be released to the subjects primary physician with the subject's permission and written release.

At the end of the study, study staff will arrange for any additional (or new) psychiatric follow up, as clinically indicated.

At each study visit, the study staff will enter the data into case report forms on REDCap. All laboratory values will be reviewed by the Principle Investigator or another physician co-investigator. All study data will be stored securely on REDCap and de-identified prior to data analysis and only group data will be reported. Paper files for each subject, including the consent form, screening materials, and any additional correspondence will be stored in a locked filing cabinet in the office of the study staff at Brigham and Women's Hospital.

During all portions of this research study, the privacy and confidentiality of all participants will be maintained.

X. References:

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