Protocol Title:
Tocilizumab, An Il-6 Receptor Antibody, As Add-On Treatment For Residual Positive, Negative, And Cognitive Symptoms Of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Version Date:
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Protocol Number:
6729

Clinic:
Translational Imaging

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Cover Sheet

Choose from the following that is applicable to your study
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Translational Imaging
Within the division/department, what Center or group are you affiliated with, if any?
Translational Imaging

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
N/A

Application for Continuation of Research

Status

Current Status of Study:
Enrollment of new subjects is closed. Research procedures and/or interventions are ongoing for subjects currently enrolled.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
We have completed enrollment for this study. The last subject will complete her last visit at the beginning of 2/17. After that time we will proceed with data analysis.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
Yes
Please describe them and indicate resultant protocol modifications made.
One patient, IL656, stopped his antipsychotic and antidepressant midway through the trial. He developed suicidal ideation and was hospitalized. In the hospital, he restarted his medications and recovered promptly. He was withdrawn from the trial. There were no sequelae. This was reported to the IRB.
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?

Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
75 enrollees, 36 completers
Total number of participants enrolled to date
58
Number of participants who have completed the study to date
35
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
Schizophrenia
Total number of participants enrolled from this population to date
58
Gender, Racial and Ethnic Breakdown
16 F, 42 Males. 35 AA, 18C, 4 M, 1 As; 9 Hispanic

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
19
Number of participants currently enrolled
1
Did the investigator withdraw participants from the study?
Yes
Circumstances of withdrawal:
There were 8 total. 7 were withdrawn as they were screen fails. 1 had the SAE described above.
Did participants decide to discontinue study involvement?
Yes
Circumstances of discontinuation:
There were 3 total. Two withdrew before any study drug was administered as they decided against doing the study. One withdrew after one administration of study drug as he decided he did not want to participate any longer.

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ Audio or Videotaping
✓ Off-label Use of Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults who may have impaired decision-making ability
✓ Adults
✓ Adults over 50
✓ Individuals with Psychosis
✓ Inpatients

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study
2

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Foundation
Sponsor
Stanley Medical Research Institute
Select one of the following
Single Site

Business Office
CU
Does the grant/contract involve a subcontract?
No

Funding Source #2

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Other
Sponsor
irving Institute
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

Schizophrenia (SZ) is a prevalent, debilitating, and costly illness. Currently available treatments are often either only partially effective or associated with significant side effects. Thus, newer treatments are desperately required.

All current treatments for SZ function primarily by blocking D2-type dopamine receptors. An alternative theory of SZ comes from studies of microbial pathology and SZ that postulate disturbances of cytokines and inflammatory mediators in SZ. Ecologic data have suggested associations between early pregnancy infection and the development of SZ in offspring of infected mothers. Additionally, lifetime infection with

Toxoplasma gondii substantially increases the risk of SZ, while epidemiologic data, studies on the effects of Toxoplasma gondii infection in humans and rodents, and results of the effects of antipsychotic medications on Toxoplasma gondii implicate this organism in risk for SZ.

One of the main mediators of the effects of infection/inflammation in the human body is cytokines. Recent data suggest that cytokines, and in particular IL-6, may mediate the effects of lifetime or prenatal infection on SZ risk. Preclinical models of SZ support a convergence between a role for IL-6 in the pathophysiology of SZ and the major neurochemical hypotheses of SZ-the dopamine and glutamate hypotheses. Namely, IL-6 dysfunction or excess promotes SZ-like behaviors and SZ-like biochemical and electrophysiological profiles, while IL-6 knockout or neutralization mitigates these abnormalities. Furthermore, plasma IL-6 levels are elevated in acutely psychotic but not treated patients, and Positron Emission Tomography (PET) studies have shown active inflammation in the brains of individuals with psychosis. Finally, treatment of individuals with SZ with non-specific anti-inflammatory agents, such as celecoxib and aspirin, has suggested a role for anti-inflammatory agents in SZ. These data also suggest that studies of immunologic agents that more specifically target the underlying pathophysiology of SZ may be more efficacious. Tocilizumab (Actemra®) is an FDA-approved humanized monoclonal antibody against the IL-6 receptor used for treatment of rheumatoid arthritis in individuals who have not responded to at least one TNF-alpha therapy and for juvenile idiopathic arthritis. We will conduct a randomized, placebo-controlled, double-blind clinical trial of tocilizumab as add-on treatment for residual positive, negative, and cognitive symptoms in SZ. After a two-week baseline measurement, a 12-week treatment phase (i.e., three doses of study drug), adjunctive to antipsychotics, will begin, with 18 individuals randomly assigned to tocilizumab and 18 individuals to placebo. The primary study hypothesis is that individuals receiving tocilizumab will show greater improvements in their PANSS total scores than those taking placebo. Secondary outcomes will include comparisons on specific clinical, cognitive, and biochemical (i.e., cytokines) outcomes, as well as relationships between baseline IL-6 levels and treatment outcome. To our knowledge, this is the first investigation of immune modulation as a treatment in SZ and the first direct test of the immunologic/inflammatory/infectious theory of SZ, and therefore has great implications for the study of drug development, etiology and pathophysiology of the illness.

Background, Significance and Rationale

Background, Significance and Rationale
Birth cohort studies have identified associations between schizophrenia (SZ) and early pregnancy exposure to infectious agents, including influenza (Brown, Begg et al. 2004), herpes simplex virus type 2 (Buka, Tsuang et al. 2001; Buka, Cannon et al. 2008), and Toxoplasma gondii (Brown, Schaefer et al. 2005; Mortensen, Norgaard-Pedersen et al. 2007). The most parsimonious model suggests that there are common effects of infection that may increase the risk of SZ (Brown and Derkits 2010). These effects are hypothesized to be mediated by cytokines (Gilmore and Jarskog 1997). Cytokines are a family of soluble proteins that play an important role as the systemic mediators of host response to infection (Brown and Derkits 2010). Cytokines, including interleukin-6 (IL-6), may be produced in the CNS, have numerous effects on both glial and neuronal components of the CNS and have effects on both normal and abnormal brain development (Frei, Malipiero et al. 1989; Benveniste, Sparacio et al. 1990; Hopkins and Rothwell

1995; Rothwell and Hopkins 1995; Gilmore and Jarskog 1997). In the maternal immune activation model of SZ, lipopolysaccharide- and poly (I:C) administration induce elevated levels of IL-6 in fetal brain (Patterson 2009). IL-6 levels are elevated in the plasma of both first-episode (effect size = 1.4) and acute relapsed (effect size = 0.96) patients, while they decrease after treatment (effect size = -0.31) (Miller, Buckley et al. 2011). These data suggest that IL-6 is a state marker of SZ, normalizing with treatment. In addition, Positron Emission Tomography (PET) studies of the peripheral benzodiazepine receptor, which is upregulated during microglial activation, have also supported persistent inflammation in the brains of individuals with SZ (van Berckel, Bossong et al. 2008; Doorduin, de Vries et al. 2009; Takano, Arakawa et al. 2010). Finally, treatment studies of non-specific anti-inflammatory agents also support the development of treatments aimed at underlying inflammation (Muller, Riedel et al. 2002; Akhondzadeh, Tabatabaee et al. 2007; Laan, Grobbee et al. 2010; Muller, Krause et al. 2010). Therefore, pharmacologic agents that potently inhibit the activity of specific cytokines, in particular IL-6, represent a novel approach to the treatment of schizophrenia and may offer greater therapeutic benefit.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Study Goals:

1) Establish the feasibility of using tocilizumab**,** and targeting the IL-6 receptor in general, as treatment for positive, negative and cognitive symptoms and impairments in daily functioning in SZ (i.e., as measured by PANSS, GAF, CGI, UPSA, and MATRICS) and determine effect sizes for a more definitive clinical trial.

2) Refine the study procedures and inclusion/exclusion criteria for a future, definitive clinical trial, using clinical/neuropsychological measures and laboratory analyses of cytokine levels.

3) To evaluate the safety of tocilizumab in schizophrenia.

4) To examine the effects of tocilizumab on hippocampal CBV and glutamate.

Description of Subject Population

Sample #1

Specify subject population
Schizophrenia, Schizoaffective Disorder
Number of completers required to accomplish study aims
36
Projected number of subjects who will be enrolled to obtain required number of completers
75

Age range of subject population
18-59

Gender, Racial and Ethnic Breakdown
Based on the expected breakdown from 5-South and the Lieber Schizophrenia Research Clinic, we expect to enroll 65% males and 35% females; with a racial profile of 44% Caucasian, 22% Hispanic, 26% African American, 6% Asian, and 2% Other.
Description of subject population
Patients with Schizophrenia or schizoaffective disorder. All will undergo a screening history and physical, structured diagnostic interview, baseline laboratory work, and a urine drug screen. We will use the available information already obtained on subjects via clinical admission procedures or participation in other research protocols whenever possible.

Recruitment Procedures

Describe settings where recruitment will occur

Patients are recruited from various sources by referral from departments of the Columbia University Medical Center (CUMC) and from affiliated hospitals (Harlem Hospital Center and St. Luke's-Roosevelt) and local mental health clinics, day programs, community residences, family and mental health advocacy groups.

We could also recruit stable, English-speaking patients from outpatient clinics, from the Inwood or Audubon Clinics of the Washington Heights Community Service, or from the Lieber Research Clinic if they meet criteria for participation and are willing to participate. We could also recruit individuals who are inpatients on the 5-South inpatient unit at NYSPI, the 4-South inpatient unit at PI, or other inpatient units, if the patients meet criteria for the study, have capacity to make informed consent, and are interested in participating in this study.

In other terms this study can be conducted on an inpatient or outpatient basis but recruitment could be from either the inpatient or the outpatient settings. The patient will be approached by a member of the clinical team for permission to be approached by the research team. Capacity to provide informed consent will be evaluated by a psychiatrist not associated with the research team.
How and by whom will subjects be approached and/or recruited?
see above
How will the study be advertised/publicized?
NYSPI IRB approved advertisements/flyers may be posted in local or national media (e.g., Village Voice), Internet, other electronic media, or on bulletin boards or distributed at locations described above.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

We will also recruit patients who are actively participating in #6334R (Schizophrenia Research Clinic (LSR) Outpatient Umbrella Protocol) or in **#6691 MOSAIC: THE MANAGEMENT OF SCHIZOPHRENIA IN CLINICAL PRACTICE A Prospective, Non-interventional Registry of Diverse Patients with Schizophrenia Across the Disease Spectrum in Usual Care Settings: Course of Disease, Treatments, and Burden of Illness**

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Patients
Create or insert table to describe the inclusion criteria and methods to ascertain them

Criteria	**Assessment**
1. Males or females between 18 and **59** years old	History
2. Fulfill DSM-IV criteria for schizophrenic illness, schizoaffective disorder	Per history, clinical impression SCID and/or DIGS criteria
3. A negative urine toxicology	Urine toxicology
4, Capacity to understand the study and to give written informed consent	History and clinician's assessment
5. Must be on a stable dose of any combination of antipsychotic medications, up to two medications, except for clozapine, for at least 4 weeks if oral or 2 cycles if depot prior to the study. Mood stabilizers, benzodiazepines and antidepressants are allowed as long as the drugs have not been changed for 4 weeks before screening.	History
6. Moderate level of symptomatology	PANSS $\geq$ 60

Create or insert table to describe the exclusion criteria and methods to ascertain them

Criteria	**Assessment**

1. Pregnancy or lactation, lack of effective birth control during the 15 days before the initial day of the study (Day 0) and for the duration of the drug trial	**Blood pregnancy test, assessment**
2. Unstable medical or neurological condition (Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids , ANC < 1500, platelet count < 120,000, severe liver disease or AST/ALT greater than 1.5 times the ULN at baseline, a current severe infection, intestinal diverticula, or tuberculosis (latent or active-patients with a positive ppd but negative chest x ray may participate)), or a live vaccine within one month of receiving study drug.	**Medical and neurological history, EKG, blood chemistry, ppd**
3. Any current non medicinal use of amphetamines, opiates, cocaine, sedative-hypnotics, cannabis, or other psychoactive drugs (other than nicotine)	**History, urine toxicology**
4. Currently taking a medication known to cause neutropenia (clozapine, carbamazepine), or another disease modifying anti-rheumatic drugs (DMARD)	**History**
5. Any history of substance dependence (other than nicotine or cannabis) within the previous 6 months or a history of substance abuse within the previous 1 months (other than nicotine)	**History**
6. Impaired intellectual functioning	**WTAR < 6 (will only be obtained if there is a history of impaired intellectual functioning or if a study physician feels that the study subject may have impaired intellectual functioning; it will not be obtained if there is no indication of impaired intellectual functioning)**
7. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization.	**History**
8. Treatment with any investigational agent within 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of screening	**History**
9. Previous treatment with any cell-depleting therapies, including investigational agents or approved therapies, some examples are CAMPATH, anti-CD4, anti-CD5, anti¬CD3, anti-CD19 and anti-CD20.	**History**
10. Treatment with intravenous gamma globulin, plasmapheresis or Prosorba column within 6 months of baseline.	**History**
11. Previous treatment with tocilizumab (an exception to this criterion may be granted for single dose exposure upon application to the sponsor on a case-by-case basis).	**History**
12. Any previous treatment with alkylating agents such as chlorambucil, or with total lymphoid irradiation.	**History**
13. History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies.	**History**

14. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (include uncontrolled diabetes mellitus) or gastrointestinal disease (including complicated diverticulitis, ulcerative colitis, or Crohn's disease.)	**History, labs, EKG**
15. Current liver disease as determined by principal investigator unless related to primary disease under investigation	**History, labs**
16. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, Hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds).	**History, labs**
17. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening.	**History**
18. Active TB requiring treatment within the previous 3 years. Patients will be screened for latent TB and, if positive, treated following local practice guidelines prior to initiating tocilizumab. Patients treated for tuberculosis with no recurrence in 3 years are permitted.	**History, ppd**
19. Primary or secondary immunodeficiency (history of or currently active) unless related to primary disease under investigation.	**History, labs**
20. Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including hematological malignancies and solid tumors, except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured), or breast cancer diagnosed within the previous 20 years unless related to primary disease under investigation.	**History**
21. Neuropathies or other conditions that might interfere with pain evaluation unless related to primary disease under investigation.	**History**
22. Patients with lack of peripheral venous access.	**Physical exam**
23. Body weight of > 150 kg.	**Weight**
24. Serum creatinine > 1.6 mg/dL (141 µmol/L) in female patients and > 1.9 mg/dL (168 µmol/L) in male patients. Patients with serum creatinine values exceeding limits may be eligible for the study if their estimated glomerular filtration rates (GFR) are >30.	**Labs**
25. Total Bilirubin > ULN	**Labs**
26. Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)	**Labs**
27. White Blood Cells < 2.5 x 10^9/L (3000/mm3)	**Labs**

28. Absolute Lymphocyte Count < 0.5 x 10^9/L (500/mm3)	**Labs**
29. Positive Hepatitis BsAg, or Hepatitis C antibody	**Labs**
Additional Exclusion Criteria for MRI Portion	
1. Metal Implants or a history of metal working	**Physician evaluation**
2. Lifetime diagnosis of asthma with asthmatic symptoms within the past 3 years	**Physician evaluation**
3. Lifetime diagnosis of renal failure or renal disease	**Physician evaluation**
4. Lifetime diagnosis of hypertension or diabetes	**Physician evaluation**
5. Renal insufficiency (Crcl <50mL/min/1.73m2) Crcl=[[140-age(yr)]*weight(kg)]/[72*serum Cr(mg/dl)]	**Serum Cr and formula**
6.**More than one previous gadolinium scan**	**History**

For females of child bearing age:

The pregnancy test is performed during the screening procedure and repeated every day study drug is administered.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process

The consent process is a multistep process, whereby information about the risks and benefits of the study will be provided to potential subjects across several sessions. The number of sessions over which this information will be provided will depend on how well the subject understands and retains the information. The process begins with the subject initiating contact via telephone. The research staff will provide a brief description of the study. Thereafter, potentially eligible candidates are scheduled for a face-to-face interview. Subjects will be informed of all potential risks and benefits of participation. Subjects will be required to read the informed consent form, and the investigator additionally describes the risks and discomforts.

Describe Study Consent Procedures
See above.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Brown, Alan, MD
Girgis, Ragy, MD
Type in the name(s) not found in the above list

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
Yes
Methods/procedures for capacity assessment

Any licensed psychiatrist (MD) **or psychologist (PhD)** who works in the New York State Psychiatric Institute and has completed CITI training may assess capacity.

Study Procedures

Describe the procedures required for this study

Subjects will be randomized to the two groups (i.e., placebo or tocilizumab). Patient assignment will be performed by Mark Slifstein, PhD, who has no contact with the patients. The drug and placebo will be identically packaged.

The study will involve (summarized in table 1):

- A screening assessment (only tests that are not already acquired will be performed. No tests will be repeated). These procedures may be done on more than one day.

- 3 total days of treatment with placebo or tocilizumab

- 2 safety follow up visits (e.g. safety tests, EKG)*

* If necessary, patients could return for a further follow up visit 2 weeks after study completion.

Table 1) Timetable of phase II of the study

TABLE 1: PROCEDURES							
Study Week	Screening[a]	0	2	4	8	12	14[b]
Informed Consent	X						
Study Drug		X		X	X		
Efficacy Aims							
PANSS	X		X	X	X	X	
CGI/GAF	X		X	X	X	X	
MATRICS/UPSA	X		X	X	X	X	
Safety Aims							
SMA20/CBC/TSH/C-SSRS/Urinalysis	X		X	X	X	X	X
Physical Exam	X		X	X	X	X	X
Vitals	X	X	X	X	X	X	X
SAFTEE	X	X	X	X	X	X	X
SAS/EKG	X			X	X	X	X
Cytokine Levels/Toxoplasma Ab	X			X	X	X	
Urine Toxicology/Pregnancy	X	X	X	X	X	X	X
MRI (optional)		X				X	

a A WTAR will be performed for any individuals suspected of having intellectual impairment.

b These procedures will be performed only if there were abnormalities from the Week 12 assessments that require follow up.

Specific procedures.

Screening.

Patients will receive the routine clinical characterization. Study subjects will be initially evaluated with a medical history, review of symptoms, and physical and neurological exam to determine if an underlying treatable medical condition is prohibiting the use of tocilizumab. Laboratory studies will be obtained to exclude metabolic or neuroendocrine disturbances, specifically TSH, electrolytes, CBC, LFTs, BUN, fasting lipid panel, hepatitis panel, urinalysis, and creatinine. If medical review of systems suggests HIV risk factors, then an HIV test will be obtained. If an HIV test is obtained, a study physician will provide pre- and post-test counseling.

All patients will also receive a ppd test. Patients with positive ppd tests may receive a chest x ray to rule out TB. Patients who have known positive ppds may have a chest x ray without placing an additional ppd.

Neuropsychological Test Battery and clinical assessment.

Baseline assessments

To obtain a research diagnosis, we will use the SCID and/or DIGS information, in addition to history and clinical impression. Additional information will be collected through the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Clinical Global Impression (CGI) scale (Guy 1976), WTAR (WTAR 2001), Global Assessment of Functioning (GAF) (APA, 2000), the University of California Performance-based Skills Assessment (UPSA) (Patterson et al., 2001) and the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2007).

Clinical assessment

Clinical assessment will be performed at baseline and weeks 2, 4, 8, and 12. At each time, PANSS, the CGI scale, the GAF, CSSRS, MATRICS, and UPSA will be performed.

Neuropsychological Test Battery

The MATRICS battery was chosen by a panel of experts on cognition in schizophrenia, and the battery is specifically designed to assess treatment-related changes in cognition in patients with schizophrenia. It assesses cognitive functions in the following domains using the following tests: Speed of Processing: Category Fluency, Brief Assessment of Cognition in Schizophrenia (BACS) – Symbol-Coding, Trail Making A. Attention/Vigilance: Continuous Performance Test – Identical Pairs (CPT-IP). Working Memory: University of Maryland – Letter-Number Span, Wechsler Memory Scale (WMS) - III Spatial Span. Verbal Learning: Hopkins Verbal Learning Test (HVLT) – Revised. Visual Learning: Brief Visuospatial Memory Test (BVMT) ¬– Revised. Reasoning and Problem Solving: Neuropsychological Assessment Battery (NAB) – Mazes. Social Cognition: Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)– Managing Emotions. This battery takes 60 to 90 minutes to administer.

Study Drug administration

At day 0, week 4 and week 8 subjects will receive study drug (placebo or tocilizumab) based on random assignment. Study drug will be administered intravenously via an iv drip over 60 min as per clinical guidelines. Blood pressure and heart rate will be obtained before and after administration. A study physician or nurse will be present during the administration. The infusion will take place in the clinical room of the Division of Translational Imaging, the ECT suite, or the 5 South treatment room. A study physician will be present for the entire infusion.

All subjects randomized to tocilizumab will receive 8mg/kg during their infusions, unless the subject is experiencing side effects that, in the opinion of the subject and study physician, are intolerable and likely to improve at a lower dose. In these cases 4mg/kg of tocilizumab, or the placebo equivalent, will be administered. Placebo will consist of a normal saline solution and will be administered in a similar manner. The maximum dose used will be 800mg.

Because of the very low risk of anaphylaxis (see figure for criteria), as well as fever, chills, nausea, or vomiting due to the tocilizumab infusion itself (hypersensitivity reaction), the study physician will have parenteral epinephrine and diphenhydramine available during each administration, as well as acetaminophen, and patients will be monitored by a study physician or nurse for one hour after the administration. Patients will also be called by the study physician the day after their administration to check in on their status.

All patients will provide samples for anti-tocilizumab antibody testing at baseline and at termination. In addition, samples for PK/PD will be tested for each time point when an anti-tocilizumab antibody test is done. All patients experiencing events related to serious hypersensitivity or anaphylactic reactions that cause the patient to be withdrawn from study drug treatment will have anti-tocilizumab and PK/PD testing at time of event, and also 6 weeks after the last dose for anti-tocilizumab and PK/PD testing.

Patients withdrawn from study drug due to a reduced neutrophil count will be monitored for signs of infection, with treatment as deemed appropriate by the PI or sponsor, and will have a repeat white blood cell count with differential performed weekly until the ANC is above 1500 cells/mm^3 (1.5 x 10^9/L). If the ANC drops below 1.0 *10^9/L, biweekly CBCs will be performed and a heme consult will be obtained. In addition, if the ANC does not return to above 1000 cells/mm^3 (1.0 x 10^9/L) within 2 months (or sooner if deemed necessary by the sponsor or PI), a hematology referral will be obtained.

Patients withdrawn from study drug due to a reduced platelet count will have a repeat platelet count performed weekly until the count is above 100,000 cells/mm^3 (100 x 10^9/L). If the platelets do not return to above 100,000 cells/mm^3 (100 x 10^9/L) within 2 months (or sooner if deemed necessary by the sponsor or PI), a hematology referral will be obtained.

Patients withdrawn from study drug due to elevated liver function tests will have repeat tests performed, as clinically appropriate, until levels return to baseline. If the patient's liver function tests have not returned to

baseline within 6 months (or sooner, if deemed necessary by the sponsor or designee), an ultrasound and/or liver biopsy will be considered.

Safety monitoring and follow-up visits

Safety monitoring will include the procedures described above in addition to a full evaluation including the following: a complete medical and psychiatric interview, medical exam, extrapyramidal symptoms, routine blood tests (25 mL) with LFTs and lipids and EKG and urine at weeks 2, 4, 8, and 12. If clinically indicated, subjects may be asked to participate in extra follow-up visits as determined by the study physician. Vital signs urine toxicology, urine pregnancy, and adverse events via the SAFTEE will be assessed at every visit.

All patients who participate in this protocol will be managed by a study physician. If a subject who participates in this protocol has another psychiatrist before beginning the study, the study physician will coordinate care with that psychiatrist, although all patients will be seen for medical/psychiatric assessments at a minimum as per the schedule described above.

Patients withdrawn from study drug due to a reduced neutrophil count will be monitored for signs of infection, with treatment as deemed appropriate by the PI or sponsor, and will have a repeat white blood cell count with differential performed weekly until the ANC is above 1000 cells/mm^3 (1.0 x 10^9/L). If the ANC does not return to above 1000 cells/mm^3 (1.0 x 10^9/L) within 2 months (or sooner if deemed necessary by the sponsor or PI), a hematology referral will be obtained.

Patients withdrawn from study drug due to a reduced platelet count will have a repeat platelet count performed weekly until the count is above 100,000 cells/mm^3 (100 x 10^9/L). If the platelets do not return to above 100,000 cells/mm^3 (100 x 10^9/L) within 2 months (or sooner if deemed necessary by the sponsor or PI), a hematology referral will be obtained.

Patients withdrawn from study drug due to elevated liver function tests will have repeat tests performed, as clinically appropriate, until levels return to baseline. If the patient's liver function tests have not returned to baseline within 6 months (or sooner, if deemed necessary by the sponsor or designee), an ultrasound and/or liver biopsy will be considered.

Early Termination Visits

In the case that patients must terminate the study early, every effort will be made to obtain the next scheduled clinical/neuropsychological/safety assessments as soon as possible after early termination, as well as the next study drug administration if it has been at least 3 weeks since the last administration and continue through the protocol, if possible and if they are willing to do so, as per the regular schedule.

Audio/Videotaping Option

Patients who participate in this protocol may be asked to consider having a clinical/neuropsychological rating session associated with this study audio or videotaped, and would sign a separate consent for this. These audio/videotapes will be used only for educational/training purposes. Any patient who declines will still be eligible to participate in all other components of this study. Audio/video tapes will be kept for up to ten 10 years. They will be kept in locked file cabinets, and available only to research staff.

Cytokine and Toxoplasma Levels

At the baseline and week 4, 8, and 12 visits, blood will be obtained for cytokine levels and toxoplasma antibody.

MRI Option

Patients who meet the additional MRI exclusion criteria and are interested will be presented the optoin of participating in the MRI option. Of note, participating in the MRI option is not required to be a part of the clinical trial. This will be clearly stated to patients.

For this option, patients will receive an MRI scan (as detailed below) at baseline and within one month of receiving their last dose of study drug. If they terminate early and after receiving at least one dose of study drug, they will be asked to have their follow up MRI scan.

MRI with gadolinium contrast. Subjects will obtain MRI images on the NYSPI 3.0T GE scanner. CBV, ASL, and MRS sequences will be obtained. After a T1 scout image, needed to determine patient position, we will acquire the following images:
(1) Standard structural images will be used to obtain tissue content information needed to convert the ASL signal into CBF value in physiological units. Next, pseudo Continuous ASL (pCASL) images will be acquired. Total imaging time for ASL will be ~10mins.
(2) For acquisition of left hippocampal glutamate using MRS, we will use standard MRS sequences. Total imaging time for MRS will be 15~30min.
(3) For CBV mapping, subjects will receive pre-gadolinium and post-gadolinium T-1 weighted images after receiving I.V. gadolinium (0.1mmol/kg). Total imaging time for CBV will be ~20 min.

All scans will be examined at the image console for gross structural abnormalities such as the presence of mass effects, hydrocephalus, and vascular malformations by Dr. Girgis. Images will be read for gross structural brain abnormalities by neuroradiologist within one month of the scan. Should there exist a gross structural brain abnormality, a neuroradiologist will immediately inform the principal investigator Dr. Girgis. The neuroradiologist will immediately provide an oral report followed by a handwritten or typed note to the PI and the Director of the MRI Unit. A final written transcript of the clinical reading will be provided within two weeks of the oral report. Appropriate follow-up with the patients primary care physician or appropriate sub-specialist and care setting will be immediately arranged for further diagnostic testing/treatment recommendations by Dr. Girgis in consultation with the neuroradiologist. For routine scans with no findings, the subject will be informed of the result by letter if they choose or through reviewing the letter's findings with Dr. Girgis at a research follow-up appointment.

Additional Gadolinium Information

Because of the FDA safety announcement, we will inform all subjects who are currently enrolled, about this new safety announcement. We will use the following template to begin the discussion:

"The Food and Drug Administration (FDA) has issued an announcement stating they are investigating a possible risk of adverse health effects from repeated use of gadolinium for MRI. Though the FDA has not reached a conclusion at this time, you should not participate in this study if you have previously had more than 1 MRI scan with gadolinium."

From this point we will have a discussion with the subject about his/her willingness to continue to participate. If they do not want to continue their participation, they will be discontinued from the study.

In addition, to ensure that individuals are systematically queried about previous gadolinium scans, we will ask all individuals who are currently enrolled or interested in the study whether they had an MRI with an i.v. injection (i.e., "Did they give you an injection?") in case people do not know the term "gadolinium."

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Subjects will be withdrawn from the study if:

a. They request it for any reason

b. The PI judges that it is medically unwise to continue in the study, including, but not limited to for severe rash, infection, or other side effect

c. ANC < 1000

d. AST/ALT > 3x Upper limit of normal

e. Platelet count < 100,000

f. His/her psychiatric condition deteriorates to the point that he/she loses capacity to consent for this trial.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

Baseline, Weeks 4, 8, and 12 Visits	Weeks 0, 2 and 14 Visits	Total (mL)	Total (oz)	Total (tablespoons)
50mL per visit * 4 visits = 200mL	15mL per visit * 3 visits = 45mL	245mL	8.28	16.57

Table 2 summarizes blood sampling (mL) over the course of the study for each procedure. The total blood sampled is 245 mL, over a 90 day period, which is less than a typical blood donation (500 mL). In the consent form, volumes are given in mL, ounces (1 ounce = 29.5 mL) and tablespoons (1 tablespoon = 15 mL), with all volumes rounded up to the next integer.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

CGI-3 minutes

GAF-3 minutes

CSSRS-5 minutes

MATRICS-60-90 minutes

PANSS-15-30 minutes

UPSA-5 minutes

SCID-60 minutes

DIGS-90 minutes

WTAR-5 minutes

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
tocilizumab
Manufacturer and other information
Manufactured by Chugai/Roche. FDA approved for the treatment of rheumatoid arthritis in individuals who have not responded to at least one TNF-alpha therapy and for juvenile idiopathic arthritis. We will apply for an IND with exemption from the FDA.
Approval Status
No IND is required
Choose one of the following options
FDA has determined that IND is not required

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study

Patients will continue on their medication regimen as before the study as long as it is clinically indicated. The treating clinician can make changes if needed due to clinical deterioration or side effects. All patients who complete the study will be offered at least 4 months of free treatment (free except for the cost of medications) with a psychiatrist and psychotherapist in the Lieber Schizophrenia Research Clinic. They will also be offered referrals to other providers if they request them.

Clinical Treatment Alternatives

Clinical treatment alternatives
Patients who do not participate in this study may receive their normal clinical care, including with

medications, therapy, and other interventions. Biological agents, such as tocilizumab, are available for use but have not yet been studied in individuals with schizophrenia.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

a. Tocilizumab administration

Tocilizumab is FDA-approved for the treatment of rheumatoid arthritis in individuals who have not responded to previous DMARD therapy, as well as for juvenile idiopathic arthritis. Therefore, there is substantial information on tocilizumab use, and tocilizumab has been found to be generally well tolerated, and its risks well characterized. We would also like to clarify that individuals who have received tocilizumab in clinical studies or in practice are generally more medically infirm (tocilizumab is indicated only for adults who have failed another biologic agent) and often receiving another immune modulator, such as methotrexate. Therefore, their risks of side effects are generally much higher than for our subjects who will be medically healthy and only receiving tocilizumab. A substantial proportion of serious side effects that occur while taking tocilizumab occur in individuals who are already immunocompromised, have CHF, or are predisposed or already have cancer.

There are several risks of tocilizumab use. Risks of the administration include anaphylaxis (0.4%) as well as an acute hypersensitivity reaction (0.2%) including chills, fever, nausea, and vomiting. The emergence of anti-tocilizumab antibodies has been reported in clinical studies (RA: 18 of 601 patients (3.0 %), pJIA: 1 of 19 patients (5.3 %), sJIA: 11 of 128 patients (8.6 %); and Castleman's disease: 1 of 35 patients (2.9%).

Common and mild side effects of tocilizumab administration including mild infection including nasopharyngitis, hypertension, rash, abdominal pain, diarrhea, mild elevated AST/ALT, headache, and dizziness, elevated lipids. More serious side effects including injection site reaction (5-8%), gastrointestinal perforation (rare), thrombocytopenia (1.3-1.7%), neutropenia (1.8-3.4%), tuberculosis (rare), upper respiratory tract infection (6-8%), cancer (rare, and does not separate from placebo, Lopez-Olivo et al., 2012), other serious/opportunistic infection (rare), demyelinating disorders (rare, unclear if related to tocilizumab), pleurisy (rare), cardiac failure (rare; and in meta-analyses with other immune modulators, does not separate from placebo (Singh et al., 2011).

Tocilizumab should not be administered to pregnant or nursing females.

We will also break the blind after 5 subjects and report to the IRB in order to determine whether or not there are any psychiatric side effects of tocilizumab.

Elevated levels of IL-6 have been known to inhibit CYP450 enzymes, with a preference for those NOT involved in the metabolism of antipsychotic medications (e.g., CYP3A4). Treatment with tocilizumab has been known to restore CYP450 functioning to normal levels in situations in which elevated IL-6 levels were inhibiting CYP450 enzymes, but has not been known to over stimulate these enzymes. Most psychiatric

medications are metabolized by CYP450 enzymes NOT affected by IL-6 to a great degree (e.g., CYP2D6), although some are metabolized to a minor degree by CYP450 enzymes affected by IL-6 (e.g., CYP3A4). Therefore, while we do not expect a change in antipsychotic blood levels during the course of this trial, we will be vigilant about monitoring for a change in mental status of all participants in this trial.

There is also the possibility that patients will experience an exacerbation of symptoms while in this trial.

b. Venous Blood sampling

Intra-venous sampling or lines (heplock or IV) can cause bleeding, occlusion, infection, or clotting. They may also cause discomfort.

c. Interviews

Patients may experience boredom and fatigue during the administration of neuropsychological assessments and ratings scales.

d. Audio/videotaping

There is a slight risk of loss of confidentiality to subjects who participate in this optional component of the protocol.

e. MRI Imaging: The Magnetic Resonance (MR) scanner uses strong magnetic fields and radio waves to take measurements in the brain. MRI involves lying on a table that slides into a large magnet shaped like a cylinder. Before beginning the procedure, we will determine that patients do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and they will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). In addition, they will complete a brief interview at the time of study inclusion to determine if they have Asthma or a history of renal failure that may exclude their ability to receive an injection of Gadolinium (see below section). These questions will be repeated on the day of the scan. For the scanning procedure, they will be asked to lie flat on the back in the MRI scanner for approximately 60 minutes and to remain as still as possible. Some people have reported sensations during MRI scans, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in the body. With any MRI scan, on occasion, some people experience nervousness or discomfort due to the scanner's small space and the need to lie still. Except for pacemakers, some types of metallic implants, and medication patches, we are not aware of any other potentially dangerous interactions or hazards associated with the MRI scan. The MRI scanner also produces a loud noise.

f. Gadolinium compounds do have side effects such as nausea and vomiting, observed in less than 2 people out of every 100 injected. (1.8% estimate). Dry mouth (less than 2%), dizziness (0.7% up to 3.6%), and headache (2.2% up to 5.8%) are infrequent, yet possible side-effects. An additional side effect is hives, observed in less than 1 person out of every 100 injected with Multihance (0.7% estimate). All of these side effects resolve within 20 minutes to several hours. People with asthma or

known sensitivities to contrast agents are at increased risk for more serious side rare side effects (less than 1/10,000 injections estimate), such as severe allergic reaction that may result in sudden difficulty breathing, and therefore will not be injected with Gadolinium. Some patients with acute renal failure or end-stage renal disease have developed a serious medical condition known as nephrogenic systemic fibrosis (NSF) after the use of gadolinium for MRI. The primary concern regarding risks to renal function from gadolinium-based contrast agents (GBCAs) is specific to this population of patients who have end-stage renal disease (ESRD) on hemodialysis, or acute, florid, clinical renal failure, and then are exposed to gadolinium. This population of patients is by definition excluded from this study by virtue of medical history and general review of systems. Renal dysfunction as a result of gadolinium in a population without history of end-stage renal disease or acute renal failure has not been described in the medical literature. In a retrospective study conducted at two large medical centers, 74,124 patients were
injected with a standard dose of gadolinium (0.1mmol/kg, the same dose used in our research studies) who had no screening for renal function, with a rate of zero/74,124 cases of renal complications (e.g., nephrogenic systemic fibrosis (NSF) or other renal dysfunction) post injection (Prince, Zhang et al. 2008). All 15 cases of NSF that were found in this retrospective study all had severe, clinical renal failure at the time of gadolinium injection. No cases of NSF have been identified in persons with normal renal function or with moderate renal dysfunction.

Regarding this specific risk, the FDA recommends:
1. Become familiar with the patient populations at risk for NSF.
2. Avoid using gadolinium in patients with known risks for developing NSF.
3. Prior to administering gadolinium, evaluate patients for renal dysfunction by assessing their renal function, either by obtaining a medical history or conducting laboratory tests that measure renal function.
4. When administering gadolinium, do not exceed the recommended dose in product labeling and allow a sufficient period of time for elimination of the agent from the body prior to any further gadolinium
administration.

The American College of Radiology recommends, as of July 2007, pre-screening patients prior to the administration of Gadolinium-Based MR Contrast Agents (GBMCA) their glomerular filtration rate (GFR) for the following patient groups:
1. Renal disease (including solitary kidney, renal transplant, renal tumor)
2. Age >60
3. History of Hypertension
4. History of Diabetes
5. History of severe hepatic disease/liver transplant/pending liver transplant. For patients in this category only, it is recommended that the patient's GFR assessment be nearly contemporaneous with the MR examination for which the GBMCA is to be administered.

The dosing guidelines are as follows: CNS (Central Nervous System) Adults: The recommended dose of Multihance 0.1mmol/kg (0.2 mL/kg) administered as a rapid bolus intravenous injection. According to the Multihance package insert and the recent literature, repeated dosing of mutihance up to a total dose of .3mmol/kg (in three doses of 0.1mmol/kg) can be immediate given within a short

time-span with no adverse effects. The elimination half-life of the compound is 1-2 hours. Prior to readministration, the FDA recommends 'sufficient time for drug elimination'. Our study design of a single baseline dose at 0.1mmol/kg followed by repeated injection after finishing study drug administrations at least one month to three months later is more than adequate time for elimination of contrast agent, which should be complete by two days, and is well below the maximal dosing guidelines that have been shown to be safe with repeated dosing in prior studies.

Describe procedures for minimizing risks

All subjects are given contact information for the PI and study physician (primarily Dr. Girgis) so that they can contact him at any time if necessary.

a. In order to minimize risk, each patient will be monitored and the drug infusion stopped immediately should there be any safety concern. We will obtain frequent laboratory analyses, including lipids, liver tests, and cbc, adverse event queries, and EKGs during this study. Patients will be terminated from the study if their LFTs (i.e., AST/ALT) rise above 3x ULN or the ANC below 1000 or platelet count <100,000, or they develop side effects that are, in the opinion of the PI, preclusive of continuing in this protocol. Patients with baseline severe liver disease, elevated AST/ALT (1.5x ULN), ANC<**15**00, thrombocytopenia (platelet < 100,000), known intestinal diverticula or an immunologic disorder which impairs the immune system will be excluded from this study. Patients will be instructed not to obtain any live vaccines between 1 month before the study and 3 months after receiving study drug. All patients will have a ppd before beginning study drug administration, and positive ppds will be followed by chest xrays. Subjects with positive ppds and active disease or latent disease will not be included in this study, subjects with positive ppds and negative chest x rays may be included.

These criteria will ensure that the safety of the subjects who participate in this trial is maximized and will not increase the risks to subjects. There are are additional general and specific safeguards in place to maximize the safety of all individuals of this trial, as well as several important safety considerations.

First, the vast majority of the data on tocilizumab related neutropenia, transaminitis, and thrombocytopenia were obtained in very medically infirm patients on both tocilizumab and another DMARD (often methotrexate or prednisone which are comparatively more toxic). Therefore, all of the side effects that we will be discussing here are likely to occur at lesser rates and with lesser severity than described. In addition, tocilizumab is widely approved and it is now not possible to quantify the number of people who have received it. In addition, while the maximum dose in this trial is 8mg/kg given every 4 weeks, 12mg/kg is routinely given every 2 weeks to children with arthritis, attesting to the relative safety of this medication. Similarly, the FDA has indicated that this study is exempt from needing an IND, in part related to the safety of and experience with tocilizumab. Moreover, we have proposed very conservative exclusion criterion to ensure that no individuals with any predisposing condition or on any predisposing medication can be included in this trial, including exclusion cutoffs of an ANC of **15**00 and AST/ALT of 1.5xULN.

We will now address each of these criterion individually.

Regarding platelet counts, the mechanism by which tocilizumab increases platelet counts is not completely clear, however, elevated IL-6 levels are thought to stimulate thrombopoietin (Kaser et al., 2001), so blocking IL-6 with tocilizumab may mitigate this activity. However, tocilizumab is not a bone marrow suppressor and only potentiates thrombopoietin. Therefore, antagonizing IL-6 only leads to a minor decrease in platelet counts, if at all, and one that is not related to serious bleeding events and rarely decreases below 100K. The frequency of this event is 1-4% in individuals receiving both tocilizumab and another DMARD, while in this trial subjects will only be receiving tocilizumab, which is relatively mild compared to typical DMARDS (e.g., methotrexate, prednisone). In addition, tocilizumab related decreases in platelet counts are not related to serious bleeding events and are readily reversibly after discontinuing treatment. In summary, tocilizumab related thrombocytopenia is an extremely uncommon event, is mild when it occurs, is fully reversible after discontinuing treatment, and has no substantial clinical relevance.

Regarding decreases in neutrophil counts, the mechanism by which tocilizumab decreased neutrophil counts is not clear. However, it is thought that IL-6 demarginates neutrophils and accelerates their release from marrow (Suwa et al., 2000), so blocking IL-6 would mitigate these effects. **In addition, recent data show that anti IL6 treatments (such as tocilizumab) do not cause phagocytosis or reduced functioning of neutrophils (Wright et al., 2014), confirming these data. Additionally, clinical data from Genentech (attached) also show that while Tocilizumab dose decrease ANC, the decrease in ANC has not been associated with severe infection.** Also, tocilizumab is not a bone marrow suppressor and does not affect the overall concentration of neutrophils. Therefore, antagonizing IL-6 only leads to a minor decrease in neutrophil counts on laboratory analysis but does not decrease neutrophils overall, and any decrease does not lead to serious events. Consistent with this mechanism, agranulocytosis is not considered a risk of tocilizumab. In addition, decreases in neutrophil counts are readily reversibly after discontinuing treatment. In summary, tocilizumab related neutropenia is an uncommon event, is mild when it occurs, is fully reversible after discontinuing treatment, and has no substantial clinical relevance.

Regarding transaminitis, tocilizumab is known to irritate the liver, and we expect approximately 33% of individuals on tocilizumab (~6 in this trial) to reach up to 3xULN and one percent to reach between 3-5x ULN (~0-1 in this trial). However, tocilizumab is not overtly toxic to the liver, and hepatitis or fulminant liver failure are not considered risks of tocilizumab. When it occurs, transaminitis is mild, reversible, and has no clinical relevance. In summary, tocilizumab related transaminitis is a relatively common event though much less common above 3xULN, is mild when it occurs, is fully reversible after discontinuing treatment, and has no substantial clinical relevance.

Because of the very low risk of anaphylaxis, as well as fever, chills, nausea, or vomiting due to the tocilizumab infusion itself (hypersensitivity reaction), the study physician will have parenteral epinephrine and diphenhydramine available during each administration, as well as acetaminophen, and patients will be monitored by a study physician or nurse (at the bedside) for one hour after the administration. For the one hour time period after the administration, when a nurse is at the bedside of the patient, the study physician will be in the immediate proximity (i.e., on 5 South if using 5 South, in the vicinity of the ECT suite if using the ECT suite, and in the Division of Translational Imaging if using the Division of Translational Imaging, so that, if necessary, the study physician can be at the bedside within 30 seconds). During the one hour infusion, the study physician will be present at all times. Patients will also be called by the study physician the day after their administration to check in on their status.

In addition, while we do not expect a change in antipsychotic blood levels during the course of this trial, we will be vigilant about monitoring for a change in mental status of all participants in this trial.

b. These risks are minimized by using proper techniques. In addition, the primary study physician (in most cases Dr. Girgis) will assess the IV catheter placement. IV catheters will be removed immediately after administration of the study drug is complete (approximately 1 hour after placement).

c. In order to avoid boredom caused by the administration of neuropsychological tests and ratings scales, patients will be allowed frequent and regular breaks. If necessary, particularly during the screening/baseline visit, patients will be allowed to finish the session on a different day.

d. In order to minimize the risks of loss of confidentiality for those patients who participate in the optional audio/videotaping component of this protocol, tapes will be kept in locked drawers, and made available to research staff only. Personal identifying information will not be included on the tapes.

e. MRI Imaging: Before beginning the procedure, we will determine that patients do not have a pacemaker or any unsafe metallic implants such as an aneurysm clip or heart valve and certain tattoos, and they will be asked to remove any metal or magnetized objects (such as keys, chains, jewelry, retainers, medication patches, hairpins or credit cards). In addition, they will complete a brief interview at the time of study inclusion to determine if they have Asthma or a history of renal failure that may exclude their ability to receive an injection of Gadolinium (see below section). These questions will be repeated on the day of the scan. The MRI scanner also produces a loud noise; earplugs will be provided to reduce this discomfort. If a patient experience any discomfort and wish to stop the scan, he/she can tell the MRI technologist who will stop the scan immediately. In our experience, no one has had sensations from the MRI that did not stop when the scanning stopped.

f. Gadolinium -A trained physician (currently Dr. Girgis) will inject the gadolinium and remain with the patient for the entire duration and for 15minutes after the scanning session is complete. Prior to scan, all participants being considered for participation in this study will continue to have a complete medical history prior to MRI to screen for renal failure/history of renal disease, diabetes, or hypertension, as well as screening labs. Patients with a diagnosis of acute renal failure are invariably severely medically ill and hospitalized, and are not eligible for study participation. In the current protocol, we administer Multihance according to the patient's weight at a dose of 0.1mmol/kg. Based

upon the amount administered, we do not exceed the recommended dosage. In addition, an Epi Pen will be available at all times during scanning with gadolinium.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
We use coded records and keep signed consent forms in a locked file cabinet; patients with a positive drug screen are not entered in the study. We do, however, point out to prospective subjects that we cannot assure that their drug histories and other personal records might not become known.

Subject names and diagnoses are stored in an electronic database that is accessible only with a password. Only the clinical/research staff involved in studies at the Division of Translational Imaging have access to the database. Subject names, along with scan information is stored on desktop computers in the division. These computers are kept in locked offices. Additionally, personal identifying information is stored in the password-protected database at NYSPI (R2Net).

The safety data (e.g., data on adverse events and laboratory values) will be shared with Genentech. All correspondences with Genentech will have no more personal identifying information except for a non identifying study number. Genentech will not receive any other identifying information.

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects

It is possible that subjects who participate in this study will experience an improvement in symptoms. However, any such benefits would be expected to be temporary and short-lived.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

$50 for each baseline (**up to 2)**, week 2, 12, or 14, which include only assessments.

$100 for each week 0, 4, 8 visit during which they receive study drug, which will include both assessments and study drug administrations.

Compensation schedules are based on time commitment during the respective visits.

$100 for each MRI scan for those individuals who participate in MRI scans.

We will also reimburse for reasonable, local transportation costs.

In total, subjects will receive up to $5**5**0 or $700 if they participate in the MRI scans. Compensation will be paid by cash or check mailed to the subject's address 4-6 weeks after the procedure. If subjects do not complete all procedures, payment will be pro-rated for participation.

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