An Open-Label, Pilot Trial of Adjunctive Tocilizumab in Schizophrenia

To the Editor: Interest and enthusiasm for research on the immunology of schizophrenia has, arguably, taken a prominent role in the field. Adjunctive antiinflammatory treatment may be associated with improvement in psychopathology and cognition in some patients with schizophrenia.[1,2] Interleukin-6 (IL-6) is an inflammatory cytokine produced by blood leukocytes and central nervous system microglia and astrocytes. IL-6 levels are elevated and associated with psychopathology, smaller hippocampal volume, and poorer cognition in schizophrenia.[3–5] We hypothesized that adjunctive tocilizumab—a humanized IL-6 receptor monoclonal antibody—would improve cognition in schizophrenia, an important determinant of quality of life and functioning.

Method. With Institutional Review Board approval and an Investigational New Drug waiver from the US Food and Drug Administration (FDA), we conducted an 8-week open-label trial of adjunctive tocilizumab in schizophrenia (ClinicalTrials.gov Identifier NCT01696929). All subjects provided written informed consent, and a Data Safety Monitoring Board, which included a psychiatrist and rheumatologist, provided study oversight.

Tocilizumab is FDA approved for adults with rheumatoid arthritis and juvenile idiopathic arthritis and is administered as an intravenous infusion every 4 weeks. Subjects were aged 18–55 years, had a *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder, were taking a non-clozapine antipsychotic, had no psychiatric hospitalizations in the past 3 months, and were on stable psychotropic medications for ≥ 1 month.

Exclusion criteria were taking scheduled immunomodulatory agents; having a history of immune disorder; using an illicit drug in the past month; having unstable medical conditions; having active or chronic infections; and being pregnant, breastfeeding, or being a reproductive-age female not using contraception.

After screening, subjects received 4 mg/kg of tocilizumab at baseline and 4 weeks. Psychopathology (Positive and Negative Syndrome Scale[6] [PANSS], cognition (Brief Assessment of Cognition in Schizophrenia[7] [BACS], alternate forms of testing) and fasting serum high-sensitivity C-reactive protein (hsCRP) and cytokine levels were assessed at baseline and weeks 2, 4, and 8. Changes in psychopathology and cognition were analyzed using a paired *t* test, 2-sided, using a last-observation carried forward approach; *P* values were considered statistically significant at the $\alpha = .05$ level.

Table 1. Demographic and Clinical Characteristics of the Study Sample

Characteristic	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6
Age, y	43	32	52	22	39	23
Sex	Female	Male	Female	Male	Female	Male
Race	African descent	White	White	African descent	African descent	African descent
Body mass index	31.0	39.6	35.6	33.6	25.1	35.2
Smoking (cigarettes/d)	5	0	0	0	10	0
Highest education	High school diploma	Some high school	Some college	Some college	Some high school	High school diploma
Diabetes	No	Yes	No	No	No	No
Diagnosis	Schizophrenia	Schizoaffective	Schizophrenia	Schizoaffective	Schizoaffective	Schizophrenia
Age at first hospitalization, y	32	18	41	16	18	17
Antipsychotic	Ziprasidone, 60 mg, orally, 2 times/d	Haloperidol, 1 mg orally, 3 times/d	Lurasidone, 40 mg, orally, once daily	Paliperidone, 117 mg, intramuscularly, once monthly Quetiapine, 50 mg, orally, at bedtime	Paliperidone, 156 mg intramuscularly, once monthly Fluphenazine, 5 mg, orally, 2 times/d	Iloperidone, 12 mg, orally, once daily Lurasidone, 80 mg, orally, once daily
Baseline hsCRP (mg/dL)	7.44	2.23	11.20	4.09	1.56	2.27

Visit								
Variable	Baseline		Week 2		Week 4		Week 8	
PANSS, mean (SD) score								
Positive	13.5 (1.6)		12.0 (1.8)		12.3 (3.1)		12.8 (2.8)	
Negative	12.3 (6.7)		12.7 (5.6)		13.5 (6.1)		13.6 (8.2)	
General	31.0 (5.5)		28.0 (4.3)		28.3 (5.2)		27.6 (5.5)	
Total	56.8 (10.9)		52.7 (9.5)		54.2 (12.7)		54.2 (13.9)	
BACS, mean (SD) score	Raw Score	*Z*-Score	Raw Score	*Z*-Score	Raw Score	*Z*-Score	Raw Score	*Z*-Score
Verbal memory	38.0 (9.6)	−1.2 (1.0)	41.5 (14.4)	−0.7 (1.7)	40.7 (14.4)	−0.9 (1.7)	42.2 (16.1)	−0.6 (1.9)
Digit sequence	13.7 (5.0)	−2.9 (1.1)	14.8 (3.9)	−2.8 (0.9)	16.5 (5.3)	−2.2 (1.4)	16.7 (5.6)	−2.3 (1.3)
Token motor	61.0 (23.4)	−1.6 (2.6)	72.3 (11.7)	−0.4 (1.4)	67.3 (12.2)	−0.9 (1.5)	74.0 (9.9)	−0.2 (0.9)
Verbal fluency	20.0 (11.3)	−3.2 (1.2)	22.5 (13.4)	−3.0 (1.5)	24.7 (1.05)	−2.6 (1.1)*	20.8 (8.5)	−2.9 (0.6)
Digit symbol coding	35.7 (13.2)	−2.4 (1.3)	46.7 (12.3)	−1.4 (1.2)*	46.2 (11.2)	−1.4 (1.2)*	47.2 (12.9)	−1.4 (1.2)*
Tower of London[a]	10.8 (5.8)	−2.5 (2.8)	11.5 (3.9)	−2.0 (1.7)	10.7 (4.5)	−2.3 (1.8)	10.3 (5.9)	−2.5 (2.5)
Composite		−2.3 (1.4)		−1.7 (1.0)		−1.7 (1.0)*		−1.6 (1.1)*
hsCRP, mean (SD) mg/dL	4.8 (3.8)				2.5 (2.7)		4.3 (5.4)	
Cytokine, mean (SD) pg/mL								
IL-2	0.0 (0.0)				0.4 (1.1)		0.0 (0.0)	
IL-6	0.3 (0.7)				8.4 (12.1)		2.7 (3.3)	
IL-8	1.2 (0.9)				1.0 (0.7)		1.2 (0.7)	
IL-10	1.4 (1.1)				2.7 (4.0)		1.8 (2.1)	
TNF-α	1.2 (2.9)				0.9 (1.8)		1.1 (1.8)	

*$P \leq .01$ compared to baseline.
Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, hsCRP = high-sensitivity C-reactive protein, IL = interleukin, PANSS = Positive and Negative Syndrome Scale.

Results. Eight subjects were enrolled; 2 were excluded after screening. Although 6 subjects entered the trial, 1 was removed after the first infusion because psychosocial stressors required psychiatric hospitalization. All week-4 study assessments were completed by the subject; however, a second infusion was not administered. Thus, 5 subjects completed the trial. Demographic and clinical characteristics are presented in Table 1. Infusions were well tolerated without clinically significant adverse effects. Compared to baseline, there was significant improvement in BACS verbal fluency at 4 weeks; digit symbol coding at 2, 4, and 8 weeks; and composite score at 4 and 8 weeks (see Table 1). There were no significant changes in psychopathology scores or hsCRP or cytokine levels, and baseline immune measures did not predict changes in cognition. The most likely explanations for these negative associations are the small sample size and that 5 of 6 subjects did not have detectable baseline IL-6 levels. Since tocilizumab is an IL-6 receptor antagonist, IL-6 levels increased from baseline (4 of 6 subjects had detectable IL-6 levels after infusions), most likely reflecting endogenous IL-6 production.

Adjunctive tocilizumab was associated with significant improvement in cognition. Improvements were observed in all 6 subjects for digit symbol coding, which were robust in magnitude,[8–10] and in 5 subjects for global cognition. Digit symbol coding is a measure of processing speed not associated with specific brain regions or functional neurocircuitry,[11] and greater impairments predict poorer prognosis and functional disability.[12] Our findings suggest that tocilizumab may be a viable adjunctive treatment for cognitive impairment in schizophrenia, although safety and cost (approximately $1,000 per 4 mg/kg dose) are important considerations regarding its clinical utility. Given the serious potential adverse effects due to immunosuppression, which include life-threatening infections, ulcers, and malignancy, use of this medication required a formal risk evaluation and mitigation strategy. An important strength of our study is that, unlike nonsteroidal antiinflammatories, tocilizumab has no relevant off-target (ie, non–immune system) effects. Potential limitations are the open-label design and possible practice effects, although we used alternate forms of the BACS.[13] Tocilizumab was not associated with improvements in psychopathology; however, subjects were clinically stable with mild baseline illness severity. In rheumatoid arthritis, tocilizumab dosing is increased to 8 mg/kg after the first infusion. Because subjects received 4 mg/kg for both infusions, improvements may have plateaued. Evidence of baseline inflammation was not an inclusion criterion, although it was present for 3 of 6 subjects (hsCRP ≥ 3 mg/dL). In depression, monoclonal antibody therapy with infliximab may improve symptoms in patients with baseline inflammation.[14] A larger "proof-of-concept" randomized, placebo-controlled trial of patients with a higher dose of tocilizumab and for a longer duration is warranted. Including only subjects with baseline inflammation may increase the signal-to-noise ratio and would be a step toward more personalized medicine for patients with schizophrenia.

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