The Case for Adjunctive Monoclonal Antibody Immunotherapy in Schizophrenia

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KEYWORDS

• Schizophrenia • Psychosis • Immune • Inflammation • Cytokine
• Monoclonal antibody • Treatment • Adjunct

KEY POINTS

- There is robust evidence that schizophrenia is associated with immune system dysfunction throughout the lifespan.
- There is need to more extensively evaluate the hypothesis that immune dysfunction may be involved in the pathophysiology of schizophrenia.
- Monoclonal antibodies act by directly neutralizing cytokines or by binding cytokine receptors.
- Monoclonal antibodies do not have any off-target effects; therefore, improvements in psychopathology in response to these agents would further directly implicate inflammatory pathways in the pathophysiology of schizophrenia.
- Overall, there is a compelling rationale for well-designed, carefully conducted trials of monoclonal antibody immunotherapy in schizophrenia.

INTRODUCTION

In a recent seminal finding in neuroscience, two independent studies found functional lymphatic vessels lining the dural sinuses of dissected mouse brain meninges—that is, a "direct connection" between the brain and immune system.[1,2] The presence of a functional and classical lymphatic system in the central nervous system (CNS) is a paradigm-shifting finding that challenges basic assumptions in neuroimmunology and how clinicians perceive brain-immune interactions. If confirmed in humans, it may follow that dysfunction of meningeal lymphatic vessels contributes to the pathophysiology of a variety of CNS disorders associated with immune system involvement,

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including schizophrenia, and would enable a more mechanistic approach to the study of the neuroimmunology of these disorders.

The investigation of immune system abnormalities in schizophrenia, although ongoing for decades, has more recently become a popular area of research. This interest has been at least partially stimulated by increased understanding of the interactions that occur between the immune system and the brain in other chronic medical disorders, and furthered by the recent discovery of meningeal lymphatic vessels. Schizophrenia is associated with immune system dysfunction throughout the lifespan. Advances in genetics have led to the identification of associations between genes involved in the regulation of the immune system and increased risk of schizophrenia.[3] Prenatal maternal infection with a variety of different infectious agents is a replicated risk factor for the development of schizophrenia in the offspring,[4] and may act synergistically with family history of psychosis on schizophrenia risk.[5] An association between schizophrenia and infections seems to be bidirectional: hospital contact for infection during childhood or adolescence is associated with an increased risk of schizophrenia in adulthood,[6] and schizophrenia is also a risk factor for infections.[7] Patients with schizophrenia have immune abnormalities in the blood, cerebrospinal fluid, and CNS, including immune cell numbers, inflammatory markers, and antibody titers.[8] Acutely ill patients with schizophrenia seem to have an increased prevalence of certain comorbid infections (eg, lower urinary tract infections).[9,10] Schizophrenia is also associated with increased mortality from infectious diseases, including pneumonia and influenza.[11,12]

Presently, all approved antipsychotics for the treatment of schizophrenia are antidopaminergic agents. Although these medications are effective for many patients, particularly positive symptoms, many other patients have some degree of treatment resistance. Thus, there is a great impetus to identify other effective pharmacologic treatments for schizophrenia, especially for negative symptoms and cognitive dysfunction. Several trials have also found that treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or agents with anti-inflammatory properties, including aspirin, celecoxib, estrogen, and *N*-acetylcysteine, in adjunct with antipsychotics, may be associated with significant improvement in psychopathology in schizophrenia.[13,14] Importantly, in two studies, baseline blood levels of cytokines, key signaling molecules of the immune system that regulate inflammation, predicted response to adjunctive NSAID treatment.[15,16] Essentially, patients who had evidence in the blood of increased inflammation baseline were more likely to improve with NSAIDs. Taken together, these findings suggest a need for more extensively evaluation of the hypothesis that immune dysfunction may be involved in the pathophysiology of schizophrenia.

This evidence, energy, and enthusiasm, coupled with advances in molecular biology, has afforded the field an unparalleled opportunity to investigate this immune hypothesis, toward identifying new potential treatments to alleviate symptoms and improve quality of life in patients with schizophrenia. Currently, several humanized monoclonal antibodies are approved for the treatment of autoimmune disorders and cancers. These antibodies act by directly neutralizing cytokines or by binding cytokine receptors. Cytokines are key signaling molecules of the immune system that exert effects in the periphery and brain. They are produced by immune and nonimmune cells, and exert their effects by binding specific receptors on a variety of target cells. Cytokine receptors also exist in soluble forms, which can inhibit (eg, soluble interleukin-2 receptor [sIL-2R]) or enhance (eg, sIL-6R) the biologic activity of cytokines. There are endogenous cytokine receptor antagonists (eg, IL-1 receptor antagonist [IL-1RA]) that compete with cytokines for membrane receptors. Cytokines are key