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# MONOCLONAL ANTIBODY THERAPY IN AUTOANTIBODY-ASSOCIATED PSYCHOTIC DISORDERS AND SCHIZOPHRENIA: NARRATIVE REVIEW OF PAST AND CURRENT CLINICAL TRIALS

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***SUMMARY***

*Neural cell-surface autoantibody-associated psychiatric disease and a subgroup of psychotic disorders are probably caused by an immune dysregulation such as B-cell related autoantibody production. In this review we describe past and current randomized placebo-controlled trials investigating monoclonal antibodies as therapy for autoantibody-associated psychiatric disease and psychotic disorders, aiming to delineate the current landscape of such monoclonal antibodies in autoantibody-associated psychiatric disease and psychotic disorders, as well as perspectives for future trials. Rituximab and ocrelizumab are now being tested in clinical trials, whereas the initial results on tocilizumab are controversial, as they demonstrated a cognitive-function benefit in an open label study in schizophrenic patients – results that were not replicated in a randomized placebo-controlled trial. Adalinumab as TNF-alpha blockage was effective in treating positive and negative symptoms in schizophrenia. These findings demonstrate that monoclonal antibody therapy is a potentially promising option to treat subgroups of schizophrenia and autoantibody-associated psychiatric patients, but it should be investigated in more placebo-controlled, double-blind trials with large cohorts.*

***Key words:*** *autoantibody - psychiatric disease - psychotic disorder - schizophrenia - clinical trial*

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## AUTOANTIBODY-ASSOCIATED PSYCHIATRIC DISEASE

Neural autoantibodies in psychiatric disease are attracting growing interest in the field of immunopsychiatry. Autoimmune psychosis is a type of a psychotic disorder that originates from a probable autoimmune inflammation in the central nervous system (CNS) along with the confirmed presence of autoantibodies in the serum or cerebrospinal fluid (CSF) (Pollak et al. 2020). Pollak et al. (2020) proposed specific criteria classifying a psychotic disorder into a possible, probable, or definitive autoimmune origin (Pollak 2020). According to Pollak (2020), when making a diagnosis, it is important that the patient revealed an abrupt onset of psychotic symptoms less than 3 months previously, in addition to any one of these anomalies: tumor, movement disorder, an adverse response to antipsychotic drugs, seizures, a disturbed level of consciousness, severe cognitive dysfunction, or autonomic dysfunction; one of these must be present to classify a psychotic disorder as a possible autoimmune psychosis. To categorize a psychotic disorder as a probable autoimmune psychosis, one of two more criteria like pleocytosis in the CSF or bilateral brain abnormalities must be fulfilled. Alternatively, two of the following items should be present: electroencephalography (EEG) abnormalities (focal slowing or focal epileptic potentials), signs of intrathecal immunoglobulin G (IgG) synthesis in the CSF, or neural autoantibodies detected via a cell-based assay. To diagnose a definitive autoimmune psychosis according to Pollak's recent criteria (Pollak et al. 2020), we need proof of an anti-neural autoantibody from the IgG subtyped. These criteria may thus help to evaluate the significance of serum or CSF autoantibodies in psychotic disorders. To date, however, there is no study evidence on monoclonal antibody therapy in patients with autoantibody-associated psychosis. Therefore, our review addresses ongoing studies to answer the question of whether immunotherapy with monoclonal antibodies might be helpful to improve clinical outcomes in patients with autoantibody-mediated psychotic disorders. Our review also aims to analyze the clinical outcomes of completed studies with monoclonal autoantibodies in schizophrenia and to describe planned studies on applying monoclonal autoantibodies in schizophrenia. Schizophrenia is a heterogeneous disease that severely affects cognition, behavior, and emotions, leading to an often chronic condition entailing dire living conditions and intellectual disabilities. We focus on monoclonal autoantibodies in schizophrenia as modulatory components of the immune system, as several studies indicate immune system's substantial involvement in schizophrenia (Van Mierlo et al. 2020, Woo et al. 2020, Tomasik et al. 2016). We provide readers with a brief overview of ongoing and completed studies on the use of monoclonal autoantibodies in patients with psychotic disorders in the context of psychotic disorders associated with autoantibodies and schizophrenia. Each autoantibody's rationale for use is discussed in more

detail in the appropriate sections. This topic has garnered increasing interest over the last few years, and reviews and hypotheses years ago addressed the issue of the concomitant use of monoclonal antibodies in psychotic disorders and schizophrenia (Miller & Buckley 2016, Chaves & Vieira-Coelho 2020, Müller 2018, Chauchan et al. 2021, Sastry et al. 2004).

## AIMS AND METHODS OF THE REVIEW

The aim of our study is to provide an overview of current and previous important trials registered in ClinicalTrials.gov that carried out immunotherapy with monoclonal antibodies in patients with (1) autoantibody-associated psychotic disorders and (2) schizophrenia. In schizophrenia's case, we required no evidence of neural autoantibodies as an inclusion criterion for this review. We specifically selected autoantibody-associated psychotic disorders because there is often a potential reason for an autoimmune genesis (Hansen et al. 2020, Masdeu et al. 2016, 2017), although an autoimmune basis is not likely in every patient with autoantibodies and schizophrenia. For autoantibody-associated psychotic disorders, monoclonal autoantibody therapy is an established third-line therapy for escalating treatment and for patients who failed to benefit from first- and second-line immunotherapy (Pollak et al. 2020). A recent study showed that autoantibody-associated psychotic disorders are a common phenomenon in patients with schizophrenia and schizoaffective spectrum, occurring in approximately 17% (346 of 2043 patients), according to a recent study of 7000 patients with 49 autoantibodies (Daguano Gastaldi et al. 2022). In addition, several studies indicate alterations in immune responses involving elevated interleukins such as IL6 or 23 and upregulated T-helper cells Th17 in schizophrenia patients (Al-Hakeim et al. 2022), making immunotherapy with monoclonal autoantibodies that interfere with interleukins a promising and rational therapy. In the next section, immune dysregulation in schizophrenia is described in more detail (see next paragraph). For our narrative review, we searched for articles in PubMed and studies in ClinicalTrials.gov, a database of publicly funded clinical trials.

## IMMUNE DYSREGULATION IN SCHIZOPHRENIA

A variety of genetic (Ahangari et al. 2022, Li et al. 2022, Bishop et al. 2022) and immunological studies investigating diverse immune biomarkers (Elkjaer Greenwood Ormerod et al. 2022, Carnac et al. 2022, Li et al. 2022, Ermakov et al. 2022, Räuber et al. 2022) have revealed hints of an immune dysregulation and blood-brain barrier dysfunction in schizophrenic patients. The immune phenotypes of autoimmune diseases like Crohn's disease are positively associated genetically with schizophrenia (Tylee et al. 2022) indicating genetic similarities between autoimmune diseases like Crohn´s and schizophrenia. Several pathways and aspects of immune dysregulation have been identified in schizophrenia, such as altered cytokines (Elkjaer Greenwood Ormerod et al. 2022) and immune cells (Carnac et al. 2022). A recent interesting small pilot study by Husain-Krautter et al. (2022) found that antibodies produced by CSF B-cells in schizophrenic patients were distinct from those of healthy controls. These findings will have to be confirmed in larger cohorts, but they might imply a specific production by B-cells of antibodies in a subgroup of schizophrenic patients. CD20+ cells, for instance, were detected in the hippocampus of schizophrenic patients (Busse et al. 2012) confirming B-cells as relevant targets in modulating immunologic reactions in schizophrenic patients. B-cells are especially relevant, as they might alter the composition of autoantibodies. Another recent interesting therapeutic target are T regulatory cells (Tregs) in psychotic disorders (Kelly et al. 2018, Sahbaz et al. 2020). Tregs are important for regulating CNS inflammation, and are relevant in CNS autoimmunity. IL-6 is increased in the blood of patients with transient psychosis and schizophrenia (Kale et al. 2022). Furthermore, according to a recent hypothesis by Corsi-Zuelli (Corsi-Zuelli et al. 2021), IL-6 might contribute to less activated Tregs (hypofunctional Tregs) in psychotic disorder. Blockage of the IL-6 cascade by antibodies therefore seems to be an amazing target for modulating the Tregs activation state. By doing this, an autoimmune condition evoked by hypofunctional Tregs could be dampened and symptoms arising from autoinflammation in schizophrenia might be reduced. Taken together, immune dysregulation in schizophrenia is heterogeneous and offers different targets for admistering monoclonal antibodies.

## ANTIBODY THERAPY IN AUTOANTIBODY-POSITIVE PSYCHOTIC DISORDER

### Rituximab

An ongoing randomized, placebo-controlled, double-blind phase 2 trial termed SINAPPS2 (Principal investigator: A. Coles, Great Britain) that started in 2017 is investigating the effect of intravenous immunoglobulins versus placebo or rituximab in autoantibody-associated psychosis (Lennox et al. 2019, NCT03194815) (Table 1). Rituximab is a monoclonal anti-CD20 antibody targeting the depletion of B-cells. Targeting B-cells in autoantibody-associated psychiatric disease is relevant in those autoantibody-associated psychiatric syndromes believed to be B-cell-dependent. For example, membrane-surface autoantibodies like anti-NMDAR are relevant to the pathogenesis of encephalitis (Al-Diwani et al. 2022, Feng et al. 2021). In SINAPP2, the neural autoantibodies can be present in serum or CSF. Eligible patients are aged 16-60 years. The rituximab dosage

applied is 1g via two infusions starting between 28 to 35 days after IVIG application, with a second infusion two weeks later. Each infusion is accompanied by 100 mg methylprednisolone. The psychotic episode should not have occurred more than two weeks ago, and no episode should have occurred longer than 24 months ago. The trial has two additional key exclusion criteria quite difficult to fulfill, such as an ongoing acute encephalopathy and co-existing neurological disease, as neuropsychiatric features and encephalopathy often coincide in autoimmune psychosis. It is a monocentric trial lasting about 20 weeks with follow-up of treatment lasting up to one year. The primary outcome is a relevant treatment response effect according to the Positive and Negative Symptoms Scale (PANSS). Other functional outcomes will be assessed in addition via the Clinical Global Impression - Improvement scale and Personal and Social Performance Scale (Table 1). This ongoing trial's results are expected in 2024. We are describing the study here because we can learn from it whether or not the underlying autoantibody subclass, such as membrane surface-related autoantibodies, which are thought to have B-cell immune-pathogenesis, play a role in the beneficial effects of monoclonal autoantibodies. In addition, we find it of potential interest to determine whether serious side effects limit the use of these drugs in future studies. Additional initial data from a case series showed that rituximab is a very seldom followed option, as it is used in just 4% of patients with antibody-related psychiatric autoimmune encephalitis, but it appears to be a very effective option - one that alleviated symptomology in 100% of patients suffering from probable psychiatric autoimmune encephalitis (Endres et al. 2022).

### Ocrelizumab

Another randomized, placebo-controlled therapeutic trial (NCT03971487) (Principal investigator: J.C. Masdeu, United States) in phases 1 and 2 (Table 1) was performed to investigate two intravenous doses of 300 mg of ocrelizumab in patients with schizophrenia or a schizoaffective psychosis type associated with autoantibodies. Ocrelizumab is also a monoclonal antibody against the CD20 antigen belonging to B-lymphocytes developed to treat multiple sclerosis. Thus, its function resembling rituximab and ocrelizumab is believed to help stop autoantibody production in patients with schizophrenia or schizoaffective disorder associated with membrane-surface autoantibodies. The trial's primary outcome is the PANSS score as a measurement of psychotic symptoms. The trial will probably finish in this year, and their results will soon be published. We are eager to obtain these highly anticipated results to see if ocrelizumab's efficacy is similar to rituximab's in membrane surface autoantibody-associated schizoaffective disorder or in schizophrenia for a future investigation.

## ANTIBODY THERAPY IN PSYCHOTIC DISORDERS AND IN SCHIZOPHRENIA

### Rituximab

An open-label study that started in 2019 and finishing this year is assessing rituximab in an age-restricted cohort of patients aged 18-40 years presenting two years of an ongoing schizophrenia-spectrum disorder (NCT03983018) (Principal investigator: S. Bejerot, Sweden). As delineated above, B-cells-related antibody mechanisms differ between schizophrenia and controls, thus this study's rationale is to reduce antibody production by depleting B-cells via rituximab. This trial's primary outcome is a change from baseline assessed by the PANSS scale (Table 1). In addition to assessing functional outcomes, B-cell subpopulations will be determined in relation to the clinical response, which will give insights into the relationship between B-cell subpopulations and clinical symptomatology. This study will therefore be of great importance in assessing the importance of B-cell mechanisms and related treatment strategies in schizophrenia. These results will help us to plan future research on the use of rituximab in schizophrenic patients and to find out whether certain patient subgroups benefit from such immunotherapy depending on their clinical characterization.

### Siltuximab

Siltuximab is a monoclonal antibody against interleukin-6 (IL-6) being tested in a phase 1 randomized controlled clinical trial to prove its safety, tolerability, and efficacy as an adjunct to an antipsychotic treatment regimen over a 9-week period in a 30-patient subgroup with schizophrenia or schizoaffective disorder presenting increased peripheral inflammation assessed by high-sensitivity C-reactive protein (hsCRP) > 0.5 mg/dl (NCT02796859) (Principal investigator: B. J. Miller, United States). As IL-6 supposedly interacts with the regulation of Tregs activity, it seems logical to minimize these populations indirectly by an IL-6 antibody to lower autoinflammation in schizophrenic patients. The hypothesis is that siltuximab would induce better cognition than a placebo. Furthermore, they expect higher IL-6 levels in patients given siltuximab. The dampened inflammation state will also be assessed, and lower hsCRP is expected to be detected in siltuximab-treated patients. The treatment period will last about 9 weeks with three siltuximab infusions: at baseline, and again after three and six weeks. This trial's results are anticipated in December 2023. This study is extremely important for planning and performing future investigations, as the hypothesis that the IL-6 antibody interacts with Tregs activity, leading to lower inflammation as measured by hsCRP, can be indirectly investigated. Influencing Tregs activity through the indirect application of IL-6 monoclonal antibody is an advanced target for future schizophrenia therapy and therefore of great importance for the design of future studies.

**Table 1.** Trials with monoclonoal antibodies in schizophrenia and autoantibody associated psychiatric disease

| Trial | Drug | Co-hort | Study phase, trial type | Study duration | Primary and secondary outcome | Results | Nct number | Principal investigator | Publi-cation |
|---|---|---|---|---|---|---|---|---|---|
| Anti-neural membrane autoantibody associated psychosis | Rituximab and IVIGs | N=80 | 2, Interventional, Randomized, Placebo controlled, Double blind | 2017-2024 | Relevant treatment response in PANSS<br>Primary outcome:<br>PANSS reduction<br>Secondary outcome:<br>a) time to first treatment response, 18 m<br>b) relapse rate, 18 m<br>c) number of adverse effects, 18 m<br>d) proportion of patients reaching 20% reduction in PANSS, 12 m<br>e) proportion of patients reaching 30% reduction in PANSS, 12 m<br>f) proportion of patients reaching 40% reduction in PANSS, 12m<br>g) Changes in Global Impression Scale, 12 m<br>h) Changes in the Young Mania Rating Scale, 12 m<br>i) Changes in antipsychotic non-neurological side effects scale, 12m<br>j) Changes in BACS<br>k) Changes in GAF, 12 m | Ongoing study, currently no results | NCT03194815 | Alastdair Coles, University of Cambridge, Great Britain | Lennox et al. 2019 |
| Schizophrenia and schizoaffective disorder associated with autoantibodies | Ocrelizumab | N=40 | 1, 2, Interventional, Randomized, Placebo controlled | 2017-2024 | Improvement in PANSS<br>Primary Outcome:<br>Score on PANSS, 6 m<br>Secondary Outcome:<br>a) Score on quality of life scales for psychiatric patients, 6 m<br>b) Score on NIH Cognitive Toolbox, 6m<br>c) Antipsychotic-equivalent medication ordered by patient's psychiatrist, 6 m | Ongoing study, currently no study results | NCT03971487 | Joseph C. Masdeu, Houston Methodist Neurological Institute, US | - |
| Schizophrenia | Rituximab | N=9 | 1, Interventional, Open label | 2019-2022 | Change from baseline assessed by the PANSS<br>Primary outcome:<br>Change measured by PANSS, 40% reduction regarded as respone, week 20<br>Secondary outcome:<br>a) Personal and Social Performance scale, week 20<br>b) Clinical Global Impression severity, week 20<br>c) Clinical Global Impression -Improvement in relationship to inflammatory markers<br>d) Clinical Global Impression-Improvement, proportion of responders, week 20<br>e) Clinical Global Impression<br>f) Adverse reaction: any adverse reactions | Ongoing study, currently no study results | NCT03983018 | Susanne Bejerot, Region Örebro County, Sweden | - |

*Abbreviations:* BACS = Brief Assessment of Cognition; GFA = global assessment of functioning; IVIG = intravenous immunoglobulins; m = months; N = number; PANSS = Positive and Negative Symptoms Scale in Schizophrenia; UPSA-B score = University of California, San Diego Performance-Based Skills Assessment B score

**Table 1.** Continues

| Trial | Drug | Co-hort | Study phase, trial type | Study duration | Primary and secondary outcome | Results | Nct number | Principal investigator | Publi-cation |
|---|---|---|---|---|---|---|---|---|---|
| Schizophrenia | Siltuximab | N=30 | 1, Interventional, Randomized, Placebo controlled | 2016-2023 | Change in cognition (BACS)<br>Primary outcome:<br>Change in cognition BACS at baseline and 9 weeks<br>Secondary outcome: change in total psychotic symptoms at baseline and 9 weeks by PANSS<br>A positive change reflects an increase and a negative changes depicts a decrease of psychopathology | Ongoing study, currently no study results | NCT02796859 | Brian J Miller, Augusta University, Georgia, US | - |
| Schizophrenia | Tocilizumab | N=20 | 1 Randomized, Controlled trial | 2016-2023 | Improvement in cognitive function compared to placebo<br>Primary outcome:<br>Change in cognition BACS at baseline and 12 weeks<br>Secondary outcome: change in total psychotic symptoms at baseline and 12 weeks by PANSS<br>A positive change reflects an increase and a negative changes depicts a decrease of psychopathology | Ongoing study, currently no results | NCT02874573 | Brian J Miller, Augusta University, Georgia, USA | - |
| Schizophrenia | Tocilizumab | N=59 | 4, Randomized, Placebo-controlled, Interventional | 2014-2018 | Change in PANSS<br>Primary outcome:<br>Clinical response by PANSS<br>Secondary outcome:<br>Cognitive symptoms overall MATRICS t score change at baseline and 12 weeks<br>UPSA-B score skills at baseline and 12 weeks | No effect on behavioral outcome, completed | NCT02034474 | Ragy R Girgis, New York State Psychiatric Institute, USA | Girgis et al. 2018 |
| Schizophrenia | Tocilizumab | N=8 | 1, Interventional, Open label | 2012-2014 | Change in cognition BACS<br>Primary outcome:<br>Change in cognition BACS at baseline and 8 weeks<br>Secondary outcome: change in total psychotic symptoms at baseline and 8 weeks by PANSS<br>A positive change reflects an increase and a negative changes | Improve-ment in cognitive function | NCT01696929 | Brian J Miller, Augusta University, Georgia, US | Miller et al. 2016 |

*Abbreviations:* BACS = Brief Assessment of Cognition; GFA = global assessment of functioning; IVIG = intravenous immunoglobulins; m = months; N = number; PANSS = Positive and Negative Symptoms Scale in Schizophrenia; UPSA-B score = University of California, San Diego Performance-Based Skills Assessment B score

### Tocilizumab

This study is a randomized, controlled phase 1 clinical trial applying antipsychotic treatment as a recombinant humanized monoclonal interleukin 6 antibody in 20 patients with schizophrenia or schizoaffective disorder administered by intravenous infusion to investigate tocilizumab's safety, tolerability, and efficacy (NCT02874573) (Principal investigator: B.J. Miller, United States). The trial, initiated in 2016, is ongoing with estimated completion in 2023. Its duration is 12 weeks, and tocilizumab is being given adjunct to antipsychotic treatment. These patients also suffer increased peripheral inflammation, evident in elevated hsCRP exceeding 0.5 mg/dl. The anticipated primary outcome is improved cognitive function compared to placebo. Tocilizumab will be applied intravenously. The results of this study are essential because the results of previous studies have been inconsistent and contradictory. An completed randomized, placebo-controlled, double-blind phase 4 trial demonstrated that tocilizumab as add-on treatment for schizophrenic patients presenting residual positive, negative, and cognitive symptoms (NCT02034474). However, this trial's published findings revealed that tocilizumab exerted no effect on schizophrenic behavior (Girgis 2018). In contrast, another finished small-cohort, open-label trial with six patients showed generally improved cognition after tocilizumab application (NCT01696929) (Miller 2016).

### Combination therapy: risperidone with adalimumab

Another interesting target is to block the tumor necrosis factor alpha (TNF-alpha) by means of the adalimumab antibody, as in schizophrenia, dysregulated proinflammatory cytokines (such as TNF-alpha) are suspected (Carnac et al. 2022). A randomized, placebo-controlled trial that took place for over a year from 2020 to 2021 showed that a subcutaneous adalimumab injection of 40 mg by a pen injector was superior in reducing positive and/ or negative symptomatology and in lowering general psychopathology scores (Motamed et al. 2022). However, no inflammatory parameter, ie, C-reactive protein, interleukin-1ß, IL-6, interleukin-8 or TNF-alpha, was lower after adalimumab application, thus putting the mechanism of reducing inflammation in schizophrenia in doubt.

## DISCUSSION

Two trials on schizophrenia involving tocilizumab application (NCT02034474, NCT01696929) yielded inconsistent results. The inconsistent results of these studies (NCT02034474, NCT01696929) could also be due to different primary outcome assessment strategies with different contents (psychotic versus cognitive symptoms) and scales (PANSS or BACS) (Girgis et al. 2018, Miller et al. 2016). The placebo and randomized controlled trial indicated that tocilizumab is not beneficial in behavioral-outcome terms in schizophrenia. Yet as the small open-label trial revealed a benefit in cognitive function after tocilizumab, we are keen to see the results of the ongoing trial with tocilizumab (NCT02874573), whose results are due in 2023. Note that the anti-TNF-alpha antibody adalimumab delivered evidence in a randomized trial of its efficacy in treating negative and positive symptoms in schizophrenia when added to the antipsychotic standard therapy with risperidone, as described above (Motamed et al. 2022). The trials investigating autoantibody-associated psychiatric diseases such as bipolar and psychotic disorder are still running, and their results should show whether antibody therapy is a viable option in autoantibody-associated psychiatric disease, as it is in autoimmune encephalitis, where antibody therapy has effectively in lowered relapse rates (Trewin et al. 2022). However, the first evidence from a case series seem to indicate the impressive usefulness of monoclonal antibodies like rituximab in treating psychiatric autoimmune encephalitis with antibodies (Endres et al. 2022). Methodological differences between studies make comparison difficult, such as different periods of symptom assessment (baseline and 9, 12, or 8 weeks, and 6 or even 18 months, Table 1). Longer study duration seems more appropriate to assess the long-term effects of monoclenal therapy, although this tends to mask short-term effects when assessed at short intervals after baseline (e.g., 8-12 weeks) (Table 1). A few studies can be directly compared thanks to their similar outcome parameters, such as tocilizumab (NCT02874573) and siltuximab (NCT 02796859) in schizophrenia patients (Table 1). The SINAPP2 trial seems to be a very well-designed study (NCT0319481), as it has a long-term observation interval and detailed analysis plan with primary and multiple secondary outcome parameters. In fact, an investigation of ocrelizumab patients with autoantibody-associated schizoaffective and schizophrenic disorder appears to have a similar long-term observation period and very specific secondary outcome parameters (Table 1, NCT03971487).

## CONCLUSIONS

This review demonstrates that a promising therapeutic option entailing monoclonal autoantibodies has emerged for a subgroup of psychotic and schizophrenia spectrum disorders associated either with neural autoantibodies, or presumably immune-mediated. However, the overall efficacy of monoclonal antibody therapy for autoantibody-associated psychosis must still be proven. More research is needed to investigate the immune pathways involved, so that we can learn which specific autoantibody is playing a key role in psychosis or schizophrenia, and then to use this knowledge to develop monoclonal antibody-based treatment strategies.

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### *Contribution of individual authors:*

Niels Hansen wrote the manuscript.

Berend Malchow revised the manuscript for important intellectual content.

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