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Monoclonal antibody precision therapy targeting inflammation for bipolar disorder: a narrative review

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***Abstract*:** Bipolar disorder (BD) is a severe mental disorder with various hypotheses regarding its pathogenesis. This article provides a summary of numerous studies on the variations in inflammatory cytokine levels in patients with BD and the effects of treatment with antipsychotics, mood stabilizers, and antidepressants on these levels. In addition, patients with autoimmune diseases who use anti-inflammatory monoclonal antibodies experience symptoms, such as depression, anxiety, and insomnia. These pieces of evidence suggest a potential association between immune inflammation and BD and offer new possibilities for therapy. Building upon this relationship, the authors propose an innovative approach for treating BD through individualized and precise therapy using anti-inflammatory monoclonal antibody drugs. To support this proposal, the authors compile information on pharmacological effects and relevant studies, including trials of various anti-inflammatory therapeutic monoclonal antibody drugs (e.g. infliximab, tocilizumab, and canakinumab) for the potential treatment of BD and its associated side effects in psychiatry. The authors categorize these anti-inflammatory monoclonal antibody drugs into levels I–IV through a comprehensive analysis of their advantages and disadvantages. Their potential is examined, and the need for further exploration of their pharmaceutical effects is established.

Keywords: bipolar disorder, immune system, inflammatory cytokines, monoclonal antibody, precision therapy

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Introduction

Bipolar disorder (BD) is a chronic, episodic disorder characterized by recurrent alternating episodes of mania and depression. It can lead to psychotic symptoms, such as hallucinations and delusions. The onset of the disorder typically occurs at an early age. Research has shown that the suicide rate among patients with BD is more than 20 times higher than that among the general population.[1] The exact cause of BD is still unknown but various studies have linked it to genetic, biorhythmic, biochemical, and environmental factors. Multiple hypotheses exist regarding the development of BD, which involves various pathological mechanisms, including neuronal–glial plasticity, monoamine signaling, inflammatory homeostasis, cellular metabolic pathways, and mitochondrial dysfunction.[2]

Recent studies have suggested that BD is associated with immune dysfunction. Changes in immune markers, particularly an increase in pro-inflammatory cytokines, have been observed in the nervous system of individuals with BD.[3] In 1981, Horrobin and Lieb[4] hypothesized that immune dysfunction may be a critical factor in the disease progression of BD and that relapse or remission of BD is driven by the immune system. Since then, many researchers have begun to investigate the relationship between BD and immune dysfunction and focused on inflammatory cytokines. Current studies indicate that inflammatory cytokines in the immune system, such as interleukin (IL), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), play a crucial role in the pathogenesis of BD.[5,6] Patients with BD have a high prevalence of multisystem

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inflammatory diseases, which led Leboyer *et al.*[7] to conclude that BD is a multisystem inflammatory disease that affects many systems, including mood, cognition, cardiovascular health, metabolism, and sleep. The immune inflammatory hypothesis opens up new possibilities for treating BD, including the discovery of potential drugs and the design of targeted and effective therapeutic regimens.[8] This review provides an overview of the association between BD and inflammatory cytokines and the latest advancements in monoclonal antibody therapies that target BD-related inflammatory cytokines. Accordingly, we propose precision therapies for BD with monoclonal antibody drugs based on the immune inflammation hypothesis. Studies were included based on the population, intervention, comparison, outcomes, and study design criteria, as shown in the Supplemental Table.

Methods

We performed a forward literature search in ScienceDirect, Springer, PubMed, and China National Knowledge Infrastructure and a backward literature search in the reference lists of retrieved articles published until 31 August 2023. The search strategy included the following intentionally broad terms: (inflammatory factors OR cytokines OR pro-inflammatory molecules OR inflammatory mediators) OR (monoclonal antibodies OR monoclonal antibody therapy OR monoclonal antibody drugs OR monoclonal antibody treatment) AND (bipolar disorder OR manic depression OR manic-depressive illness OR bipolar affective disorder). Duplicate references were excluded. The remaining articles were screened by their titles and abstracts, and the full texts were further inspected to determine if they matched the topic of this narrative review. Papers had to include psychiatry and inflammatory trait research or should have established a link or correlation between psychiatry and inflammatory or immune-related biomarkers. We included all study designs apart from social news reports and conference abstracts. Given the multifaceted nature of the research question, the inclusion criteria were nonsystematic, and papers were included based on the query results or the references cited in the selected articles.[9]

Relationship between BD and different inflammatory cytokines

Cytokines, which are proteins or glycoproteins secreted by immune cells in response to noxious stimuli, play a crucial role in mediating the interaction between immune and neuroendocrine systems.[10] Inflammatory mediator theory, which was proposed in 1988, links cytokines to the inflammatory reaction. This theory suggests that a large number of cytokines released by immune cells form a complex inflammatory cascade that ultimately leads to an inflammatory reaction. Although many cytokines are involved in the inflammatory process, they have different roles. Based on the roles of cytokines in the inflammatory process, they can be categorized as proinflammatory and anti-inflammatory. Proinflammatory cytokines include IL-1β, TNF-α, IL-6, IL-8, IFN-γ, IL-17, IL-18, and IL-33, and anti-inflammatory cytokines include IL-4, IL-10, and IL-1 receptor antagonist (IL-1RA). When the levels of these cytokines are normal, they help restore damage and resist pathogens, but when their levels are abnormal, they may contribute to the development of diseases and the onset of pathological changes. For example, oversecretion of proinflammatory cytokines promotes tryptophan depletion and serotonin catabolism, activates aberrant neuroimmune mechanisms involved in specific neural circuits related to mood regulation, and leads to the dysfunction of noradrenergic and 5-hydroxytryptophanergic neurotransmission in the brain, which is mostly reflected in patients with depressive symptoms.[11] Moreover, in the presence of high inflammation, microglia are abnormally activated, and abnormal pathologic neural protrusion pruning and impaired neuroplasticity may occur and eventually induce the onset of BD.[12,13]

Systematic studies have been conducted on the applications of Mendelian randomization and have suggested a causal relationship among a proinflammatory state, elevated C-reactive protein (CRP), and the risk of developing BD.[14,15] The hypothalamic–pituitary–adrenal (HPA) axis, for example, plays an important role in the connection between inflammation and BD.[16,17] Proinflammatory cytokines (TNF-α, IL-6, etc.) considerably upregulate HPA activity, thereby increasing systemic cortisol levels.[18] In inflammation, chronic hypercortisolemia downregulates glucocorticoid receptor synthesis, translocation, and sensitivity in the pituitary and hypothalamus, effectively inhibiting the negative feedback loop of the HPA axis.[19] The loss of the negative feedback loop ultimately contributes to BD symptoms, such as mood disorders and cognitive impairment.[17] Furthermore, inflammation may

affect brain structures and lead to a dysregulated stress response, potentially causing emotion dysregulation disorders.[9] For instance, a systematic review has shown that immune markers are linked to functional and structural magnetic resonance imaging alterations in BD, particularly in brain areas involved in affective and somatomotor processing.[20] A study that reviewed diffusion tensor imaging found immune system activation, especially within peripheral proinflammatory cytokines (IL-1β, TNF-α, IL-8, and IFN-γ) and CRP, which correlate with white matter microstructural impairments during depressive episodes of BD.[21] Thus, proinflammatory cytokines are relevant to BD because they may affect brain networks and reveal the pathophysiological mechanisms of BD.

This review aims to explore the relationship between cytokines and BD, to provide a theoretical foundation for the potential use of monoclonal antibodies in the treatment of BD. Table 1 summarizes the results of recent studies on inflammatory cytokine levels in patients with BD to help evaluate the correlation between inflammatory reaction and BD. Overall, most studies showed that the expression levels of proinflammatory cytokines, such as IL-1β, IL-6, TNF-α, IL-8, IL-17, IL-18, and IFN-γ, and anti-inflammatory cytokines IL-10 and IL-1RA are elevated in patients with BD.[5,22–44] Inconsistent results on IL-4 level have been obtained for patients with BD, whereas consistent results have been derived from studies on IL-1β, IL-6, and TNF-α.[5,6,24,25,27,32–41,45] After BD medication, the expression of proinflammatory cytokines IL-1β, IL-6, and TNF-α decreases, whereas the expression of anti-inflammatory cytokines IL-4 and IL-10 increases.[46–56] The relationship between BD symptomatic improvement after drug treatment and the variation trends of pro/anti-inflammatory cytokine levels suggests a connection between immune inflammation and BD. Although abnormal changes in the levels of inflammatory cytokines are closely related to BD, considerable individual differences still exist. For instance, some studies have reported that there are no significant abnormal changes in inflammatory cytokines among some patients with BD, and studies have suggested that inflammatory cytokines in BD patients may be related to obesity rather than their symptoms.[34,39,41,44,57] In other words, BD is not inevitability associated with individuals and their inflammatory cytokines. Bishop *et al.* showed that inflammatory and immune processes are dysregulated in schizophrenia and related psychoses. However, current research is going beyond the univariate analysis of a single inflammatory marker and attempting to identify the relationship between immune inflammation and mental disorders by considering discrete differences in multiple inflammatory markers.[58] In this case, patients need to be subdivided into subgroups in accordance with the changes in each inflammatory cytokine, and precise individualized treatment must be applied based on the patients' specific inflammatory cytokines.

BD and proinflammatory cytokines

IL-6. The soluble IL-6 receptor (sIL-6R), a soluble receptor for IL-6, enhances the information transduction of IL-6 by binding IL-6. Therefore, sIL-6R levels can reflect IL-6 levels to some extent.[26] Several studies have shown that sIL-6R levels are elevated in patients with BD; they indirectly reveal increased IL-6 levels.[24,27] IL-6 exerts

Table 1. Summary of findings related to inflammatory cytokines in patients with BD.

Inflammatory cytokines	Manic episode	Depressive episode	Mixed seizure	Remission period	Unclassified
IL-1β	Elevated[6,32]	Elevated[6,32]	Elevated[32]	–	Elevated[15,32,33] No change[34]
IL-1RA	Elevated[33]	Elevated[33]	–	–	Elevated[5,31] No change[27]
IL-4	Elevated[32] No change[41]	Elevated[32]	Elevated[32]	No change[41]	Decreased[45] Elevated[27]

(Continued)

Table 1. (Continued)

Inflammatory cytokines	Manic episode	Depressive episode	Mixed seizure	Remission period	Unclassified
IL-6	Elevated[35,59]	Elevated[37–37]	Elevated[35,38]	Elevated[38]	Elevated[5,24,25,34]
sIL-6R	–	–	–	No change[39]	Elevated[5,24,25]
IL-8	Elevated[40]	Elevated[37,40]	–	–	Elevated[40] No change[5,27]
IL-10	Elevated[29]	–	–	Elevated[30]	No change[27]
IL-17	Elevated[60]	–	–	Decreased[61]	Elevated[62]
IL-18	Elevated[59]	Elevated[35]	–	–	–
IL-33	Elevated[63]	–	–	–	–
TNF-α	Elevated[34,35,40]	Elevated[34–36,40]	Elevated[35]	Elevated[30] No change[34]	Elevated[5,24,25,27]
sTNFR1	Elevated[28,42] No change[44]	Elevated[42,43] No change[44]	–	Elevated[28,39]	Elevated[25,27]
sTNFR2	Elevated[28]	Elevated[43]	–	Elevated[28]	Elevated[24] No change[27,64]
IFN-γ	–	–	–	–	Elevated[24] No change[27]

'–' indicates that no relevant study was found. This table summarizes the changes in various inflammatory cytokines based on a large number of papers and other academic materials. The changes in these cytokines are divided into different episode periods to guide precise treatment.
IFN-γ, interferon-γ; IL-1β, interleukin-1β; IL-1RA, interleukin-1 receptor antagonist; sIL-6R, soluble IL-6 receptor; sTNFR1, soluble necrosis factor receptor 1; sTNFR2, soluble necrosis factor receptor 2; TNF-α, tumor necrosis factor-α.

a neuroprotective effect at low concentrations and promotes neurodegenerative processes at high concentrations.[65] IL-6 is implicated in neurogenesis and synaptic plasticity regulation and mediates hippocampal-dependent learning and memory formation, so it plays specific functions in cognitive processes.[66] The inflammatory microenvironment in the brain induced by IL-6 may progressively damage the hippocampus and other neural circuits involved in cognitive function.[67] High levels of IL-6 are associated with cognitive impairment due to neurological damage and further alter the patient's cognitive patterns, possibly contributing to mood disorders, such as BD.

IL-1β. The proinflammatory cytokine IL-1β is primarily secreted by monocytes and macrophages during the formation of antigen–antibody complexes. As a crucial member of the IL-1 family, IL-1β can impair spatial learning and contextual memory in the hippocampus by inhibiting its long-term potentiation effects.[64] IL-1β can contribute to the decline in cognitive function caused by inflammatory reactions by affecting neurogenesis in the hippocampus.[68] Viviani *et al.* demonstrated that IL-1β increases *N*-methyl-D-aspartate receptors (NMDAR), leading to an uncontrolled rise in calcium inward flow through NMDAR channels. This condition ultimately results in excitotoxicity and impaired neuroplasticity.[69]

TNF-α. The proinflammatory cytokine TNF-α can also inhibit the long-term enhancement of the hippocampus and impair its spatial learning and contextual memory.[70] In addition to its involvement in the body's inflammatory reaction and immune response, TNF-α promotes the production of other proinflammatory cytokines that can lead to tissue damage. TNF-α is toxic to neuronal cells because it initiates apoptotic mechanisms through the activation of apoptotic proteases, which result in demyelinating changes in neuronal cells, by participating in neuronal apoptosis, which reduces frontal lobe volume and activity.[71–73] Soluble necrosis factor receptor 1 (sTNFR1) and soluble necrosis factor receptor 2

(sTNFR2), as soluble receptors for TNF-α, can transduce their signals into intracellular signals and may reflect the activity of TNF-α to some extent.[28] The levels of sTNFR1 and sTNFR2 are considerably elevated in patients with BD and correlated with the duration of BD, further suggesting that inflammatory mechanisms may be involved in the pathophysiology of BD.[5,24,28]

BD and anti-inflammatory cytokines

IL-4. The anti-inflammatory cytokine IL-4, produced by a subpopulation of Th2 cells and mast cells among others, has multiple effects. However, its biological mechanisms of action are complex and modulate various pathophysiologic processes. A study revealed that IL-4 levels in patients with BD are negatively correlated with the Hamilton Depression Scale and the Bipolar Rating Scale.[45] In addition, the IL-4 levels of patients with BD are lower than those of normal individuals, implying that IL-4 plays a regulatory role in maintaining cellular and humoral immune homeostasis in patients.[45] Another study reported elevated levels of IL-4 in patients with BD; these elevated levels are believed to increase the activation of the downstream inflammatory signaling pathway nuclear factor-κB (NF-κB) and enhance the monocyte infiltration of neurons.[32]

IL-10. IL-10 is a cytokine with anti-inflammatory properties. It is derived from multiple cells and has multiple functions. It can suppress nonspecific and specific immunity by inhibiting the function of immune cells, thereby exerting anti-inflammatory properties.[74] Several studies showed that patients with type I BD have considerably elevated levels of serum IL-10, which suggests that the body may produce IL-10 as a compensatory mechanism to combat inflammation.[29,30]

Interleukin-1 receptor antagonist. The IL-1RA, an antagonist of the IL-1 receptor, is typically found in peripheral blood in a soluble form. Its role is to counteract the proinflammatory effects of IL-1 by binding to the IL-1 receptor, exerting anti-inflammatory effects. Consequently, it is also recognized as an anti-inflammatory cytokine. A meta-analysis demonstrated that patients with BD have high levels of IL-1RA.[5] Another study conducted on elderly patients with euthymic BD revealed elevated serum IL-1RA levels and posited that IL-1RA is associated with cognitive function deterioration.[31]

Changes in inflammatory cytokine levels after BD treatment

In existing BD treatments, the use of antipsychotics, mood stabilizers, and antidepressants is effective in ameliorating depressive and manic symptoms and attenuating inflammatory reactions in patients with BD. Among the common combinations of antipsychotics and mood stabilizers, the combination of ziprasidone and valproate has been shown to decrease the levels of IL-1β and TNF-α while increasing the levels of IL-4.[46,47] The combination of quetiapine and valproate increases the levels of IL-4 and IL-10 while decreasing the levels of TNF-α and IL-1β.[48,49] Another combination, quetiapine and lithium carbonate, decreases TNF-α, IL-1β, and IL-6 while increasing IL-4 and IL-10.[50–52] The combination of lithium carbonate and valproate decreases IL-6 and TNF-α levels while increasing IL-10.[53,54] In addition, the combination of aripiprazole and olanzapine can effectively decrease IL-1β and TNF-α levels in patients with BD with manic episodes.[55] The combination of citalopram and sodium valproate alleviates clinical symptoms in patients with depressive episodes of recurrent BD, which is potentially associated with decreased levels of IL-1β and IL-6.[56] Different therapeutic agents for BD improve patients' depressive and manic symptoms through various pharmacologic effects. Moreover, existing literature suggests that all these agents affect the levels of inflammatory cytokines. This strong evidence implies an intrinsic link between BD and immune inflammation.

Inflammatory cytokine-based anti-inflammatory drug therapy for BD

Nonsteroidal anti-inflammatory drugs (NSAIDs), *N*-acetylcysteine, infliximab, pioglitazone, and minocycline have been extensively studied in clinical trials to validate their effectiveness in treating BD.[75] These trials have demonstrated the efficacy of anti-inflammatory treatments for BD to a certain extent but have highlighted certain issues with existing drugs. For instance, NSAIDs and *N*-acetylcysteine exert adverse gastrointestinal effects or give rise to cardiovascular disease risks according to clinical trials.[76,77] Clinical trials on pioglitazone and minocycline were limited to certain high-baseline subgroups, short durations, small sample sizes, or case studies that confirmed some degree of effectiveness of anti-inflammatory drugs in depressive or manic symptoms but large sample sizes and long-term studies have failed to find notable differences in the treatment of depressive and manic symptoms.[78–81]

In summary, current anti-inflammatory drugs clinically used for the treatment of BD have the following problems: broad drug targets, insufficient drug targeting, and lack of precision medication. These problems lead to limited therapeutic efficacy and increased adverse effects. Considering the relationship between inflammatory cytokines and BD, some scholars hypothesized that tocilizumab, a monoclonal antibody IL-6 antagonist, can be a potential treatment option for BD.[75,82] Therefore, we propose to target BD-related inflammatory cytokines and advance the research on monoclonal antibody anti-inflammatory drug therapy for BD based on these cytokines.

Monoclonal antibodies are antibodies that are cloned from a single B cell. They exhibit high homogeneity and can target a specific antigenic epitope with high specificity. Furthermore, they have a clear mechanism of action and few toxic side effects. Currently, monoclonal antibodies are widely used in targeted therapy for autoimmune diseases, tumors, and other diseases.[83] In this review of inflammatory cytokines as therapeutic targets, we introduce monoclonal antibodies against the cytokines associated with BD and investigate their potential efficacy, side effects, and risk of adverse reactions in the treatment of BD. The relevant findings are summarized in Table 2.

Table 2. Potential monoclonal antibody drugs for BD anti-inflammatory therapy.

Monoclonal antibody drugs	Pharmacological effect	Advantages	Disadvantages	Test recommendation level[a]
Infliximab[84–89]	Binds sTNF-α and membrane-type TNF-α (mTNF-α) and inhibits their binding to TNF receptors, thereby blocking the inflammatory signaling induced by TNF-α.	Clinical application is long enough, and it improves depressive symptoms mainly in patients with BD with elevated TNF-α.	Frequent depression and insomnia are common adverse reactions.	I
Tocilizumab[82,90–93]	Blocks the interaction of IL-6 with the IL-6 receptor (sIL-6R) to inhibit the inflammatory reaction.	It has a medium–long clinical application time. It improves the depression and anxiety symptoms of patients with rheumatoid arthritis, the manic symptoms and cognitive impairment of relapsing polychondritis patients, and the overall cognitive function of patients with schizophrenia. No psychiatric symptoms have been observed.	No studies have applied it to patients with BD.	I
Adalimumab[94,95]	Specifically binds to sTNF-α and blocks its interaction with the TNF receptor, thereby effectively blocking the inflammatory effects of TNF-α.	Clinical application is long enough, and it improves depressive symptoms in patients with major depression.	No studies have applied it to patients with BD, and frequent mood changes, anxiety, and insomnia are common.	II
Canakinumab[96,97]	Specifically binds to IL-1β and blocks its binding to the IL-1 receptor to neutralize its activity.	Amelioration of positive symptoms in schizophrenic patients with elevated IL-1β and no adverse psychiatric symptoms have been observed.	Clinical use is short.	II

(Continued)

Table 2. (Continued)

Monoclonal antibody drugs	Pharmacological effect	Advantages	Disadvantages	Test recommendation level[a]
Siltuximab[98,99]	Binds to human IL-6 with high affinity and specificity, thereby neutralizing it.	Improvement of depression in patients with multicenter Castleman's disease and lack of adverse psychiatric effects.	Clinical application is relatively short, and no studies have applied it to psychiatric patients.	III
Sarilumab[100–102]	Binds to IL-6Rα with high affinity and inhibits IL-6/IL-6Rα complex formation.	Improvement of depressive symptoms in patients with rheumatoid arthritis.	Its clinical application time is relatively short, it has not been applied to psychiatric patients, and frequent insomnia and hypothyroidism are common.	III
Certolizumab pegol[90,103,104]	Binds sTNF-α and mTNF-α and blocks TNF-α-mediated inflammatory signaling pathways.	May improve depressive symptoms in patients with psoriasis, and the frequency of anxiety and mood disorders is occasional.	Relatively short time in clinical use and no studies have been conducted on psychiatric patients.	III
Golimumab[90,105]	Inhibits inflammation by targeting and neutralizing TNF-α.	Advanced preparation technology.	Its clinical application time is short, it has not been applied to psychiatric patients, and frequent depression and insomnia are common.	IV
Satralizumab[106,107]	Binds to IL-6Rs specifically.	Potential to treat depressive symptoms.	Its clinical application is short, no study has applied it to psychiatric patients, and frequent depression is common.	IV

This table compares the advantages and disadvantages of various anti-inflammatory monoclonal antibodies. After comparing and weighing the advantages and disadvantages, we set test recommendation levels based on trial priority. We recommend high trial priority for drugs with obvious advantages and few disadvantages.
[a]Recommendations to prioritize drug trials for BD treatment are given levels. I recommends very high priority, II recommends priority, III recommends low priority, and IV does not recommend priority at all.
BD, bipolar disorder; IFN-γ, interferon-γ; IL-1β, interleukin-1β; IL-1RA, IL-1 receptor antagonist; mTNF-α, membrane tumor necrosis factor-α; sIL-6R, soluble IL-6 receptor; sTNF-α, soluble TNF-α.

Monoclonal antibodies against TNF-α

Anti-TNF-α drugs, such as monoclonal antibodies, exert anti-inflammatory effects through multiple pathways. These pathways include neutralization of soluble and membrane-bound TNF-α, inhibition of T-cell activation and pro-inflammatory cytokine release, induction of antibody- or complement-dependent cytotoxicity, apoptosis of T cells and macrophages, enhancement of the intestinal barrier function, and induction of regulatory T-cell differentiation.[108] Four anti-TNF-α monoclonal antibodies have been approved by the Food and Drug Administration (FDA). They are infliximab, adalimumab, certolizumab pegol, and golimumab; they are commonly used to treat diseases, including rheumatoid arthritis, Crohn's disease, and psoriasis.[90]

Infliximab. Infliximab, the first anti-TNF-α monoclonal antibody to receive marketing approval, is a human–mouse chimeric antibody consisting of a human Immunoglobulin G1 (IgG1) crystallizable Fragment (Fc) region and a mouse variable Fragment (Fv) region. The antibody, with a murine variable region and a human constant region, binds soluble TNF-α (sTNF-α) and membrane TNF-α (mTNF-α), thereby blocking their binding to TNFR and inhibiting inflammatory signaling triggered by TNF-α.[84,85] Recent anti-inflammatory studies have shown that infliximab is effective in patients with BD.[86]

In 2013, Raison *et al.*[87] conducted a double-blind, randomized clinical trial (RCT) that demonstrated infliximab's potential to improve depressive symptoms in certain patients with BD with high-baseline inflammatory biomarkers. Another double-blind, controlled RCT also revealed that infliximab has high antidepressant efficacy in patients with BD with elevated plasma expression of inflammatory markers, such as TNF-α.[88] The two studies suggest that infliximab can be effective for patients with BD with elevated levels of TNF-α and indicate that classification using inflammatory biomarkers may help in implementing precise individualized adjunctive therapy for BD patients with varying levels of inflammation.

In 2019, McIntyre *et al.*[89] conducted the first study that evaluated the inflammatory evidence on the use of infliximab for adult patients with BD. However, the subjects included in this study needed to meet only one of the various inflammatory characteristics and were not further categorized into subgroups based on the specific inflammatory characteristics. This lack of precise subgrouping may partly explain why the study failed to confirm that adjunctive use of infliximab considerably improves depressive symptoms in patients with BD. However, a *post hoc* analysis of the study showed that infliximab exhibits high, long-lasting antidepressant efficacy in patients with a history of childhood abuse, particularly physical abuse. This finding further suggests that by precisely subgrouping patients with BD, clinical researchers may be able to identify individuals who can benefit from infliximab.

Overall, infliximab is likely to be an adjuvant drug for individualized precision therapy for the treatment of BD but its efficacy has not been clarified because of the lack of precise RCTs with large sample sizes.

Adalimumab. Adalimumab is the world's first fully human anti-TNF-α monoclonal antibody to be approved for marketing, and its properties include good efficacy and low immunogenicity. Adalimumab's mechanism of action is similar to that of infliximab, which specifically binds to sTNF-α and blocks its interaction with TNFR, thus effectively blocking the inflammatory effects of TNF-α.[94] Recently, Abbasian *et al.*[95] conducted a 6-week double-blind RCT, in which 36 patients with major depression were equally assigned to either the adalimumab or placebo group. The results indicated that adjunctive therapy with adalimumab considerably improves patients' depressive symptoms. However, no clinical studies have examined the direct use of adalimumab for patients with BD.

Certolizumab pegol. Certolizumab pegol is a humanized Fab-engineered antibody fragment with two molecules of polyethylene glycol attached to extend its plasma half-life. It binds to sTNF-α and mTNF-α, effectively blocking the TNF-α-mediated inflammatory signaling pathway.[90] A recent study found that the use of certolizumab pegol improves depressive symptoms in patients with psoriasis.[103] A meta-analysis demonstrated high comorbidity between psoriasis and BD.[104] Given that psoriasis and BD roughly share immune inflammatory mechanisms, perhaps these results could indicate the potential efficacy of certolizumab pegol in the treatment of BD. However, clinical studies on the application of certolizumab pegol to patients with BD are still lacking. Furthermore, because of the high comorbidity probability of psoriasis and BD,

certolizumab pegol may offer a new approach to cure psoriasis and BD simultaneously.

Golimumab. Golimumab is a fully human anti-TNF-α monoclonal antibody produced by transducing mice with the human IgG motif. The technology used to prepare it is more advanced than the technology for preparing other monoclonal antibodies.[90] Golimumab inhibits inflammation primarily by targeting and neutralizing TNF-α. Although little clinical experience in golimumab is available, substantial evidence supports its effectiveness and tolerability in patients with rheumatoid arthritis.[105] However, no studies have demonstrated that golimumab can treat symptoms of depression or mania associated with BD.

Monoclonal antibodies against IL-6

Currently, two types of monoclonal antibodies are centered around IL-6 anti-inflammatory therapies: one targets IL-6, and the other targets IL-6R. These monoclonal antibodies can inhibit the inflammation-mediated effects of IL-6 by specifically binding to and blocking its action. To date, four monoclonal antibodies against IL-6 have been approved and are available on the market: tocilizumab, siltuximab, satralizumab, and sarilumab.

Tocilizumab. Tocilizumab, a humanized anti-IL-6R monoclonal antibody, can inhibit the inflammatory reaction by blocking the interaction between IL-6 and the IL-6 receptor (sIL-6R). It is mainly used in the treatment of rheumatoid arthritis and cytokine release syndrome.[90] Clinical trials conducted by Tiosano *et al.*[91] revealed that tocilizumab improves depression and anxiety symptoms in patients with rheumatoid arthritis. Liu *et al.*[92] found that tocilizumab usage improves manic symptoms and cognitive deficits in patients with relapsing polychondritis. In addition, based on clinical trial results showing that tocilizumab can improve the overall cognitive function of patients with schizophrenia, Miller *et al.*[93] posited that tocilizumab can be advanced as a personalized therapeutic agent for schizophrenia after conducting large-sample-size longitudinal studies on individuals with baseline inflammation. Considering the upregulation of IL-6 expression levels in patients with BD, some scholars suggested that tocilizumab may be a potential therapeutic option for BD.[82] Meanwhile, IL-6 is associated with rheumatoid arthritis, relapsing polychondritis, schizophrenia, and BD. Previous clinical trials and case reports have indicated that tocilizumab can effectively alleviate symptoms, such as depression, mania, anxiety, and cognitive impairment. Consequently, tocilizumab holds promise as a personalized medication with the potential to be developed for the treatment of cognitive function impairment, mania, and mood symptoms in patients with BD.

Siltuximab. Siltuximab is an anti-IL-6 human–mouse chimeric monoclonal antibody that can bind to IL-6 with high affinity and specificity. By neutralizing IL-6, it reduces the level of unbound IL-6 and prevents it from binding to the receptor, thereby blocking its downstream signaling pathway. It is usually used to treat HIV and HHV-8-negative multicenter Castleman's disease.[98] Double-blind RCT results indicate that siltuximab is considerably superior to placebos in improving depressed mood, fatigue, and anhedonia in patients with multicenter Castleman's disease.[99] However, no clinical trials have been conducted to evaluate the efficacy of siltuximab in the treatment of patients with BD.

Satralizumab. Satralizumab, a novel recombinant humanized IgG2 monoclonal antibody, is primarily used to treat optic chiropractic inflammation; it inhibits the onset of the neuroinflammatory reaction by specifically binding to IL-6R.[106] Some scholars reported that IL-6R is a promising target for the treatment of depressive symptoms and concluded that satralizumab may have great potential for treating depression.[107] However, further studies are needed to validate this claim.

Sarilumab. Sarilumab is the first fully human monoclonal IgG antibody that directly targets the alpha subunit of the IL-6 receptor complex (IL-6Rα). It binds to IL-6Rα with high affinity, inhibits the formation of the IL-6/IL-6Rα complex, and interrupts the cytokine-mediated inflammatory signaling cascade for the treatment of rheumatoid arthritis.[109] A clinical trial demonstrated a reduction in the incidence of depressive symptoms and an improvement in fatigue symptoms among patients using sarilumab.[100,101] Moreover, an RCT revealed that sarilumab leads to greater improvements in health-related quality of life scores compared with adalimumab in patients with rheumatoid arthritis with high baseline IL-6 levels.[102] However, studies on the effectiveness of sarilumab in treating BD are lacking.

Monoclonal antibodies against IL-1β

IL-1β plays an essential role in the inflammatory reaction. The use of an anti-IL-1β monoclonal antibody can effectively reduce the biological activity of IL-1β and inhibit the inflammatory reaction. To date, the only globally approved and marketed IL-1β monoclonal antibody is canakinumab.

Canakinumab. Canakinumab is a human IgGκ monoclonal antibody that targets IL-1β. By specifically binding to IL-1β and blocking its interaction with the IL-1 receptor, canakinumab neutralizes its activity and inhibits inflammation. Canakinumab is commonly used in the treatment of cryopyrin-associated periodic syndromes, juvenile arthritis, and other diseases.[96] In a double-blind RCT conducted by Thomas *et al.*,[97] patients with schizophrenia or schizotypal affective disorder were included when they had elevated levels of peripheral markers of inflammation, such as IL-1β, at baseline. The results of the trial showed that canakinumab suppresses the inflammatory reaction and considerably improves positive symptoms in such patients. These findings imply that canakinumab has a relatively strong effect on inflammation suppression and positive symptom improvement. Hence, we speculate that canakinumab may be effective for the individualized treatment of mental disorders.

Psychiatric adverse reactions of monoclonal antibodies

In discussions of the treatment of BD with monoclonal antibodies, the therapeutic advantages and limitations in terms of the psychiatric side effects of these antibodies must be acknowledged.[110,111] A notable advantage is the potential to improve depressive symptoms, as indicated by studies on natalizumab.[112] One of the limitations is that natalizumab and other monoclonal antibodies can induce suicidal thoughts and behavior by triggering the secretion of proinflammatory cytokines.[113] Compared with other monoclonal antibodies, those that target the immune system are more likely to cause depression and suicide, which are associated with imbalances in inflammatory cytokines.[110] The authors posit that monoclonal antibodies targeting the immune system can regulate levels of inflammatory cytokines and can have positive or negative effects.

In other words, because monoclonal antibodies targeting the immune system can effectively affect brain inflammation and cause changes in affective and cognitive systems, such as depression and suicide, after natalizumab use, the treatment of BD with anti-inflammatory monoclonal antibodies exerts opposite effects. Adverse psychiatric reactions can be avoided by closely monitoring these effects and making informed decisions, and BD could even be treated. However, if inflammatory cytokine levels are not carefully monitored during treatment, an increase in proinflammatory cytokines may lead to adverse psychiatric reactions. In conclusion, no contradiction exists between adverse psychiatric reactions and BD treatment potential. Misuse of these antibodies may lead to inflammation in the central nervous system, which may result in depression and suicide. However, when these antibodies are used correctly to suppress inflammation, they could be employed to treat BD. The authors acknowledge the limitation, namely, adverse psychiatric reaction, of monoclonal antibodies and regard it as a problem to be solved in the future.

Conclusion

This review summarizes a large number of existing reports on inflammatory cytokines that support the immune inflammation hypothesis on the pathogenesis of BD, including TNF-α, IL-6, and IL-1β. Based on the sufficient literature evidence from the BD efficacy trials of anti-inflammatory drugs, this review posits that the effectiveness of anti-inflammatory therapy is closely related to the targeting of drugs and the accuracy of personalized medication. Hence, we review three monoclonal antibodies, namely, infliximab, tocilizumab, and canakinumab, that target the three above-mentioned inflammatory cytokines. We recommend their use for the precise treatment of cognitive impairment, depression, and mania in BD because of their high targeting ability and few side effects.

Prospect

As modern medicine enters the era of precision medicine, the field of drug research and development and clinical medication is gradually shifting toward individualized precision targeted therapy. Individualized precision therapy has become the development direction of this field and the most

effective among different clinical treatments. Given the complex nature of BD's pathogenesis, which involves various etiological factors and considerable individual variations among patients, precision therapy is necessary. The use of individualized monoclonal antibody-assisted therapy that is customized based on the specific levels of certain inflammatory cytokines shows promise in improving the precision, effectiveness, and safety of BD treatment. This approach offers a valuable strategy for rational drug utilization. However, many problems still need to be verified and solved in the process of realizing this goal (section 'Limitations' provides the details). Extensive clinical trials and studies are required to validate the actual effectiveness of monoclonal antibodies in the precise treatment of BD. Notably, adverse reactions to monoclonal antibody drugs are still common, and these include adverse psychosomatic reactions, such as depression, anxiety, and even mania. Therefore, the issue of adverse reactions needs to be thoroughly considered and addressed when monoclonal antibody drugs are actually applied to BD patients. Nevertheless, we believe that in the future, individualized adjuvant use of monoclonal antibodies will broaden the application of precision immunotherapy in BD and will offer patients targeted, efficient, safe treatment options.

Limitations

The review has several limitations that need attention. First, this review has a narrative nature, so it is exposed to the risk of bias and may not comprehensively cover all existing literature due to the lack of systematic methods. Second, conclusive evidence, such as sufficient RCTs and meta-analyses, on the topic is lacking. Third, the underlying pathophysiological mechanisms of specific cytokines in BD remain unclear. Although some studies suggested the potential therapeutic effects of using monoclonal antibodies, they did not consider the issue of population heterogeneity, such as bipolar I and II subtypes. Fourth, the authors focused on the potential therapeutic effects of BD based on similarities in symptoms and did not consider the subjects, sample sizes, and durations of the included studies. Last, some studies on monoclonal antibodies found that these antibodies have no efficacy for patients with BD and may even have side effects, especially when patients are not subdivided into certain biotype subgroups.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Shijin Wu: Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

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Reference

1. Pompili M, Rihmer Z, Innamorati M, *et al.* Assessment and treatment of suicide risk in bipolar disorders. *Expert Rev Neurother* 2009; 9: 109–136.
2. McIntyre RS, Berk M, Brietzke E, *et al.* Bipolar disorders. *Lancet* 2020; 396: 1841–1856.
3. Barbosa IG, Machado-Vieira R, Soares JC, *et al.* The immunology of bipolar disorder. *Neuroimmunomodulation* 2014; 21: 117–122.
4. Horrobin DF and Lieb J. A biochemical basis for the actions of lithium on behaviour and on immunity: relapsing and remitting disorders of inflammation and immunity such as multiple sclerosis or recurrent herpes as manic-depression of the immune system. *Med Hypotheses* 1981; 7: 891–905.
5. Modabbernia A, Taslimi S, Brietzke E, *et al.* Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biol Psychiatry* 2013; 74: 15–25.
6. Söderlund J, Olsson S, Samuelsson M, *et al.* Elevation of cerebrospinal fluid interleukin-1β in bipolar disorder. *J Psychiatry Neurosci* 2011; 36: 114–118.
7. Leboyer M, Soreca I, Scott J, *et al.* Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord* 2012; 141: 1–10.
8. Haozhe L. The relationship between inflammatory cytokines and therapeutic effect of bipolar disorder with acute manic episode. *PhD Dissertation, Shanghai Jiao Tong University School of Medicine, China*, 2015.
9. Saccaro LF, Schilliger Z, Dayer A, *et al.* Inflammation, anxiety, and stress in bipolar disorder and borderline personality disorder: A narrative review. *Neurosci Biobehav Rev* 2021; 127: 184–192.
10. Wu H, Yi-ru F. Research progress of immunological mechanisms of bipolar disorder. J Shanghai Jiaotong Univ (Med Sci) 2011; 31(11): 1540.
11. Leonard BE. The immune system, depression and the action of antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; 25: 767–780.
12. Li Z and Huaqing M. Immunological research development of the bipolar disorder. *Sichuan Mental Health* 2017; 30: 85–89.
13. Kokkosis AG and Tsirka SE. Neuroimmune mechanisms and sex/gender-dependent effects in the pathophysiology of mental disorders. *J Pharmacol Exp Ther* 2020; 375: 175–192.
14. Saccaro LF, Gasparini S and Rutigliano G. Applications of mendelian randomization in psychiatry: a comprehensive systematic review. *Psychiatr Genet* 2022; 32: 199–213.
15. Wium-Andersen MK, Ørsted DD and Nordestgaard BG. Elevated C-reactive protein(CRP) and late-onset bipolar disorder in 78 809 individuals from the general population. *Br J Psychiatry* 2016; 208: 138–145.
16. Silverman MN and Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann NY Acad Sci* 2012; 1261: 55–63.
17. Rosenblat J and McIntyre R. Bipolar disorder and immune dysfunction: epidemiological findings, proposed pathophysiology and clinical implications. *Brain Sci* 2017; 7: 144.
18. Beishuizen A and Thijs LG. Endotoxin and the hypothalamo-pituitary-adrenal (HPA) axis. *J Endotoxin Res* 2003; 9: 3–24.
19. Pace TWW and Miller AH. Cytokines and glucocorticoid receptor signaling: relevance to major depression. *Ann NY Acad Sci* 2009; 1179: 86–105.
20. Saccaro LF, Crokaert J, Perroud N, *et al.* Structural and functional MRI correlates of inflammation in bipolar disorder: a systematic review. *J Affect Disord* 2023; 325: 83–92.
21. Aronica R, Enrico P, Squarcina L, *et al.* Association between diffusion tensor imaging, inflammation and immunological alterations in unipolar and bipolar depression: a review. *Neurosci Biobehav Rev* 2022; 143: 104922.
22. Sayana P, Colpo GD, Simões LR, *et al.* A systematic review of evidence for the role of inflammatory biomarkers in bipolar patients. *J Psychiatric Res* 2017; 92: 160–182.
23. Castaño-Ramírez OM, Sepúlveda-Arias JC, Duica K, *et al.* Inflammatory markers in the staging of bipolar disorder: a systematic review of the literature. *Revista Colombiana de Psiquiatría* 2018; 47: 119–128.

24. Yontao Y. Screening of clinical and biological markers and establishment of diagnostic predictive models for bipolar and unipolar depressive disorders. *Master Thesis, Jining Medical University, China*, 2021.
25. Yun W, Haiyan L, Ying W, *et al*. Correlation between inflammatory markers and emotional status in patients with bipolar disorder. *Clin Educ Gen Pract* 2019; 17(05):432-434+438
26. Hodes GE, Ménard C and Russo SJ. Integrating Interleukin-6 into depression diagnosis and treatment. *Neurobiol Stress* 2016; 4: 15–22.
27. Munkholm K, Braüner JV, Kessing LV, *et al*. Cytokines in bipolar disorder vs. healthy control subjects: A systematic review and meta-analysis. *J Psychiatr Res* 2013; 47: 1119–1133.
28. Barbosa IG, Huguet RB, Mendonça VA, *et al*. Increased plasma levels of soluble TNF receptor I in patients with bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* 2011; 261: 139–143.
29. Jesudas BR, Nandeesha H, Menon V, *et al*. Relationship of elevated neural cell adhesion molecule 1 with interleukin-10 and disease severity in bipolar disorder. *Asian J Psychiatr* 2020; 47: 101849.
30. Tatay-Manteiga A, Balanzá-Martínez V, Bristot G, *et al*. Clinical staging and serum cytokines in bipolar patients during euthymia. *Prog Neuropsychopharmacol Biol Psychiatry* 2017; 77: 194–201.
31. Lotrich FE, Butters MA, Aizenstein H, *et al*. The relationship between interleukin-1 receptor antagonist and cognitive function in older adults with bipolar disorder: IL-1RA, bipolar disorder, and cognition. *Int J Geriatr Psychiatry* 2014; 29: 635–644.
32. Zhang C, Wei C, Cheng W, *et al*. Changes of serum S100B, total bilirubin IL-1β and IL-4 levels in patients with bipolar disorder. *Chin J Health Care Med* 2019; 21: 158–160.
33. Goldsmith DR, Rapaport MH and Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry* 2016; 21: 1696–1709.
34. Solmi M, Suresh Sharma M, Osimo EF, *et al*. Peripheral levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-1β across the mood spectrum in bipolar disorder: a meta-analysis of mean differences and variability. *Brain Behav Immun* 2021; 97: 193–203.
35. Luo Y, He H, Zhang M, *et al*. Altered serum levels of TNF-α, IL-6 and IL-18 in manic, depressive, mixed state of bipolar disorder patients. *Psychiatr Res* 2016; 244: 19–23.
36. Chen P, Chen F, Chen G, *et al*. Inflammation is associated with decreased functional connectivity of insula in unmedicated bipolar disorder. *Brain Behav Immun* 2020; 89: 615–622.
37. Tang G, Chen P, Chen G, *et al*. Inflammation is correlated with abnormal functional connectivity in unmedicated bipolar depression: a resting state FMRI study. Preprint, In Review. *Epub ahead of print* 20 May 2020. DOI: 10.21203/rs.3.rs-28937/v1.
38. Jacoby AS, Munkholm K, Vinberg M, *et al*. Cytokines, brain-derived neurotrophic factor and C-reactive protein in bipolar I disorder – Results from a prospective study. *J Affect Disord* 2016; 197: 167–174.
39. Hua M-H, Chen M-H, Hsu J-W, *et al*. Proinflammatory cytokine dysregulation and cognitive dysfunction among patients with remitted bipolar I and II disorders. *J Affect Disord* 2021; 281: 738–743.
40. Wang T-Y, Lee S-Y, Chen S-L, *et al*. The differential levels of inflammatory cytokines and BDNF among bipolar spectrum disorders. *IJNPPY* 2016; 19: pyw012.
41. Erzin G, Aydemir MÇ, Yüksel RN, *et al*. Serum 15-d-PGJ2 and PPARγ levels are reduced in manic episode of bipolar disorder while IL-4 levels are not affected. *Psychiatr Clin Psychopharmacol* 2019; 29: 298–306.
42. Doganavsargil Baysal O, Erdogan A, Cinemre B, *et al*. Levels of TNF alpha, soluble TNF receptors (sTNF-R1, sTNF-R2) in bipolar disorder. Archives of Neuropsychiatry. *Epub ahead of print* 2019. DOI: 10.29399/npa.24844.
43. Teixeira AL, De Souza RT, Zanetti MV, *et al*. Increased plasma levels of soluble TNF receptors 1 and 2 in bipolar depression and impact of lithium treatment. *Hum Psychopharmacol Clin Exp* 2015; 30: 52–56.
44. Jun Y, Jin L, Qi L, *et al*. The correlation between serum levels of CD30, BAFF, sTNF-R1, CXCL10 and different emotional states in patients with bipolar disorder. *J Int Psychiatr* 2023; 50: 418–421.
45. Jun L, Yingying H, Wenguang H, *et al*. Serum cytokine levels and clinical significance in patients with different clinical phases of bipolar disorder. *Exp Lab Med* 2022; 40: 733–735.
46. Li Y and He X. Efficacy of valproic acid combined with ziprasidone on bipolar disorder and its effect on serum total bilirubin albumin and inflammatory factors. *HeBei Med* 2020; 26: 1307–1312.

47. Li Q and Yu J. Effects of ziprasidone combined with sodium valproate on clinical symptoms and inflammatory markers in patients with bipolar disorder. *Drug Eval* 2023; 20: 177–179.

48. Xu J and Le S. Effect of valproate plus quetiapine on the degree of mania and serum levels of BDNF, IL-4 and IL-10 in patients with bipolar disorder with manic episodes. *Mod Med Health Res* 2021; 5: 78–80.

49. Meng Q and Shi G. The clinical efficacy of quetiapine combined with magnesium valproate in the treatment of bipolar disorder. *Chin J Drug Abuse Prev Treat* 2022; 28: 1843–1847.

50. Huang C, Liu W, Ma X, *et al.* Effect of Quetiapine combined with Lithium Carbonate on inflammatory response and manic symptoms in patients with bipolar disorder. *China Mod Med* 2021; 28: 89–91.

51. He L, Yang Y and Jiang F. Effects of quetiapine combined with lithium carbonate on manic degree and inflammation Iindexes in patients with bipolar disorder manic episode. *Heilongjiang Med J2021*; 45: 694–696.

52. Zhang G and Qiu X. Effect of combined systemic care of lithium carbonate and quetiapine on cognitive function and inflammatory factor levels in patients with bipolar disorder and manic episodes. *Mod Med Health Res* 2022; 6: 123–127.

53. Chen D, Xian C and Li J Y. Clinical effect of lithium carbonate combined with magnesium valproate in bipolar disorder. *Chronic Pathematology J* 2022; 23: 1314–1316+1319.

54. Shao G. Efficacy analysis of lithium carbonate extended-release tablets and magnesium valproate extended-release tablets in patients with manic episodes of bipolar disorder. *Mod Diagn Treat* 2021; 32: 1210–1212.

55. Xu S, Xia W and Jin H. Effect of aripiprazole tablets combined with olanzapine tablets on cognitive function and serum inflammatory factors in patients with bipolar disorder. *Clin Educ Gen Pract* 2022; 20: 595–598.

56. Liu X, Yan BR and Jin LI. Effect of citalopram hydrobromide tablets on cognitive function and inflammatory factors in patients with recurrent bipolar disorder. *Drug Eval Res* 2017; 40: 1631–1634.

57. Knight EL, Engeland CG, Yocum AK, *et al.* Heightened inflammation in bipolar disorder occurs independent of symptom severity and is explained by body mass index. *Brain Behav Immun Health* 2023; 29: 100613.

58. Bishop JR, Zhang L and Lizano P. Inflammation subtypes and translating inflammation-related genetic findings in schizophrenia and related psychoses: a perspective on pathways for treatment stratification and novel therapies. *Harv Rev Psychiatry* 2022; 30: 59–70.

59. Munkholm K, Weikop P, Kessing LV, *et al.* Elevated levels of IL-6 and IL-18 in manic and hypomanic states in rapid cycling bipolar disorder patients. *Brain Behav Immun* 2015; 43: 205–213.

60. Li H Z, Hong W, Wang Z W, *et al.* Correlation between expression of peripheral IL-17 protein and aggression of bipolar mania. *Fa yi xue za zhi* 2016; 32: 40–44.

61. Keshri N, Nandeesha H and Kattimani S. Elevated interleukin-17 and reduced testosterone in bipolar disorder. Relation with suicidal behaviour. *Asian J Psychiatr* 2018; 36: 66–68.

62. Anderson G and Maes M. Bipolar disorder: role of immune-inflammatory cytokines, oxidative and nitrosative stress and tryptophan catabolites. *Curr Psychiatr Rep* 2015; 17: 1–9.

63. Barbosa I G, Morato I B, de Miranda A S, *et al.* A preliminary report of increased plasma levels of IL-33 in bipolar disorder: further evidence of pro-inflammatory status. *J Affect Disord* 2014; 157: 41–44.

64. Lynch MA. Neuroinflammatory changes negatively impact on LTP: a focus on IL-1β. *Brain Res* 2015; 1621: 197–204.

65. Misiak B, Beszlej JA, Kotowicz K, *et al.* Cytokine alterations and cognitive impairment in major depressive disorder: from putative mechanisms to novel treatment targets. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; 80: 177–188.

66. McAfoose J and Baune BT. Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev* 2009; 33: 355–366.

67. Hayley S, Hakim AM and Albert PR. Depression, dementia and immune dysregulation. *Brain* 2021; 144: 746–760.

68. Hueston CM, Cryan JF and Nolan YM. Stress and adolescent hippocampal neurogenesis: diet and exercise as cognitive modulators. *Transl Psychiatry* 2017; 7: e1081–e1081.

69. Viviani B, Bartesaghi S, Gardoni F, *et al.* Interleukin-1β Enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *J Neurosci* 2003; 23: 8692–700.

70. Prieto GA, Tong L, Smith ED, *et al.* TNFα and IL-1β but not IL-18 suppresses hippocampal long-term potentiation directly at the synapse. *Neurochem Res* 2019; 44: 49–60.

71. Cacci E, Claasen J-H and Kokaia Z. Microglia-derived tumor necrosis factor-α exaggerates death of newborn hippocampal progenitor cells in vitro. *J Neurosci Res* 2005; 80: 789–797.

72. Smith JA, Das A, Ray SK, *et al*. Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. *Brain Res Bull* 2012; 87: 10–20.

73. Morgan JA, Singhal G, Corrigan F, *et al*. TNF signalling via the TNF receptors mediates the effects of exercise on cognition-like behaviours. *Behav Brain Res* 2018; 353: 74–82.

74. Ouyang W and O'Garra A. IL-10 Family Cytokines IL-10 and IL-22: from basic science to clinical translation. *Immunity* 2019; 50: 871–891.

75. Yang K, Li LH and Qiu Y . Research advances in progress of immunotherapy for bipolar disorder. *J Inter Neurol Neurosurg* 2021; 48: 81–85.

76. Mousavi SY, Khezri R, Karkhaneh-Yousefi M-A, *et al*. A randomized, double-blind placebo-controlled trial on effectiveness and safety of celecoxib adjunctive therapy in adolescents with acute bipolar mania. *J Child Adolesc Psychopharmacol* 2017; 27: 494–500.

77. Kishi T, Miyake N, Okuya M, *et al*. N-acetylcysteine as an adjunctive treatment for bipolar depression and major depressive disorder: a systematic review and meta-analysis of double-blind, randomized placebo-controlled trials. *Psychopharmacology* 2020; 237: 3481–3487.

78. Zeinoddini A, Sorayani M, Hassanzadeh E, *et al*. Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: a randomized, double-blind, placebo-controlled trial: Research Article: Pioglitazone for Bipolar Depression. *Depress Anxiety* 2015; 32: 167–173.

79. Rosenblat JD and McIntyre RS. Efficacy and tolerability of minocycline for depression: a systematic review and meta-analysis of clinical trials. *J Affect Disord* 2018; 227: 219–225.

80. Husain MI, Chaudhry IB, Khoso AB, *et al*. Minocycline and celecoxib as adjunctive treatments for bipolar depression: a multicentre, factorial design randomised controlled trial. *Lancet Psychiatry* 2020; 7: 515–527.

81. Aftab A, Kemp DE, Ganocy SJ, *et al*. Double-blind, placebo-controlled trial of pioglitazone for bipolar depression. *J Affect Disord* 2019; 245: 957–964.

82. Brietzke E, Scheinberg M and Lafer B. Therapeutic potential of interleukin-6 antagonism in bipolar disorder. *Medical Hypotheses* 2011; 76: 21–23.

83. Singh S, Kumar NK, Dwiwedi P, *et al*. Monoclonal antibodies: a review. *CCP* 2018; 13: 85–99.

84. Su Q, Huang Z and Tang G. Recent progress in clinical application of Anti-TNF antibody McAb. *Medical Recapitulate* 2006;05: 293–295.

85. Siegel SA, Shealy DJ, Nakada MT, *et al*. The mouse/human chimeric monoclonal antibody cA2neutralizesTNFin vitro and protects transgenic mice from cachexia and TNF lethality in vivo. *Cytokine* 1995;7: 15–25.

86. Colpo GD, Leboyer M, Dantzer R, *et al*. Immune-based strategies for mood disorders: facts and challenges. *Expert Rev Neurother* 2018; 18: 139–152.

87. Raison CL, Rutherford RE, Woolwine BJ, *et al*. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 2013; 70: 31.

88. Bavaresco DV, Uggioni MLR, Ferraz SD, *et al*. Efficacy of infliximab in treatment-resistant depression: a systematic review and meta-analysis. *Pharmacol Biochem Behav* 2020; 188: 172838.

89. McIntyre RS, Subramaniapillai M, Lee Y, *et al*. Efficacy of Adjunctive Infliximab vs Placebo in the treatment of adults with bipolar I/II depression: a randomized clinical trial. *JAMA Psychiatry* 2019; 76: 783.

90. Jin C, Mian X, Lujun L, *et al*. Biologics for targeting inflammatory cytokines and their clinical application. *Chinese J Biotechnol* 2019; 35:1009–1020.

91. Tiosano S, Yavne Y, Watad A, *et al*. The impact of tocilizumab on anxiety and depression in patients with rheumatoid arthritis. Eur J Clin Invest. *Epub ahead of print* September 2020. DOI: 10.1111/eci.13268.

92. Liu L, Liu S, Guan W, *et al*. Efficacy of tocilizumab for psychiatric symptoms associated with relapsing polychondritis: the first case report and review of the literature. *Rheumatol Int* 2016; 36: 1185–1189.

93. Miller B J, Dias J K, Lemos H P, *et al*. An open-label, pilot trial of adjunctive tocilizumab in schizophrenia. *J clin Psychiatry* 2016; 77(2): 13353.

94. Mitoma H, Horiuchi T, Tsukamoto H, *et al*. Molecular mechanisms of action of anti-TNF-α agents – Comparison among therapeutic TNF-α antagonists. *Cytokine* 2018; 101: 56–63.

95. Abbasian F, Bagheri S, Moradi K, *et al.* Evidence for anti-inflammatory effects of adalimumab in treatment of patients with major depressive disorder: a pilot, randomized, controlled trial. *Clin Neuropharmacol* 2022; 45: 128–134.

96. Dhimolea E. Canakinumab. mAbs 2010; 2: 3–13.

97. Thomas W, Isabella J, Rhoshel L, *et al.* S33. Reduction in peripheral C-reactive protein levels with canakinumab administration is related to reduced positive symptom severity in patients with schizophrenia and inflammation. *Schizophr Bull* 2019; 45(SUPnan): S318–S318.

98. Deisseroth A, Ko C-W, Nie L, *et al.* FDA Approval: Siltuximab for the treatment of patients with multicentric Castleman disease. *Clin Cancer Res* 2015; 21: 950–954.

99. Sun Y, Wang D, Salvadore G, *et al.* The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. *Brain Behav Immun* 2017; 66: 156–164.

100. Strand V, Hagino O, Guillonneau S, *et al.* SAT0207 Depressive symptoms in patients with rheumatoid arthritis in sarilumab target and mobility trials and impact of treatment. In: Saturday, 16 June 2018. BMJ Publishing Group Ltd and European League Against Rheumatism, 1–964.

101. Choy EHS and Calabrese LH. Neuroendocrine and neurophysiological effects of interleukin 6 in rheumatoid arthritis. *Rheumatology* 2018; 57: 1885–1895.

102. Strand V, Boklage SH, Kimura T, *et al.* High levels of interleukin-6 in patients with rheumatoid arthritis are associated with greater improvements in health-related quality of life for sarilumab compared with adalimumab. *Arthritis Res Ther* 2020; 22: 250.

103. Armstrong A, McBride S, Spelman L, *et al.* 33259 Improvements in anxiety and depression among patients with moderate to severe plaque psoriasis treated with certolizumab pegol: three-year results from 2 phase 3 trials (CIMPASI-1 and CIMPASI-2). *J Am Acad Dermatol* 2022; 87(3): AB175.

104. Chen M, Jiang Q and Zhang L. The prevalence of bipolar disorder in autoimmune disease: a systematic review and meta-analysis. *Ann Palliat Med* 2021; 10: 350–361.

105. Pelechas E, Voulgari P and Drosos A. Golimumab for rheumatoid arthritis. *JCM* 2019; 8: 387.

106. Heo Y-A. Satralizumab: first approval. *Drugs* 2020; 80: 1477–1482.

107. Lesmana MHS, Le NQK, Chiu W-C, *et al.* Genomic-analysis-oriented drug repurposing in the search for novel antidepressants. *Biomedicines* 2022; 10: 1947.

108. Billmeier U, Dieterich W, Neurath MF, *et al.* Molecular mechanism of action of anti-tumor necrosis factor antibodies in inflammatory bowel diseases. *WJG* 2016; 22: 9300.

109. Scott LJ. Sarilumab: First global approval. *Drugs* 2017; 77: 705–712.

110. Minnema LA, Giezen TJ, Souverein PC, *et al.* Exploring the association between monoclonal antibodies and depression and suicidal ideation and behavior: a VigiBase study. *Drug Saf* 2019; 42: 887–895.

111. Shayowitz M, Bressler M, Ricardo AP, *et al.* Infliximab-induced depression and suicidal behavior in adolescent with Crohn's disease: case report and review of literature. *Pediatr Qual Saf* 2019; 4: e229.

112. Hoepner R, Faissner S, Salmen A, *et al.* Efficacy and side effects of natalizumab therapy in patients with multiple sclerosis. *J Cent Nerv Syst Dis* 2014; 6: 41–49.

113. Nagesh O, Bastiampillai T, Fisher L, *et al.* Cyclical suicidal ideation following natalizumab infusion for multiple sclerosis. *Aust N Z J Psychiatry* 2015; 49: 668–669.

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