PPN

Personalized Psychiatry and Neurology

Review

Hyperexpression of Proinflammatory Cytokines in Blood as a Biomarker of Systemic Inflammatory Response in Schizophrenia: Scoping Review

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Citation: Shnayder, N.A.; Rusanova, G.V.; Nasyrova, R.F. Hyperexpression of Proinflammatory Cytokines in Blood as a Biomarker of Systemic Inflammatory Response in Schizophrenia: Scoping Review. *Personalized Psychiatry and Neurology* **2024**, *4 (2)*: 13-24. https://doi.org/10.52667/10.52667/2712-9179-2024-4-2-13-24.

Chief Editor: Nikolaj G. Neznanov, D Med Sci, Professor

Received: 23 April 2024
Accepted: 10 June 2024
Published: 15 June 2024

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Abstract: Introduction: An imbalance of the genetically determined cytokine response plays a key role in the etiology of treatment-resistant schizophrenia (TRS). In recent years, an attempt has been made to evaluate the prognostic role of systemic inflammation in the development of TRS. The problem requires a multidisciplinary approach on the part of the specialists in the following clinical disciplines: psychiatry, immunology, experimental medicine and pharmacogenetics. The solution of this problem is possible with the involvement of preventive and personalized medicine. The purpose: Evaluation the prognostic role of genetic polymorphisms of pro-inflammatory cytokines in the development of TRS. Materials and Methods: We conducted a keyword-based analysis of the English and Russian-language articles published within the past 5 years. The following databases were used in the study: PubMed, MedLine, Web of Science Core Collection (Clarivate Analytics), Web Science, Russian Science Citation Index, Scopus, Scientific Research, Google Scholar, Oxford Press, and eLibrary. Results: In a number of the analyzed works, an increased level of pro-inflammatory cytokine production was noted in patients with TRS. Based on this, single nucleotide variants (SNVs), their influence on the expression of pro- and anti-inflammatory cytokine genes, as well as their predictor role in the development of TRS. The most promising SNVs for further studies were identified. Conclusion: The risk of developing TRS is associated with a genetically determined status of the cytokine response and its regulation. Studies of the association of various SNVs of genes encoding pro-inflammatory cytokines in the Russian Federation need to be continued.

Keywords: interleukin, genetics, treatment-resistant schizophrenia, systemic inflammation, hematological biomarkers, single nucleotide variant (SNV), personalized medicine

1. Introduction

Schizophrenia (Sch) is a severe psychiatric disorder that affects cognitive, behavioral and emotional functioning and is associated with a substantial socioeconomic burden. [1]. Sch affects approximately 24 million people or 1 in 300 people (0.32%) worldwide. This rate is 1 in 222 people (0.45%) among adults [2]. It is not as common as many other mental disorders. Onset is most often during late adolescence and the twenties, and onset tends to happen earlier among men than among women [3]. On one side it is associated with the development of serious drug-induced adverse reactions (ADRs) and on the other side it is associated with the development of therapeutic resistance [4].

Treatment-resistant schizophrenia (TRS) is a condition in which the mental disorder is not cured or corrected despite an adequate course of treatment [5]. Despite the proven

efficacy of antipsychotic drugs, 30%-50% of patients with Sch obtain a scarce benefit from conventional treatments. TRS implicates an important burden at 3 levels, as follows: (1) clinical: negative attitude to medication, drug abuse, and nutritional/physical health problems; (2) economic: hospitalizations and polytherapy; and (3) humanistic: depression and social isolation. As a result, dealing with TRS involves a high emotional burden for patients and their caregivers, affecting their quality of life. The shortcomings of the current health care and social support systems cannot provide adequate and effective solutions to these patients [6]

TRS represents a major clinical challenge. The broad definition of TRS requires nonresponse to at least 2 sequential antipsychotic trials of sufficient dose, duration, and adherence. Several demographic, clinical, and neurologic predictors are associated with TRS. Primary (or early) TRS is present from the beginning of therapy, while patients with secondary (or later-onset) TRS initially respond to antipsychotics but become resistant over time, often after relapses. Guidelines worldwide recognize clozapine as the most effective treatment option for TRS, but clozapine is underused due to various barriers. Importantly, studies indicate that response rates are higher when clozapine is initiated earlier in the treatment course. ADRs are common with clozapine, particularly in the first few weeks, but can mostly be managed without discontinuation; they do require proactive assessment, intervention, and reassurance for patients. Furthermore, plasma leucocyte and granulocyte levels must be monitored weekly during the first 18–26 weeks of treatment, and regularly thereafter, according to country regulations. Therapeutic drug monitoring of (TDM) clozapine trough plasma levels is helpful to guide dosing, with greatest efficacy at plasma clozapine levels ≥350 μg/L, although this level is not universal. Notably, plasma clozapine levels are generally greater at lower doses in nonsmokers, patients with heavy caffeine consumption, in women, in obese people, in those with inflammation (including COVID-19 infection), and in older individuals. Earlier and broader use of clozapine in patients with TRS is an important measure to improve outcomes of patients with this most severe form of the illness [7]. Patients with TRS have higher rates of unemployment, worse quality of life, and poorer social and occupational functioning than people who respond to treatment. Researchers have estimated that the direct healthcare costs for TRS in the US is 3–11-fold higher than for the schizophrenia population as a whole, with multiple hospitalisations accounting for a large proportion of this cost. In England, 25–50% of the National Health Service's (NHS) £11.8 billion mental health budget is allocated to schizophrenia services and TRS is thought to contribute a large proportion of these costs [8].

Recently, evidence linking Sch to autoimmunity has been highlighted; autoimmune-related antibodies anticardiolipin, antinuclear, anti-DNA, antihistone, and anti-NMDA receptors have been reported present in the serum of Sch patients. Gene polymorphisms of several cytokines are associated with the development of the Sch syndrome. In patients with schizophrenia, presence of gene polymorphisms of proinflammatory cytokines, such as IL-1β and IL-6, have been linked to high serum levels of these cytokines. An emerging literature suggests that prenatal and postnatal exposure to pathogens may contribute to the etiopathogenesis of Sch via the actions of cytokines. In fact, cytokines produced in response to infection are not only involved in the inflammatory response but also in the development and function of the central nervous system (CNS) [9].

A study of ILs in cerebrospinal fluid (CSF) showed that IL-6 and IL-8 levels were elevated in SH but were not significantly elevated in affective disorders [10], and a meta-analysis of cytokines in CSF showed higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines in patients with TRS [11].

It is well-known that dopaminergic dysfunction is an important feature of the pathophysiology of TRS [12]. The interaction between cytokines and neurotransmitters in specific brain regions and during brain development is important in the pathophysiology of TRS [13]. In patients with Sch, a meta-analysis study showed that IL-1β, IL-6, and transforming growth factor-β functioned as state cytokine markers, but IL-12, interferon

(IFN)-γ, and tumour necrosis factor alpha (TNF-α) functioned as trait cytokine markers. The state cytokine markers were elevated in first-episode patients and normalized after antipsychotic drug treatment. Conversely, the trait markers were elevated during acute exacerbation and remained elevated even after treatment with antipsychotic drugs. These cytokines have been linked to mental illnesses. IL-2 regulates neurotransmitter metabolism, including dopamine metabolism, and IL-6 acts as a neurotrophic factor in the CNS [14].

Irregularities in the cytokine system are characteristic of patients with TRS [15] [16]. Significantly elevated serum levels of IL-2 and IL-6 are usually found, which is probably associated with activation of the inflammatory response system (IRS). Moreover, serum levels of IL-2 or IL-6 and cortisol are positively correlated with the severity of Sch, supporting the hypothesis that hypercortisolemia may also be caused by hyperproduction of proinflammatory cytokines [17].

In first episode psychosis, Mondelli et al. measured brain-derived neurotrophic factor (BDNF), IL-6 and TNF-α in 46 patients. Compared to healthy controls, patients had reduced *BDNF* gene expression and increased IL-6 and TNF-α. History of childhood trauma was associated with lower BDNF mediated through IL-6 [18]. In a more recent review, Goldsmith et al. investigated acute and chronic cytokine changes in schizophrenia, bipolar disorder and depression, which included 40 studies on acute Sch [19]. In meta-analysis, IL-6, sIL2r, IL-1RA and TNFα were all significantly raised in acute schizophrenia, bipolar disorder and depression. There was more heterogeneity in FEP samples than acute relapse of established schizophrenia [19]. These findings suggest that the association of increased inflammatory cytokines transcend traditional diagnostic boundaries; for a discussion on the trans-diagnostic effect of inflammation please, see below [20]

Cytokines function together with specific cytokine inhibitors and soluble cytokine receptors to regulate the immune response in humans [21]. Their physiologic role in inflammation and pathologic role in systemic inflammatory responses are now well established. An imbalance in cytokine production or cytokine receptor expression and/or dysregulation of the cytokine process contribute to the development of various pathologic disorders, including TRS [22]. Cytokines are classified as pro-inflammatory and anti-inflammatory. Time-dependent pro- and anti-inflammatory imbalance determines the outcome of the inflammatory response in the development of TRS [23]. However, it should be emphasized that the division of cytokines into pro- and anti-inflammatory is rather conventional, because depending on certain conditions, the same cytokine can behave as pro- or anti-inflammatory (e.g., IL-6) [24]. In fact, the amount of cytokines, the nature of the activating signal, the nature of the target cell, the nature of the cytokines produced, the timing, the sequence of cytokine action, and even the experimental model are parameters that strongly influence the properties of cytokines, and, consequently, the risk of developing CH and TRSs [25].

Aim of this scoping review is an assessment of the prognostic role of genetic polymorphisms of pro-inflammatory cytokines in the development of TRS.

2. Materials and Methods

We analyzed both Russian and English-language articles on a given topic.

Inclusion criteria in the search: 1) full-text original articles cited in databases: PubMed, MedLine, Web of Science Core Collection (Clarivate Analytics), Web of Science, Russian Science Citation Index, Scopus, Scientific Research, Google Scholar, Oxford Press, and eLibrary; 2) articles in Russian and English; 3) search depth 5 years 4) keyword matching: interleukin, genetics, treatment-resistant schizophrenia, systemic

inflammation, hematological biomarkers, single nucleotide variant (SNV), personalized medicine. Exclusion criteria: abstracts, monographs, manuals, guidelines.

A total of 307 publications were found. However, only 148 works met the purpose of our research. In accordance with all the abovementioned search criteria, we analyzed 77 original full-text articles.

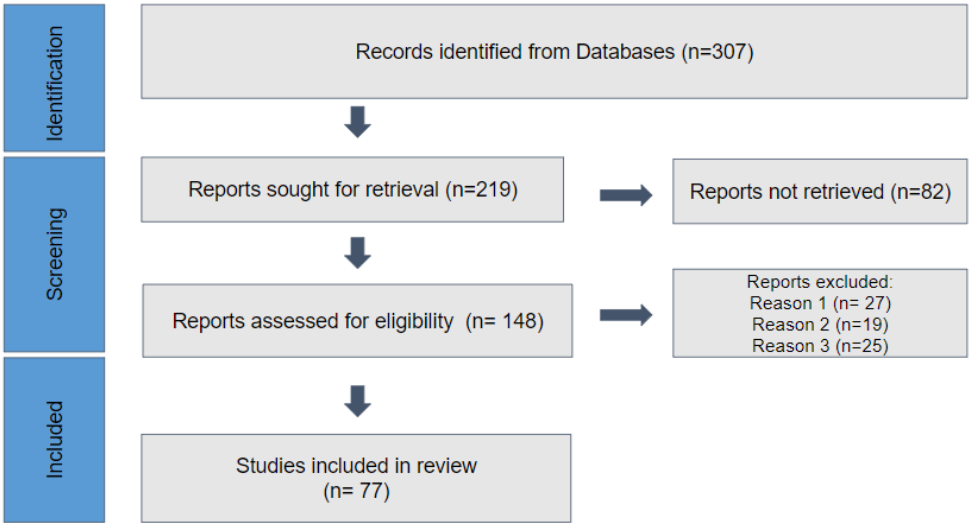

Figure 1. – Block diagram PRISMA.

3. Results

Proinflammatory cytokines play a central role in neuroinflammatory diseases of infectious or noninfectious origin. Proinflammatory cytokines are produced predominantly by activated macrophages and are involved in the regulation of acute and chronic inflammatory reactions [26]. These cytokines serve to localize and resolve inflammatory foci by activating the local response and IRS. Proinflammatory cytokines can directly modulate the activity of different classes of neurons in the CNS, including dopaminergic neurons [27]. The most well-studied proinflammatory cytokines responsible for early responses are IL1-α, IL1-β, IL-6, and TNF-α. Other proinflammatory mediators include members of the IL-20 family, IL-33, leukemic inhibitory factor (LIF), IFN-γ, oncostatin M (OSM), ciliary neurotrophic factor (CNTF), transforming growth factor beta (TGF-β), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-11, IL-12, IL-17, IL-18, IL-8, and a host of other chemokines that chemoattract inflammatory cells. These cytokines either act as endogenous pyrogens (IL-1, IL-6, TNF-α), increase the synthesis of secondary inflammatory mediators and pro-inflammatory cytokines by both macrophages and mesenchymal cells, stimulate the production of acute phase inflammatory proteins, or attract inflammatory cells [28]. IL-1β, TNF-α, IFN-γ, IL-12 and IL-18 are well characterized as pro-inflammatory cytokines in TRS and Sch.

3.1. Interleukin 1β

IL-1β is produced by blood myeloid cells, pathogenic lymphocytes, resident microglia and CNS astrocytes in autoimmune diseases, neurodegeneration and metabolic disorders. It is a key pro-inflammatory cytokine involved in the regulation of the innate immune response [29]. IL-1β is a pleiotropic cytokine capable of activating microglia and astrocytes and leading to the subsequent synthesis of other proinflammatory cytokines and chemotactic mediators in the CNS [30]. IL-1β leads to aberrant release and

accumulation of glutamate, which subsequently leads to neuronal death in most neurodegenerative diseases [31].

In a cross-sectional study by Enache et al. [32], which studied the association of plasma levels of cytokines with TRS, no association of IL-1β with TRS was found, but other studies obtained alternative results demonstrating a significant association between high serum levels of IL-1β and the development of TRS [33].

The *IL-1RA* allele 2 homozygous genotype and *IL-1RA* allele 2 frequencies were non-significantly higher among Sch patients than in controls. The *IL-1RA* allele 2 was known to be related to severe clinical outcomes in chronic inflammatory diseases. Furthermore, it was documented that the presence of the *IL-1RA* allele 2 is associated with enhanced IL-1β production. It has been documented that a higher expression of the *IL-1RA* allele 2 was related to bifrontal-temporal gray matter volume and generalized white matter tissue deficits in allele 2 carrier Sch patients [34].

The *IL-1β* C-511T polymorphism is associated with higher IL-1β plasma concentrations, on the one hand, there is evidence suggesting that levels of IL-1β may vary with clinical status along with the concentration of other cytokines, such as IL-6 and TGF-β. Specifically, acute exacerbations seem to create an increase in their values [35]. Also, a significant association founds between serum levels of IL-1β and negative rather than positive Sch symptoms [36][37].

3.2. Tumor necrosis factor alpha

TNF-α regulates a number of processes including sleep, learning, memory, synaptic plasticity, and astrocyte-induced synaptic amplification in the healthy CNS [38]. The biological functions of TNF-α are mediated through its two major receptors: tumor necrosis factor receptor 1 (TNF-R1 or p55) and tumor necrosis factor receptor 2 (TNF-R2 or p75). TNF-R1 activation triggers inflammatory, apoptotic and degenerative cascades, while TNF-α signaling through TNF-R2 is an anti-inflammatory and cytoprotective biomarker, resulting in the induction of proliferation, differentiation, angiogenesis and tissue repair [39].

TNF-α is also an important proinflammatory cytokine produced by both neurons and glial cells in the CNS. Association genetic studies have confirmed the presence of TRS associated SNVs genes in the innate and adaptive immune systems [40]. In a recent study investigating the association between SNV 238 G/A, a gene encoding TNF-α, and response to antipsychotics, it was shown that although SNVs 238 G/A and 308 G/A are not associated with Sch, SNV 238 G/A may be associated with a high risk of TRS and suicide attempts in Turkish patients [41]. In another study on the prognosis of TRS, it has been shown that TRS is associated with a specific cytokine and chemokine profile, namely increased levels of C-C motif chemokine ligand 11 (CCL11), macrophage inflammatory protein-1 alpha (MIP-1α), soluble tumor necrosis factor receptor 1 (rTNF-R1) and soluble tumor necrosis factor receptor 2 (rTNF-R2), and reduced levels of interferon-gamma induced protein 10 (IB-10), TNF-α, IL-2 and IL-4 [42]. However, data from a cross-sectional study showed that increased TNF-α expression was observed in patients with TRS and ultra-resistant to therapy Sch (UTRS) [43].

Furthermore, poor cognitive functioning and disability in daily life activities are negatively associated with increased peripheral TNF-α and IL-12p70 levels in patients with schizophrenia [44]. The TNF-α level negatively correlated with various cognitive functions, including attention span, verbal memory, executive function, sustained attention, and psychomotor speed. These findings are consistent with those of a previous study showing a positive association between cognitive dysfunction and TNF-α levels in patients with TRS [45]. TNF-α produced by microglia appears to act in cognitive dysfunction in patients with TRS [46].

3.3. Interferon gamma

IFN-γ is a soluble cytokine that is predominantly released from type 1 (Th1) helper T cells, cytotoxic T lymphocytes, and natural killer cells. IFN-γ stimulates microglia, which is associated with a variety of cellular adaptations, including changes in morphology, receptor regulation, and increased levels of proinflammatory cytokines [47]. The evidence on IFN-γ levels in TRS remains inconsistent. Upthegrove et al. [48] showed that elevated IFN-γ levels are associated with TRS. However, another study reported that IFN-γ was not associated with the expected response to antipsychotics [20].

The expression of IFN-γ was found significantly reduced in patients with Sch as compared to the normal controls [49].There is an association between several inflammatory and autoimmune diseases and a SNP in the first intron of the human *IFNG* gene with nuclear factor-KB (NFKB)-binding region [50]. Jemli et al., in a study on the Tunisian population, observed that *IFNG* +874T/A variant *TT* genotype and *T* allele showed higher frequencies in all paranoid Sch patients than those in the male controls [51]. However, another study found no significant association between genotype distribution of *IFNG* +874T/A variant and risk of Sch [52]. Decreased IFN-γ levels may be related to enhanced cognitive performance in Sch [53]. On the contrary, in APP/PS1 mice, intraperitoneal injection of IFN-γ restores microglial autophagy, promotes amyloid-β clearance, and improves cognition [54]. Previous meta-analyse also found that serum IFN-γ levels were lower in patients with Sch than in healthy controls [15]. However, some studies showed that Sch patients had higher or no difference in IFN-γ levels compared with control group [55] [56].

3.4. Interleukin 12

IL-12 is secreted mainly by macrophages and dendritic cells in response to bacterial cell wall components. IL-12 stimulates proliferation and activates and increases the cytotoxicity of NK cells and T cells, promoting the differentiation of the latter into Th1 cells. It is also known to induce secretion of IFN-γ and TNF-α and has a synergistic effect with IL-18 [22]. When studying the plasma level of IL-12, it was found to be elevated in TRS and UTRS [48] . IL-12 were significantly decreased in TRS disorder. The proposed state marker IL-12, which was differentially altered between acute and chronic illness stages, have integral roles in T-cell functioning and activity [57]. Decreased IL-12 concentrations in TRS might suggest that a different type of lymphocyte cellular activity occurs, or these might be the result of the immunomodulating effect of antipsychotics [58]. Meta-analyse of the effect of antipsychotics on IL-12 serum levels where no stratification by population or administered pharmacotherapy is applied seem to yield inconsistent results, suggesting their elevated [19] [59]. In addition, in their meta-analysis including the largest sample, Romeo et al. described no changes in IL-12 serum levels in ARCh patients, and their elevated values in those treated with risperidone [15].

3.5. Interleukin 18

Researches of IL-18 expression in the CNS began soon after its discovery as a stimulator of INF-γ production in the immune system. IL-18 was investigated because of its similarity to IL-1β as a possible mediator of behavior in psychiatric disorders and local inflammatory responses associated with neuronal damage. IL-18 contributes to loss of appetite, sleep, and inhibition of long-term potentiation, and is produced and active in microglia, possibly contributing to neurodegeneration. IL-18 represents a link between the immune and nervous systems, as IL-18 and its receptors in the CNS mediate neuroinflammation, modulating homeostasis and behavior [59]. There is some evidence that serum IL-18 levels are elevated in patients with TRS but are not causative of the development of the psychiatric disorder itself [60], although it is likely that elevated serum IL-18 levels may be a biomarker for TRS.

The IL-18 protein levels in the blood of Sch patients are significantly elevated. The first episode psychosis Sch subgroup achieved borderline significance. It must be noted that overall IL-18 levels are higher in chronic Sch than in first episode psychosis (FEP)

patients and only one of the three studies investigating FEP Sch reported a significant increase in serum IL-18 levels, however, combined with the other studies the FEP Sch group display a borderline significant increase in serum IL-18 levels. Our results suggest that IL-18 may have utility as a biomarker for Sch [61].

Even though five of the seven studies failed to find any significant association between increased IL-18 serum levels and PANSS (Positive and Negative Syndrome Scale), they did however, find a significant correlation between increased IL-18 levels and various other indicators of cognitive decline such as total PANSS and its subscales of immediate/delayed memory [62], decreased verbal fluency [63], depression [64], total PANSS and its immediate/delayed memory, attention and language sub-scores [65].

An Increased IL-18/IL-18BP ratio may induce a pro inflammatory state because elevated levels of free IL-18 stimulate nuclear factor-κB-dependent transcription of inflammatory cytokines, chemokines, adhesion molecules and inflammatory enzymes [66].

3.6. Interleukin 8

IL-8 is secreted predominantly in response to antigen by macrophages, T-lymphocytes, neutrophils, and other cells; IL-8 is also the most potent human chemokine [67]. IL-8, as a pro-inflammatory cytokine, enhances the migration of neutrophils, T-lymphocytes, and monocytes, whose enzymes produce free oxygen radicals and thus increase oxidative stress, which can lead to neuronal death [68]. IL-8 significantly predicts non-response to antipsychotic therapy and positively correlates with negative Sch symptoms [32] and can be considered as a potential biomarker of TRS.

3.7. Interleukin 17

IL-17 is secreted by T-helper cells (Th17) and stimulates macrophages and microglia to secrete proinflammatory cytokines [69]. There is no effect of antipsychotics on peripheral IL-17 levels [70]. However, it has been reported that activation of the IL-17 pathway may be present from the debut of SH and appears to increase as the disease progresses until the development of TRS and UTRS. The IL-23/IL-17 pathway is considered as a therapeutic target for patients with TRS, especially since many anti-inflammatory drugs have been proposed as adjuvant treatments for TRS symptoms, such as N-acetylcysteine, which has been shown to reduce IL-17 production [47].

4. Discussion

Imbalance of cytokine response has an important role in the etiology of schizophrenia in general, and treatment-resistant schizophrenia in particular. Hyperexpression of proinflammatory endogenous mediators (cytokines) can be detrimental to a patient with "non-dopamine" Sch and lead to the development of TRS.

The genetic predisposition that determines the balance of proinflammatory cytokines in a particular patient with Sch, and hence susceptibility to TRS, is of great clinical importance. SNV risk alleles have been identified in genes encoding proinflammatory cytokines and cytokine receptors that significantly alter their expression. Also SNV genes may determine the imbalance of proinflammatory and anti-inflammatory cytokines in the neuroinflammatory response in patients with "non dopamine" and "dopamine Sch.

To date, therapeutic strategies targeting pro-inflammatory cytokines may be effective in the treatment of TRS. Proinflammatory cytokines are known to play a crucial role in triggering the neuroinflammatory response. However, their levels in the CNS may have reached their absolute or relative peak before the clinical signs of TRS become evident to the psychiatrist. In addition, therapies that block proinflammatory cytokines may paradoxically lead to increased inflammation [71]. Various inflammatory paradoxes have been reported, including new foci of inflammation and amplification of the chronic inflammatory response, occurring when: (1) genes encoding certain cytokines and

inflammatory regulators are mutated [72]; (2) patients have somatic mutations [73] responsible for the inflammatory response [74]; (3) expression of proinflammatory cytokines is reduced due to carrying low-producing SNVs in the genes encoding them [75]; (4) therapies that block the production of proinflammatory cytokines are used, etc. [76].

Proinflammatory cytokines and inflammatory regulators are interrelated during evolution. At the same time, drug blockade of one cytokine can lead to a significant change in the regulation of a long list of genes and signaling pathways, presumably the "second wave of inflammation" [77]. For example, the second wave of inflammation may be a major mechanism for the development of the acute inflammatory response observed in patients receiving Mab therapy that blocks proinflammatory cytokines [71]. Nevertheless, recent studies provide new insights into the role of the imbalance between pro- and anti-inflammatory cytokines in the pathogenesis of Sch and the formation of TRS, as well as new approaches to the prognosis and early diagnosis of TRS development, and new targets for future therapeutic interventions in "non-dopamine" Sch. These guidelines demonstrate that the problem of assessing the contribution of proinflammatory and anti-inflammatory cytokines to the maintenance or alteration of cytokine balance may become a new key to unraveling the mystery of "non-dopamine" Sch and developing new therapeutic strategies for the treatment of Sch and TRS, as well as psychosis in acute and chronic neuroinflammation.

5. Conclusions

Our scoping review demonstrates that the problem of evaluating the contribution of pro-inflammatory cytokines to maintaining or changing the cytokine balance can become a new key in unlocking the mystery of "non-dopamine" Sch and developing new therapeutic strategies for the treatment of TRS and psychosis in acute and chronic neuroinflammation. In addition, the inconsistency of the results of previous studies on the role of pro-inflammatory cytokines indicates that the TRS biomarker, most likely, is not the serum level of one or several cytokines, but the cytokine balance. We have demonstrated a hypothesis that the cytokine imbalance is one of the most important TRS biomarkers. Partially, this hypothesis is supported by the variable response to immunomodulators in patients with TRS, which were prescribed without taking into account the cytokine balance of the relation between serum levels of the most important pro-inflammatory and anti-inflammatory cytokines for TRS. Studies of the association of various SNV of genes encoding proinflammatory cytokines need to be continued.

Author Contributions: Conceptualization, N.A.S.; methodology, R.F.N; software, G.V.R.; validation, G.V.R.; formal analysis, G.V.R.; investigation, G.V.R. and N.A.S.; resources, R.F.N.; data curation, R.F.N.; writing—original draft preparation, G.V.R.; writing—review and editing, N.A.S.; supervision, R.F.N.; project administration, R.F.N.; funding acquisition, R.F.N. All authors have read and agreed to the published version of the manuscript.

Funding: The research is supported by State assignment of Bekhterev National Medical Research Center for Psychiatry and Neurology of Russian Ministry of Health 2024-2026 (XSOZ 2024 0012)

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds ... are available from the authors.

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