Pre-treatment plasma cytokine levels as potential predictors of short-term remission of depression

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ABSTRACT

Objectives: The response to antidepressants varies significantly among individuals and is difficult to predict before treatment. In this randomised control trial, we explored cytokines that correlate with the therapeutic effect of mirtazapine (MIR) and selective serotonin reuptake inhibitors (SSRIs) and whether they could be predictors of remission for each antidepressant.

Methods: Plasma cytokines, such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) were assayed in 95 participants before medication and assayed by the enzyme-linked immunosorbent assay. The Hamilton Rating Scale for Depression assessed depressive symptoms over 4 weeks.

Results: In the SSRI group, the baseline GM-CSF level was significantly higher in the remission group than in the non-remission group (p = 0.022). In the MIR group, the baseline level of TNF-α was significantly higher (p = 0.039) and IL-2 was lower (p = 0.032) in the remission group than in the non-remission group. In patients prescribed with MIR, the cut-off values of TNF-α (10.035 pg/mL) and IL-2 (1.170 pg/mL) calculated from the receiver operating characteristic curve suggested that the remission rate, which corresponds to a positive predictive value, could be increased from 31.3% to 60.0% and 50.0%, respectively. For those prescribed with SSRIs, the remission rate was 37.0% and using the cut-off value of GM-CSF (0.205 pg/mL), the remission rate could be almost doubled to 70%.

Conclusions: Our study shows that pre-treatment plasma concentrations of TNF-α, IL-2, and GM-CSF may suggest the predictability of remission by SSRIs or MIR.

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Introduction

Background

Major depressive disorder (MDD) is an important public health issue that causes a significant burden, not only on patients but also on society, accounting for approximately one-fifth of the years lived with disability among adults aged ≥15 years (World Health Organisation 2008), it also causes an increase in mortality. According to the present diagnostic criteria, MDD has relatively high heterogeneity and innovating new antidepressant agents or renewing treatment guidelines does not significantly improve the remission rate (Ferrier 1999; Entsuah et al. 2001; Kato et al. 2005; Thase et al. 2005, 2010; Guaiana et al. 2013; Kato et al. 2017). Recently, the inflammatory hypothesis has been widely recognised as an important pathogenesis of MDD as an alternative to the monoamine hypothesis (Dooley et al. 2018). Patients with MDD have an abnormal peripheral immune system (Zunszain et al. 2013), with weak cellular immunity and high levels of proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interferon-γ, and interleukin (IL)-1, IL-2, IL-6, and IL-8 (Liu et al. 2012). In addition, proinflammatory cytokines affect pathophysiological features, such as neuroendocrine...
function, neurotransmitter metabolism, and regional brain activity, all of which can contribute to the pathogenesis of MDD (Dantzer et al. 2008). In addition, several investigations in humans and animals have supported this theory; specifically, exposure to high levels of proinflammatory cytokines induces depression-like symptoms and behaviour, patients with inflammation-based treatments are inclined to experience depressed mood or depressive disorder, and antidepressants possess anti-inflammatory features that can reverse cytokine-induced major depression in humans and depressive-like behaviours in animals (Pollak and Yirmiya 2002; Schiepers et al. 2005). Although granulocyte-macrophage colony-stimulating factor (GM-CSF) is a well-known haematopoietic growth factor, its actions are diverse, and its involvement in the inflammatory and immune systems has attracted much attention. In addition, GM-CSF has been shown to mediate the stress response to chronic exposure to social adversity (Powell et al. 2013), exhibit a neuroprotective effect against programmed cell death (Schabitz et al. 2008), and promote brain-derived neurotrophic factor production (Bombeiro et al. 2018). There is also much interest in its role in the central nervous system.

The inflammatory hypothesis is consistent with the monoamine hypothesis, as the inflammatory system strongly influences tryptophan metabolism. For example, inflammatory cytokines inhibit the production of serotonin by enhancing decomposition of tryptophan, a precursor of serotonin, mediated by indoleamine 2,3-dioxygenase (IDO). Therefore, the inflammatory hypothesis of MDD may indirectly support the monoamine hypothesis. It may indicate various therapeutic responses due to the different reactions to drugs with different behaviours.

Some previous reports have examined the association between pre-treatment cytokines or CRP and the therapeutic effects of antidepressants, but these were not conducted in randomised controlled trials and did not compare the differences between SSRIs and MIR (Xu et al. 2019; Zhang et al. 2019).

In this study, we focus on the inflammatory hypothesis and analyse the correlation between pre-treatment plasma cytokine levels and therapeutic response to antidepressants in untreated patients with MDD to identify specific cytokines that contribute to the therapeutic response to mirtazapine (MIR) or selective serotonin reuptake inhibitors (SSRIs), which may lead to more appropriate interventions.

**Materials and methods**

**Participants**

This study is part of the Genotype Utility Needed for Depression Antidepressant Medication (GUNDAM) study (Kato et al. 2017), an open-label, randomised, flexible-dose, 4-week study that was conducted from September 1, 2011 to April 30, 2015. Full details of the methods can be found in the previously published study (Kato 2011). In brief, this study was a randomised controlled trial conducted at Kansai Medical University Medical Centre, Kansai Medical University Hospital, and Seishokai Sephiroth Hospital in Japan. The study was registered in the UMIN (University Hospital Medical Information; No. 000006417). The participants included in the study were 20–75-year-old outpatients, meeting the diagnosis of MDD according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I Disorders (SCID-I/P) (First et al. 2002), Japanese, scoring at least 14 on the 17-item Hamilton Rating Scale for Depression (HAMD17) (Hamilton 1960) and had been free of psychotropic drugs for at least 14 days before entering the study. Participants with clinically significant unstable medical illness, pregnancy, a principal psychiatric diagnosis other than major depression, a history of substance abuse or dependence active within the previous 6 months, history of treatment-resistant depression, defined as non-response to two or more antidepressant, and electroconvulsive therapy within the last 6 months were excluded. Diagnoses were assigned by two independent senior psychiatrists and confirmed by a third psychiatrist. Participants were randomly prescribed either MIR or SSRIs (paroxetine or sertraline). The initial doses of MIR, paroxetine, and sertraline were 15, 10, and 25 mg/day, respectively. The dose was increased to 30 mg/day for MIR, 20 mg/day for paroxetine, and 50 mg/day for sertraline within 2 weeks and increased to 45 mg/day for MIR, 40 mg/day for paroxetine, and 100 mg/day for sertraline between 2 and 4 weeks, if there was no intolerability. If the participants did not tolerate a certain dose, the same dose was continued without increasing the dose. All patients were evaluated at baseline and bi-weekly thereafter until the end of the study, using the HAMD17. The primary efficacy outcome was the rate of remission, defined as a HAMD17 score of ≤7, at week 4. The HAMD17 assessment was performed by trained senior psychiatrists (M.K., S.S., H.B., K.N., and Y.T.).
**Cytokine measurements**

Human plasma samples were derived from pre-treatment patients with MDD. The plasma levels of TNF-α, IL-1β, and IL-8 were assayed by the enzyme-linked immunosorbent assay using a Milliplex MAP Kit (HSYTMAG-60K) on a Milliplex Analyser 4.2 MAGPIX machine (Millipore) according to the manufacturer’s instructions in the Department of Psychiatry, School of Medicine, University of Occupational and Environmental Health, Japan. The plasma levels of IL-2, IL-4, IL-6, and GM-CSF were measured using the Human Cytokine Magnetic 10-Plex Panel (Thermo Fisher Scientific) according to the manufacturer’s instructions. We added the same plasma sample to each plate for the cytokine multiplex assay and calculated the interassay coefficient of variation (%). We performed duplicate measurements in all subjects. As a quality control, when a cytokine was detected in less than 90% or a quality control, when a cytokine was detected in only a portion of the participants (less than 90%) or there was high interassay variability (51% or more), the assay of the cytokine was regarded as unreliable. These cytokine measurements were performed using Filgen (Nagoya, Japan). Values were expressed as pg/mL.

**Statistical analysis**

All randomised patients assigned to the treatment group at baseline and after 4 weeks of the HAMD17 assessment were included in the analyses. All included participants were divided into remission and non-remission groups. All cytokine levels were collected before treatment and measured for analysis.

For the primary outcome, the analysis of covariance (ANCOVA) controlling for background characteristics, such as the sex, age, age at the first episode, history of previous MDD episodes, smoking and drinking status, body mass index, and HAMD17 score at baseline were examined to evaluate the association of respective values of baseline plasma cytokine levels with each antidepressant treatment response. Correlation coefficients between the baseline HAMD17 scores and respective cytokine levels or participants’ background data were calculated using Spearman’s rank correlation coefficients or Pearson’s correlation. For other continuous data, we performed the analysis of variance or Wilcoxon rank-sum test if the assumption of normality was violated. For binary outcomes, differences in proportions between the two groups were analysed using chi-square and Fisher’s exact tests, as required. We then evaluated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of baseline cytokine levels for the remission achieved by each antidepressant. Their values were calculated from the cut-off points obtained using the receiver operating characteristic curve (ROC curve). The optimal cut-off value was defined on the basis of the maximal Youden index (sensitivity + specificity − 1) (YOUDEN, 1950), which provided a good trade-off between sensitivity and specificity. The results were considered significant at \( p < .05 \). All statistical analyses were performed using SPSS software (SPSS version 23.0; SPSS, Tokyo, Japan). A priori power analysis was performed using G*POWER version 3.1. At this significance level, our sample had a power of 0.80 to detect a large effect size of \( d = 0.86 \) in the SSRI sample and a large effect size of \( d = 0.82 \) in the MIR sample (Cohen 1988).

**Ethics statement**

This study was approved by the relevant Institutional Ethics Committee of each centre and was conducted following the Declaration of Helsinki for Human research. Written informed consent was obtained from all participants after information regarding the nature of the study procedures was fully explained.

**Results**

**Baseline analysis**

Of the MDD outpatients randomised to receive MIR or SSRIs in Step I of the GUNDAM study (Kato et al. 2017), plasma cytokines were obtained from 95 participants at the study baseline, before medication. Of these, 9.1% of the SSRI group and 5.9% of the MIR group dropped out due to adverse events. Finally, 59 participants passed the quality control and were used in the analysis: 27 in the SSRI group (paroxetine = 14, sertraline = 13) and 32 in the MIR group (Table 1).

|               | Total (n = 59) | SSRIs (n = 27) | MIR (n = 32) | \( p \) |
|---------------|---------------|---------------|-------------|-------|
| Sex (female)  | 61.0%         | 59.3%         | 62.5%       | n.s.  |
| Smoking       | 5.1%          | 0.0%          | 9.4%        | n.s.  |
| Age (years)   | 50.0 16.7 51.3 16.4 48.9 17.2 | n.s.  |
| Age at first episode (years) | 46.2 16.8 46.7 17.1 45.7 16.8 | n.s.  |
| Previous episode (times) | 0.5 0.8 0.6 0.8 0.4 0.8 | n.s.  |
| BMI (kg/m²)   | 23.2 4.8 23.6 4.8 23.0 4.9 | n.s.  |
| Baseline HAMD17 score | 20.0 4.9 18.5 3.8 21.2 5.4 | 0.05 |

SSRIs, selective serotonin reuptake inhibitors; MIR: mirtazapine; BMI: Body Mass Index; HAMD17: 17-item Hamilton Rating Scale for Depression. The \( p \)-value was calculated from a comparison between the SSRI group and the MIR group.
The average dose of each drug at 4 weeks was 33.0 mg/day for paroxetine, 76.9 mg/day for sertraline, and 35.6 mg/day for MIR, and most of the subjects were able to increase the dose to the maximum. Ten of 27 participants (37.0%) treated with SSRIs and 10 of 32 participants (31.3%) treated with MIR achieved remission after 4-week of treatment.

There were no differences in the socio-clinical background data of the analysed participants between the remitters and non-remitters in each antidepressant group, nor between MIR and SSRIs, except for the HAMD17 score (\(p < .05\)). No biomarkers showed a correlation with baseline severity, as assessed by the HAMD17 score. Meanwhile, since the baseline HAMD17 score was correlated with the response to treatment, the baseline HAMD17 score was entered into the statistical model as a covariate for the subsequent ANCOVA. Baseline level of TNF-\(\alpha\) was significantly correlated with IL-6 (\(r_s = 0.276, p = .035\)) and IL-8 (\(r_s = 0.329, p = .011\)), IL-2 with IL-4 (\(r_s = 0.286, p = .028\)) and IL-6 (\(r_s = 0.517, p = 2.7 \times 10^{-5}\)), IL-8 with IL-1\(\beta\) (\(r_s = 0.340, p = .008\)) and IL-6 (\(r_s = 0.409, p = .001\)), and GM-CSF with IL-4 (\(r_s = 0.516, p = 2.8 \times 10^{-5}\)), respectively (Figure 1).

**Cytokines on treatment response**

In the SSRI group, GM-CSF (\(F = 6.03, p = .022\)) was significantly correlated with the remission rate. The average plasma concentration of GM-CSF at baseline was significantly higher in the remission group than in the non-remission group.

In the MIR group, TNF-\(\alpha\) (\(F = 4.69, p = .0039\)) and IL-2 (\(F = 4.66, p = .032\)) were significantly correlated with the remission rate. The baseline TNF-\(\alpha\) level was significantly higher and the IL-2 level was lower in the remission group than in the non-remission group (Table 2). Of these, TNF-\(\alpha\) levels were significantly correlated with remission after 2 weeks in the MIR group, but GM-CSF and IL-2 levels were not. IL-2 level was also associated with remission rate after 4 weeks in total sample (\(F = 3.18, p = .047\)). When each SSRI was analysed separately, GM-CSF remained significantly correlated with remission in the paroxetine group, but not in the sertraline group. IL-6 level was negatively correlated with remission after 4 weeks in total sample (\(F = 6.82, p = .026\)).

**Figure 2** indicates the concentration of cytokines between the remission and non-remission groups using the MIR \(\times\) TNF\(\alpha\), MIR \(\times\) IL-2, and SSRIs \(\times\) GM-CSF combinations.

**Predictor analysis**

According to the ROC analysis (Supplementary Figure 1), the thresholds of the above-mentioned statistically

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**Table 2. Comparison of baseline cytokine levels in patients treated with each antidepressant in the remission and non-remission groups.**

|                      | SSRIs Remission (\(n = 10\)) | Non-remission (\(n = 17\)) | p-value | SSRIs Remission (\(n = 10\)) | Non-remission (\(n = 22\)) | p-value |
|----------------------|------------------------------|----------------------------|---------|------------------------------|-----------------------------|---------|
| baseline TNF-\(\alpha\) | 6.25 (3.31)               | 11.53 (13.25)             | .002    | 13.64 (7.72)               | 8.44 (5.04)                 | .039*   |
| baseline IL-1\(\beta\)  | 2.06 (1.79)               | 2.43 (3.41)              | .541    | 2.69 (3.74)               | 2.46 (1.93)                 | .788    |
| baseline IL-2          | 2.41 (2.99)               | 3.30 (4.70)              | .558    | 0.93 (0.87)               | 3.27 (4.19)                 | .052*   |
| baseline IL-4          | 6.24 (2.80)               | 5.22 (2.09)              | .504    | 4.51 (0.70)               | 6.17 (4.05)                 | .071    |
| baseline IL-6          | 1.37 (0.84)               | 2.13 (1.16)              | .089    | 2.71 (2.28)               | 1.98 (1.78)                 | .355    |
| baseline IL-8          | 10.89 (14.43)            | 5.56 (6.62)              | .090    | 20.63 (24.43)            | 23.17 (32.59)               | .796    |
| baseline GM-CSF        | 0.26 (0.10)               | 0.16 (0.04)              | .022*   | 0.19 (0.08)               | 0.23 (0.13)                 | .316    |

'SD' indicates standard deviation; 'p' indicates the p-value; *p < 0.05. SSRIs, selective serotonin reuptake inhibitors; MIR, mirtazapine; TNF-\(\alpha\): tumour necrosis factor \(\alpha\); IL: interleukin; GM-CSF: granulocyte-macrophage colony-stimulating factor.
significant cytokines GM-CSF (SSRI), IL-2 (MIR), and TNF-α (MIR) were 0.205, 10.035, and 1.170, respectively.

For the SSRI × GM-CSF combination, analysis based on the cut-off value of baseline GM-CSF levels ≥ 0.205 showed 70% sensitivity, 82.4% specificity, 70.0% PPV, and 82.4% NPV (p = .007). In the combination of MIR × TNF-α, the cut-off point of baseline TNF-α levels ≥ 10.035 showed 66.7% sensitivity, 81.0% specificity, 60.0% PPV, and 85.0% NPV (p = .011). In the MIR × IL-2 combination, the positive cut-off was IL-2 levels ≤ 1.170, showing 87.5% sensitivity, 63.2% specificity, 50.0% PPV, and 70.4% NPV (p = .016) (Table 3).

Figure 3 shows the number of discriminated patients according to the cut-off values in each group.

### Table 3. Results of cut-off values and the sensitivity, specificity, positive predictive value, and negative predictive value.

| Cytokine | Cut-off Positive (pg/mL) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|----------|--------------------------|-----------------|-----------------|---------|---------|
| TNF-α    | ≥ 10.035                 | 66.7            | 81.0            | 60.0    | 85.0    |
| IL-2     | ≤ 1.170                  | 87.5            | 63.2            | 50.0    | 70.4    |
| GM-CSF   | ≥ 0.205                  | 70.0            | 82.4            | 70.0    | 82.4    |

PPV: positive predictive value; NPV: negative predictive value; TNFα: tumour necrosis factor α; IL-2: interleukin-2; GM-CSF: granulocyte-macrophage colony-stimulating factor.

Discussion

In this randomised control trial, we explored cytokines that correlate with the therapeutic effect of MIR and SSRIs and whether they could be predictors of remission for each antidepressant. Interestingly, the results of this study showed that the pre-treatment levels of specific cytokines, such as TNF-α and IL-2 for MIR and GM-CSF levels for SSRIs, were different between patients in the remission and non-remission groups after 4 weeks of antidepressant treatment.

In this study, 31.3% achieved remission after 4 weeks of MIR treatment and using the cut-off values for TNF-α (10.035 pg/mL) and IL-2 (1.170 pg/mL) determined from the ROC, the remission rate, which corresponds to PPV, could be increased to 60.0% and 50.0%, respectively. The remission rate was 37.0% for patients who were prescribed SSRIs, and using the cut-off value of GM-CSF (0.205 pg/mL), the remission rate could be almost doubled to 70%. Although baseline levels of TNF-α, IL-2, and GM-CSF were associated with other cytokine levels, these three factors were the only ones correlated with treatment effect, suggesting that these three are representative cytokines associated with treatment effect. As for the relationship between cytokines, the results of this study were consistent with previous studies in depression that found a correlation between TNF-α and IL-6 (Quinn et al. 2020) (Goldsmith et al. 2016). In addition, both IL-2 and IL-6 were reported to be higher in manic states (Brietzke et al. 2009). However, there is still no consensus on the correlation between cytokines in mood disorders. In our results, one of the points of interest is that the pre-treatment cytokines that predict the therapeutic response were different between SSRIs and MIR. This difference may be partially due to the different pharmacodynamic and pharmacokinetic features of SSRIs and MIR. Pharmacodynamically, SSRIs are mainly serotonin reuptake inhibitors, while MIR block alpha2 receptors, serotonin 2A receptors, and histamine receptors. In terms of pharmacokinetics, SSRIs and cytokines are substrates of P-glycoprotein (Pgp), which is encoded by the ATP-binding cassette subfamily B member 1 (ABCB1) gene, but not MIR.
(Weiss et al. 2003; O’Brien et al. 2013; Pollak et al. 2018). That is, the transition of the former to the brain is regulated by Pgp at the blood-brain barrier (BBB), while the latter is not. When the BBB permeability is increased by depression or inflammation, this difference in regulation by Pgp may be correlated with our result that baseline cytokine characteristics differ in response to treatment with each drug.

There are reports that GM-CSF levels correlate with anxiety symptoms (Tang et al. 2018). There are also reports that SSRIs are effective for anxiety symptoms, and some of the result of this study may have been predictive of remission by SSRIs. On the other hand, there are reports that high GM-CSF levels are associated with treatment-resistant depression (Király et al. 2017) and that IDO activation and tryptophan action are reduced (Schefold et al. 2010). Thus, it is controversial with regard to GM-CSF and its effects on the serotonin nervous system. Although it is not fully understood, GM-CSF may have affected the serotonin nervous system, leading to the present results. Although some previous reports have not found a significant correlation between pre-treatment GM-CSF levels and antidepressant treatment responses (Chen et al. 2018; Ricken et al. 2018), Schmidt et al. reported results similar to ours (Schmidt et al. 2016). In contrast to the study by Schmidt et al., which reported the association of treatment response with various antidepressants, we examined the effect of GM-CSF on remission by antidepressant type, which is new and brings us closer to the clinical use of drug selection using cut-off values.

Similar to this study, the study by Carloni et al. reported that high baseline TNF-α levels predicted the response to paroxetine (Carloni et al. 2019). Meanwhile, the result is inconsistent, as several studies have reported that baseline TNF-α levels are not correlated with the antidepressant response (Brunoni et al. 2014; Schmidt et al. 2016; Gadad et al. 2017; Chen et al. 2018; Ricken et al. 2018). The results of this study may differ from those of other studies because MIR was used as an antidepressant, the short-term effect of 4 weeks was examined, and remission was used as the outcome. Previous meta-analyses have shown that antidepressant treatment reduces TNF levels, especially in responders. An increased number of patients with high pre-treatment TNF levels achieved remission after treatment with MIR, possibly because high TNF levels were more likely to be reduced by treatment than low TNF levels (Marini et al. 2016). In animal studies, it has been reported that intraperitoneal administration of TNF-α increases slow-wave sleep. Furthermore, it has been reported that high TNF-α levels activate noradrenergic presynaptic receptors and attenuate noradrenergic neurotransmission (Reynolds et al. 2005). MIR is a unique antidepressant that acts on noradrenergic presynaptic receptors and may positively affect sleep, which may have influenced our results.

Several studies have investigated the associations between baseline IL-2 levels and response to SSRI or SNRI and have found no correlation between them (Fornaro et al. 2013; Brunoni et al. 2014; Schmidt et al. 2016; Chen et al. 2018), and our results with SSRIs were consistent with these studies. However, it is interesting to note that low levels of IL-2 were associated with treatment response to MIR, a drug with a unique pharmacological mechanism. Furthermore, it is intriguing that the pre-treatment cytokine levels that
Specifically, by measuring GM-CSF levels for SSRI suggests the predictability of remission by SSRI or MIR. Plasma concentrations of TNF-α may be useful in predicting remission in depressed patients with a history of suicide attempts having higher TNF-α levels and lower IL-2 levels than those without a history of suicide attempts (Janelidze et al. 2011). This differential increase or decrease of the two pro-inflammatory cytokines according to the characteristics of depression may explain our results showing different characteristics of these two pre-treatment cytokines in patients in remission with MIR. MIR is effective in depressed patients with suicidal ideation and is used as a first-line drug in Japan (Sakurai et al. 2020), suggesting that it has a modifying effect on high TNF-α and low IL-2 levels in these patients.

A limitation of our study is the relatively small sample size. As in previous cytokine studies, this is partially due to the exclusion of samples with cytokine levels below the measurement threshold from the analysis. The power of our sample was sufficient to detect differences of approximately 2.62 pg/mL for IL-2 and 10.12 pg/mL for TNF-α in the MIR samples and 0.016 pg/mL for GM-CSF in SSRI samples between remission and non-remission; therefore, smaller effects could have been missed. Furthermore, the results reported here are exploratory, as they were not adjusted for multiple testing and would need to be confirmed in future studies with larger samples. In addition, although our study excluded smokers, obese patients and patients with comorbidities, all factors that could affect inflammation status and depression symptoms, it did not analyse other possible confounders such as nutrition and degree of physical activity. Moreover, the duration of this study was 4 weeks, and the results are based on the relationship between pre-treatment cytokines and the acute response and cannot address the relationship with the long-term course required for the treatment of depression. One of the strengths of this study is that it was conducted in a Randomised Controlled Trial design; therefore, there was no drug selection bias, and there was a decreased influence of known patient characteristics and unknown events on the results.

In conclusion, our study shows that pre-treatment plasma concentrations of TNF-α, IL-2, and GM-CSF may suggest the predictability of remission by SSRI or MIR. Specifically, by measuring GM-CSF levels for SSRI treatment and TNF-α and IL-2 levels for MIR treatment in the peripheral blood, it may be possible to optimise antidepressant selection. Further research is needed to reveal the relationship between cytokines, depression, and reactivity to antidepressants.

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**Statement of interest**

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The other authors declare that they have no competing interests.

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