

THE TNF-ALPHA INHIBITOR ETANERCEPT AS MONOTHERAPY IN TREATMENT-RESISTANT DEPRESSION – REPORT OF TWO CASES

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INTRODUCTION

Growing evidence links affective disorders and the immune system. Pro-inflammatory cytokines are implicated in the pathogenesis of depression by activation of the tryptophan- and serotonin-degrading enzyme indolamine-2,3-dioxygenase (IDO) (Kiank et al. 2010) and by up-regulating serotonin transporter activity (Zhu et al. 2006), leading to reduced availability of serotonin. Pro-inflammatory cytokines may play future roles in the therapy of depressive disorder, as biomarkers, and as targets for cytokine inhibitors and modifiers of cytokine signalling (Lichtblau et al. 2013).

Levels of tumor necrosis factor- α (TNF- α) and its soluble receptors p55 and p75 are increased in acutely depressed patients (Himmerich et al. 2008) and TNF- α was increased in depressed compared to healthy females (Kahl et al. 2006). In animals, induction of depressive behaviour by administration of TNF- α was reversed by anti-TNF- α antibody (Kaster et al. 2012). In humans, treatment for psoriasis with the anti-TNF- α agent etanercept, a TNF- α receptor p75-Fc fusion protein, was found to have antidepressant effect (Tyring et al. 2006). In an animal model of depression, treatment with etanercept reduced depression-like behaviour (Krügel et al. 2013). In bipolar depression (BD), TNF- α -levels are considered as potential trait markers for the disorder, and modulation of TNF- α may be a target for antidepressant treatment (Soczynska et al. 2009).

The aim of this investigation was to explore possible antidepressant effects of etanercept in two patients suffering from depressive episodes, one in the context of major depressive disorder (MDD), the other bipolar disorder (BD). Following a drug-free wash-out period of 14 days, severity of depressive symptoms was investigated before (baseline = BL) and after 7 (T1), 14 (T2) and 21 (T3) days of etanercept monotherapy. Measures of depression comprised observer-rated Hamilton Depression Rating Scale (HAMD-21) and self-rated Beck Depression Inventory (BDI-II). Participants gave informed consent for off-label treatment with the TNF- α -inhibitor etanercept. Detailed information was provided on the absence of

approval of the drug for the treatment of depressive episodes. This procedure was in conformity with German legal requirements governing consent to unapproved treatments (BVerfG 2005, Az 1 BvR 347/98).

CASE REPORTS

Patient 1

A 58-yr old, unemployed, divorced mother of 2, was admitted with a depressive episode. She had a history of 6 previous inpatient admissions, diagnosed with a recurrent depressive disorder and a history of poly substance abuse of benzodiazepines, opiates and alcohol. Recently instituted pharmacotherapy comprising trimipramine 100 mg and citalopram 40 mg daily and a series of 12 ECTs only led to partial remission with rapid relapse into benzodiazepine abuse. Following lack of response, antidepressants were discontinued for 2 weeks. Following exclusion of contraindications (Miyasaka et al. 2006), treatment with etanercept 25 mg subcutaneous twice a week as monotherapy was instituted. Compared to BL (HAMD-21 33 points, BDI-II 27 points) depressive severity reduced during course of treatment (T1 HAMD-21 7 points, BDI-II 14 points; T2 HAMD-21 14 points, BDI-II 27 points; T3 HAMD-21 13 points, BDI-II 27 points) (Figure 1). Therapy with etanercept was discontinued after 3 weeks, following a relapse into alcohol but not benzodiazepine dependence during the therapy. Therefore, following cessation of etanercept, a depression-focused pharmacotherapy with tiapropridine 3 x 12.5 mg daily was commenced.

Patient 2

A 62-yr old retired, married patient with 23 previous admissions for bipolar disorder (BD) since age 30. Hospitalised with a recent exacerbation of a severe depressive episode, characterized by increased anhedonia, tearfulness, extensive rumination, disruption of sleep, loss of appetite and suicidal thoughts. Following a lack in response to first- and second-line pharmaco-

therapy, treatment with tranylcypromine 40 mg, lamotrigine 100 mg and aripiprazole 10 mg, partial sleep deprivation twice a week plus daily bright light therapy and 12 sessions of ECT three times weekly had no marked antidepressive effect. Following 14 days drug-free, etanercept 25 mg was commenced, twice a week. HAMD-21- and BDI-II-scores slightly decreased during the three weeks (HAMD-21-scores: 24 points at BL, 21 at T1, 20 at T2, 17 at T3; BDI-II-scores: 31 points at BL, 26 at T1, 34 at T2, 24 at T3) (Figure 1). TNF- α levels at BL (6.9 pg/ml) was within the reference limit of <8.1 pg/ml and rose during treatment (T1 92.2 pg/ml; T2 138.0 pg/ml; T3 209 pg/ml). No side effects were observed. Medication with mirtazapine and lithium was recommenced rapidly after the 3 weeks of etanercept treatment, based on a past history of response. The therapeutic option of deep brain stimulation was discussed with the patient.

DISCUSSION

We report the administration of the anti-TNF- α drug etanercept in two patients suffering from depressive episodes, in MDD and in BD. Though the literature supports a significant antidepressant effect of anti-TNF- α drugs in animal models of depression and reduced depressive symptoms in patients with psoriasis, etanercept treatment in these 2 cases did not lead to an unequivocal response.

When interpreting the results, it should be noted that both patients had a low probability of antidepressant response, given lengthy past psychiatric histories and non-response to prior conventional treatment. Secondly, HAMD-21 scores dropped in both patients, in patient 1 formally meeting the criteria for response with a reduction of 60 % after 3 weeks. In

contrast, BDI-II scores remained around baseline levels. Since patients with chronic or enduring depressive episodes often have difficulties in perceiving small changes in symptoms, as outlined in the ‘theory of mind’ (Foerstl 2009), it is possible that improvements were not recognized by the patients. Further, the observational period of 3 weeks might have been too short to demonstrate a marked effect. Tying reported an antidepressive effect after 8 weeks of etanercept treatment (Tying et al. 2006), and an antidepressive-like response in rats was observed after 35 days of drug-administration (Krügel et al. 2013). Alternatively, the rapid but short-lasting response seen at day 7 in MDD patient 1 may be attributed to a rapid blockade of circulating TNF- α . The paradoxical, previously reported (Bhatia & Kast 2007) and hypothetically autoregulatory increase in TNF- α -levels, as observed in patient 2, may have contributed to a relapse in depressive symptoms during treatment.

Further, an influence of the previous drug abuse in patient 1 and previous medication on TNF- α -levels and etanercept effects (Munzer et al. 2013), extending beyond the 14 day wash-out period, cannot be ruled out.

The effectiveness of etanercept treatment may also be influenced by baseline levels of TNF- α . Normal baseline levels in patient 2 potentially reduced the sites for etanercept action from the outset. Further, the response to treatment may have been negatively influenced by the paradoxical effect of etanercept in inducing TNF- α -elevations. Unfortunately, TNF- α -levels were not determined in patient 1.

In the future, the effect of anti-TNF- α -medication could be compared between patients with and without elevated TNF- α -levels preceding therapy, and the course of TNF- α -levels during treatment should be registered as possible covariate.

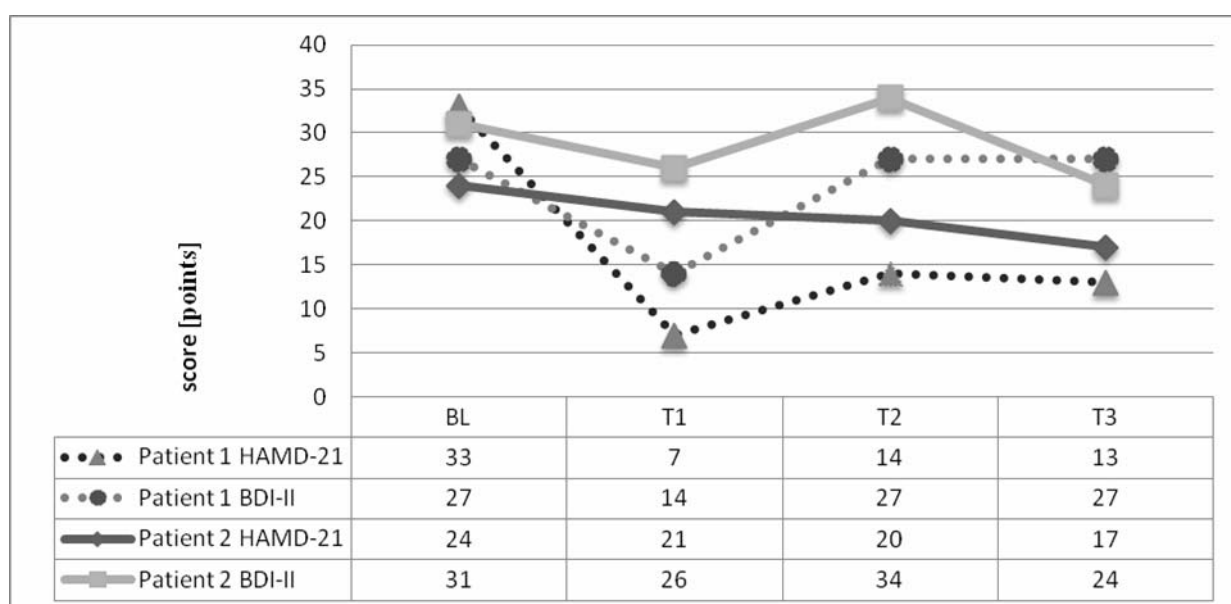


Figure 1. Course of HAMD-21 and BDI-II depression ratings at baseline (BL), 7 (T1), 14 (T2) and 21 (T3) days of etanercept treatment, in patient 1 and patient 2

CONCLUSIONS

In conclusion, this first-time application of etanercept in two patients suffering from unipolar and bipolar disorder revealed equivocal antidepressant effects. This should be reassessed in a clinical trial on etanercept or other non-antibody anti-TNF- α drugs in antidepressant treatment.

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Conflict of interest:

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