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Journal of Clinical Case Studies

ISSN 2471-4925 | Open Access

CASE REPORT

Volume 9 - Issue 2

Infliximab-Induced Depression and Suicidal Behaviour: A Serious Adverse Event to Consider

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Received: 13 Mar, 2024 | **Accepted:** 20 Apr, 2024 | **Published:** 27 Apr, 2024

Citation: Maissa T, Wissal BY, Yosra H, Salem B, Oumayma C, et al. (2024) Infliximab-Induced Depression and Suicidal Behaviour: A Serious Adverse Event to Consider J Clin Case Stu 9(2): doi: dx.doi.org/10.16966/2471-4925.275

Abstract

Infliximab (INF) is a biological widely used in the treatment of various auto-immune diseases including Behçet's disease. INF and other pro-inflammatory cytokines, has been retained in some cases as a factor in the pathogenesis of various neuropsychiatric conditions. Herein we present the case of an adult man with Behçet's Disease (BD) who developed acute depression leading to suicide after the fourth infusion of infliximab. The patient did not experience disabling depressive syndrome, or suicidal thoughts before. He has never made a prior suicide attempt. He denied any previous episodes of mania or psychosis or a history of trauma. Our patient received a serotonin reuptake inhibitor with a good response which allowed us to maintain infliximab therapy.

Infliximab-induced depression and Suicidal behaviour: a serious adverse event to consider

Introduction

Infliximab (INF) is a biological widely used in the treatment of various auto-immune diseases including Behçet's disease [1]. Opportunistic infections, malignancies and neurodegenerative diseases are the most sever reported adverse events and physicians should be awarened of these complications [2]. Neuropsychiatric effects reported with biological agents in general and infliximab specifically are rare. The diagnosis is challenging as there is frequently an associated psychiatric comorbidities related to the medical conditions for which biological agents are initially prescribed. Various pro-inflammatory cytokines including Infliximab have been retained in some cases as factors in the pathogenesis of various neuropsychiatric conditions.

The pathophysiological mechanism of psychiatric symptoms including depression and suicidal behavior associated with infliximab are still unknown [2-6]. Herein we present the case of an adult man with Behçet's Disease (BD) who developed acute depression leading to suicide after the fourth infusion of infliximab.

Case report

A 39-years-old Caucasian male, with no previous personal or familial psychiatric disorders, was diagnosed Behçet disease in 2011. He initially complained about bouts of joint pain and bipolar aphthosis and was initiated on colchicine and corticosteroids. After an evolution of 7 years, he experienced a panuveitis necessitating association of two immunosuppressive drugs including ciclosporine and azathioprine.

Few months later, he developed retinal detachment of the right eye with occlusive vasculitis complicated by intraviterical haemorrhage. Infliximab at the dosage of 5mg/kg was initiated and the patient received subsequent infusions after 2 then 6 weeks. The outcome was partially favourable with a mild improvement in his ocular symptoms.

However, one week after the third infusion, the patient developed persistent insomnia, irritability and a depressed mood with passive suicidal thoughts revealed, as he did not improve after treatment.

Within two weeks of his fourth infusion, his depressive symptoms significantly worsened, and his suicidal thoughts became intrusive. In attempt to commit suicide, the patient was fortunately rescued by his family members. The patient was hospitalized. Other etiological causes including thyroid screening panel, complete metabolic tests and urine toxicology, complete blood count, were all ruled out and were within normal ranges. A cerebral angiography MRI was performed and has not shown any abnormalities.

The patient reported that before beginning infliximab, he was stressed, very nervous, and had periods of depressed mood due to

the decreased visual acuity with the severe symptoms of his ocular disease.

The patient did not experience disabling depressive syndrome, or suicidal thoughts before. He has never made a prior suicide attempt. He denied any previous episodes of mania or psychosis or a history of trauma. The patient reported that he was in conflict with his wife and has problem of funding after his visual acuity decrease as he loosed his job. No herbal or medication intake was found.

The patient was discharged home with an appointment to the department of psychiatry and escitalopram 10 mg/day was prescribed. On follow-up, his depressive symptoms improved significantly and he has no longer experienced suicidal thoughts. He tolerated the next infliximab infusions and had no recurrent psychiatric illness since this event.

Discussion

Infliximab (IFX) is an anti-Tumor Necrosis Factor-Alpha (TNF-α) inhibitor [7] with a numerous well-identified adverse events, such as opportunistic infections and malignancy. However, less is known about their psychiatric adverse events are limited reports.

The diagnosis is often challenging as autoimmune diseases such as inflammatory bowel disease, vasculitis and rheumatoid arthritis are associated with psychiatric disorders in general and depression in particular. In our patient, severe depression induced by infliximab was probable according to the Naranjo probability scale [8]. The temporal relationship between infliximab therapy and symptoms, differential diagnosis that were ruled out and were all negative and the outcome after drug withdrawal are retained in our patient.

In our literature review, few case reports have described suicide thoughts and attempts [4, 9,10] and manic episodes [11,12] associated with the use of IFX or other TNFa inhibitors [13,14].

We believe that the incidence of infliximab-induced depression is under reported [15]. In a recent retrospective observational study, incidence of psychiatric disorders was of 9.87% confirming a potential elevated risk of psychiatric adverse events [15].

Many case reports have shown that rapid delay and onset of neuropsychiatric disorders within months after TNF- α inhibitor initiation may indicate a shared pathogenesis [4,5].

Along with other pro-inflammatory cytokines, TNF-α has been identified as a factor in the pathogenesis of many neuropsychiatric disorders [16,17].

Behavioural changes-induced by TNF-α are complex and are related to a direct effect on the metabolism of neurotransmitters involved in depression and suicide in both the limbic system and the basal ganglia. Proinflammatory cytokines have also been shown to have direct effects on the hormones of the hypothalamic-pituitary axis and corticotropin-releasing hormone, which may also contribute to depression [18].

TNF-α is a potent pro-inflammatory cytokine and it can cross the Blood-Brain Barrier (BBB) without disrupting the BBB and affecting brain function [19]. Some studies revealed that TNF-α is elevated in serum of depressed suicide attempters [20] and Cerebrospinal Fluid (CSF). TNF-α level can serve as a predictor of suicidal ideation [21]. Genetic predisposition was also studied. The gene of TNF-α is one of the most fundamental shared genes that involve depression and suicidal behaviour [22].

Examination of postmortem brains of suicide victims revealed 2.5-fold higher expression of TNF-α in the dorsolateral prefrontal cortex of patients who died by suicide compared with controls [23].

Moroever, animal studies have also shown that TNF-α can have neuroprotective effects at different regions of the brain [17].

However, a recent study has analysed the effects of infliximab on brain neurochemistry of adults with bipolar depression. Authors showed that treatment with IFX did not affect prefrontal N-Acetylaspartate (NAA) concentration in adults with bipolar depression and exploratory analysis suggested a potential effect of treatment on the glutamate system [23]. Some studies have even suggested that IFX treatment is related with improved quality of life in patients suffering from treatment-resistant mood disorders [24,25].

In their literature review, Soczynska JK, et al. concluded that IFX treatment had a beneficial effect on the symptoms of bipolar disorder [25].

These beneficial effects can be explained by the pathologic elevation of blood interleukin-6 and C-reactive protein levels in psychotic disorders, and IFX's ability to reduce these elevated levels [26,27]. An antidepressant effect has also been suggested for other TNFa inhibitors, such as etanercept [28].

So, and according to these findings, psychiatric effect of anti-TNF still controversial and necessitate more scientific and clinical studies.

In our case, Behçet's disease increases the risk of developing depression associated to IFX therapy so it should be necessary to screen patients before starting IFX therapy. For example, American College of Gastroenterology guidelines recommends that all patients with inflammatory bowel disease should be screened for psychiatric disorders [29].

Patients should also be closely monitored in the early stages of treatment so that emerging neuropsychiatric symptoms can be detected and treated at an early stage. In addition, his family members must be warned about his behavior after treatment. Hence patient and family education are crucial is such situations and clinicians should be aware of the risk of psychiatric disorders related to biological therapies and especially IFX. Psychiatric follow up may be useful and is considered as a prevention measure. In some cases, physicians may indicate preventive pretreatment for patients who had a high-risk to develop psychiatric adverse effects to IFX in order to improve its tolerability [5]. Our patient received a serotonin reuptake inhibitor with a good response which allowed us to maintain infliximab therapy.

Conclusion

The characterization of psychiatric adverse events is essential for adequately assess the risk benefit ratio and improving the management of these adverse events when they occur under IFX therapy.

Clinicians should be aware of these risks and a prompt management should be initiated in order to prevent fatal outcome.

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