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### ► To cite this version:

Cécile Marie Yelnik, Louise Gaboriau, Nadine Petitpain, Hélène Théophile, Emmanuel Delaporte, et al.. TNF- $\alpha$  inhibitors and psychiatric adverse drug reactions in the spectrum of bipolar (manic) or psychotic disorders: Analysis from the French pharmacovigilance database. *Therapies*, 2021, 76 (5), pp.449-454. 10.1016/j.therap.2020.09.003 . hal-04398833

**HAL Id: hal-04398833**

**<https://hal.science/hal-04398833v1>**

Submitted on 22 Jul 2024

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## THERAPIES

### HEADING: Pharmacovigilance

# TNF- $\alpha$ inhibitors and psychiatric adverse drug reactions in the spectrum of bipolar (manic) or psychotic disorders: analysis from the French pharmacovigilance database

TNF- $\alpha$  inhibitors and manic or psychotic disorders

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Received June 15, 2020; accepted August 27, 2020

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## **Summary**

*Objective.*- This study aimed to describe reports of psychiatric adverse drug reaction (ADR) in the spectrum of bipolar (manic features) or psychotic disorders that occurred under tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors therapy. *Methods.*- We searched the French pharmacovigilance database for reports of psychiatric ADR in the spectrum of bipolar (manic features) or psychotic disorders during treatment with TNF- $\alpha$  inhibitors. Psychiatric symptoms were divided in 2 categories: (i) confirmed diagnosis of manic episode or acute psychosis and (ii) psychiatric symptoms with psychotic or manic features but not meeting sufficient criteria for diagnosis of psychosis or manic disorder. *Results.*- Overall, 9942 reports of ADR were registered in the French pharmacovigilance database with TNF- $\alpha$  inhibitors, including 243 reports of psychiatric ADR. Among them, we identified 41 reports of psychotic or manic disorders as define above: 9 characterised manic episodes and 32 psychiatric disorders with psychotic or manic features. TNF- $\alpha$  inhibitors were the only medication suspected in 23 reports (56%). The delay between starting TNF- $\alpha$  inhibitors treatment and onset of symptoms varied from hours to years with a median time of 40 days. Psychiatric symptoms improved in 22/23 patients in whom the TNF- $\alpha$  inhibitor was withdrawn. *Conclusion.*- Depressive disorders are well-known ADR of TNF- $\alpha$  inhibitors, but we report, here, 41 reports of psychiatric ADR diagnosed as manic or psychotic disorders or in the spectrum of bipolar or psychotic disorders with these treatments. Epidemiological studies are needed to confirm this signal.

## **KEYWORDS**

TNF- $\alpha$ ; TNF- $\alpha$  inhibitors; adverse drug reaction; psychotic disorders; Psychosis; Pharmacovigilance

## **Abbreviations**

ADA: adalimumab

ADR: adverse drug reaction

ETN: etanercept

FPVD: French pharmacovigilance database

IBD: inflammatory bowel disease

IFX: infliximab

IQR: interquartile range

MedDRA: medical dictionary for regulatory activities

NSAIDs: non-steroidal anti-inflammatory drugs

RA: rheumatoid arthritis

SA: ankylosing spondylitis

SD: standard deviation

SmPC: summary of product characteristics

SOC: system organ class

TNF- $\alpha$ : tumor necrosis factor alpha

## Introduction

Tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors are indicated for the treatment of autoimmune and inflammatory systemic disorders, such as rheumatoid arthritis (RA), ankylosing spondylitis (SA), psoriatic rheumatism, psoriasis and inflammatory bowel disease (IBD) and therefore largely prescribed. Five treatments are currently available in France: infliximab (IFX), etanercept (ETN), adalimumab (ADA), golimumab and certolizumab.

According to Medic' am data (from 2010 until 2017), TNF- $\alpha$  inhibitors are widely used: more than 3 million boxes sold for adalimumab, more than 2 million for etanercept, 400,000 for golimumab and among 250,000 for certolizumab. In 2015, more than 700,000 boxes were sold for infliximab (data from transparency committee). Psychiatric complications in the summary of product characteristics (SmPC) of TNF- $\alpha$  inhibitors, especially symptoms in the spectrum of depressive disorders are reported to be frequent. Other psychiatric complications, such as manic and psychotic disorders are not included in the SmPC, even though some case-reports of such complications have been described [1-6].

This study aimed to describe reports of psychiatric ADRs in the spectrum of psychotic disorders during treatment with TNF- $\alpha$  inhibitors registered in the French pharmacovigilance database.

## Patients and methods

### Definition of the psychiatric ADRs of interest

Psychiatric ADRs in the spectrum of bipolar (manic features) or psychotic disorders were defined as follows: i) diagnosis of acute manic episode or acute psychosis; ii) Psychiatric symptoms with manic or psychotic features but not meeting criteria for firm diagnosis, including: disturbances in thinking and perception, personality disorders and disturbances in behaviour, deliria, dissociative disorders, sexual dysfunctions and disturbances (according to medical dictionary for regulatory activities [MedDRA] dictionary).

## Study design and data collection

This was an observational, retrospective study. Eligible reports were identified using the French pharmacovigilance database (FPVD), which gathers all consecutive ADRs reported by healthcare professionals and patients, and collected by the 31 regional pharmacovigilance centers since 1985 [7]. Every registered ADR was analysed by a college of pharmacologists and causality was assessed for every suspected drug according to the French imputability method [8]. ADRs were encoded using the MedDRA classification.

Reports were selected using the MedDRA system organ class (SOC) term « psychiatric disorders ». Reports that reported one of the five TNF- $\alpha$  inhibitors (IFX, ETN, ADA, golimumab and certolizumab) as a suspected or a concomitant drug in the FPVD until 31<sup>th</sup> December 2017 was included. All reports were individually reviewed with a psychiatrist and only reports strictly in the spectrum of bipolar (manic features) or psychotic disorders were selected. To note, a same patient could present several psychiatric symptoms simultaneously.

We collected the following clinical characteristics: gender, age, prior history of psychiatric disorders, underlying disease, name of TNF- $\alpha$  inhibitor, concomitant treatments (in particular corticosteroids), description of the manic or psychotic disorders, time between start of TNF $\alpha$  inhibitor and onset of psychotic disorders, evolution of psychotic disorders, and TNF- $\alpha$  inhibitor management (withdrawal or not, change, rechallenge).

Causality assessment was evaluated using the French method for causality assessment of ADRs [8]. We presented only intrinsic score, which include chronological criteria (for example: symptoms started after the suspected drug was administered, improvement was observed after stopping it) and semiological criteria (for example: other aetiologies have been excluded) because bibliographic data are discussed later. Intrinsic score range from I0 to I3 (I0 = incompatible causality; I1 = dubious causality; I2 = plausible causality; I3 = likely causality). Causality scores were evaluated by each pharmacologist and only for suspected drugs (but not concomitant drugs).

A case was considered severe if it has resulted in death, in hospitalization or prolonged hospitalizations, invalidity or incapacity, was life threatening or if it represents another severe situation (evaluated by the pharmacologist).

## Statistical analysis

Data were expressed as number (percentage of the total), mean (standard deviation, SD) or median (interquartile range [IQR]). Univariate analysis of factors associated with favorable psychiatric outcome was done with the Fisher's exact test for categorical variables. Statistical testing was done at the two-tailed  $\alpha$  level of 0.05. Data were analysed using SPSS software package 22.

## Results

### Study population

Among 9942 reports of ADRs registered in the FPVD with TNF- $\alpha$  inhibitors, psychiatric disorders concerned 243 reports, and of these, 41 concerned psychiatric disorders of interest. Depressive disorder was the most frequent cause for exclusion (all exclusion causes are shown in Fig. 1).

Characteristics of the study population are shown in Table 1. TNF- $\alpha$  inhibitors were prescribed mostly for rheumatic disease (59%). Others indications were Behçet's disease, Takayasu's disease, panuveitis and Still disease. IFX, ETN and ADA accounted for 90% of prescriptions and were prescribed within the recommended doses and frequency of administration according to the pathology of the patient. Eleven (27%) patients had prior history of psychiatric illness.

As causality might be assessed only if TNF- $\alpha$  inhibitors are classified as suspected drug, causality analysis was available for 35/41 reports. Among these, 11 (31%) had a causality score  $\geq 2$  (plausible or likely). Regarding reports in which causality score for TNF- $\alpha$  inhibitor was low, causality scores for others concomitant suspected drugs were not higher.

### Description of psychiatric ADRs

Nine (22%) patients had a diagnosis of manic episode whereas 32 patients (78%) had psychiatric disorders in the spectrum of manic or psychotic disorders but not meeting criteria for characterised diagnosis (Table 1).

Of the 9 reports selected, the MedDRA labels were “manic episode” (N = 5), “manic state” (N = 1), “manic reaction” (N = 1), “acute mania” (N = 1), bipolar affective disorder (N = 1), and “behavioral disorders” (N = 1, associated with the “manic episode” label). No psychiatric history or psychotropic treatment was reported for 5 of the 9 patients. Of the remaining 4, 1 patient had a history of depressive disorder for which she was being treated with antidepressant and anxiolytic medication. Another patient, with a history of bipolar disorder, presented with a manic episode on antidepressant while she had no mood stabilizer coverage. In this particular case, the suspected drug causing the manic episode was the antidepressant, with ETN being present primarily as concomitant therapy. Another patient was presented as having “psychiatric weaknesses” with no notion of bipolar disorder per se. In this patient, the occurrence of two manic episodes, the first on ADA and the second on certolizumab, led to the initiation of mood stabilizer (valpromide). Finally, a patient was being treated with lamotrigine but as part of the treatment of epilepsy.

Initial symptoms occurred from few hours to several years after initiation of TNF- $\alpha$  inhibitors, with a median time of 40 days (IQR = 142.5). Of note, for one of the reports, the manic episode occurred 10 years after ETN onset. More than half reports (N = 24) were considered severe including: 62.5% (N = 15) hospitalizations or prolonged hospitalizations, 29 % (N = 7) others severe situation and 8.3% (N = 2) life threatening situations.

Of the 23 patients who stopped the treatment, 22 improved their psychiatric ADRs, of which 7 with an anxiolytic and/or antipsychotic treatment (Table 2). Among the 12 patients who pursued the TNF- $\alpha$  inhibitor, half of patients did not improve and 4 improved (of which 2 with an anxiolytic and/or antipsychotic treatment). Rechallenge with the same drug was performed in 4 patients, and 1 had a relapse of psychiatric disorders. To note, there were also 8 patients with recurrent psychiatric disorders after each perfusion. In 3 patients, another TNF- $\alpha$  inhibitor was tried and relapse occurred in one of them. In 23/41 (56%) patients, TNF- $\alpha$  inhibitor was the only drug suspected to explain these ADRs. In 20 reports, other drugs (1 to 7 drugs) were also suspected or concomitant in the psychiatric ADR. We specifically search for concomitant corticosteroid prescription. Corticosteroids were associated in 10 patients (24%): they were suspected in 2 reports, considered as a concomitant drug in 3 reports, and were only mentioned in narratives in the last 5 patients. Among other drugs which can have psychotic effects [9] but are less well-known, we found: proton pump inhibitors (N = 5), non-steroidal anti-inflammatory drugs (NSAIDs, N = 4), imipraminic



antidepressants (N = 2), opiates (N = 2) and betablockers (N = 2). Among other drugs which can have manic effects [10], we found: antidepressant (N = 3) and dopaminergic agonists (N = 1).

## Discussion

To our knowledge, this is the first description of 41 reports of manic or psychotic disorders associated with TNF- $\alpha$  inhibitors therapy.

Outside depression, psychiatric ADRs with TNF- $\alpha$  inhibitors have been poorly documented in clinical trials [11-13]. In literature, a cohort of 734 patients treated with IFX for rheumatic disorders, did not report psychiatric ADRs [14]. In the study conducted by Farrel *et al.* among the 55 ADRs in 100 IBD patients treated by IFX only one report of anxiety was described [15]. In our publication review, we identified 7 reports of acute manic episodes or acute psychosis that occurred during treatment with TNF- $\alpha$  inhibitors (3 reports were treated by ETN and 4 reports by IFX) [1-6]. In all of those reports, psychiatric symptoms appeared or worsened under TNF- $\alpha$  inhibitor therapy and significantly improved or disappeared after TNF- $\alpha$  inhibitor withdrawal. Two case reports state that rechallenge with TNF- $\alpha$  inhibitor did not result in a relapse of the symptoms [2-4]. However, in the first case follow-up after rechallenge was shorter than required for symptom appearance [2] and in the other case only two further injections were administered [4]. Three reports of resolution of psychotic disorders after the initiation of TNF- $\alpha$  inhibitor have been also described [16-18]. In our study, the 9 reports were presented as manic episodes. Nevertheless, the distinction between manic or psychotic episode can be difficult to make, as formal diagnoses, using this experimental design with missing data. Dubious causality was predominant (I1) but this is what is usually observed when using the French causality assessment [19]. Importantly, the fact that psychotic disorders improved after TNF- $\alpha$  inhibitor withdrawal in all (except one) of our patients, which was a strong chronological argument in favour of the TNF- $\alpha$  inhibitor implication, made difficult to rechallenge TNF- $\alpha$  inhibitor.

Regarding confounding factors, confusional state was excluded in our study, as well as in reports previously described in literature [1-6]. Concomitant drugs, which can have played a role in the onset of the ADR, were present in almost half of our reports. As this type of TNF- $\alpha$  inhibitor's ADR is not recognised so far, we also searched for reports where TNF- $\alpha$  inhibitor was allocated as

a concomitant (and not a suspected drug). Among them, concomitant corticosteroids therapy may be the main confounding factor as these are a well-known cause of psychotic disorders. It concerned only 10 patients and was suspected in only 2 reports. Moreover, in one report of manic episode previously described, the suspected drug causing the manic episode was the antidepressant whose risk of manic decompensation is well described. As well, concomitant inflammatory disease, with potential neurological manifestations, may also be a confounder but only 2 of our patients had such disease (Behçet's disease). Finally, even if patients could be psychologically affected by their somatic severe disease, it tends more toward a depressive disorder than a manic or a psychotic disorder.

From the physiopathological point of view, clinical and bench studies indicated a possible role for TNF- $\alpha$  in mood regulation. Indeed, although conflicting, inflammatory injury and cytokine release in depression and schizophrenia have been reported [6,20].

Our study has some limitations: its retrospective design, a non-systematic data collection based only on FPVD spontaneous declarations, a small sample size that might be explained by the fact that prescribing physicians of TNF- $\alpha$  inhibitors are unaware of potential psychotic disorders ADR, which may lead to under-report those ADR to the FPVD [21].

The strengths of our study include the use of a national database for the identification of reports and a comprehensive description of each report in the database. This database collects standardized information from spontaneous reports, which are validated by a college of pharmacologists and clinicians before recording. Spontaneous reports are a useful tool in pharmacovigilance to raise a potential, rare or yet unrecognized, signal or warning. Moreover, in order to limit under recognition of reports in this database, we included TNF- $\alpha$  inhibitors considered as a "concomitant" drug (and not just a "suspected" drug).

In conclusion, our results suggest that manic and psychotic disorders might be induced by TNF- $\alpha$  inhibitors therapy. Prospective pharmaco-epidemiological studies are required to confirm this signal. In case of manic or psychotic disorders that appear in patients treated with TNF- $\alpha$  inhibitors, the potential causality of TNF- $\alpha$  inhibitors might be questioned.

## Acknowledgements

The authors acknowledge the assistance of all 31 regional centers of the French pharmacovigilance system through the "*Association française des centres régionaux de pharmacovigilance*" (AFCRPV).

## Disclosure of interest

Authors have no conflict of interest to declare.

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**Table 1.** Description of the 41 reports of psychotic disorders associated with TNF- $\alpha$  inhibitors therapy.

| <b>Characteristics</b>                      | <b>Patients<br/>n (%)</b> |
|---|---------------------------|
| <b>Mean age (standard deviation), years</b> | 44,35 (16,7)              |
| <b>Gender male / female</b>                 | 21/20                     |
| <b>Underlying disease:</b>                  |                           |
| - Rheumatic disease                         | 24 (59%)                  |
| - Psoriasis                                 | 3 (7%)                    |
| - Inflammatory bowel disease                | 4 (10%)                   |
| - Others                                    | 6 (15%)                   |
| - Missing data                              | 4 (10%)                   |
| <b>History of psychiatric illness</b>       | 11 (27%)                  |
| <b>TNF-<math>\alpha</math> inhibitors:</b>  |                           |
| - Infliximab                                | 13 (32%)                  |
| - Etanercept                                | 14 (34%)                  |
| - Adalimumab                                | 12 (29%)                  |
| - Certolizumab                              | 2 (5%)                    |

|  |                        |
|--|------------------------|
| <b>Coprescription of glucocorticosteroid</b>   | 10 (24%)               |
| <b>Median time to initial symptoms onset (interquartile range), days</b>   | 40 (142,5)<br>17 (41%) |
| <b>Missing data</b>  |                        |
| <b>Classification of psychiatric adverse drug reaction:</b>  |                        |
| <b><u>Diagnosis of:</u></b>  |                        |
| • <i>Manic episode</i>   | 9 (22%)                |
| <b><u>Psychiatric symptoms in the spectrum of a psychotic and manic disorder but not meeting criteria for diagnosis:</u></b> |                        |
| • <i>Disturbances in thinking and perception:</i>  |                        |
| - <b>Hallucinations</b>  | 15 (37%)               |
| - <b>Delusion of persecution</b>   | 2 (5%)                 |
| • <i>Personality disorders and disturbances in behaviour:</i>  |                        |
| - <b>Aggressiveness</b>  | 9 (22%)                |
| - <b>Inconsistency</b>   | 1 (2%)                 |
| - <b>Paranoia</b>  | 1 (2%)                 |
| - <b>Desinhibition</b>   | 1 (%)                  |
| • <i>Others:</i>   |                        |
| - <b>Depersonnalization</b>  | 2 (5%)                 |
| - <b>Psychomotor agitation</b>   | 4 (10%)                |
| - <b>Deliria</b>   | 2 (5%)                 |
| - <b>Libido exacerbation</b>   | 1 (2%)                 |
| - <b>Hypersexuality</b>  | 1 (2%)                 |

**Table 2.** Issue of psychiatric adverse drug reaction.

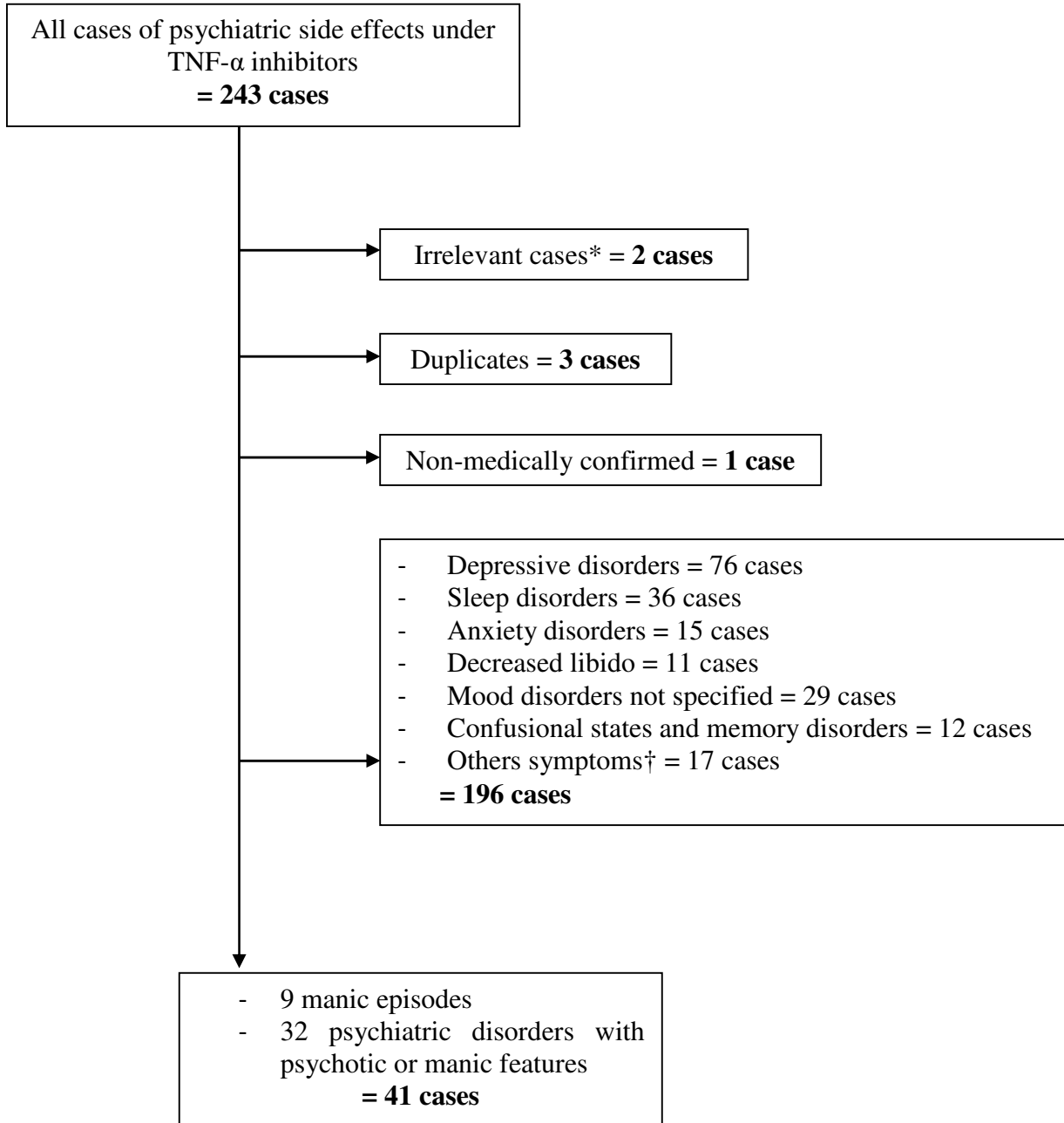
|   | Improvement or resolution | No improvement or resolution | Missing data on issue |           |
|---|---------------------------|------------------------------|-----------------------|-----------|
| <b>TNF<math>\alpha</math> inhibitor withdrawn</b> | 22                        | 0                            | 1                     | 23        |
| <b>TNF<math>\alpha</math> inhibitor pursued</b>   | 4                         | 6                            | 2                     | 12        |
| <b>Missing data on treatment</b>                  | 3                         | 2                            | 1                     | 6         |
|   | 29                        | 8                            | 4                     | <b>41</b> |

TNF- $\alpha$ : tumor necrosis factor- $\alpha$

**Figure 1. Flowchart of the study**

**Legend** \* After update, symptoms or treatment of interest was no longer suspected

† Events without a clear link with a diagnosis of acute psychosis or a manic episode (for example: stuttering, photophobia...)



TNF- $\alpha$  : tumor necrosis factor- $\alpha$