The Nocebo Effect in Rheumatology: An Unexplored Issue

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ABSTRACT: We described the features of nocebo, and its impact in studies of transition from the originator to the respective biosimilar in inflammatory rheumatic diseases. Investigations in healthy volunteers as well as in the neurology and anesthesiology fields demonstrated the involved cerebral areas and the neurotransmitter pathways responsible for the nocebo response. Whether these findings are applicable to patients with inflammatory rheumatic diseases remains to be demonstrated. Nocebo may account for part of the after-switching biosimilar failures. However, in the absence of validated classification or diagnostic criteria, specific neurochemical and neuroimaging studies, the lack of data on serum tumor necrosis factor and drug levels, and the disease improvement after the switching back to the originator biologic observed in some patients, the nocebo diagnosis remains the role of the individual clinician. Investigations on nocebo pathophysiology and diagnosis are required to address its impact in after-transition biosimilar studies in rheumatology.

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During the past 5 years, the patents of several branded biologics, including infliximab (Remicade®), etanercept (Enbrel®), rituximab (Mabthera®), and adalimumab (Humira®) expired. Meanwhile, respective biosimilars were developed and approved by the U.S. Food and Drug Administration (FDA) and European Medicine Agency (EMA). Biosimilars have been shown to be highly similar to the original products by studies on pharmacokinetics, pharmacodynamics, and randomized head to head, non-inferiority, controlled trials (RCTs). The results of these trials have been extrapolated to grant approval for all indications labelled for the reference biologic. Both FDA and EMA stated the therapeutic equivalence of biosimilars, thus opening the way to the switching (or transition) from the originator to the respective biosimilar. Consequently, owing to the relevant low price of biosimilars, the transition to the biosimilars was highly recommended or forced by the governments of different countries, despite the marginal evidence of efficacy and safety of transitioning in real-life clinical practice [1,2].

Nocebo has been investigated in healthy volunteers within the fields of neurology and anesthesiology. Extrapolation of nocebo pathophysiology to rheumatic disorders seems speculative

To date, multiple biosimilars of reference biologics, including etanercept (re-ETN), infliximab (re-IFX), adalimumab (re-ADA), and rituximab (re-RTX), are available worldwide for the treatment of inflammatory rheumatic diseases. However, data from observational trials of switching from the originator product to its biosimilar revealed a consistent percentage of patients in clinical remission or low disease activity who experienced disease flares leading to biosimilar discontinuation after transition [3]. In most reports the discontinuations were attributed, at least in part, to the nocebo effect (hereafter indicated as nocebo), although in the majority of the cases the related clinical manifestations attributable to nocebo were not precisely addressed, thus remaining a diagnosis of exclusion after other reasons were eliminated [4].

In this review we described the features of the nocebo phenomenon including its definition, pathophysiology, diagnosis, and impact on the outcome in studies reviewing the consequences of switching from the originator to the respective biosimilar in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthritis (SpA).

The literature on the different aspects of nocebo, including the existing definitions and classification/diagnostic criteria, the neuropsychiatric pathophysiology, the nocebo clinical measures, and the reported frequency of nocebo in clinical trials of switching from originators to biosimilars in rheumatic diseases, was reviewed. Data were extracted from controlled trials (RCT), observational trials, and national registries. The following drugs were investigated: infliximab biosimilar (bio-IFX), etanercept biosimilar (bio-ETN), adalimumab biosimilar (bio-ADA), and rituximab biosimilar (bio-RTX).

DEFINITION OF NOCEBO

Despite some small differences among the reports, nocebo has been defined as the worsening of previous symptoms or the onset of new negative clinical features induced by non-pharmacological and pharmacological interventions as the results of the patient's negative attitude toward the treatment. In other words, the nocebo effect is universally perceived as the opposite of the placebo effect, and most of the clinical manifestations are considered the result of subjective psychological conditioning that cannot be objectified [5]. However, this definition relates the negative reactions to psychological factors and does not include the evidenced neurochemical pathways [6], neuroimaging features showing the different cerebral areas involved by nocebo as compared to placebo [7], and sex differences [4].

CLASSIFICATION AND DIAGNOSTIC CRITERIA

Nocebo has long been investigated in the anesthesiology and neurology fields. Depending on the different conditions, the clinical manifestations of nocebo are variable and include pain exacerbation, drowsiness, nausea, headache, insomnia, migraine, or motor performance deterioration [6]. The rate of nocebo in neurology trials ranged from 18.5% up to 78.3% in patients with different brain disorders, leading to dropout from the study in 0.3% to 8.8% of the cases [8].

Several reports evaluated the burden of nocebo in clinical trials of patients with fibromyalgia. Two reviews of RCTs of fibromyalgia showed that nocebo was responsible for 67.2% to 81.7% of adverse events observed in the active drug arms [9,10], and 9.5% of dropouts were attributed to disease worsening without clinical reasons. These rated were significantly higher compared to the rates observed in RCTs of multiple sclerosis, migraine, and painful diabetic peripheral neuropathy [9,10]. Dizziness, nausea, constipation, headache, dry mouth, arthralgias, and insomnia were the most frequent symptoms attributed to nocebo [9]. However, most of these symptoms might be related to the labelled side effects of the drugs, including duloxetine, milnacipran, pregabalin, gabapentin, and pramipexole [9]. In addition, several confounding factors, including the frequent fibromyalgia-associated depression and the different assessment strategies, limited the correlation to the nocebo effect [10].

There is an absence of neurochemical and neuroimaging studies in the rheumatology field

The variability of clinical features, the non-specificity of symptoms, and the different conditions where the phenomenon was investigated did not allow formulation of classification/diagnostic criteria and appropriate outcomes measures useful to address the real burden of nocebo accurately. Hence, its diagnosis and prevention remain entrusted to the individual clinician.

PATHOPHYSIOLOGY OF NOCEBO

The underlying mechanisms responsible for nocebo have been investigated in healthy volunteers, in patients with neurological disorders, and in patients with analgesia through neurochemical and neuroimaging studies.

Experimental studies on rats and healthy humans showed the role of cholecystokinin type A and type B receptors in modulating pain perception through their opposite action on dopamine activity [11]. When stimulated by cholecystokinin, which is present in elevated concentrations in the limbic area, the B-receptor exerts an inhibitory action on dopamine release and increases the perception of pain. Proglumide, a nonspecific cholecystokinin antagonist, and diazepam can inhibit this action [6]. Positron emission tomography (PET) using carbon 11 labeled carfentanil radiotracer performed in healthy volunteers showed a deactivation of opioid and dopaminergic neurotransmission in nocebo, whereas they were stimulated by placebo [11]. Similar findings were found by using electrophysiologic deep brain stimulation in patients with Parkinson's disease [12]. As opposed to the placebo response, endogenous opioids are not implicated in nocebo [13].

Hyperalgesia in nocebo is also exerted by the hyperactivity of the hypothalamic–pituitary–adrenal axis, as expressed by the decreased levels of adrenocorticotropic hormone and cortisol in diazepam-exposed nocebo conditions [7].The cyclooxygenase-prostaglandins pathway plays a role in nocebo. In an experimental study, salivary levels of prostaglandins and pain intensification were evaluated in a nocebo group (36 healthy subjects) and in 38 controls. Both groups were evaluated for hypobaric hypoxia headache at an altitude of 3500 meters. A significant increase of salivary prostaglandins and thromboxane was observed in the nocebo group compared with non-nocebo controls [14].

Confirming the different neurotransmitter pathways in nocebo in comparison with placebo effect, neuroimaging studies in healthy subjects using functional magnetic resonance and PET showed distinct nocebo-activated brain areas, such as the anterior insula, anterior cingulate gyrus, prefrontal cortex, inferior frontal gyrus, thalamus, amygdala, and hippocampus [11]. Host-related variables including female gender, depression and anxiety, pessimism, quality of the informed consent, and physicians' verbal information also predispose to nocebo [8].

To the best of our knowledge, with the exclusion of fibromyalgia, no studies investigating the pathophysiology of nocebo in patients with inflammatory rheumatic disorders have been published.

NOCEBO OCCURRENCE AND DIAGNOSIS IN TRIALS OF BIOSIMILARS IN PATIENTS WITH RA, PSA, AND SPA

As reported in a review of RCTs and their open label extension phase, and of real-world observational studies of transitioning from the originator biologics to the respective biosimilars, (including bio-IFX, bio-ETN, and bio-RTX), the discontinuation rates ranged from 5% to 33.3%. A higher percentage of

discontinuation was observed in open label trials as compared with RCTs, with a median value of 14.3% (range 0.0–33) and 6.95% (range 5.2–11), respectively [15]. Since most of the discontinuations were not attributable to drug-related adverse events, the patients' negative expectation toward the switch leading to nocebo was used to explain the treatment failures [15].

Several observational trials of switching from an originator biologic to the respective biosimilar have supported the evidence for the nocebo effect as a reason for discontinuation [16-27]. As shown in Table 1, nocebo accounted for up to 83.6% of biosimilar withdrawals. Since nocebo-attributed discontinuations were not reported in any of the trials of switching of bio-ADA and bio-RTX, only the results related to bio-IFX and bio-ETN were included in Table 1 The number of nocebo-attributed withdrawals was not specified in one study [27], and the diagnosis of nocebo was mostly based on patients' subjective symptoms with no evidence of disease worsening. None of these studies investigated the neurochemical pathways and the neuroimaging features attributed to nocebo. As listed in Table 2, a detailed description of subjective symptoms leading to nocebo diagnosis were available in four studies [18,23-25]. The most frequent manifestations were subjective arthralgias, followed by painful injection, headache and malaise without any objective evidence.

The outcome of patients who switched back to the originator was assessed in two studies. In the report from Cochin University Hospital, Paris, France [22], no changes of disease activity were recorded in 5 patients with RA, while bath ankylosing spondylitis disease activity index (BASDAI), ankylosing spondylitis disease activity score (ASDAS) and global disease activity significantly improved in 33 patients with SpA. No differences were observed in 120 back-switchers from bio-ETN to re-ETN in the DANBIO registry [27]. However, the retention rate in back-switchers was high, with 104 out 120 (87%) patients still receiving re-ETN over a median follow-up of 236 days. In other studies, no information on the follow-up of patients with nocebo-attributed discontinuations was available. Scherlinger et al. [26] evaluated the long-term transitions from re-IFX to CT-P13 and observed that most of discontinuations attributed

Table 1. Nocebo-attributed discontinuations after switching from originators to biosimilars in published clinical trials of rheumatoid arthritis, psoriatic arthritis and spondyloarthritis

Author/year [reference]	Disease	Biosimilar	Patient (N)	Overall discontinued N (%)	Non-Nocebo N (%)	Nocebo N (%)	Nocebo diagnosis	Neurochemical and neuroimaging investigations
Nikiphorou 2015 [16]	RA, PsA, SpA	Bio-IFX CT-P13	39	11 (28.2)	5 (45.5)	6 (54.5)	Subjective reasons; no objective worsening	No
Abdalla 2017 [17]	RA, PsA, SpA	Bio-IFX CT-P13	34	5 (14.7)	3 (60)	2 (40)	Subjective reasons; no objective worsening; Dizziness (negative MRI)	No
Schmitz 2017 [18]	RA, PsA, SpA	Bio-IFX CT-P13	27	7 (25.9)	6*	1	Subjective reasons; no objective worsening	No
Glintborg 2017 [19]	RA, PsA, SpA	Bio-IFX CT-P13	802	132 (16.4)	37 (28)	NA	An unspecified number of withdrawals attributed to nocebo	No
Scherlinger 2018 [20]	RA, PsA, SpA	Bio-IFX CT-P13	89	25 (28)	14 (56)	11 (44)	Subjective reasons; no objective worsening	No
Boone 2018 [21][§]	RA, PsA, SpA	Bio-IFX-CT-P13	24	NA	NA	3 (12.5)	Perceived diminished effect and new-onset headache	No
Avouac 2018 [22][§§]	RA, PsA, SpA	Bio-IFX-CT-P13	182	43 (23.6)	9 (21)	34 (79)	Patients' experience inefficacy	No
Tweehuysen 2018 [23]	RA, PsA, SpA	Bio-IFX-CT-P13	192	47 (24)	22 (46.8)	25 (53.2)	Subjective reasons; no objective worsening.	No
Kaltsonoudis 2019 [24]	SpA	Bio-IFX CT-P13	45	5	1 (20)	4 (80)	Subjective reasons; no objective worsening.	No
Tweehuysen 2018 [25]	RA, PsA, SpA	Bio-ETN SB4	635	55 (8.7)	9 (16.4%)	46 (83.6)	Subjective reasons, no objective worsening.	No
Scherlinger 2018 [26]**	RA, SpA	Bio-ETN SB4	44[§§§]	3	3 (100)	0 (0)	NA	No
Glintborg 2018 [27]	RA, PsA, SpA	Bio-ETN SB4	1621	299 (18.4)	77 (25.7)	NA	Authors defined as due to "subjective reasons" the majority of SB4 withdrawals	No

*Two patients were withdrawn due to unspecified different diseases

**Phone survey

[§]This study was conducted on 73 patients with Crohn's disease, 28 with ulcerative colitis, and 24 with RA, PsA, and SpA. Data reported in the table are limited to patients with rheumatic diseases

[§§]This study included 260 patients, 64 with inflammatory bowel diseases, 14 with other diseases, and 182 with inflammatory rheumatic diseases. Data in the table are related to patients with rheumatic disorders

[§§§]Of the initial 52 patients included in the study 6 refused the switch for personal reasons and 2 did not participate

bio-IFX = infliximab biosimilar, bio-ETN = etanercept biosimilar, NA = not available, PsA = psoriatic arthritis, RA = rheumatoid arthritis, SpA = spondyloarthritis

Table 2. Reported subjective symptoms attributable to nocebo response after transition to biosimilars

Author/year [reference]	Biosimilar	Nocebo N	Symptoms (patient N)
Schmitz 2017 [18]	Bio-IFX CT-P13	1	Hyperventilation (1)
Tweehuysen 2018 [23]	Bio-IFX CT-P13	25	Arthralgia, fatigue, pruritus, myalgia, headache, malaise, cough, dry eyes, dyspnea, nausea, paresthesia, diarrhea, mood disturbances, dizziness, rhinitis*
Kaltsonoudis 2019 [24]	Bio-IFX CT-P13	4	Headache, somnolence, dizziness, arthralgias, fatigue, pain
Tweehuysen 2018 [25]	Bio-ETN SB4	46	Arthralgia (9), painful injection (6), malaise (5), pruritus (4), headache (3), nausea (3), cough (2), dizziness (2), dyspnea (2), fatigue (2), paresthesia (2), palpitations (2), hair loss (1), myalgia (1), mood disturbances (1), vision disturbances (1)

*These symptoms were reported in the text as features of nocebo without any indication on the number of patients discontinuing the therapy

bio-IFX = infliximab biosimilar, bio-ETN = etanercept biosimilar

to nocebo occurred over the first weeks, suggesting patients' reluctance to accept the switch [28].

To the best of our knowledge, prior to the introduction of biosimilars, the effect of nocebo as a cause of treatment failure has not been assessed in trials of originator biologics in RA, PsA, and SpA.

It should be stressed that the pathophysiology of nocebo has been investigated almost exclusively in neurological disorders and in healthy volunteers. Whether these findings may be applied to patients with different pathologic conditions such as RA, PsA, and SpA remains to be demonstrated, especially if we consider the different pathologic background of these diseases. For example, the loss of dopaminergic neurons of the substantia nigra pars compacta represents the pathological basis of Parkinson's disease [29], while RA does not affect the dopaminergic system. In a recent meta-analysis of 236 randomized controlled trials of 17,381 placebo-receiving patients with Parkinson's disease the nocebo response rate was 56% [30], while the magnitude of nocebo in RA was usually lower [22]. Confirming the different pathologic mechanisms, in a large population-based study from Denmark of 13,695 patients with Parkinson's disease, a decreased risk for the neurodegenerative disorder was found in patients with RA [31]. Conversely, a significant increased risk of RA was found in patients with myasthenia gravis who underwent thymectomy [32]. The increased risk of RA after thymectomy, with the consequent interleukin-17 (IL-17) suppression [32], may be explained by the enhancement of the pathogenic role of other cytokines such as tumor necrosis factor (TNF)-α, and interleukin-6 (IL-6), or it may be due to a reduced control of regulatory T cells [33].

In a nationwide cohort study from Taiwan [34], an increased incidence of RA was found in patients with multiple sclerosis (hazard ratio 1.78, 95% confidence interval 1.24–2.56, $P = 0.002$), and this association was attributed to the shared increased serum levels of IL-17 between the two diseases. However, IL-17 has a limited pathogenic role in RA, as expressed by the weaker efficacy of IL-17 blockade as compared with non-anti-IL-17-targeted biologics [35].

Other host-related confounding factors may influence the nocebo response. Similar to fibromyalgia, up to 35% of RA patients have depression, anxiety, and other psychiatric disorders [36]. These co-morbidities are associated with significantly higher TNF-α, interleukin-10 (IL-10), IL-6, and IL-17 serum levels as compared with healthy subjects [36]. Therefore, in absence of specific investigations, it seems questionable whether the nocebo mechanisms observed in healthy subjects may be extrapolated to patients with RA. Moreover, complex mechanisms are involved in the physiopathology of pain in RA, including the synovial inflammation, the gut microbiota, the vagal nerve-mediated inflammation reflex, and the synovial fluid acidosis induced by synovial fibroblasts under cytokine stimulation [37]. Experimental models confirm the complexity of nociception in RA [37]. TNF-α levels are elevated in RA, and several investigations correlated the role of this cytokine in pain perception, that may be separated from the anti-inflammatory action of TNF-α in the joints [38], suggesting a direct action on sensory neurons. Therefore, an insufficient TNF-α blockade exerted by reduced serum levels of anti-TNFs may increase the nociception giving a biological reason for symptoms attributed to nocebo in RA, PsA, and SpA.

Comparable serum levels of both re-IFX and bio-IFX CT-P13 were found in one switching study on a small sample size of 27 patients [18]. This study reported the lowest percentage of nocebo-attributed treatment failures, with only one patient discontinuing bio-IFX for subjective symptoms Serum levels of TNF-α and of anti-TNF biosimilars were not assessed in the other trials of switching, thus part of nocebo discontinuations could be due to insufficient TNF-α blockade.

Several nocebo-related symptoms may be objectified. At least part of the nocebo-attributed biosimilar failures should be reconsidered

Rheumatoid factor and anti-citrullinated proteins/peptides antibodies contribute to an increase of the nociception through the induction of aberrant neutrophil extracellular traps with release of cytokines that stimulate sensory neurons by binding to chemokine receptors of peripheral nociceptors [39].

Based on the previous considerations, studies investigating the nocebo mechanisms in RA, PsA and SpA should assess whether the complicated immune-mediated pathogenesis of these disorders may imply different cerebral pathways as compared with patients with neurological diseases.

Beyond the different pathological background of inflammatory rheumatic disorders, several concerns on nocebo as a cause of discontinuations in trials of transition from the reference products to biosimilars may be raised, including the nocebo-associated symptoms and diagnosis, the lack of neurochemical and neuroimaging investigations, the low-grade of evidence, and the prevalent absence of data on the outcome of discontinuers.

As detailed in Table 2, several symptoms categorized by the investigators as subjective health complaints or perception of disease worsening, are perplexing. Arthralgia is a rather generic term that may imply tender joints and may be an objective symptom. Tender joint count has long been used to assess the joint involvement in inflammatory rheumatic disorders, and it is included in all composite scores currently used to measure the disease activity in RA and PsA. This item is widely accepted as part of patient global assessment with consistent repercussion on patient-reported outcomes. Similarly, other symptoms including dyspnea, cough, diarrhea, hair loss, and rhinitis could all be objectified in clinical practice. About the diagnosis of subjective perception of disease worsening, data on switching back to the originator, showing a significant improvement of outcome measures in SpA [22], suggesting that, at least in part, the nocebo-attributed discontinuations were sustained by a real biosimilar failure. The uncertainties related to nocebo in inflammatory rheumatic disorders are summarized in Table 3.

CONCLUSION

Nocebo may account for part of the treatment failures in studies of transition from an originator biologic to the respective biosimilar in patients with RA, PsA, and SpA. However, as we previously suggested [40], there are several reasons that nocebo is such a challenging diagnosis. These reasons include the absence of classification/diagnostic criteria, the different pathologic background of inflammatory rheumatic disorders with respect to other conditions where nocebo was investigated, and the absence of specific neurochemical and neuroimaging studies. Furthermore, the substantial lack of drug and TNF-α levels evaluation, and the observed disease improvement after the switching back to the originator biologic also confound diagnosis. Accordingly, nocebo diagnosis remains entrusted to the individual clinician decision.

Table 3. Unclarified issues of nocebo in rheumatology

Item	Evidence
Definition	• Generic: subjective reaction opposite to placebo effect • Neurochemical and neuroimaging features not included
Diagnosis	• Substantially a diagnosis of exclusion • Lack of classification criteria and outcome measures • Several nocebo-related symptoms may be objectified
Pathogenesis	• Whether the pathophysiology resulting from studies on healthy subjects, and in neurology may be applied to rheumatic disorders remains to be demonstrated • The complexity of pain mechanisms in RA may activate different nociception pathways
Trials of switching from originators to biosimilars	• Nocebo-attributed discontinuations are determined by the individual clinician decision • Absence of neurochemical, and neuroimaging studies in the rheumatology field • Substantial absence of data on drug and TNF levels in studies of nocebo-attributed discontinuations • At least part of nocebo diagnosis may be due to real drug failure

TNF = tumor necrosis factor

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Capsule

Thymus development, cell by cell

The human thymus is the organ responsible for the maturation of many types of T cells, which are immune cells that protect us from infection. However, it is not well known how these cells develop with a full immune complement that contains the necessary variation to protect us from a variety of pathogens. By performing single-cell RNA sequencing on more than 250,000 cells, **Park** et al. examined the changes that occur in the thymus over the course of a human life. They found that development occurs in a coordinated manner among immune cells and with their developmental microenvironment. These data allowed for the creation of models of how T cells with different specific immune functions develop in humans.

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Capsule

Concern about swine fever vaccines

African swine fever (ASF) is a lethal hemorrhagic disease that affects swine, including wild boar and domestic pigs. Beginning in the mid-2018 with the introduction of the ASF virus to China, an outbreak of ASF has devastated pig farming in Asia. The disease is spreading into Europe and may soon become a global threat to the pig population. Efforts to prevent the spread of ASF virus are challenged by residual infection in the wild boar population and difficulties in preventing the movement of pig products. In a perspective, **Gavier-Widén** and co-authors discussed strategies to develop a vaccine that can be used in bait for wild boar and be administered to farmed animals to effectively overcome ASF. However, in the rush to generate a vaccine, there are concerns that the existing options under development may make matters worse.

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