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Psoriasis, inflammatory bowel disease, and uveitis as paradoxical adverse effects induced by TNF inhibitors in patients with immune-inflammatory rheumatic conditions

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ABSTRACT

Despite their known benefits, tumor necrosis factor alpha inhibitors (TNFi) may cause certain unexpected side effects, such as the aggravation of pre-existing autoimmune conditions or inducing the onset of new inflammatory conditions, these reactions being called "paradoxical adverse effects'' (PAEs). The spectrum of TNFi-induced PAEs is vast and may include dermatological disease (frequently - psoriasiform skin reactions), gastroenterological disease (inflammatory bowel disease), ophthalmological disease (uveitis) and other autoimmune conditions (lupus-like reactions, vasculitis). PAEs are characterized by complex physiopathological mechanisms which remain a matter of further research and may significantly impact the patients' evolution and quality of life. Importantly, a large number of patients require the cessation of TNFi treatment, as well as other types of therapeutic interventions. The present review aimed to analyze recent findings regarding certain paradoxical adverse effects (psoriasis, inflammatory bowel disease, and uveitis) in patients with RA, ankylosing spondylitis (AS), and PsA treated with TNFi.

Keywords: paradoxical adverse effects, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, inflammatory bowel disease, uveitis

INTRODUCTION

Biological therapy with TNFi (tumor necrosis factor alpha inhibitors), has revolutionized the therapeutic management of various chronic inflammatory diseases in the fields of rheumatology, gastroenterology and dermatology [1]. TNFi such as infliximab, etanercept, adalimumab, golimumab, and certolizumab, have become a benchmark for the treatment of rheumatoid arthritis (RA), spondyloarthritides (SpA), Crohn's disease (CD), ulcerative colitis (UC), psoriasis, psoriatic arthritis (PsA), having a great impact on reducing the symptoms and inflammation marker levels (thus lowering disease activity), as well as improving the patients' quality of life and slowing the progression of certain manifestations [2,3]. Moreover, apart from their efficacy, TNFi demonstrate good safety profiles, as shown in numerous clinical studies [1].

Despite their known benefits, TNFi may cause certain unexpected side effects, such as the aggravation of pre-existing autoimmune conditions or inducing the onset of new inflammatory diseases [3,4]. These are so-called "paradoxical adverse effects" (PAEs), with an increasing number of cases reported. The PAEs represent an exacerbation or the development of a new inflammatory disease triggered by biologics that are commonly used to treat the above-mentioned inflammatory condition. The spectrum of TNFi-induced PAEs is vast and may include dermatological disease (frequently - psoriasiform skin reactions), gastroenterological disease (inflammatory bowel disease), ophthalmological disease (uveitis) and other

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autoimmune diseases (lupus-like reactions, vasculitis) [1,5].

A PAE may be referred to as "true" when it is directly induced by a therapy that may be used to treat it (psoriasis, CD, and hidradenitis suppurativa), while a "borderline" paradoxical reaction is triggered by a biological treatment that is not effective in that specific condition (uveitis, scleritis, sarcoidosis, granulomatous diseases, vasculitis, alopecia areata). The latter is defined as a particular immune-mediated effect developed under biological treatment [6]. Importantly, PAEs are often resolved not only by cessation of the drug or switching to another biologic agent, but also by using additional therapies [6].

The pathogenesis of these reactions remains unclear. However, several cases of PAEs have been reported not only in association with anti-TNFα agents but also with other biologics (rituximab, ustekinumab, secukinumab and ixekizumab). Prior to considering an adverse effect as paradoxical, it is necessary to apply a standardized tool, such as the Naeanjo Adverse Drug Reaction Probability Scale, to evaluate the causality of the manifestations [7-11].

The present review aimed to analyze recent findings regarding certain paradoxical adverse effects (psoriasis, inflammatory bowel disease, and uveitis) in patients with RA, ankylosing spondylitis (AS), and PsA treated with TNFi.

PSORIASIS AS A TNFI-RELATED PAE

Paradoxical psoriasis represents the prototypical cutaneous PAE, described as a class effect of TNFi, being the first described and the most common manifestation induced in rheumatologic and non-rheumatologic patients treated with TNFi [4]. Paradoxical psoriasis is a rare, immune-mediated therapy-induced reaction that may be either *new-onset psoriasis*, or *an exacerbation of preexisting psoriatic lesions* [12].

New-onset psoriasis or *de novo* psoriasis represents a temporary condition that occurs in patients without a history of psoriasis, treated with anti-TNFα agents for an immune-mediated rheumatic or non-rheumatic disease. The literature reported that *de novo* psoriasis may adopt different clinical phenotypes [7]. This type of reaction is the most common and the most reported in the literature. The TNFi-related worsening of psoriatic lesions represents a condition that occurs in patients with a history of psoriasis prior to the initiation of biological treatment. The exacerbation of psoriasis after administration of TNFi may appear with or without changes regarding the morphology of psoriasis lesions [12-15].

Perez de Lis et al. found that paradoxical psoriasis was the most frequent biological treatment-induced PAE (of 12731 cases included in the study, 6375 developed psoriasis). The authors also established that TNFi were the most frequent biologic agents involved, in almost 9133 cases [15]. In 2018, Mylona et al. observed that between 2–5% of patients treated with anti-TNFα agents developed paradoxical psoriasis [3,4,16].

In most cases, this reaction does not depend on the underlying disease or the type of TNFi used and it regresses when the treatment is discontinued (which emphasizes that it is not a new immune-mediated disease, but a treatment-induced reaction) [3]. Some studies reported that the patients treated with TNFi in association with a conventional synthetic DMARD (disease-modifying antirheumatic drug) such as methotrexate, have a lower risk to develop PAEs compared to the patients under TNFi monotherapy [17]. Other studies reported that the co-medication with methotrexate has no clear protective role [6].

The risk for a rheumatic patient to develop a paradoxical skin reaction such as psoriasis during the administration of TNFi therapy is higher during the first year of treatment (60%) [4] and it occurs on average about 14 months after beginning the therapy [18-20].

Regarding the distribution by sex, it has been observed that female patients had a higher risk of paradoxical psoriasis during TNF blockade therapy than male patients [21].

According to the classification of inflammatory skin disease, the appearance of paradoxical cutaneous reactions to TNFi can be explained by the interaction between several factors such as genetic predisposition, treatment-induced immune changes and an abnormal cellular immune response pattern [22-24]. The pathogenesis of this type of reaction is considered to be different from that of classical psoriasis [20]. The most widely accepted pathogenic hypothesis was the imbalance of the TNFα and type I-Interferons or IFNα (being typical for early psoriasis), with the overexpression of IFNα and the accumulation of plasmacytoid dendritic cells (pDC) in the skin lesion [4,25,26]. The hypothesis regarding the overexpression of IFNα was confirmed by skin biopsy, which illustrated different results compared to classic psoriatic findings [27-30].

At the level of the skin lesion, keratinocytes and neutrophils release antimicrobial peptides (AMPs) that form complexes with "self" genetic material originating from damaged cells. The pDC are then stimulated to release large quantities of IFNα and the conventional dendritic cells (cDCs) produce TNFα and IL23 (interleukin 23) [3,26] which subsequently leads to the perpetuation of the inflammato-

ry process and the release of other proinflammatory cytokines (such as Th17, IL17, IL22) that induce a hyperproliferation of keratinocytes, favor the accumulation of neutrophils at the level of the skin and upregulate AMPs production [3].

In psoriasis lesions, TNFα may stimulate the maturation of cDCs and pDCs (which lose the capacity to produce IFNα). TNFi block the maturation of pDCs and stimulate an aberrant production of IFNα in the skin, inducing the appearance of skin lesions in some patients [3]. This type of reaction becomes a trigger for the psoriatic skin phenotype. In paradoxical psoriasis, TNFα fails to activate the maturation of cDCs. This may lead to a failure to activate T cells. Therefore, paradoxical psoriasis is mostly independent of T-cells, contrary to the pathogenesis of classical psoriasis [3,26].

According to the literature, there are various rates of development of cutaneous paradoxical reactions during the treatment with anti-TNFα agents that depend on the observation period, the patients examined and specific patient-related factors, the biological agent administered and the period of administration [11,31,32,33].

Paradoxical psoriasis under TNFi appears to be more frequent in patients with RA without a history of comorbid cutaneous inflammatory disease [6, 11]. Collamer and Battafarano found that, of 207 such cases, 43% were RA patients, 26% were SpA patients, and 20% were inflammatory bowel disease (IBD) patients; 59% of these patients were treated with infliximab, followed by adalimumab (22%), and etanercept (19%). The most frequently reported cutaneous paradoxical reaction was pustular psoriasis, followed by plaque psoriasis, and guttate lesions [34]. Brown et al. included in their review 216 cases of de novo psoriasis induced by TNFi. Similar to previous studies, the authors confirmed that most cases were RA patients (37%). Furthermore, the most frequently reported paradoxical cutaneous reactions were plaque psoriasis (44,8%), followed by palmoplantar pustular psoriasis (36,3%), psoriasiform lesions (19.9%), and guttate psoriasis in 11% of cases [19,35]. Regarding the anatomical sites, the authors showed that the most widely involved body areas were the plantar region (45.8%), extremities (45.4%), palms (44.9%), scalp (36.1%) and trunk (32.4%) [19].

Li et al. found that the prevalence of paradoxical skin reactions during TNFi in RA patients was 2,3%-5%. According to studies, the most widely described cutaneous paradoxical reaction is plaque psoriasis (15.8%–50% of cases), palmoplantar pustular psoriasis (PPP) (33.3%–45% of cases), psoriasiform lesions (in 19.9% cases) and guttate psoriasis (in 7%–15 of cases) [32]. Notably, the most frequently involved anti-TNFα agents were infliximab (52.6%–62.5%), followed by adalimumab (14.4–34%) and etanercept (12–29%).

The currently available literature also describes cases in which the administration of TNFi led to a worsening of preexistent psoriasis [6,12,32,34]. The TNFi most frequently implicated in these cases were etanercept (62%), infliximab (23%), and adalimumab (15%) [7,32].

Since these cutaneous paradoxical reactions have been reported with all TNFi, TNFα inhibitor-induced psoriasis is considered to be a class effect [36].

Baganz et al. analyzed a German RA cohort and concluded that the RA patients that received anti-TNFα treatment had a higher risk to develop paradoxical psoriasis compared to those treated with conventional synthetic DMARDs or other biologics. The authors also demonstrated that the female gender and current smoking status may constitute considered additional risk factors for paradoxical psoriasis in RA patients [37].

Bae et al. conducted a retrospective cohort study showing that the risk of the patients with AS developing de novo psoriasis or PPP was significantly increased, approximately 1.8% of AS patients reporting new-onset psoriasis lesions during the treatment with TNFi. Furthermore, the authors found that younger patients had a higher risk under treatment with infliximab [38].

Based on literature data, most patients who developed paradoxical psoriasis discontinued the treatment with TNFi [19,20]. Commonly, the prognosis of paradoxical psoriasis is favorable and it is not always necessary to discontinue the therapy, especially when the underlying inflammatory disease is well controlled and the patient does not have severe skin lesions [7]. Nevertheless, the therapeutic of paradoxical psoriasis represents a challenge for clinicians. Apart from treating the cutaneous eruption and the associated symptoms (pruritus, pain), it is important to consider some relevant factors such as: the severity of the skin lesions, the activity of the underlying rheumatic disease, the patients' quality of life, their comorbidities, other options to treat the rheumatologic conditions, the risk of losing the treatment response in case of switching or discontinuing the TNFi, the treatment of the psoriatic eruption [4,39].

The therapeutic options for paradoxical psoriasis include not only local treatment, symptomatic therapy and corticoids, but also in some case the cessation of the TNFi treatment. In milder cases, where the affected body surface area (BSA) is less than 5%, or in moderate cases (BSA 5-10%), it is not recommended to stop the biological treatment, but it is necessary to apply a topical therapy (topical steroids, keratolytic agents, immunomodulators, vita-

min D analogs) [7,12,34,40]. In moderate to severe cases, the treatment may require UV-phototherapy or systemic treatment (cyclosporine, methotrexate, retinoids and systemic steroids, biologics). The systemic agents are required in 5% of cases [4]. In cases of severe lesions (BSA more than 10%) such as severe plaque psoriasis or generalized pustular psoriasis which may significantly impact the patients' quality of life, it is recommended to discontinue the treatment with anti-TNFα agents. However, there are some patients who demonstrate only a partial improvement after the cessation of biological treatment [1,4,19].

To control the underlying rheumatologic disease, the clinician may consider the change from one TNFi to another one. In these cases, studies show the improvement of the skin lesions only in 15% of cases, while 64% of patients showed an improvement after switching to a biologic with a different mechanism of action. In this last case, the most effective biologic used in cases of paradoxical psoriasis were anti-IL12/23 and anti-IL6 agents [1,41,42,43].

Based on literature data, almost half of the patients with paradoxical reactions will present a spontaneous improvement of cutaneous lesions after the cessation of the triggering biologic and only 45% of patients with paradoxical psoriasis may present persistent skin lesions [4]. Because there is a risk of recurrence of the paradoxical reaction when using the same biologic after the remission of paradoxical psoriasis, it is important to evaluate the treatment options by a double perspective: the underlying rheumatic disease and the availability of alternative biological therapy options [4,44].

INFLAMMATORY BOWEL DISEASE-LIKE CHANGES AS TNFI-RELATED PAES

Another example of a paradoxical reaction induced by BA is the development of inflammatory bowel disease (IBD). The latter are chronic, relapsing intestinal inflammatory conditions including Crohn's disease (CD) and ulcerative colitis (UC) [45,46]. These diseases have many common features and can be differentiated by the location and the nature of intestinal inflammation [47,48]. UC is a lifelong superficial ulcerative disease, affecting only the colon, and is characterized by the inflammation of the mucosa and submucosa, extending proximally in a continuous manner [49]. UC may produce serious complications such as bleeding, toxic megacolon, fulminant colitis or colon carcinoma, which are serious causes of morbidity and mortality in IBD patients [50]. CD involves not only the colon, but may affect any part of the gastrointestinal tract. Usually, CD is characterized by a transmural inflammation which is extending deep into the intestinal wall, in a discontinuous manner. It is associated with granuloma formation [51] and, similar to UC, may produce some complications, such as fibrotic strictures, fistulas, abscesses or carcinoma [48]. The etiology of IBD is not fully elucidated. However, it has been shown that disease progression depends on various factors such as environmental triggers, certain genetic factors, microbial flora, and aberrant immune responses [52].

According to the literature, IBD (UC and CD) may constitute a paradoxical reaction to biologics in rare cases (especially associated with TNFi). Perez de Lis et al. showed that IBD induced by biologics was the second most frequent paradoxical reaction developed in rheumatic patients (845 cases of 12.731) [15]. Of all cases of IBD–like changes, the most frequent presentation was CD (355 cases), followed by UC (228 cases), and non-classified IBD or nonspecific colitis [53-55].

It has been stated that there are no clinical, endoscopic or histopathologic differences between classical IBD and paradoxical IBD [56]. The gastrointestinal reaction induced by biologics is considered to be uncommon, affecting more frequently the populations with AS, PsA or psoriasis, as an extraarticular manifestation of these diseases [57]. It may also affect the individuals treated or retreated with etanercept rather than with other TNFi [55,58]. The association between other autoimmune diseases and IBD has been well studied, in particular with AS, which is connected to IBD clinically, pathologically and genetically [59].

Tolu et al. estimated that the prevalence of new-onset IBD under TNFi in AS patients was around 0.15%, and the incidence was estimated at 2.2/100 patient-years with etanercept, and 0.2/100 patient-years with infliximab. Additionally, AS patients with a history of IBD had a ten-fold risk increase for developing IBD flares during treatment with etanercept [60]. Furthermore, some studies emphasized that the lesions of CD have been seen in up to 50% of patients. Also, approximately 40%-60% of AS patients demonstrated endoscopic and histopathological lesions identical to those of IBD [55].

Seeing as these paradoxical adverse effects are rare, their pathomechanism is poorly understood. Nonetheless, both diseases (CD and UC) have digestive inflammation in common as a pathogenic mechanism [53]. The normal intestinal mucosa is in a dynamic balance between factors that activate the host immune system (such as luminal microbes, diets) and the host defense systems that reduce the inflammation and maintain the integrity of the intestinal mucosa. Once this balance is disturbed, it can lead to changes in the mucosal physiology and cause the development of many gastrointestinal disorders, including IBD [61].

It is widely accepted that the pathogenesis of IBD is related to an aberrant immune response, through the activation of CD4+ (Cluster of Differentiation 4) T cells against the commensal microbiota [56,62]. Studies have revealed that the tissue of patients with active intestinal inflammation has higher levels of CD3+ CD4+ T cells than healthy individuals [51]. This dysregulated immune response has an important role in the pathogenesis of IBD. It has been hypothesized that the intestinal inflammation observed in CD could be explained by macrophage and/or neutrophil dysfunction, based on impaired secretion of TNFα, which may incompletely remove the bacterial antigens found in tissues [63]. CD4+ T cells have a major role in the beginning and the development of this pathologic response. The capacity of CD4+ T cells (such as T helper cells Th1, Th2 and Th17) to initiate and to shape the immune response is related to the production of different cytokines [64,65].

According to the literature, the gut inflammation in CD involves especially Th1 cells which produce an aberrant production of IFNγ and TNFα which activate innate immune cells, such as neutrophils and macrophages. Th1 is an important factor involved in the protection against intracellular pathogens [66]. The intestinal inflammation of UC is characterized by an aberrant production of Th2 cytokines, especially IL4, IL5 and IL13 being involved in allergic disorders or asthma and in the protection against extracellular microbes [66]. In the intestinal mucosa of CD patients there is an increased level of TNFα, interferon IFNγ and IL12, IL17A, IL21, IL23, while intestinal mucosa of UC patients is an increased level of the cytokines IL13, IL5 [67,68].

Furthermore, some studies have emphasized a correlation between the disease severity in patients with CD and the levels of IFNγ in their blood. In contrast, in UC patients no similar association was found [64].

Another important factor involved in the IBD pathogenesis is Th17, which plays a significant role in protection against microbial pathogens and is considered to be a driver of autoimmune disease, being correlated to multiple inflammatory conditions [51]. One of the cytokines secreted by Th17 cells is IL17A that plays an important role in chronic infection and in mediating autoimmunity [69,70]. According to the literature, patients with active CD and UC have a significantly higher number of IL17+ cells compared to inactive forms of disease. Moreover, the levels are undetectable in healthy individuals [64,66].

Hutchings et al. estimated that TNFi-induced paradoxical gastrointestinal reactions (new-onset IBD or IBD flares) appear after approximately 4-40 months of treatment (with a median value of 27 months) [53].

Epidemiological studies have revealed a link between AS or PsA and inflammatory bowel disease–like changes [71]. The AS or PsA patients have a significant independent risk (4 times higher) to develop CD or UC [56,72], but the connection between these immune diseases is not clearly understood [73]. Paradoxical IBD occurs more frequently among patients that are genetically susceptible and are treated with TNFi, with etanercept showing a stronger connection to these reactions compared to monoclonal antibodies [73].

Recent studies show that the administration of etanercept is ineffective in CD. Etanercept produces a cytokine imbalance and may provoke an alteration of the inflammatory cytokine expression in the bowel mucosa, leading to the development of IBD. So, etanercept not only may trigger the development of CD, but also, may accelerate this disease in genetically susceptible patients [73].

O'Toole et al. identified 49 cases of paradoxical IBD under etanercept (44 CD, 5 UC). The most frequent immune rheumatic inflammatory disease involved was AS (11 CD, 3 UC), JIA (juvenile idiopathic arthritis, 11 CD), RA (9 CD), RA (3 CD), PsA (7 CD, 2 UC), and psoriasis (3 CD). The mean duration before paradoxical IBD onset was 3.58 months. After the development of IBD, 34 patients discontinued the treatment with etanercept, 19 patients switched to another TNFi and 3 patients responded to the treatment with 5-aminosalicylic acid and continued the administration of etanercept [74].

Puig identified 16 cases of new-onset IBD in patients with inflammatory rheumatic disease after the administration of TNFi. The most frequent paradoxical IBD was CD, reported in AS patients after receiving etanercept. Paradoxical UC was reported in psoriasis patients during treatment with adalimumab [75].

Korzenik et al. examined a population-based cohort (17 018 individuals) and concluded that there was a higher risk to develop de novo IBD among rheumatologic or dermatologic patients during the administration of TNFi. Specifically, they found that etanercept was frequently associated with the development of new-onset UC and CD. Also, the risk was lower for patients treated with infliximab or adalimumab [62]. In 2019, Hutchings et al. found that 3 of their patients developed paradoxical reactions under TNFi: 2 were affected by inflammatory bowel disease-like changes, and 1 patient developed sarcoid-like granulomas. After the cessation of the treatment with TNFi, all three patients showed clinical improvement [53].

Recently, some case reports and clinical studies have reported new-onset enterocolitis as a severe form of paradoxical gastrointestinal reaction during biological treatment. At least 158 cases of new-onset enterocolitis were identified in patients with JIA

and RA from the U.S. FDA registers (United States of America Food and Drug Administration), frequently during administration of etanercept (82%) [11].

In general, there were described two therapeutic solutions for the patients with paradoxical IBD treated with etanercept for an underlying rheumatic disease. If the patient is treated with etanercept in monotherapy, then it is recommended to stop etanercept and add azathioprine and corticosteroids as a solution. If the patients received etanercept in combination with other disease-modifying antirheumatic drugs, then etanercept can be discontinued without adding any new drugs [55].

UVEITIS AS A TNFI-RELATED PAE

Another common paradoxical reaction to TNFi is uveitis, an inflammatory eye disease that is responsible for 10% of legal blindness [76]. Uveitis occurs due to inflammation of the uvea (the iris, ciliary body, choroid) [77] and may be infectious or non-infectious [78]. Uveitis can constitute a manifestation of various systemic diseases, such as RA, AS, PsA, UC, CD, or sarcoidosis [79]. Between 23–63% cases of uveitis are idiopathic (associated with inflammatory, traumatic and infectious conditions) [80], while 40% of uveitis is associated with systemic autoimmune diseases [77].

According to the International Uveitis Study Group, uveitis may be classified depending on the anatomic position of inflammation: anterior, intermediate, posterior or involving all parts (panuveitis) [81]. The anatomical classification is clinically essential, as it helps in the differential diagnosis of its etiology and therapeutic approach. In 2005, the Standardization of Uveitis Nomenclature (SUN) refines the anatomical classification of uveitis by defining descriptors based on clinical onset (sudden or insidious), duration (limited <3 months, or persistent >3 months), and course (acute, recurrent and chronic) [82].

Choi et al. estimated a rate of new-onset and recurrence of uveitis in AS patients at about 5.0% and 38.2%, over 46.7 months [83]. Based on the literature data, anterior uveitis (AU) is the most frequent, being estimated at 50% of uveitis cases, while posterior uveitis is the least frequent [84]. Of all types of uveitis, AU prevalence is slightly higher in AS patients, accounting for approximately 33% of cases, while in patients with PsA the prevalence is about 6–9%, and 2–5% in patients with IBD [85]. Usually, in AS patients, the uveitis is unilateral, while in IBD or PsA patients, the uveitis is often bilateral [85].

Regarding the distribution by gender, there are different results published. One meta-analysis described the prevalence of uveitis to be higher in women (33%) than in men (29%). However, there are studies that reported that the prevalence is higher in male patients, while other research established no difference between genders [86].

Paradoxical uveitis is defined as a rare, immune-mediated therapy-induced non-infectious reaction [78,79]. A number cases of uveitis have been reported as paradoxical reactions to biologics, especially after TNFi therapy. Iqbal et al. state that certain drugs may induce the appearance of uveitis in about 0.5% of cases [87] and, sometimes, may trigger a severe lesion that can be easily misdiagnosed [81]. Because these paradoxical adverse effects are uncommon, the pathogenesis remains poorly understood [88].

There are several theories regarding the development of different types of uveitis. In general, uveitis can be explained through the interaction between genetic predispositions, some trigger factors (such as the microbiome, bacterial infection or stress), and an abnormal response of the innate and adaptive immunity [86,88].

According to the literature, the major genetic factor involved not only in AS, PsA, but also in uveitis, is HLA-B27 (Human Leukocyte Antigen) [89]. The prevalence of uveitis in HLA-B27 positive SpA patients is about 50% and only 14% in HLA-B27 negative SpA patients [86]. One hypothesis regarding the development of uveitis in AS patients could be the presence of abnormal forms of HLA-B27 that introduce the 'uveitic' antigens to CD4+ T cells and natural killer cells (NK) cells causing their autoreactivity. In this manner they are able to induce inflammation in the joints or eye [90].

The pathogenesis of drug-induced uveitis remains unclear. However, several hypotheses have been proposed. One of them is that the drugs may induce uveitis by direct mechanism, when the drug has direct contact with the eye (topical, intravitreal or intracameral administration) or through indirect mechanism when the drug may stimulate the immune system to produce an anti-drug antibody [91]. Another possible mechanism involved in the development of uveitis could be an aberrant inflammatory response of both adaptive and innate immune systems or auto-inflammatory disease, which was suggested as a mechanism for different types of uveitis [90].

Some authors proposed the hypothesis that the microbiome plays an important role in the development of SpA and uveitis [92]. The destruction of the intestinal barrier function allows the transfer of intestinal immune cells to extra-intestinal sites, such as the eye, where they may induce a local inflammatory cascade. Another hypothesis that confirmed the implication of the microbiome to the pathogenesis of uveitis is the theory regarding the molecular mimicry between HLA-B27 and some bacteria such as *Klebsiella* [86].

Normally, there is a balance between inflammatory mechanisms and regulatory mechanisms. Once

this immune balance is destroyed, the development of uveitis may begin. In the context of intraocular inflammation, the blood-retina barrier (BRB) is compromised by pro-inflammatory agents such as cytokines IL1, IL6 and TNFα, causing an accumulation of these cytokines [93]. For that reason, in order to treat non-infectious uveitis, it is fundamental to reduce the level of inflammatory cytokines [94]. The latter can be produced by Th cells of the CD4+ lineage. CD4+ T cells may be differentiated into Th1, Th17 or Th2. Th1 and Th17 cells play an important role in inflammatory and the development of autoimmune uveitis, both of them being considered to be pathogenic effectors, inducing, tissue lesions independently [95,96]. Furthermore, the Th17 line predominantly enrolls granulocytic inflammatory infiltrate into the eye, while the Th1 line favors the formation of mononuclear infiltrates [96].

The Th1 cells produce a large quantity of IFNγ, which is responsible for cellular immunity, Th2 produces IL4, IL 5, IL13 and is responsible for humoral immunity, and Th17 produce IL17, IL21, and IL22 [97]. Another important cytokine is IL23, whose level is elevated in the serum of the patients with uveitis and AS. IL23 is produced by dendritic cells and macrophages. It is known to play an important part in the development of pathogenic Th17 cells. Without the presence of IL23, Th17 cells will develop, but would not be pathogenic [97].

Some studies reported that TNFα is an activity marker in patients with uveitis. The concentration of TNFα in the aqueous humor of patients with idiopathic uveitis or HLA-B27+ individuals is increased [94]. TNFα is considered a key factor of intraocular inflammation, activating macrophages and T cells and inducing the destruction of the BRB, which causes the development of uveitis [77].

Drug-induced AU is frequently associated with all TNFi, the inflammation being more frequently reported under etanercept, but may also be induced under infliximab and adalimumab [81]. Commonly, anti-TNFα therapy is administered to reduce the inflammation in patients with severe acute AU or in patients with recurrent acute AU. To explain this reaction, it has been proposed the hypothesis that the decreased TNFα levels produce an increased level of interferon and a disparity of cytokines that lead to autoantibody formation and increased inflammation.

Etanercept is the most frequently incriminated agent, being associated with paradoxical uveitis in AS patients. Additionally, observational studies emphasize that etanercept is not as effective as infliximab or adalimumab in preventing uveitis [83].

In the RHAPSODY trial, the authors demonstrated that treatment with Adalimumab reduces the occurrence of AU flare (in about 50% of the cases) in patients with AS [98]. In 2016, a multicenter, double-blind, randomized, placebo-controlled phase 3 trial (VISUAL II) found that adalimumab is safe and effective compared to corticosteroid therapy, having a decreased risk of inducing the recurrence of uveitis. Studies highlighted that adalimumab is more effective in preventing uveitis flares and in maintaining remission, being also well tolerated by patients with different autoimmune diseases [99].

In 2017, Prez de Lis et al. showed in their review that paradoxical uveitis occurred in 182 cases. They established that the main underlying disease associated with this type of reaction was RA or JIA, about 69% [15].

Lie et al. reported in their study that the risk of occurrence of uveitis in AS patients after administration of etanercept was 4 times higher compared to those treated with Adalimumab during the first 2 years of therapy. Also, the risk of uveitis in AS patients after treatment with etanercept was 2 times higher for AS patients compared to those treated with Infliximab [100]. The protective role of monoclonal anti-TNF antibodies against AU compared with the soluble TNF receptor was described previously in several studies. Frant et al. confirmed the conclusions of other similar previous studies that the patients treated with etanercept have a significant risk to develop uveitis compared to monoclonal antibody treatment (infliximab or adalimumab) [101].

In 2020, Choi et al. highlighted the occurrence (new-onset and recurrence) of non-infectious uveitis after administration of different types of TNFi (adalimumab, etanercept, infliximab or golimumab) in an AS cohort of 175 patients. Of all 175 AS patients, 27 developed uveitis after receiving infliximab, adalimumab, golimumab or etanercept. The authors reported (contrary to previous study results) that the etanercept is not associated with a high risk of development of uveitis compared with other TNFi. Also, they demonstrated that in the group with a high risk of new-onset of uveitis, there was no significant difference between the patients receiving different anti-TNF agents. On the contrary, the risk of recurrence of uveitis was 5.4 times higher in AS patients after the administration of infliximab than in those treated with adalimumab or golimumab [83].

In 2020, Gonzalez et al. conducted an observational study of 320 PsA patients finding 10 patients with uveitis. Of these 10 patients, only 2 received biologics and developed uveitis during the treatment. One patient developed new-onset uveitis during etanercept, and the second one had a history of recurrent uveitis and developed new flares under adalimumab, certolizumab and golimumab [102].

In general, the therapeutic solution for paradoxical uveitis included (in almost all cases) the cessation or switching to another biological agent [78].

CONCLUSION

A large spectrum of PAEs has been reported in patients with various immune-inflammatory diseases under administration of biologic therapy, especially under TNFi drugs. This type of reaction is characterized by complex physiopathological mechanisms which remain a matter of further investigation. These paradoxical reactions may have a serious impact on the patients' quality of life and, as a consequence, require adequate knowledge and attention from the clinician in choosing the therapeutic management.

The main priorities for the rheumatologist include the close surveillance of patients treated with biologics in order to prevent, identify, monitor and treat possible PAEs, while also ensuring the optimal control of the underlying inflammatory rheumatic disease.

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