Anti-TNF-α induced paradoxical psoriasis in patients with ankylosing spondylitis: a systematic review

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ABSTRACT

Background. The approval of TNF-a inhibitors (TNFi) was a breakthrough in the treatment of ankylosing spondylitis (AS). Although also effective in psoriasis, drug-related adverse events of onset of psoriasiform skin lesions – paradoxical psoriasis (PP) under TNFi have been reported.

Methods. We performed an electronic data search in MEDLINE via Pubmed and Cochrane library scientific databases from inception to January 2023, following the PRISMA guidelines. We assessed the distinct characteristics and frequency of risks for PP appearance in AS patients treated with different TNFi.

Results. *PP* was found in 0.5–1% of TNFi-treated AS patients and the latency period was 2–11 months. The safest TNFi in terms of PP induction was certolizumab, whereas the one most commonly associated with PP was infliximab.

Conclusion. *PP* is an uncommon adverse reaction to TNFi treatment in AS patients and responds well to drug withdrawal. More large data studies need to be conducted though, to shed light on PP nature and management.

Introduction

Ankylosing spondylitis (AS) is a chronic, inflammatory disease that typically affects the axial skeleton (1, 2). It is characterised by new bone formation that eventually leads to joint ankylosis and spine fusion, which manifest clinically as increased spinal rigidity and decreased range of motion (3, 4). The pharmacological armamentarium utilised to induce remission, relieve symptoms and reduce functional disability was previously limited to non-steroidal anti-inflammatory drugs (NSAIDs); these agents are still considered the first line treatment option by the current, state of the art EULAR guidelines (5). In this light, substantial advances in preclinical and translational research in the last two decades changed the therapeutic landscape of the disease with the introduction of targeted therapies, with the potential to control disease activity (6, 7). More specifically, the approval of the TNF- α inhibitors (TNFi), other biologics such as IL-17-antagonists and small molecules that inhibit Janus kinases heralded a new era in the treatment of AS, substantially improving symptoms and quality of life (8).

TNF- α is a potent orchestrator of inflammatory responses, secreted primarily from macrophages and monocytes (9). Early reports in patients with spondyloarthritis showed elevated TNF- α concentrations in the serum and synovial tissue while TNF- α mRNA was found to be overexpressed in the cellular infiltrate in patients with sacroiliitis (10). Taken together, these data suggested a critical role for this cytokine in immunopathogenesis and justified subsequent clinical studies on TNF-a blockade in patients with AS. In the early 2000s, the success of the TNF- α antagonist infliximab in the treatment of patients with active AS (11) provided evidence that blocking a single proinflammatory mediator such as TNF- α could potentially be of a game changing therapeutic significance in inflammatory arthritides. At present, there are five approved TNF- α antagonists for the treatment of AS in the market, namely infliximab, golimumab, adalimumab, etanercept and certolizumab. The number of available TNFi was further increased during the last years with the introduction of biosimilars.

Although spinal inflammation and damage constitute the principal features of AS, up to one third of patients have

a positive history of one or more extraarticular manifestations, such as anterior uveitis, inflammatory bowel disease (IBD) and psoriasis (12). Especially, history of either IBD or psoriasis was associated in recent studies with higher disease activity and functional impairment, while patients with these comorbidities were treated more frequently with TNFi (13, 14). The efficacy of TNF blockade in achieving remission and preventing new flares differs between the extra-articular manifestations (15). Since TNFi are typically highly efficacious in psoriasis treatment, the development of new psoriasiform lesions or the exacerbation of chronic psoriasis under TNF-a blockade is referred to as paradoxical psoriasis (PP). This phenomenon is reported in up to 5% of patients with a variety of primary diagnoses with newly initiated TNFi while the majority of cases occur within the first year of treatment (16). In this systematic review, we explore the available epidemiological data of new onset PP in patients with AS, summarise the potential pathogenetic mechanisms and propose therapeutic interventions.

Methods

This systematic review was performed in accordance with the Cochrane Handbook for the systematic reviews of Interventions and the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was registered on the International Prospective Register of Systematic Reviews (PROSPERO identifier: CRD42022337988).

Aim of the study

The research question was agreed upon by all authors and formulated using the PICO strategy.

The focused PICO question was:

Is the use of TNF- α inhibitors in patients with AS associated with an increased risk of new psoriasis?

Population/patient: patients with AS. Intervention: treatment with TNF- α inhibitors.

Comparison: treatment with placebo or other drugs.

Outcome: percentage of patients with new psoriasis.

Literature search

We conducted an electronic search of articles indexed in MEDLINE via Pub-Med and Cochrane library scientific databases from inception to January 2023. The detailed search strategy is delineated in the Supplementary file. A brief summary is presented in the flowchart. A manual search in the reference lists of the retrieved relevant articles was conducted to assess for additional eligible articles.

Duplicates were removed using Rayyan, a web and mobile app for systematic reviews (17). Subsequently, two authors (I.S., G.I.) screened the titles and abstracts of the retrieved articles independently to identify the potentially relevant ones. Those conforming to the proposed theme were further assessed in full text to determine eligibility for inclusion according to the predefined inclusion criteria. Any disagreement among the reviewers was resolved by discussion. Additionally, studies published in any other language other than English, only in abstract form, editorials, review articles, meta-analyses, book chapters, clinical guidelines, clinical trial protocols and pre-clinical studies were excluded for the purpose of the current review.

Selection criteria

The inclusion criteria consisted of: 1. studies assessing the treatment of

patients with AS,

2. TNFi was used as treatment,

3. psoriasis was a documented side effect.

Palmoplantar pustulosis (PPP) was considered for the scope of this review as a form of psoriasis and patients who developed it were included in the final analysis.

The exclusion criteria were defined as follows: 1. Patients with axial involvement in the context of another systemic disease such as inflammatory bowel disease and psoriatic arthritis, 2. patients with any pre-existing form of psoriasis, 3. patients who developed psoriasis more than 12 months following the initiation of a TNF- α inhibitor.

Data extraction

The extraction and collection of patient characteristics and treatment data was

performed by a single author (I.S.) and included where available age, gender, previous treatments and co-treatments for AS, latency period and offending TNFi for PP.

Results

Risk of paradoxical psoriasis and potential risk factors

In the largest study published to date, Bae et al. evaluated retrospectively the incidence of psoriasiform skin lesions in a cohort of 7491 patients with AS treated with TNFi. An identically sized patient cohort who received conventional therapy was used as control. Patients treated with TNF- α inhibitors were found to be at increased risk for development of new-onset psoriasis (HR: 1.915; 95% CI: 1.390-2.637; p<0.01) and PPP (HR: 9.251; 95% CI: 3.681-23.249) after adjustment for probable confounders. Moreover, young age and female gender emerged as risk factors for the development of TNFi-associated psoriasis, the latter owing perhaps to hormonal factors or a dose-related effect, as female patients are generally treated with higher TNFi doses per kg compared to males. On the other hand, male sex was linked to a higher incidence of PPP. Nevertheless, smoking status and weight were not assessed, factors that could potentially play a role in the pathogenesis of psoriasis (18). For instance, in a cross-sectional study current smokers were 1.66 times more likely to develop psoriasis in the course of their disease (19). Of note, while Bae et al. postulated a probable association between higher disease activity in patients treated with TNF blockers and psoriasis that could account for the increased incidence of PP, recent research found no such correlation (20).

Owing to the rarity of both AS and TNFinduced psoriasis, the exact incidence of the latter is difficult to be assessed. In a retrospective exploratory analysis of an open-label phase IIIb clinical trial of 1250 patients treated with adalimumab for active AS, five patients (0.5%) were found to have new-onset, mainly mild, psoriasis (21). Moreover, in a 10-year retrospective study of 188 patients with AS treated with infliximab, etanercept or adalimumab two cases of cutaneous

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Study	no. of patients	Gender	Age (years)	Latency period	Offending agents	Type of psoriasis	Most prevalent therapeutic measure	Complete response (CR) or Partial response (PR) or No response (NR)
Bae <i>et al</i> .	137	Male: 110, Female:27	mean ± SD: 37.4 ± 12.3	N/A	Infliximab, Etanercept, Adalimumab	GPP, PPP	N/A	N/A
Braun et al.	5	N/A	N/A	Mean: 62 days	Adalimumab	N/A	N/A	N/A
Wendling et al.	6	Male: 6	46-54 (min-max)	Mean: 3 months	Adalimumab, Infliximab, Etanercept	GPP, Scalp, palmoplantar	Cessation of treatment in one patient	CR in the patient with the cessation, in the others no response with topical treatment
Wollina et al.	1	Female	24	N/A	Infliximab	Generalised Pustular Psoriasis	Cessation of treatment, PUVA	CR
Lee et al.	2	Male:2	19,45	2,4 months.	Infliximab	GPP, PPP	N/A	N/A
Aslanidis et al.	2	Male:1 Female:1	24, 57	3,8 months.	Infliximab	PPP	Topical agents/CsA	Improvement
Baeten et al.	3	Male: 2, Female:1	44,44,45	13, 34, 23 months.	Infliximab	PPP	Topical corticosteroids	2/3: CR 1/3: NR
Kobaner et al.	1	Female	45	2 months	Certolizumab	GPP	Clobetasol Levocetirizine	Palmoplantar lesions: PR Truncal lesions: CR
Pyrpasopoulou et al.	1	F	53	14 weeks	Infliximab	PPP	Cyclosporine, TNF switch	CR
Ibis et al.	1	М	NA	4 months	Adalimumab	PPP	NA	NA
Bae et al. (2020)	1	М	34	3 mo	Adalimumab	PPP	TNF switch, topical agents	CR
Cohen et al.	6	5 F 1 M	32-70 (min-max)	2-41 months (min-max)	5 Infliximab 1 Etanercept	3 erythematous scaly lesions 2 PPP 1 follicular lesion	, 3 discontinuations 5 topical treatments	CR all
Sfikakis et al.	1	F	33	9 months	Infliximab	PPP	TNF switch	PR
Capkin et al.	1	F	29	4 months	Infliximab	PPP	MTX, topical treatment	PR
Sedie <i>et al</i> .	1	F	29	10 months	Infliximab	erythematous, scaly lesions, erythema nodosum	TNF switch, oral corticosteroids	CR
Safa et al.	1	F	35	5 months	Infliximab	PPP	TNF discontinuation, MTX	PR
Volpe et al.	1	М	56	4 months	Infliximab	erythematous, scaly lesions	Topical treatment	PR
Starmans-Kool et al.	1	М	41	4 months	Infliximab	PPP	Topical treatment, temporary discontinuation	CR

Table I. Main characteristics of the included studies

GPP: generalised plaque psoriasis; N/A: not applicable

complications leading to drug discontinuation were reported which represents an incidence of approximately 1%. (22). Data coming from a specialised tertiary care facility showed that AS was the least common primary diagnosis among patients with PP under TNF-treatment (23). More details regarding the incidence of TNF-induced psoriasis in the included studies can be found in a summary depicted in Table I. Taken together, the above data suggest a lower incidence of PP in patients with AS, than the one reported in literature reviews of other primary conditions for which TNF blockers are prescribed (23). This can be due to reporting errors, male predominance in AS or

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Fig. 1. Pathophysiology of PP pathogenesis compared to classical psoriasis.

The upper panel depicts classical psoriasis pathogenesis, highlighting the importance of TNF for pDC maturation. Following pDC maturation, antigen presentation takes place, adaptive immunity is activated and cytokines such as IL-17, Il-23 orchestrate the inflammatory process leading to psoriasis. In contrast, TNF inhibition (lower panel), leads to uncontrolled IFN- α production by immature pDCs, a process driven by the innate immune system. Then keratinocyte inflammation and proliferation is mediated potentially through the JAK-STAT pathway leading to PP.

pathophysiological factors inherent to AS that render patients less prone to developing TNFi-induced psoriasis and which are still not elucidated.

Latency

In the study by Braun et al. (21) the median latency period between the first dose of adalimumab and the onset of PP was 62 days, while in a French observational study three months (range 1-6 months) (24). This temporal association infers most probably a causal relationship rather than an arbitrary event. On the other hand, the largest retrospective study to date documented a median latency of 11 months. (23). Further studies reported similar numbers, although not specific to AS (25). The reported variation in latency could be attributed to a multifactorial genesis of the adverse drug effect with involvement of additional triggers such as infections (23).

Offending agents

In line with data stemming from large case series and reviews mainly in inflammatory bowel disease, psoriasis in patients with AS is more common under infliximab treatment (HR: 2.280; 95% CI, 1.390-2.637) (18). Furthermore, infliximab seems to be associated with a much higher incidence of PPP (HR: 9.084; 95% CI, 3.681-23.249) (18). In one of the first reports of its kind, three patients on infliximab developed PPP 13, 23 and 34 weeks following treatment initiation, respectively. All three patients were HLA-B27 positive while in two patients the lesions were responsive to topical corticosteroid therapy (26). In a subsequent study, two additional cases were reported. Both patients received local treatments and/or cyclosporine, which resulted in attenuation of skin lesions (27). Data from two tertiary care university hospitals further corroborate this association (28, 29). The pathophysiological factors that could underlie this association are still largely unknown (30). Moreover, the pathogenetic insights gained from the lack of efficacy of IL12/23 (31) and IL-17 (32) inhibitors in PPP show that these cytokines of cardinal importance in classical psoriasis may not play a sufficiently vital role in PPP, hinting at a completely different immunological landscape, that may explain the disproportionately higher hazard ratio for PPP under infliximab treatment.

Among the TNF- α antagonists, certolizumab pegol may be the safest agent in terms of developing psoriasis as an adverse reaction. For example, a

pooled analysis of safety data originating from 315 patients with axial spondyloarthritis treated with certolizumab pegol revealed no cases of new onset psoriasis. (33). Our extensive literature search revealed only one reported case of a wax and waning psoriasiform skin eruption two months after commencement of treatment (34). Previous treatment with adalimumab did not lead to such lesions, pointing perhaps at a more complex pathophysiological interplay between ankylosing spondylitis, TNF- α inhibitors and the occurrence of psoriasis than mere a class effect (35). In line with the above, Pyrpasopoulou et al. (36) reported a male patient who developed extensive PPP on consecutive treatment with two TNFi. Nevertheless, a switch to a third agent of the same class, namely etanercept, achieved clinical remission of the rash.

Similar skin reactions with other TNF- α antagonists, were documented in case reports and smaller case series, the main characteristics of which are presented in Table I (37-45).

Discussion

The advent of TNFi revolutionised the treatment of AS. Although highly efficacious in improving axial inflammation and ameliorating extra-articular manifestations of the disease, these agents come with some side effects. Among them, PP, albeit uncommon, poses a major treatment challenge that reduces the quality of life and threatens a discontinuation of an otherwise effective treatment.

Despite recent advances in the field, the pathogenesis of PP remains largely unknown. It is speculated that TNFiinduced psoriasis is driven by an uncontrolled innate immune response deriving from IFNa overproduction by plasmatocytoid dendritic cells (pDCs) (46). In classical psoriasis, TNF is important for pDC maturation (47): subsequently, mature DCs perform antigen presentation to T cells. Then, through cytokine networks (TNF, IL-23, IL-17) inflammation is mediated by the adaptive immunity leading to keratinocyte proliferation (48). When TNFi is introduced in a genetically predisposed individual (49), pDCs are unable to



undergo their maturation process in the absence of TNF (50). Immature pDCs can produce high amounts of IFN α and this overproduction is thought to lead to an intense inflammatory innate response, without the TNF presence acting as a "brake" (51). Paradoxical psoriasis skin is found to have pDC and neutrophil infiltrates (52). The absence of T cell response could partially explain why PP auto-regresses after the TNFi discontinuation in most cases (16). A brief overview of the pathogenesis of classical versus paradoxical psoriasis is shown in Figure 1. Shedding light on the underlying pathophysiological mechanisms may allow in the future the development of a more targeted therapeutic approach, avoiding the usage of TNFi in patients, identified to be at increased risk for PP. Our systematic review showed that PP affects around 0.5-1% of patients with AS treated with TNFi, while young age and female sex emerged as the major risk factors. The latency period varies significantly and ranges from

two to eleven months. Moreover, our review showed that certolizumab has the lowest incidence rate in regard to development of PP. Although TNFi discontinuation resulted in resolution of the skin lesions in the vast majority of cases included in our review, a more conservative approach can also lead to clinical improvement. For instance, topicals (corticosteroids/calcipotriene/ calcineurin inhibitors) alone or in combination with the oral calcineurin inhibitor cyclosporine were in a large series (23) successful in treating PP while the inciting TNFi was continued. However, in cases with severe skin involvement the most reasonable therapeutic approach appears to be the discontinuation of the offending agent and the introduction of an alternative treatment. Since two non-anti-TNF therapeutic classes are available for AS, a switching strategy towards an IL-17 or JAK inhibitor may be considered a more effective and safe therapeutic approach compared to a cycling strategy (introduction of another TNF blocker).

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However, no evidence exists for this approach and therefore robust recommendations cannot be given based on the current literature. The largely unknown pathophysiology of the disease inflicts substantial limitations in our capacity to expand our therapeutic choices and help our patients. Nevertheless, new advances from the world of bioinformatics may provide in the future predictive tools and enhancing preventive strategies.

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We used *Biorender.com* to create the figure.

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