Paradoxical onset of psoriatic arthritis during treatment with biologic agents for plaque psoriasis: a combined dermatology and rheumatology clinical study

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ABSTRACT

Objective. *To evaluate the incidence of new cases of psoriatic arthritis (PsA) in patients with plaque psoriasis receiving biologic drugs.*

Methods. *A retrospective study was performed on 434 psoriatic patients under biologic treatment, attending the Psoriasis Care Centre of Dermatology at the University Federico II of Naples from January 2011 to November 2015. As part of the routine clinical practice, assessment of disease activity was made at baseline, and every 3 months. PsA diagnosis was performed by a rheumatologist through clinical examination, evaluation of the CASPAR criteria, laboratory and radiological assessment.*

Results. *On the basis of the inclusion and exclusion criteria, we reviewed and analysed the clinical data of 327 patients with plaque psoriasis. The biologic drugs adalimumab, etanercept, infliximab and ustekinumab were prescribed to 116 (35.5%), 88 (27.0%), 27 (8.2%), and 96 (29.3%), respectively. We found that 22 out of 327 patients with plaque psoriasis developed PsA during treatment with biologic drugs. In particular, 6 (27.2%) PsA patients were under etanercept therapy, 10 (45.4%) under adalimumab, 4 (18.2%) under ustekinumab and 2 (9.2%) under infliximab.*

Conclusion. *The results of this study show that in several psoriasis patients, biologic therapy may not be sufficient to prevent the onset of articular involvement. In most of the verified PsA cases, arthritis occurred in concomitance with severe cutaneous involvement.*

Introduction

Psoriasis is a chronic inflammatory skin disease associated with several comorbidities (1). From 6% to 48% of psoriatic patients may develop psoriatic arthritis (PsA) (2). PsA is an inflammatory arthropathy and, as well as psoriasis, represents a frequent clinical manifestation of psoriatic disease (2). It involves the peripheral and axial joints, entheses and tendon sheaths (3, 4). In two-thirds of PsA cases, skin lesions precede the onset of joint involvement by even 10 years and most often occur between the ages of 35 and 45 (5).

Diagnosis of PsA relies mainly on clinical evaluation and its key addressing findings are represented by psoriasis or familial history of psoriasis, dactylitis, enthesitis, inflammatory low-back pain and seronegative rheumatoid factor (RF) (6, 7). The ClASsification criteria for Psoriatic ARthritis (CASPAR) are usually used to classify research cohorts, having a high specificity (98.7%) and sensitivity (91.4%) (8). The CASPAR criteria have been shown highly feasible, specific, and sensitive also when adapted for retrospective use (9).

Therapy for non-severe PsA form consists of non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroids injections whereas in refractory cases conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), mainly methotrexate (MTX), sulfasalazine (SSZ), cyclosporine (CSA), and leflunomide (LFN) are used. Biological DMARDs (bDMARDs), including anti-tumour necrosis factor alpha (anti-TNF-α) agents and other biologics with different targets (anti-IL-12/23 p40 monoclonal antibody, ustekinumab and anti- IL-17 monoclonal antibodies such as secukinumab) represent therapeutic strategies recommended in resistant patients (10, 11).

bDMARDs have been shown to be effective on psoriasis, as well on all articular manifestations including enthesitis, dactylitis, and axial involvement (12-16).

The aim of the study was to evaluate the possible onset of paradoxical form of psoriatic arthritis during treatment with biologic agents for plaque psoriasis.

Patients and methods

A retrospective study was performed on 434 psoriatic patients under biologic treatment, attending the Psoriasis Care Centre of Dermatology at the University Federico II of Naples from January 2011 to November 2015.

Inclusion criteria were both sexes and stable medical conditions. Exclusion criteria was a previous diagnosis of PsA before starting biologic therapy.

The following data were collected for each psoriasis patient: age, gender, vital signs, detailed family and personal

medical history, previous and/or actual treatments, disease duration, and biologic drugs use (adalimumab, etanercept, infliximab, ustekinumab).

As part of the routine clinical practice, assessment of disease activity was made at baseline (T0), and every 3 months. In particular, clinical and laboratory assessments were recorded, including: *i*. psoriasis area and severity index (PASI), *ii*. a panel of blood biochemical parameters, including rheumatoid factor (RF), *iii*. the Early ARthritis for Psoriatic patients (EARP) questionnaire as a PsA screening tool, with a cut-off value of 3 for EARP-10 (17) and *iv*. therapeutic plan updates. Moreover, we reviewed and analysed the outcomes of rheumatologic visits performed in case of patients with painful and swollen joints, and EARP value >3.

Diagnosis of PsA was performed by a rheumatologist through clinical examination, evaluation of the CASPAR criteria, laboratory tests, and radiological assessment including x-rays, ultrasound and magnetic resonance imaging (MRI).

Results

On the basis of the inclusion and exclusion criteria, we reviewed and analysed clinical data of 327 patients with plaque psoriasis (M/F: 182/145; mean age of 49.3 years, range 16–81 years). The biologic drugs adalimumab, etanercept, infliximab and ustekinumab were prescribed to 116 (35.5%), 88 (27.0%), 27 (8.2%), and 96 (29.3%) of patients, respectively. We found that 22 (6.7%, 15 men and 7 women, mean age 51.4) out of 327 patients with plaque psoriasis developed PsA during treatment with biologic drugs. The majority of patients (19/22, 86.4%) developed a peripheral articular involvement whereas only 3/22 subjects (13.6%) manifested an axial articular disease. As regards peripheral forms of PsA, 7/19 (36.8%) oligoarthritis, 5/19 (26.3%) enthesitis, 3/19 (15.7%) dactylitis, 3/19 (15.7%) dactylitis and enthesitis, and one case of oligoarthritis and enthesitis were observed. In particular, 6 (27.2%) PsA patients were under etanercept therapy, 10 (45.4%) under adalimumab, four (18.2%) under ustekinumab and two (9.2%) under infliximab. Ten out of 22 patients had previously been treated with other biologics. Most patients (19/22) manifested a peripheral articular involvement. We found that 14/22 patients (63.6%) had PASI>10 (mean 26.8) and the onset of joint symptoms usually coincided with the worsening of skin disease. Thirteen out of 14 patients, diagnosed with PsA and with PASI>10, were switched to other biologic therapies. In particular, 6 patients to another anti-TNF-α agent, 5 patients from anti-TNF-α to anti-IL 12/23 agent, and 2 patients from anti-IL 12/23 to anti-TNF-α agents. Conversely, most patients with onset of PsA and PASI<10, along with one patient with PsA and high PASI, continued on their biologic therapy, adding methotrexate. Data are summarised in Table I.

Discussion

This study evaluates the incidence of new cases of PsA in patients with plaque psoriasis on anti-TNF-α therapy (adalimumab, etanercept and infliximab) and ustekinumab, attending our Dermatology Unit for a 5-year period.

The results show that a total of 22 (6.7%) out of 327 patients with plaque psoriasis developed PsA during biologic therapy. Among these, 27.2%, 45.4%, 18.2% and 9.2% of patients were receiving, respectively, etanercept, adalimumab, ustekinumab and infliximab.

These results outline that in several patients, biologic therapy may not be sufficient to prevent the onset of articular involvement. In most of the PsA cases, arthritis was verified in concomitance with severe cutaneous involvement under biologic therapies showing a peripheral subset.

In this study, ten out of 22 psoriasis patients developing PsA had previously been treated with other biologic agents, underlining the loss of efficacy.

In psoriasis, loss of efficacy of biological therapies over time occurs (18), and data from our study could suggest that arthritis onset can represent a possible manifestation of psoriatic flare also in patients with no previous articular involvement. Although, the major limitation of the study was the retrospective design, firm conclusions can still be drawn. These data suggest that it could be useful to evaluate the frequency and the aspect of PsA also in psoriasis patients under biologic therapy.

In recent years, treatment of psoriasis and PsA has mainly changed following the awareness of the pro-inflammatory pathogenetic mechanisms of the disease (19-22). Inhibition of TNF-α and IL 12/23 by use of antagonists has represented a key step of the therapeutic approach showing a higher level of evidence when compared with csDMARDs (10, 11).

Indeed, management of PsA with csDMARDs failed to prevent radiographic progression and to control dactylitis, enthesitis or axial disease (23).

Unlike NSAIDs and csDMARDs, TNF-α inhibitors not only provide unambiguous benefits on all PsA manifestations (peripheral arthritis, axial involvement, dactylitis, enthesopathy, and skin disease), but also prevent the progression of structural damage in peripheral joints (23). Eder *et al*. found that the proportion of patients who demonstrated progression of radiographic damage score, at 1–2 years and at 3–4 years, was higher in the methotrexate group compared to the TNF-α blockers group (23). Alternative therapies for patients who cannot tolerate or fail anti-TNF-α agents include ustekinumab that has recently been shown to be effective for several manifestations associated with PsA, including peripheral arthritis, dactylitis and enthesitis, and to inhibit radiographic progression (24).

For the ability of biologic drugs to act on disease progression, the detection and treatment of PsA in its early phases is fundamental, and cooperation between the dermatologist and rheumatologist should be emphasised to better manage PsA patients. However, despite the advantages offered by biologic drugs, our data suggest that they are not always able to prevent the manifestation of PsA. Our results are in line with those of Carija *et al*. who recently reported some cases of paradoxical psoriatic arthritis developed during ustekinumab treatment (25). This could be explained by the fact that some areas of the disease are still not understood.

Table I. Demographic and clinical characteristics of patients with plaque psoriasis who developed psoriatic arthritis in the course of treatment with biologic agents.

Patient (sex, age)	PASI	Biologic drug	Previous biologics	Therapy following diagnosis of PsA	Articular involvement
1.F, 46	23.8	ETN	None	ADA	dactylitis
2. M, 54	3.2	ETN	None	ETN+MTX	oligoarthritis
3. M, 59	2.1	ETN	None	ETN+MTX	enthesitis
4. F, 61	30.5	ETN	IFX/ADA	UST	dactylitis + enthesitis
5. M, 39	27.3	ETN	None	UST	oligoarthritis
6. F, 30	8.3	ETN	None	ADA	oligoarthritis
7. F, 55	32.7	ADA	ETN/IFX	UST	oligoarthritis
8. M, 63	5.2	ADA	None	ADA+MTX	enthesitis
9. M, 47	0	ADA	None	ADA+MTX	dactylitis
10. M, 56	15.8	ADA	None	ADA+MTX	axial involvement
11. M, 43	19.6	ADA	IFX	GOL	axial involvement
12. M, 58	29.8	ADA	None	UST	dactylitis
13. M, 67	18.8	ADA	EFAL	IFX	enthesitis + oligoarthritis
14. F, 49	25.6	ADA	ETN	UST	oligoarthritis
15. M, 52	27.9	ADA	None	ETN	dactylitis
16. M, 55	34.7	ADA	UST	ETN+MTX	enthesitis
17. F, 60	6.1	UST	ADA	GOL	axial involvement
18. M, 49	27.3	UST	ADA	ETN	oligoarthritis
19. M, 57	37.5	UST	ADA	IFX	enthesitis
20. F, 43	2.4	UST	ADA	UST+CCS	oligoarthritis
21. M, 49	9.8	IFX	None	IFX+MTX	enthesitis
22. M, 38	23.7	IFX	None	ADA	dactylitis + enthesitis

ADA: adalimumab; CCS: corticosteroids; EFAL: efalizumab; ETN: etanercept; GOL: golimumab; IFX: infliximab; MTX: methotrexate; NSAIDs: non-steroidal anti-inflammatory drugs; PASI: psoriasis area and severity index; PsA: psoriatic arthritis; UST: ustekinumab.

Firstly, about a quarter of patients with psoriasis will develop PsA, although it is currently challenging to determine *a priori* which patients will develop it. Indeed, identification of biomarkers for screening, disease activity, joint damage, treatment response and comorbidities are perceived as important clinical needs and possible therapeutic target (26). Secondly, patients who are non-responsive to anti-psoriatic therapies, including biologics (as our 14 out of 22 psoriatic patients with PASI>10), may develop an "uncontrolled" inflammation causing PsA. Recent findings suggest that inflammation of the skin may become more generalised and involve musculoskeletal structures (26). Other reports suggest that gut microbiota might have a role in joint inflammatory responses and bone remodelling in psoriatic disease (27, 28).

In conclusion, a total of 22 (6.7%) out of 327 patients with plaque psoriasis developed PsA during biologic therapy and 10 out of 22 patients had previously been treated with other biologic drugs; hence, a possible correlation with a specific agent cannot be established. Further prospective studies will be of interest to investigate these aspects.

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