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COVER PAGE

TITLE

Combined inhibition of TNFα and IL-12/23 for long-standing, refractory Psoriatic disease: a differential role for cytokines pathways?

Gabriele De Marco[1,2], Dennis McGonagle[1,2], Hannah R. Mathieson[1,2] , Mira Merashli[3] , Conor Magee[4], Oliver FitzGerald[4], Mark Goodfield[5], Helena Marzo-Ortega[1,2]

1) NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
2) Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom
3) Division of Rheumatology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon
4) St Vincent's University Hospital and Conway Institute for Biomolecular Research, University College Dublin, Ireland
5) Department of Dermatology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Address for correspondence
Helena Marzo-Ortega
LIRMM, Second floor,
Chapel Allerton Hospital,
Chapeltown Road,
Leeds LS7 4SA, United Kingdom.

Telephone: +44 (0) 113 392 4884
Fax: +44 (0) 113 392 4991
E-mail: medhmo@leeds.ac.uk

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Sir,

Psoriatic arthritis (PsA) and psoriasis are closely related chronic inflammatory conditions leading to multi-tissue involvement. Polymorphisms in genes regulating Tumour Necrosis Factor alpha (TNFα) and the interleukin-23 and -17 axis (IL-23/17) are risk factors for both musculoskeletal and cutaneous phenotypes (1). Biological drugs are effective at the population level with significant overlap in clinical response between both cutaneous and musculoskeletal involvement. Unfortunately, some patients are refractory or intolerant to TNFα inhibitors (TNFi) or to biologics targeting the IL23/17 axis. The clinical practitioner may, on occasions, encounter affected individuals showing an excellent response from one tissue target, i.e. the skin, and incomplete response or even deterioration in others, such as the joints, the uvea or bowel.

Here, we report six cases of long-lasting, complex PsA refractory and/or intolerant to several conventional synthetic and biologic disease-modifying anti-rheumatic drugs (csDMARDs and bDMARDs, respectively) who were exposed to a combination of an anti-IL-12/23 and a TNFi (Table 1). Dual targeting inhibition was considered in all cases as the TNFi worked on articular disease whereas the anti-IL12/23 only worked on skin. While combination therapy with differential cytokine inhibition mechanism showed some mild and subjective effects, it appeared to be associated with increased risk of infections.

Beyond the advent of bDMARDs, the main therapeutic challenge in real life remains the lack of response-biomarkers to support stratified intervention. Because of this, and through a trial-and-error approach, we found that some patients required dual inhibition of both TNFα and IL-12/23 to address disease activity at both the articular and the cutaneous level. This is suggestive of a TNFα-dependent arthropathy concomitant to an IL-23/17-axis-dependent psoriasis occurring in a subset of cases (2) (Figure 1). To our knowledge, there are only a few reports (3, 4) on the combination of bDMARDs in severe, refractory PsA. In our series, single-targeted inhibition was inadequate to gain full control on disease activity, triggering the decision to trial a bDMARDs combination to selectively inhibit different cytokines. The rationale behind this is partly due to the synergistic effect of the modulation of the lymphoid stress surveillance response through IL-23/IL-17 axis (1).

The small number, diverse clinical features and uncontrolled nature of these cases and different drug combinations preclude any definitive scientific conclusions being drawn regarding evidence of clinical improvement. Further, in most cases toxicity precluded treatment continuation which also carried significant cost considerations. From a mechanistic viewpoint, although there appears to be strong overlap between TNFi and anti-IL12/23 at the population level, our findings suggest a differential role of TNFα and IL-23/17 pathways in the immunopathology of articular and cutaneous involvement in some psoriatic disease cases.

Despite common tissue-specific factors in the skin and joint including Köebner responses (figure 1), some data suggest a differential involvement of pivotal innate immune cytokines, with the IL-23 pathway playing a greater role in the skin and TNFα pathway playing a greater role in the joints. We hypothesize that in some extreme cases such a polarisation may occur. Theoretical support for this comes from four strands. First, the IL-23 pathway genetics appears to be greater in psoriasis than in PsA(5). Secondly, animal models with IL-23 dysregulation develop both psoriasiform skin inflammation and arthritis, whereas TNFα transgenic models develop enthesitis, synovitis and colitis but not skin disease(6). Human immunology studies, although limited in regards of the enthesis, point towards diverse and comparatively abundant IL-23R positive cells in the skin compared to the enthesis (7). Moreover, deficiency in IL-17 pathway leads to cutaneous fungal infection, but not arthritis, suggesting an important role of the IL-23/17 axis pathway in normal skin homeostasis. Finally, these and other case series (3, 4) consistently report on the effect of TNFi on arthritis and of IL-23 inhibitor on skin disease. No reports of bDMARDs combination therapy showing TNFi efficacy in skin disease and IL-23i efficacy for joint disease exist. Thus, despite common inciting factors including cutaneous or articular micro-damage and shared cytokine networks, there may be a differential innate immune cytokine hierarchy between skin and joints in a subset of cases.

Drug development programmes confirmed the safety and efficacy of dual cytokine inhibition without superiority to conventional TNFi(8). Whereas this may apply to the population level, the need remains for single molecules with safe, dual targeting properties to be developed in PsA and psoriasis cases showing divergent therapy responses.

Key message

We hypothesize a differential cutaneous/articular cytokine hierarchy in a subset of psoriatic disease cases.

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Patients consent

All patients described in this report have provided written consent as per Rheumatology journal guidelines.

Ethics approval

Not applicable.

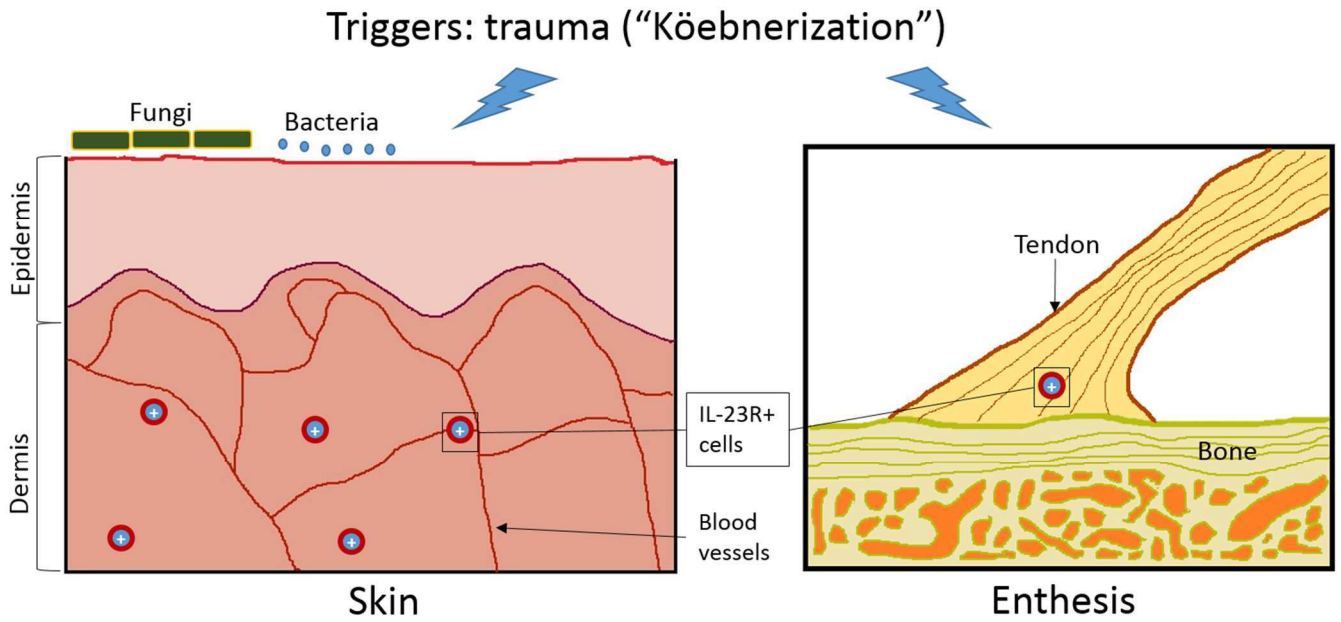
Table 1. Main clinical characteristics and treatment history of the clinical series.

	Case 1 41 year old female	**Case 2** 50 year old female	**Case 3** 63 year old female	**Case 4** 32 year old male	**Case 5** 49 year old female	**Case 6** 45 year old male
Primary disease phenotype (duration to presentation)	Polyarticular (13 years)	Polyarticular (12 years)	Axial and polyarticular (20 years)	Polyarticular (17 years)	Polyarticular (24 years)	Axial and oligoarticular (20 years)
Psoriasis (phenotype)	Plaque	Plaque	Flexural	Plaque	Plaque	Plaque, "paradoxical"*
Other extra-articular manifestations	None	Uveitis	Uveitis; Crohn's disease	None	Uveitis	Uveitis (likely secondary to ETN**)
SpA-related characteristics			HLA-B27+ve	HLA-B27+ve Family history of AS	HLA-B27+ve	
Co-morbidities	Morbid obesity	Obesity; Essential arterial hypertension	Bronchial asthma; COPD; Liver cirrhosis	Dyslipidaemia; Essential arterial hypertension	Obesity; Essential arterial hypertension	None
Previous csDMARDs	SSZ, MTX, HCQ, AZT, LEF	SSZ, MTX	AZT (for bowel)	MTX	Tacrolimus, MTX, Cyclosporin A, oral steroids	MTX, MMF, Tacrolimus, oral steroids
Previous bDMARDs	ADA (2006) (for joints): non-specific neurologic side effects (MS excluded)	INF: 2nd NR initially effective on skin and eyes; ADA: 1NR;	INF (2004) (for joints): 2nd NR;	ADA (2012) (for joints and skin) 2nd NR on both joints and skin;	INF (for joints): 2nd NR; GOL (for joints): 2nd NR	**ETN: stopped due to development of uveitis;

		GOL: 2nd NR ; UST (for skin) - LEF added for joints at this point, but stopped in 2014 (1NR)	ETN (2005-8) (for joints): stopped due to uveitis flare	INF (for joints and skin): effective on joints, 2 nd NR in skin		*ADA: developed Psoriasis; GOL: 2nd NR; INF: 2NR
Most recent bDMARD	UST (excellent control of skin, but not of joints)	UST (no control of joints)	ADA (2008-2017) (for bowel and joints), led to new flare of Psoriasis	UST (2013) (for skin)	UST helped skin but not joints	CZP prescribed for joints
Biologic co-prescribed and purpose	ETN successfully added (Feb 2014) to UST to regain control of joints	CZP (Jan 2015) successfully added to UST to regain control of joints	UST (2016) successfully added to ADA to regain control of skin	ETN (2015) added to UST to regain control of articular disease	First ETN added to UST to regain control of articular disease (not tolerated due to uveitis); Then UST+ADA (not effective on joints); Then UST+CTZ	UST added onto CZP to regain control of skin
Overall duration of exposure to bDMARDs combination	15 months	6 months	3 months	24 months	15 months	12 months
Reason for discontinuation of bDMARDs combination	Developed severe skin infection	Discontinued because of 2 chest infections	Respiratory failure with recurrent chest infections	Developed chest sarcoidosis mediastinal and hilar lymphadenopathy	2nd NR (joints) followed by bout of uveitis	Lack of significant response from skin and joints

Therapy subsequent to bDMARDs combination		APR started in October 2015, regained control of synovitis and skin Chronic pain syndrome			Ixekizumab (dramatic skin improvement, mild articular improvement)	SEC (Good improvement in skin only)
PsA = psoriatic arthritis; AS = ankylosing spondylitis; SpA = Spondyloarthritis; COPD = chronic obstructive pulmonary disease; bDMARDs = biologic disease-modifying anti-rheumatic drugs; sDMARDs = synthetic disease-modifying anti-rheumatic drugs; SSZ = sulphasalazine; MTX = methotrexate; HCQ = hydroxychloroquine; AZT = azathioprine; MMF = mofetil mycophenolate; ADA = adalimumab; MS = multiple sclerosis; INF = infliximab; 2^{nd} NR = secondary non-response; 1NR = primary non-response; GOL = golimumab; ETN = etanercept; UST = ustekinumab; CZP = certolizumab pegol; APR = apremilast; SEC = secukinumab.						

Figure 1



Genetics	**IL-23 [5] predominance**	
Gene expression data (skin, synovium)	**IL-17 [2] pathway predominance**	**TNFα [2] predominance**
Therapy	**IL-23 [3,4]**	**TNFα [3,4]**

Legend
Suggestions for a differential involvement of innate immune cytokines in psoriatic disease. The IL-23 pathway may play a greater role in the skin, while the TNFα pathway may retain a greater role in the joints.