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Dupilumab-induced enthesoarthritis and refractory atopic dermatitis successfully treated with baricitinib

Ludovico De Stefano^{1,2}, Francesca Bobbio-Pallavicini¹, Carlomaurizio Montecucco^{1,2},
Serena Bugatti^{1,2}

¹Division of Rheumatology, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

²Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

Corresponding author

Serena Bugatti, MD PhD

Associate Professor of Rheumatology

Division of Rheumatology, IRCCS Policlinico San Matteo Foundation University Hospital,
Viale Golgi 19, 27100 Pavia, Italy

serena.bugatti@unipv.it

ORCID ID <https://orcid.org/0000-0002-5396-7077>

Key message: Baricitinib was effective at controlling both dupilumab-induced arthritis/enthesitis and atopic dermatitis.

Dear Editor,

Cytokine inhibition through biological and targeted drugs has revolutionized the treatment of many chronic immune-mediated inflammatory diseases over the past 20 years. Although clinically effective and overall safe, the therapeutic manipulation of the cytokine system may trigger immune side-effects in a small albeit not negligible proportion of patients. This is the case, for instance, of tumor necrosis factor inhibitors (TNFi), which have been associated with the development of lupus autoimmunity and paradoxical psoriasis through interferon over-production.¹ Immune side-effects were also described for dupilumab, the first biological drug approved for atopic dermatitis (AD), which inhibits interleukin (IL)-4 and IL-13 signaling. In addition to the appearance of psoriasis, some authors have indeed reported the development of seronegative chronic synovitis and enthesitis in AD patients treated with dupilumab, and real-life data found immune-mediated enthesitis/arthritis in up to 6% of the patients². Inflammatory arthritis occurred early, within a few months of starting therapy, and usually persisted despite dupilumab discontinuation, requiring treatment with systemic disease-modifying anti-rheumatic drugs (DMARDs)^{3,4}.

In July 2020, a 49-year-old man with no personal or familiar history of rheumatic diseases presented to our attention with a 3-months history of swelling and tenderness of the small joints of the hands, wrists, knees and shoulders (swollen joint count 6/66, tender joint count 8/68) and right Achilles tendon enthesitis refractory to therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. He had been suffering from AD since puberty, entirely controlled (Investigator Global Assessment 0) only after starting dupilumab in February 2020 (among first-line systemic therapies, methotrexate was early interrupted because of intolerance). At the time of rheumatologic assessment, laboratory examinations showed increase in C-reactive protein (CRP) levels (2.86 mg/dl) and a stable and known increase in immunoglobulin (Ig) E levels (1932 kU/L), with a normal eosinophil count (0.1/mm³). Rheumatoid factor, anti-citrullinated protein, anti-nuclear and anti-neutrophil cytoplasmic antibodies were all negative. HLA typing revealed C06/07 and B37/49 alleles. Ultrasonography (US) confirmed polyarticular synovitis and heel enthesitis with significant Power-Doppler signal (**Figure 1A**). X-rays of the hands and feet were

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normal. In agreement with the treating dermatologist, dupilumab was discontinued, and full-dose NSAIDs plus prednisone 7.5 mg/day were prescribed, without significant improvements after two months (**Figure 1B**). Due to persistently active enthesoarthritis with features indicative of possible failure of conventional approaches, such as Power Doppler signal at US examination and increased CRP levels, and considering previous intolerance to methotrexate, in September 2020 the patient was started on secukinumab up to 300 mg. However, three months later, together with unmodified activity of peripheral arthritis and enthesitis, the patient presented with a relapse of AD (**Figure 1B,C**), with invalidating pruritus and skin pain. Skin biopsy services were not available during the COVID-19 pandemic. However, an expert dermatologist excluded an eczematous psoriasis and other confounding dermatoses, and confirmed the relapse of AD. Secukinumab was discontinued, and baricitinib 4 mg/day was started. After eight weeks of treatment, arthritis, enthesitis, and AD were completely resolved and remained inactive at the 4-months follow-up (**Figure 1B,C**). CRP levels were normal, IgE had significantly decreased to 728 kU/L, and eosinophils had remained within the normal limits.

The mechanisms linking dupilumab with the development of enthesitis/arthritis and the optimal management of the musculoskeletal side-effects of IL-4/IL-13 inhibition remain to be established. It has been hypothesized that in certain highly atopic individuals, who are probably genetically susceptible (our patient was positive for HLA C06, a haplotype associated with psoriasis), cytokine “manipulation” induced by dupilumab might lead to alterations in the relative balance of Th2 to Th17, as well as to excessive production of innate cytokines. Bridgewood et al.³ showed that enthesial-derived T-cells physiologically produce IL-4, which exerts local protective effects through down-regulation of the IL-23/IL-17 axis. Similarly, two other studies on dupilumab-induced psoriatic lesions have shown correlations between reduction in IL-4 levels and a marked increase in IL-23A,⁵ or between reduction in IL-13 and expression of IL-17A and, to a lesser extent, IL-23A and IL-12B.⁶ Evidence of the possible reciprocal compensatory switch from the Th2 to IL-23A/Th17 axis and vice versa would also seem to be provided by anecdotal case reports showing the appearance of AD-like dermatitis after treatment with anti-IL-17 for psoriasis⁷. In our patient, lack of cytokine measurements in serum, synovium and skin hampers definitive conclusions on the pathogenic mechanisms linking IL-4/IL-13 inhibition with the development of joint and enthesial inflammation. Of note, despite being highly effective in the spondyloarthritis, IL-17A inhibition failed to control dupilumab-induced

enthesitis/arthritis in our case, raising the possibility of alternative pathogenetic pathways. Accordingly, IL-4 may interfere with multiple signaling beyond IL-17 and IL-23, including interferons, IL-12 and IL-10⁸. Similarly to paradoxical psoriasis in course of TNFi², we therefore cannot exclude that dupilumab-induced rheumatic manifestations might at least in part diverge from classical spondyloarthritis in their pathogenetic drivers. By interfering with the signal transduction of a broader spectrum of cytokines, including interferons, IL-10, IL-23, IL-4 and IL-13, janus kinase inhibitors might represent valuable therapeutic options capable of controlling both the more refractory cases of dupilumab-induced arthritis/enthesitis and AD.

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LDS and SB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Contributorship: LDS conceived the work, contributed to the acquisition of patient’s data, and drafted the manuscript. FBP contributed to the acquisition of patient’s data and revised the manuscript critically. CM conceived the work and revised the manuscript critically for important intellectual content. SB conceived the work, contributed to the interpretation of data, and drafted the manuscript. All the authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

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Patient consent: Informed consent was obtained for the publication of this paper.

Data sharing statement: The authors confirm that the data supporting the findings of this study are available within the article. Original data are available from the corresponding author (SB) upon reasonable request.

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Figure legends

Figure 1. Dupilumab-induced enthesoarthritis and its management.

(A) Enthesitis of the calcaneal insertion of Achille’s tendon: longitudinal ultrasound view of the calcaneal insertion of the right Achille’s tendon showing a hypoechoic, inhomogeneous and thickened tendon with intense power Doppler signal with concomitant retrocalcaneal bursitis (white asterisk). (B, C) Variations over time in the number of swollen and tender joints (B) and in the investigator and patient global assessment of atopic dermatitis (C) in relation to different treatment approaches.

SJC66 = swollen joint count out of 66 assessed joints; TJC68 = tender joint count out of 68 assessed joints; IGA = Investigator Global Assessment (five-point scale) for atopic dermatitis; PGA = Patient Global Assessment (five-point scale) for atopic dermatitis; NSAID = non-steroidal anti-inflammatory drug; GC = glucocorticoid.

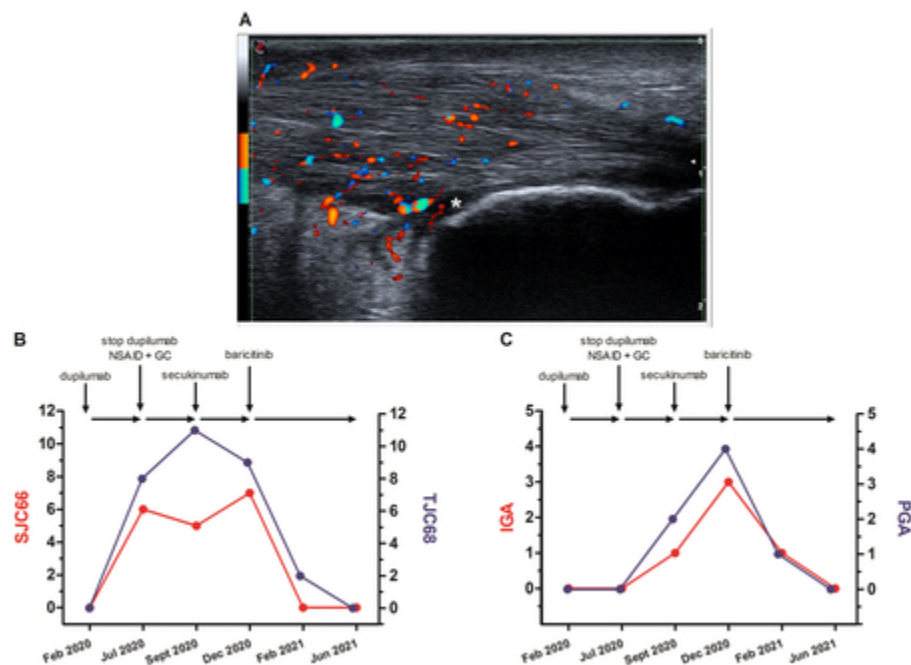


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40x30mm (300 x 300 DPI)