

DR ZENA NABEIL WILLSMORE (Orcid ID : 0000-0001-8750-804X)

DR RICHARD THOMAS WOOLF (Orcid ID : 0000-0003-3200-0075)

DR CATHERINE H. SMITH (Orcid ID : 0000-0003-1895-6070)

Article type : Research Letter

The development of inflammatory arthritis and enthesitis in patients on dupilumab: a case series

Z. N. Willsmore^{*1}, R. T. Woolf^{*1}, C. Hughes², B. Menon², B. Kirkham², C. H. Smith¹, A. E. Pink¹

*Authors contributed equally to this paper

1 St. John's Institute of Dermatology, Guy's and St. Thomas' Hospital NHS Trust, Great Maze Pond, London SE1 9RT

2 Department of Rheumatology, Guy's and St. Thomas' Hospital NHS Trust, Great Maze Pond, London SE1 9RT

Corresponding author address: Zena Willsmore, St. John's Institute of Dermatology, Guy's and St. Thomas' Hospital NHS Trust, Great Maze Pond, London SE1 9RT

E-mail: zena.willsmore@gstt.nhs.uk

Conflict of interest: none declared

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.18031

This article is protected by copyright. All rights reserved.

Accepted Article

Dear Editor, Dupilumab (Dupixent®, Sanofi), a fully human monoclonal antibody that blocks interleukin (IL)-4 and IL-13 signaling, is the first biologic approved in the UK for adult patients with moderate-to-severe atopic dermatitis (AD). In phase III studies, dupilumab was an effective treatment with 44–51% of patients achieving at least 75% improvement in Eczema Area and Severity Index (EASI).^{1–2} To date, dupilumab has been well tolerated; common adverse reactions reported from phase III data include injection-site reactions (8–19%), allergic conjunctivitis (3–19%) and oral herpes (2–5%).^{1–2} Herein we report three cases of new onset seronegative arthropathy and enthesitis that developed within 16 weeks of starting dupilumab.

Our index case (A) is a 40-year-old man with severe AD who presented with generalized joint pain and morning stiffness 16 weeks after commencing dupilumab. This resulted in a progressive decline in mobility requiring crutches whereas he was mobilizing independently prior to treatment. He had no history of joint disease, but his mother had rheumatoid arthritis. He had previously failed multiple systemic therapies (methotrexate, azathioprine, ciclosporin and mycophenolate mofetil). On dupilumab his AD had cleared (baseline EASI 36, week 12 EASI 0) with associated improvement of itch and Dermatology Life Quality Index (reduced from 26/30 to 2/30). Rheumatology examination revealed a reduced range of movement of knees, ankles and right shoulder, swelling of the small joints of hands and wrists, and enthesitis affecting the knees and Achilles tendons, consistent with an inflammatory arthropathy and enthesitis. Blood parameters were normal, including inflammatory markers (ESR, CRP), creatine kinase and negative autoimmune serology. Ultrasound (US) confirmed synovitis of both wrists and a right wrist effusion. Magnetic resonance imaging (MRI) of knees, ankles and feet did not demonstrate inflammation. Sixteen weeks after discontinuation of dupilumab and initiation of naproxen, symptoms have only mildly improved and mobility remains poor.

We present two further cases with striking clinical similarities (Table 1). A 48-year-old man (Case B) developed bilateral Achilles and left thumb tenderness at week 6 of treatment, progressing to pain and stiffness affecting the ankles, knees, left wrist and metacarpophalangeal (MCP) joints by week 8. Rheumatology examination revealed bilateral Achilles tendon, wrist and MCP joint tenderness. US scan showed low-grade mid left Achilles peri-tendonitis, with MRI showing mid portion Achilles tendinopathy. He continues to take dupilumab with partial improvement of rheumatologic symptoms on celecoxib 24 weeks after onset. A 68-year-old woman (Case C) developed generalized arthralgia 6 weeks after starting dupilumab. Rheumatological examination after 12 weeks of treatment revealed multiple symmetrical tender enthesal points throughout the body. US scan showed bilateral lateral epicondylitis. She remains symptomatic 15 weeks following discontinuation of

dupilumab. Cases B and C both had severe AD that responded to dupilumab with almost complete skin clearance (Table 1). Inflammatory markers and creatine kinase were normal, with negative autoimmune serology in both cases.

We present an unreported potential association between dupilumab and new onset seronegative arthropathy and enthesitis/tendinopathy, occurring within 16 weeks of dupilumab initiation with associated radiological changes (Table 1). To date dupilumab has been well tolerated with low rates of either serious adverse events or treatment discontinuation due to adverse events. The Summary of Product Characteristics for dupilumab makes no reference to arthritis or joint pain in the undesirable effects.³ Arthralgia was reported in phase III studies (0.8 – 4.5%) but the incidence was equivalent to placebo groups.¹⁻² A meta-analysis of adverse events reported back pain as lower in those treated with dupilumab versus placebo; whilst musculoskeletal pain was numerically lower in the dupilumab group but did not achieve significance (p value 0.27).⁴ Despite this the Dupixent® patient information leaflet includes arthralgia as a potential adverse event.

The aetiology of the arthropathy/enthesitis/tendinopathy seen in our patients is uncertain. Dupilumab blocks IL-4 and IL-13 signaling by binding the alpha subunit of the IL-4 receptor. These cytokines are predominantly produced by type 2 helper T (T_H2) lymphocytes and are central to the pathogenesis of AD. IL-4 and IL-13 have also been reported to inhibit cartilage damage and bone destruction in animal models of inflammatory arthritis.^{5,6} The counter-regulation between T_H2 and T_H1 (defined by interferon production) immune responses is well described. Recently IL-4 and IL-13 were reported to selectively suppress IL-23 production with reduced Th17 function.⁷ Although not a consistent finding, IL-4 and IL-13 have been found in synovial fluid in early seropositive arthritis.⁸ We hypothesise that in certain highly atopic individuals dupilumab, by inhibiting IL-4 and IL-13, may enhance an IL-17 mediated peripheral spondyloarthritis/psoriatic arthritis pattern of inflammatory arthritis/enthesitis. Further evaluation is needed to establish a causal link and to understand the pathogenesis.

Post-marketing pharmacovigilance remains of crucial importance with newly approved medications such as dupilumab. The development of eczema registries, such as the UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR), will facilitate the reporting of rare adverse drug reactions and should include arthritis/enthesitis as an event of special interest.

Table 1 Summary of patient characteristics

	Case 1	Case 2	Case 3
Sex	Male	Male	Female
Age (years)	40	48	68
Atopic co-morbidities	Atopic asthma	Atopic asthma	Atopic asthma
	Allergic rhinosinusitis	Allergic rhinosinusitis	Allergic conjunctivitis
	Type 1 allergy (nuts)	Allergic conjunctivitis	Type 1 allergy (multiple)
EASI score baseline week 0	36	20.6	43
EASI score dupilumab week 12	0	6	2.6
Musculoskeletal symptoms			
- Onset of after dupilumab initiation (weeks)	16	6	6
- Duration of symptoms (weeks)	Ongoing; 16	Ongoing; 24	Ongoing; 15
Inflammatory markers			
- C-reactive protein	N	N	N
- Erythrocyte sedimentation rate	N	N	N
Pattern of arthropathy			
- small joint	+	+	+
- large joint	+	+	+
Presence of enthesitis	+	+	+
Radiological findings	US: Bilateral synovitis of the wrists	US: Left Achilles peritendonitis MRI: Left Achilles tendinopathy	US: Bilateral lateral epicondylitis

EASI = eczema area and severity index, N = normal, N/A = not applicable, US = ultrasound, MRI = magnetic resonance imaging

References

1. Simpson EL, Bieber T, Guttman-Yassky E, *et al.* Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med.* 2016;375(24):2335-2348.
2. Blauvelt A, de Bruin-Weller M, Gooderham M, *et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10086):2287-2303.
3. Summary of Product Characteristics (SmPC). Dupixent. Accessed via www.medicines.org.uk on 19.02.2019
4. Ou Z, Chen C, Chen A, *et al.* Adverse events of Dupilumab in adults with moderate-to-severe atopic. *Int Immunopharmacol.* 2018 Jan;54:303-310
5. Joosten LA, Lubberts E, Durez P, *et al.* Role of interleukin-4 and interleukin-10 in murine collagen-induced arthritis. Protective effect of interleukin-4 and interleukin-10 treatment on cartilage destruction. *Arthritis Rheum.* 1997;40(2):249-260.
6. Chen Z, Andreev D, Oeser K, *et al.* Th2 and eosinophil responses suppress inflammatory arthritis. *Nat Commun.* 2016;7(1):11596.
7. Guenova E, Skabytska Y, Hoetzenecker W, *et al.* IL-4 abrogates Th17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells. *Proc Natl Acad Sci USA* 2015;112(7):2163-8.
8. Raza K, Falciani F, Curnow SJ, *et al.* Early rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. *Arthritis Res Ther.* 2005;7(4):R784-95.