

Review of dupilumab-associated inflammatory arthritis: An approach to clinical analysis and management



Ryan Jay, BA, BS,^a Jaimie Rodger, DO,^{a,b} and Matthew Zirwas, MD^{a,b}
Dublin and Bexley, Ohio

Key words: adverse effect; arthritis; arthropathy; atopic dermatitis; dupilumab; dupilumab-associated; dupilumab-induced; enthesitis; IL-4; IL-4R α ; IL-13; IL-17; IL-23; inflammatory arthritis.

INTRODUCTION

Dupilumab is a monoclonal antibody that treats atopic dermatitis by blocking interleukin (IL) 4 and IL-13 signaling.¹ Dupilumab-associated inflammatory arthritis was first reported in 2019 in 3 patients who developed seronegative arthropathy and enthesitis within 16 weeks of starting the drug.² Since then, only a few additional reports and 1 retrospective observational study have discussed this arthropathy in patients with atopic dermatitis. The pathophysiology, potential risk factors, clinical features, and response to therapy have not been well-characterized. We report 3 additional cases and present a review of the reported cases to assist providers in identifying and managing this emerging adverse event.

CASE SERIES

Table I summarizes the history, clinical presentation, and management of our patients along with the already published reports on dupilumab-associated inflammatory arthritis.

Case 1

A 32-year-old man with atopic dermatitis presented with generalized joint pain after his fourth injection of dupilumab, 2 months after his initial injection. The pain progressively worsened with each successive injection, and 13 months later, he stopped the medication because the discomfort became unbearable. Joint symptoms resolved 1 month later without any treatment, but his eczema flared 3 months after stopping dupilumab.

Abbreviation used:

IL: interleukin

Case 2

A 64-year-old man with a history of childhood-onset atopic dermatitis, seasonal allergies, and asthma developed generalized joint pain (without other symptoms of a hypersensitivity reaction) immediately after his first dose of dupilumab. After his second injection, the pain became so severe that he was bedbound. No ultrasound imaging was done, but electromyography, lumbar puncture, and extensive rheumatologic testing were all negative. The patient stopped dupilumab and was given prednisone and methotrexate for the arthropathy. It took him approximately 6 months to regain mobility and 1 year for full recovery.

Case 3

A 60-year-old woman with childhood-onset atopic dermatitis and seasonal allergies had been taking dupilumab for 19 months, without adverse effects. This treatment overlapped with concurrent azathioprine for the first 3 months. After an injection, she suddenly developed moderate, widespread joint pain that dissipated over 2 weeks and recurred after the next shot. After stopping dupilumab and treating the arthropathy with 3 weeks of dexamethasone and 8 weeks of ibuprofen and acetaminophen, her symptoms resolved and remitted 6 weeks after the last injection. Dupilumab was not restarted, and joint symptoms did not recur.

From the Department of Specialty Medicine, Ohio University Heritage College of Osteopathic Medicine, Dublin^a and Dermatologists of Greater Columbus, Bexley.^b

Funding sources: None.

IRB approval status: Not applicable.

Correspondence to: Matthew Zirwas, MD, 2359 East Main Street, Bexley, OH 43209. E-mail: matt.zirwas@gmail.com.

JAAD Case Reports 2022;21:14-8.
 2352-5126

© 2022 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2021.12.011>

Table I. Summary of patients with dupilumab-associated inflammatory arthritis in reported cases. Onset refers to the weeks after the first dupilumab injection, when symptoms started. Discontinuation refers to whether dupilumab was stopped. Resolution refers to time to improvement of arthropathy after stopping dupilumab, if applicable

Age/sex	Atopy history	Onset	Presentation	Severity	Resolution	Treatment
32/M*	AD	2 months	Generalized joint pain	Moderate	1 month	N/A
64/M*	Childhood-onset AD, asthma, seasonal allergies	After first dose	Generalized joint pain	Severe	6 months regained mobility; resolution in 1 year	Prednisone and methotrexate
60/F*	Childhood-onset AD, seasonal allergies	19 months [†]	Sudden generalized joint pain	Moderate	6 weeks	dexamethasone, ibuprofen, and acetaminophen
68/F ²	Severe AD, asthma, allergic conjunctivitis, multiple type 1 allergies	6 weeks	Generalized arthralgia	N/A	15 weeks	N/A
38/F ⁵	AD resistant to methotrexate	A few days	Started mildly, then rapid onset of “severe pain” and stiffness in 1 ankle, which gradually spread	Moderate	1 month	Celecoxib and prednisolone
47/M ⁶	Severe AD that failed azathioprine and topical steroids, asthma, allergic rhinosinusitis	1 month	Unilateral hand and wrist stiffness	Moderate	N/A	N/A
Age N/A; 14 M and 9 F ³	Moderate-to-severe AD	Mean of 4 months	Generally, combinations of arthritis, enthesitis, and tenosynovitis	Range of mild to severe	Most never discontinued and had partial resolution (only 5 of 23 discontinued permanently)	General: etoricoxib, celecoxib, or naproxen (mild cases continued full-dose dupilumab, while moderate cases reduced frequency of dupilumab)
Age and sex N/A; 6 patients ⁴	Moderate-to-severe AD	Most by week 12	Enthesitis and/or inflammatory arthritis	N/A	2 never discontinued, 1 continued at 4-weekly dosing, 3 discontinued (resolution N/A)	nonsteroidal anti-inflammatory drugs (in 2 patients who continued regular-dose dupilumab)
44/F ⁹	Long-standing AD resistant to topical and oral steroids	10 weeks	Stiffness in peripheral joints and pain in bilateral ankles	Mild to moderate	Never discontinued and had resolution in 3 months after onset of symptoms	Celecoxib

Continued

Table I. Cont'd

Age/sex	Atopy history	Onset	Presentation	Severity	Resolution	Treatment
54/M ¹⁰	AD resistant to topical and oral steroids	2 months	Generalized pain: bilateral distal and proximal interphalangeal joints, elbows, knees, left shoulder, and ankle	N/A	Never discontinued and had partial improvement	Celecoxib (ineffective), then methotrexate (partially effective)
18/F ¹¹	AD and prurigo nodularis, allergic rhinitis [‡]	2 weeks	Mild right-knee swelling, warmth, and arthralgia	N/A	Never discontinued and symptoms resolved (time N/A)	Oral diclofenac and intraarticular steroids

AD, Atopic dermatitis; F, female; M, male; N/A, not addressed.

*The first 3 cases occurred at our clinic.

[†]Patient concurrently used azathioprine in the first 2 months of using dupilumab.

[‡]Patient was being treated with dupilumab for prurigo nodularis and had a history of reactive right-knee arthritis 10 years ago that had been asymptomatic until now.

DISCUSSION

Dupilumab-associated inflammatory arthritis does not have an established management approach. Its frequency in patients starting dupilumab for atopic dermatitis is unknown, but in the single retrospective observational study reported, almost 5% of patients treated with dupilumab for atopic dermatitis were at least minimally affected by inflammatory arthritis.^{3,4} However, based on the small number of case reports in the literature and our own clinical experience, we suspect that either the frequency reported by Nathan et al³ was spuriously elevated or that the vast majority of cases are mild enough that they go unrecognized and do not require specific therapy or discontinuation of dupilumab. Cessation of dupilumab appears to reliably resolve the arthritis,^{3,5} although severe cases may take 6 months to a year after discontinuation to resolve.

The proposed pathophysiology stems from dupilumab's antagonism of the IL-4 α receptor. The drug most likely hinders the protective role of the IL-4/IL-13 axis against the IL-23/IL-17 axis, which tips the immune system toward this inflammatory pathway in predisposed patients and subsequently induces arthritis. An *in vitro* study of stimulated entheseal fibroblasts supported this pathophysiology by demonstrating that IL-4 attenuated IL-23 production.⁶ In addition, the IL-23/IL-17 axis has already been linked to autoimmune and autoinflammatory arthritis,⁷ which further supports how IL-4 α receptor antagonism by dupilumab could lead to inflammatory arthritis. While pathophysiology focuses on IL-4

blockade, uncertainty remains as to whether IL-13 signaling also plays a significant role.⁶ Further evidence and clinical experience is necessary to answer this question.

There does not appear to be an obvious relationship between severity of atopy (as determined by reports of coexistent atopic comorbidities) and the likelihood or severity of joint symptoms. Dupilumab-associated inflammatory arthritis also does not seem to be associated with age, sex, or previous joint disease. However, in many cases, there was no mention of whether patients were concurrently on other medications; hence, concomitant use of other anti-inflammatory or immunosuppressive drugs could potentially affect the risk, onset, and severity of arthritis. For instance, 1 of the patients reported in this study with onset of pain after 19 months on dupilumab was also taking azathioprine for the first 2 months of dupilumab therapy.

Joint pain generally occurred relatively early after the initiation of dupilumab therapy. Although a few cases presented many months after the initiation of therapy, most occurred in 4 months or less^{3,4,8}; some even began immediately after the first injection. Once the inflammatory arthritis was identified, it appeared that patients could be stratified based on the number of joints and the severity of the pain. The patients appeared to have either generalized, oligoarticular, or focal presentations, although generalized was the most common. Furthermore, if the symptoms were not optimally managed, focal and oligoarticular pain tended to generalize to other joints.^{2,5} The initial severity of pain also

Table II. Recommendations regarding management of inflammatory arthropathy and enthesitis in patients taking dupilumab

1. Prior to initiating dupilumab, counsel all patients about the risk of new-onset joint pain and that if it occurs, it is generally mild and easily managed. If it is more severe, the dupilumab can be discontinued, and it will resolve.
2. If a patient reports new-onset mild joint pain restricted to 1 or few joints, consider conservative management with over-the-counter nonsteroidal anti-inflammatory drugs, such as ibuprofen, on an as-needed basis.
3. If a patient reports new-onset moderate joint pain involving several joints or widespread pain, consider discontinuing the dupilumab, although in many cases it can be continued. Consider management with prescription of nonsteroidal anti-inflammatory drugs, such as celecoxib and a referral to rheumatology for comanagement.
4. If a patient reports new-onset severe joint pain that is widespread, we recommend immediate discontinuation of dupilumab, consideration of a short course of systemic steroids, and referral to rheumatology.

differed between the cases, and it appeared that the majority fell into the mild-to-moderate range that minimally affected daily function without complete debilitation.³

The initial severity of the pain appears to be predictive of the overall severity, as patients who originally had mild symptoms were generally able to continue dupilumab without significant worsening.^{3,9} Meanwhile, those with moderate or severe pain at onset were more likely to discontinue dupilumab.³ Many cases showed that the joint symptoms in mild and some moderate cases could be managed well with nonsteroidal anti-inflammatory drugs, and the clinical benefit from dupilumab outweighed any lingering inflammatory arthritis, according to the patients.^{2,3,9-11} Several recommendations can be made at this point, despite the clear need for additional information about this emerging adverse event. We have summarized our recommendations in [Table II](#).

As new systemic agents become available for the management of moderate-to-severe atopic dermatitis, the approach to management may change. It is unknown whether transitioning patients to an IL-13–only inhibitor would allow the joint pain to remit, although the theorized pathophysiology suggests that eliminating IL-4 blockade will allow IL-17/IL-23 activity to return to normal.⁶ Given that systemic Janus kinase inhibitors, such as upadacitinib, are Food and Drug Administration-approved for rheumatoid arthritis, we suspect that, if they become approved for atopic dermatitis, they would lead to rapid resolution of dupilumab-associated inflammatory arthritis. However, there are no reports on transitioning these patients to IL-13–only inhibitors or systemic Janus kinase inhibitors, and hence the effects remain speculative.

The approach to dupilumab-associated inflammatory arthritis in this review should help providers manage this largely unrecognized yet clinically significant adverse effect.

Conflicts of interest

Dr Zirwas has served as an investigator, consultant, or speaker for Regeneron/Sanofi, FitBit, Genenx/Novartis, L'Oreal, Aseptic MD, Leo, Janssen, Incyte, Vyne, UCB, Pfizer, Lilly, Asana, Avillion, Ortho Derm, AbbVie, Edessa Biotech, Galderma, Dermavant, Arcutis, Sol-Gel, Bausch Health, EPI Health, Concert, and Anaptys Bio. Author Jay and Dr Rodger have no conflicts of interest to declare.

REFERENCES

1. Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: a review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol*. 2018;78(3 suppl 1):S28-S36. <https://doi.org/10.1016/j.jaad.2017.12.022>
2. Willsmore ZN, Woolf RT, Hughes C, et al. Development of inflammatory arthritis and enthesitis in patients on dupilumab: a case series. *Br J Dermatol*. 2019;181(5):1068-1070. <https://doi.org/10.1111/bjd.18031>
3. Nathan J, Hughes C, Patel S, et al. AB0573 dupilumab-induced enthesitis/arthritis in patients with atopic dermatitis: a retrospective observational study. *Ann Rheum Dis*. 2021;80(suppl 1):1323-1324. <https://doi.org/10.1136/annrheumdis-2021-eular.1363>
4. Sears AV, Woolf RT, Gribaleva E, et al. Real-world effectiveness and tolerability of dupilumab in adult atopic dermatitis: A single-centre, prospective 1-year observational cohort study of the first 100 patients treated. *Br J Dermatol*. 2021;184(4):755-757. <https://doi.org/10.1111/bjd.19631>
5. de Wijs LEM, van der Waa JD, de Jong PHP, Hijnen DJ. Acute arthritis and arthralgia as an adverse drug reaction to dupilumab. *Clin Exp Dermatol*. 2020;45(2):262-263. <https://doi.org/10.1111/ced.14050>
6. Bridgewood C, Sharif K, Freeston J, et al. Regulation of enthesial IL-23 expression by IL-4 and IL-13 as an explanation for arthropathy development under dupilumab therapy. *Rheumatology (Oxford)*. 2021;60(5):2461-2466. <https://doi.org/10.1093/rheumatology/keaa568>
7. Tsukazaki H, Kaito T. The role of the IL-23/IL-17 pathway in the pathogenesis of spondyloarthritis. *Int J Mol Sci*. 2020;21(17):6401. <https://doi.org/10.3390/ijms21176401>
8. Chrétien B, Dolladille C, Alexandre J, et al. Dupilumab-associated arthralgia: an observational retrospective study in VigiBase®. *Br J Dermatol*. 2021;185(2):464-465. <https://doi.org/10.1111/bjd.20138>
9. Komaki R, Miyagaki T, Nakajima K, et al. Arthritis and enthesitis during dupilumab therapy completely remitted by celecoxib. *J Dermatol*. 2021;48(6):e279-e280. <https://doi.org/10.1111/1346-8138.15872>

10. Ishibashi M, Honda T, Tabuchi Y, Kabashima K. Polyenthesitis during treatment with dupilumab for atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2020;34(7):e319-e321. <https://doi.org/10.1111/jdv.16239>
11. Bostan E, Gülseren D, Özsoy Z, Ergen FB. Reactivation of inflammatory monoarthritis during dupilumab treatment used for prurigo nodularis. *Arch Rheumatol*. 2022;37(x):i-ii. <https://doi.org/10.46497/ArchRheumatol.2022.8780>