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RESEARCH LETTER

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Muscle and joint pain during dupilumab treatment for atopic dermatitis: Lack of association with antinuclear antibodies

To the Editor,

Since the increased use of dupilumab treatment in daily practice, several cases have been published on the development of dupilumab-associated inflammatory arthritis and arthropathy in patients with atopic dermatitis (AD).[1] In a large daily practice cohort of 210 AD patients treated with dupilumab, the prevalence of muscle and/or joint pain was 7.6%.[2] The question raises whether the immune-modulating effect of dupilumab, a monoclonal antibody targeting the interleukin-4 receptor alpha, might skew towards a more T helper (Th)-1/Th17-mediated response and/or promote the development of autoantibodies. In patients with humoral autoimmune diseases antinuclear antibodies (ANAs) and joint pain are commonly found.[3] In this study, we aimed to provide insight into ANA development during dupilumab treatment in AD patients.

Data of adult AD patients treated with dupilumab were extracted from the Dutch BioDay registry. All patients were treated at het University Medical Center Utrecht between October 2017 and February 2022. ANAs were measured in serum prior to dupilumab initiation, if available, and on a yearly basis during treatment by indirect immune fluorescence (IIF) using the human epithelial-20-10 cell line (EuroImmun, Lubeck, DE). A serum dilution of 1:100 was used to indicate ANA positivity. Weak positive results were considered negative.[4] In patients without ANA measurement before dupilumab treatment and a positive follow-up measurement, a serum sample prior to dupilumab initiation was tested for ANAs. Adverse events (AEs) were reported every visit. The study was approved by the local Medical Research Ethics Committee as a non-interventional study and was performed according to the declaration of Helsinki. All patients provided written informed consent.

In total, 329 patients were included of which 120 (36.5%) patients had an ANA measurement available before dupilumab initiation. The median age was 43 years (interquartile range [IQR] 29–57) and 60.2% was male. Almost all patients (92.4%) previously received oral immunosuppressive treatment, of which 39.5% used ≥2 immunosuppressive drugs (Table 1). In 8/329 (2.4%) patients, positive ANAs were found, with the longest follow-up period of 221 weeks. Six of these patients were ANA positive before dupilumab initiation of which one patient was previously diagnosed with ankylosing spondylitis (AS). During dupilumab treatment only two patients switched from ANA negative to positive after 107 and 109 weeks of dupilumab treatment, respectively, of which one patient was previously diagnosed with rheumatoid arthritis (Table 2). Approximately 6 months later, ANAs were negative again in these two patients, despite continuation of dupilumab treatment. Newly onset or progression of muscle and/or joint pain was reported in 30 (9.1%) patients of which none of the patients developed ANAs during dupilumab treatment. Patients experienced a variety of symptoms including pain and (morning) stiffness of hips, knees, shoulders and sometimes hands and feet. Several of these patients were referred to the rheumatologist for physical examination. In some patients, there was pain during palpation and a slightly decreased range of motion in one or more joints. There was no redness or swelling of the joints suggestive of inflammatory arthritis. In patients with moderate-to-severe muscle and/or joint pain, dupilumab was tapered or discontinued which led to a decrease or remission of symptoms.

In this cohort, we found a lower prevalence of 2.4% for positive ANAs compared to the healthy population (5.0–13.3% at a 1:160 and 1:80 serum dilution, respectively).[5] It has been reported that ANAs occur more frequently in AD patients compared with healthy individuals. However, studies that showed a higher prevalence of ANAs also include patients with mild AD, which make them less comparable to our results. Also, most of these studies used lower serum dilutions to measure ANA which might be an explanation for the higher ANA titers found in these studies compared to our study.[6] While ANAs are commonly found in humoural autoimmune diseases, they are not specific as ANA expression is frequently found in the healthy population,[5] women and elderly.[7] In this cohort, the development of ANAs might also be explained by different comorbidities (asthma,[3] AS,[3] decreased liver function,[7] sigmoid cancer[7]) or AEs (i.e. rosacea[8]).

Furthermore, for patients who developed muscle and/or joint pain during dupilumab treatment, ANAs remained negative suggesting that there is no induction of humoral-mediated autoimmune diseases in these patients. This finding is supported by the recently published study of Bridgewood et al. which reported that humoral-mediated autoimmune diseases were not associated with dupilumab use. They did find an association between dupilumab treatment and Th17-mediated diseases (e.g. seronegative arthritis and enthesitis/

TABLE 1 Baseline characteristics, treatment and follow-up

Total cohort, *n*	329
Baseline characteristics	
Age (years), median (IQR)	43.0 (29.0–57.0)
Male, *n* (%)	198 (60.2)
Atopic diseases at baseline, *n* (%)	
Allergic asthma	177 (53.8)
Missing	1 (0.3)
Allergic rhinitis	217 (66.0)
Missing	1 (0.3)
Allergic conjunctivitis	205 (62.3)
Missing	2 (0.6)
Food allergy	153 (46.5)
Missing	0 (0.0)
Previous use of oral immunosuppressive drugs, *n* (%)	
Total	304 (92.4)
History of ≥2 oral immunosuppressive drugs	130 (39.5)
Cyclosporine A	275 (83.6)
Methotrexate	102 (31.0)
Azathioprine	48 (14.6)
Mycophenolate mofetil	44 (13.4)
Oral tacrolimus	8 (2.4)
Other[a]	18 (5.5)
Concomitant oral immunosuppressive drugs, *n* (%)	
Total	112 (34.0)
Prednisolone	61 (18.5)
Cyclosporine A	33 (10.0)
Methotrexate	14 (4.3)
Azathioprine	4 (1.2)
Tioguanine	1 (0.3)
Follow-up	
Development of muscle and/or joint pain, *n* (%)	30 (8.7)
ANA distribution prior to dupilumab treatment, *n* (%)	
Total	120 (36.5)
Negative	114 (34.7)
Positive	6 (1.8)
ANA distribution during treatment (52 w–5 y), *n* (%)	
Total	246 (74.8)
Negative	241 (73.3)
Positive	5 (1.5)
Patients with >1 ANA measurement, *n* (%)	
Total	97 (29.5)
Shift from negative to positive	2 (0.6)
Shift from positive to negative	0 (0.0)

Abbreviations: ANA, Antinuclear Antibodies; IQR, Interquartile Range; w, week; y, year.

[a]Alitretinoin (*n* = 14), Thioguanine (*n* = 4).

Key messages

- Dupilumab-associated muscle and/or joint pain is frequently reported as a side effect in atopic dermatitis patients.
- A low prevalence (2.4%) of antinuclear antibodies was found in dupilumab-treated atopic dermatitis patients.
- We found no evidence for the development of humoral-mediated autoimmunity in these patients.

enthesopathy), suggesting that muscle and/or joint pain reported during dupilumab treatment is more likely related to a Th17-skewed response than autoimmunity.[9]

Although 329 patients were included for this study, only 2.4% of the AD patients had a positive ANA measurement at the start and/or during dupilumab treatment. The cohort with positive ANA patients is therefore rather small which may have introduced a bias in our results and is a limitation of our study.

In conclusion, we found no evidence for the development of humoral-mediated autoimmunity in terms of positive ANAs during dupilumab treatment in AD patients. None of the patients with dupilumab-associated muscle and/or joint pain developed ANAs. However, research on T-cell autoimmunity is recommended to provide further insight into other autoimmunity-related AEs during long-term dupilumab treatment.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the conception and design of this study and have been involved in drafting or revising the manuscript. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work.

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KEYWORDS

antinuclear antibodies, atopic dermatitis, autoimmunity, dupilumab, enthesitis, inflammatory arthritis

CONFLICT OF INTEREST STATEMENT

Dr. C.M. Boesjes is a speaker for Abbvie and Eli Lilly and Company. Dr. D.S. Bakker is a speaker for Sanofi and LEO Pharma. Dr. L.S. Spekhorst is a speaker for Abbvie. Prof. F. van Wijk is a speaker and/or consultant for Janssen, Johnson&Johnson and Takeda and

TABLE 2 Characteristics of eight atopic dermatitis patients with positive ANAs during dupilumab treatment.

Patient	A	B	C	D	E	F	G	H
ANA								
Start of treatment	Neg	Neg	Pos	Pos	Pos	Pos	Pos	Pos
During treatment	Pos	Pos	Pos	Pos	Pos	–	–	–
Age	28	**77**	**69**	43	43	47	**73**	49
Gender	Male	**Female**	**Female**	**Female**	**Female**	Male	Male	Male
Comorbidity	Acne	**Asthma, RA**	No	**Asthma**	HNP, herpes zoster	**↓liver function,** herpes zoster	**Sigmoid cancer,** glaucoma, arthrosis	**Asthma, AS**
Weeks between ANA1 and start dupilumab	–17[a]	–8[a]	–19[a]	–8[a]	–5[a]	0	0	2
Weeks between ANA2 and start dupilumab	109	107	209	155	103	–	–	–
Concomitant therapy	No	Inhalant pred	Pred	No	CsA	No	No	Adalimumab
AE during dupilumab	DAOSD **Rosacea**	None	DAOSD	Headache, intestinal complaints	DAOSD	None	None	Uveitis

aNegative number: ANA was measured before the start of dupilumab treatment. – not measured, two patients (F and H) discontinued dupilumab treatment prematurely, patient G did not achieve the 1-year visit yet. In bold patient characteristics, comorbidities and AEs in which ANAs are more or less frequently found.

Abbreviations: AD, Atopic Dermatitis; AE, Adverse Events; ANA, Antinuclear Antibodies; ANA1, first ANA measurement; ANA2, second ANA measurement; AS, Ankylosing Spondylitis; CsA, Cyclosporine A; DAOSD, Dupilumab-Associated Ocular Surface Disease; HNP, Hernia Nuclei Pulposi; Neg, negative; Pos, positive; Pred, Prednisolone; RA, Rheumatoid Arthritis.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The study was approved by the local Medical Research Ethics Committee as a non-interventional study (METC 18-239) and was performed according to the declaration of Helsinki. All patients provided written informed consent.

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