Articular manifestations related to anti-interleukin-5 therapies in severe asthma: a case series

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To the Editor:

Monoclonal antibodies targeting interleukin (IL)-5 (mepolizumab) or its receptor (IL-5R) (benralizumab) are biological drugs used to treat severe asthma. Both have proven efficacy in reducing exacerbations, restoring asthma control and sparing corticosteroid use, with good safety profiles [1–3]. Anti-IL-5/-5R-associated inflammatory arthritis was first reported in 2021 in six patients with severe asthma and one patient with chronic eosinophilic pneumonia [4, 5]. In our French severe asthma network CRISALIS, we have been challenged by several cases of destructive polyarthritis that developed after the initiation of anti-IL5/-5R therapies in severe asthma patients.

Therefore, to investigate the relationship between articular manifestations and anti-IL5/-5R therapies, we conducted a retrospective observational study in two ways: by issuing a call for cases to French pulmonologists from January to December 2022 and by querying the national pharmacovigilance register. We included adults receiving mepolizumab or benralizumab for severe asthma and presenting new or worsening arthralgia and/or arthritis that resulted in evaluation by a rheumatologist.

By calling for cases, we identified 22 patients receiving mepolizumab (n=15) or benralizumab (n=7) from seven different centres in France (table 1). Briefly, patients were mainly middle-aged (mean±SD age at onset of articular manifestations was 62.8±8.9 years) women (n=18, 82%), with late-onset eosinophilic (n=15) and steroid-dependent severe asthma (n=14, mean±SD daily dose 12.8±14.1 mg). All patients have attended a systematic evaluation to confirm the diagnosis of severe asthma [6]. Eight (36.4%) patients had an allergic sensitisation and four (18.2%) presented nasal polyposis. 10 (45.4%) had previously received omalizumab. All but one patient were good responders to their anti-IL5/-5R therapy.

Articular manifestations appeared (n=17) or deteriorated (n=5) at a mean±SD 11±10 months after initiation of the anti-IL5/-5R biologic. Oral corticosteroids (OCS) had been weaned in 10 (71%) of the 14 OCS-dependent patients. After specialised rheumatologist evaluation, several diagnoses were retained: calcium pyrophosphate dihydrate crystal deposition disease (CPPD) (n=6, two of whom possibly had a pre-existing condition), polymyalgia rheumatica (PMR) (n=3), anti-cyclic citrullinated peptide (CCP) seropositive rheumatoid arthritis (n=2, one of whom possibly had a pre-existing condition), psoriatic arthritis (n=1), unclassified chronic inflammatory arthritis (n=3, one of whom possibly had a pre-existing condition) and aspecific polyarthralgia (n=7, one of whom possibly had a pre-existing condition). Four patients had bone erosions on joint imaging; 11 required additional disease-modifying antirheumatic drugs (DMARDs); and 10 required low-dose OCS to control the articular manifestations. In nine patients, anti-IL-5/-5R therapies were discontinued, which led to alleviation of articular symptoms in only three of them.

To complete our analysis, we obtained data from the French pharmacovigilance database, focusing on all reported cases of musculoskeletal and connective tissue disorders with suspected anti-IL-5/-5R therapy causality. After removing duplicates from our series and excluding short-term symptoms related to injections (n=10 cases), we collected 21 additional cases of rheumatic disorders (mepolizumab n=13; benralizumab n=8). Patients were mainly women (17 out of 21, 80%), with mean±SD age 55.7±12.5 years. The following diagnoses were reported: rheumatoid arthritis (n=3), eosinophilic granulomatosis with polyangiitis (n=2), PMR (n=2), unclassified inflammatory monoarthritis or synovitis (n=2) and bursitis

Shareable abstract (@ERSpublications)
Articular manifestations should be screened before and during anti-IL-5/5R biologic treatment in severe asthma. Rigorous multidisciplinary team discussion should be carried out to assess the risk–benefit balance of withholding effective treatment. https://bit.ly/3vfPn4k

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TABLE 1 Patient characteristics, clinical and biological presentation, and outcomes from the series issued by a national call for cases

Patient number	Sex	Age years	Biologic	Previous treatment with biologic	Daily mOCS before biologic	mOCS dose mg·day^{-1}	mOCS weaned during biologic treatment	mOCS dose at rheumatologic symptom onset mg·day^{-1}	Duration of biologic treatment prior to symptom onset months	Rheumatologic diagnosis	Bone erosion on joint imaging	Biologic discontinuation	Rheumatologic treatments	Adrenal insufficiency	Follow-up (asthma)
1	M	75	Mepolizumab	Yes Omalizumab	Yes	15	Yes	5	14	Unclassified chronic inflammatory arthritis	Yes	Yes	OCS, MTX, abatacept	Absent	Peristent rheumatological symptoms requiring OCS (5 mg·day^{-1}) Switch to dupilumab 36 months after rheumatologic symptom onset
2	F	64	Mepolizumab	Yes Omalizumab	No	NR	NR	NR	16	Psoriasic arthritis	No	Yes	OCS, MTX, leflunomide, secukinumab, ixekizumab	Absent	Rheumatological symptoms controlled by ixekizumab Switch to benralizumab, with no worsening of rheumatological symptoms
3	F	65	Mepolizumab	Yes Omalizumab	Yes	20	Yes	NA	7	CPPD	No	No	Joint CS injection	Absent	Good clinical progress for rheumatological symptoms Asthma controlled by mepolizumab
4	F	69	Mepolizumab	Yes Omalizumab	Yes	20	Yes	0	10	CPPD	Yes	No	*i.v.* CS, OCS, MTX, joint CS injection, tocilizumab, sarilumab	Absent	Active rheumatological symptoms Continuation of OCS (5 mg·day^{-1}) and MTX Asthma well controlled by mepolizumab
5	F	87	Mepolizumab	Yes Omalizumab	Yes	5	Yes	0	15	Unclassified chronic inflammatory arthritis	Yes	No	OCS, MTX	Absent	Rheumatological symptoms controlled by OCS (6 mg·day^{-1}) Asthma controlled by mepolizumab and OCS
6	F	56	Mepolizumab	Yes Omalizumab	Yes	5	No	NA	7	Aspecific polyarthralgia	No	No	Joint CS injection	Not assessed	Asthma controlled by mepolizumab

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TABLE 1 Continued

Patient number	Sex	Age years	Biologic	Previous treatment with biologic	Daily mOCS before biologic	mOCS dose mg·day^{-1}	mOCS weaned during biologic treatment	mOCS dose at rheumatologic symptom onset mg·day^{-1}	Duration of biologic treatment prior to symptom onset months	Rheumatologic diagnosis	Bone erosion on joint imaging	Biologic discontinuation	Rheumatologic treatments	Adrenal insufficiency	Follow-up (asthma)
7	M	60	Mepolizumab	Yes Omalizumab	Yes	7	Yes	2.5	9	CPPD	No	No	Colchicine	Yes 11 months after rheumatological symptom onset	No recurrence of rheumatological symptoms Worsening of asthma. Diagnosis of allergic bronchopulmonary aspergillosis associated with asthma
8	F	63	Mepolizumab	Yes Omalizumab	Yes	10	Yes	0	22	Aspecific polyarthralgia	No	Yes	Hydroxychloroquine	Absent	Insufficient response to hydroxychloroquine Loss of asthma control with mepolizumab 12 months after onset of rheumatological symptoms Switch to dupilumab
9	F	60	Mepolizumab	Yes Omalizumab	Yes	10	Yes	7.5	3	CPPD	No	Yes	MTX, anakinra	Absent	OCS tapering, continuation of MTX due to arthralgia Loss of asthma control after OCS tapering Switch to dupilumab Neither asthma nor rheumatological symptoms have yet been re-assessed
10	M	56	Mepolizumab	No	No	NR	NR	NR	22	PMR	NA	Yes	OCS, MTX	Absent	Rheumatological symptoms resolution with OCS and MTX Switch to benralizumab with a good response

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TABLE 1 Continued

Patient number	Sex	Age years	Biologic	Previous treatment with biologic	Daily mOCS before biologic	mOCS dose mg·day^{-1}	mOCS weaned during biologic treatment	mOCS dose at rheumatologic symptom onset mg·day^{-1}	Duration of biologic treatment prior to symptom onset months	Rheumatologic diagnosis	Bone erosion on joint imaging	Biologic discontinuation	Rheumatologic treatments	Adrenal insufficiency	Follow-up (asthma)
11	F	65	Mepolizumab	No	Yes	20	Yes	7.5	2	CPPD	No	No	Level 2 analgesics	Absent	OCS tapering Continuation of mepolizumab
12	F	62	Mepolizumab	No	No	NR	NR	NR	7	Aspecific polyarthralgia	No	No	Etanercept	Absent	Severe asthma relapse leading to etanercept discontinuation
13	F	74	Mepolizumab	No	Yes	10	Yes	0	40	PMR	NA	Yes	OCS	Not assessed	OCS tapering initially and mepolizumab discontinuation with no loss of control of asthma, but relapse of rheumatological symptoms requiring OCS (1 mg·day^{-1})
14	F	59	Mepolizumab	No	Yes	20	No	20	3	Aspecific polyarthralgia	NA	Yes	None	Absent	Rheumatological symptoms improved after mepolizumab discontinuation Switch to benralizumab with a good result
15	F	56	Mepolizumab	No	No	NR	NR	NR	2	Aspecific polyarthralgia	No	Yes	Level 2 analgesics	Not assessed	Rheumatological symptoms improved after mepolizumab discontinuation Switch to benralizumab with good control
16	F	56	Benralizumab	Yes Dupilumab	Yes	10	No	10	4	Unclassified chronic inflammatory arthritis	No	No	*i.v.* CS, OCS	Not assessed	Difficul control of rheumatological symptoms, introduction of clomipramine hydrochloride Continuation of OCS (10 mg·day^{-1}) and benralizumab for asthma

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TABLE 1 Continued

Patient number	Sex	Age years	Biologic	Previous treatment with biologic	Daily mOCS before biologic	mOCS dose mg·day^{-1}	mOCS weaned during biologic treatment	mOCS dose at rheumatologic symptom onset mg·day^{-1}	Duration of biologic treatment prior to symptom onset months	Rheumatologic diagnosis	Bone erosion on joint imaging	Biologic discontinuation	Rheumatologic treatments	Adrenal insufficiency	Follow-up (asthma)
17	F	48	Benralizumab	No	Yes	5	No	5	0	RA (anti-CCP-positive)	Yes	No	OCS, joint CS injection, MTX, tocilizumab, rituximab, baricitinib, abatacept, etanercept	Not assessed	Active RA requiring a switch to adalimumab and continuation of OCS (10 mg·day^{-1}) Asthma controlled by benralizumab
18	F	53	Benralizumab	No	No	NR	NR	NR	6	Aspecific polyarthralgia	No	No	Level 2 analgesics, physical therapy	Absent	Good clinical progress for rheumatological symptoms Asthma controlled by benralizumab
19	F	57	Benralizumab	No	No	NR	NR	NR	26	RA (anti-CCP-positive)	Yes	Yes	Ocassional use of NSAIDs	Absent	Loss of asthma control with benralizumab and persistent rheumatological symptoms, 11 months after symptom onset Switch to tezepelumab with better asthma control Rheumatological symptoms have not yet been re-assessed
20	M	57	Benralizumab	Yes Omalizumab, mepolizumab	No	NR	NR	NR	9	Unclassified chronic inflammatory arthritis	No	No	Level 2 analgesics, physical therapy	Absent	No need for specific rheumatological treatment Asthma controlled by benralizumab

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TABLE 1 Continued

Patient number	Sex	Age years	Biologic	Previous treatment with biologic	Daily mOCS before biologic	mOCS dose mg·day^{-1}	mOCS weaned during biologic treatment	mOCS dose at rheumatologic symptom onset mg·day^{-1}	Duration of biologic treatment prior to symptom onset months	Rheumatologic diagnosis	Bone erosion on joint imaging	Biologic discontinuation	Rheumatologic treatments	Adrenal insufficiency	Follow-up (asthma)
21	F	68	Benralizumab	No	Yes	60	Yes	30	2	Aspecific polyarthralgia	No	No	Level 2 analgesics	Absent	No need for specific rheumatological treatment Asthma controlled by benralizumab
22	F	73	Benralizumab	Yes	No	NR	NR	NR	25	CPPD	No	No	Hydroxychloroquine	Absent	Good control of rheumatological symptoms by hydroxychloroquine Asthma controlled by benralizumab

mOCS: maintenance oral corticosteroids; M: male; F: female; MTX: methotrexate; NR: not relevant; NA: not available; CPPD: calcium pyrophosphate dihydrate crystal deposition disease; CS: corticosteroid; *i.v.*: intravenous; PMR: polymyalgia rheumatica; RA: rheumatoid arthritis; CCP: cyclic citrullinated peptide; NSAID: nonsteroidal anti-inflammatory drug.

(n=1), For the remaining 11 patients, no specific rheumatological diagnosis was reported except symptoms. In this group, articular manifestations developed at a mean±SD 10±16 months after treatment initiation, and six cases were classified as severe adverse events. In these spontaneous anonymous reports, information on OCS tapering and concurrent treatments was lacking.

Here we report the largest series of severe asthma patients (22 from our case series and 21 additional cases from the national pharmacovigilance database) experiencing articular manifestations associated with anti-IL-5/-5R therapy.

Rheumatic adverse events are rarely described to date in severe asthma patients receiving anti-IL5/-5R biologics, and when done so, are poorly detailed. The prevalence was similar to placebo in phase III randomised control trials (RCTs) (5–6% with mepolizumab and 2–3% with benralizumab *versus* 5% and 2% in respective placebo groups) [1, 7]. Musculoskeletal and connective tissue disorders occurred in 2–13% of cases in real life and in phase 4 long-term follow-up studies [8, 9]. The rate of arthralgia ranged from 0% to 34.7% in real-life observational studies, but the diagnosis under the term "arthralgia" is imprecise [10–12]. Outside arthralgia, our case series features varied inflammatory disorders, mostly negative for anti-CCP antibodies and rheumatoid factor, with possible bone erosions, sometimes requiring DMARDs, and occurring after 10–11 months of treatment. This relatively late onset could explain why these cases were not reported in phase III RCTs with a limited follow-up of 52 weeks.

The extrinsic causality of anti-IL-5/-5R biologics could be questioned. Indeed, nine patients discontinued biologics after onset of rheumatic symptoms, with no clinical improvement in six. In the others, despite a suspected adverse event, the treatment was maintained because asthma was well controlled. Articular manifestations were managed by rheumatologists using other ways. Moreover, the rheumatic disease could have existed before biologic initiation, as for the five out of 22 patients who deteriorated after initiation, and symptoms unmasked with OCS withdrawal. However, one-third of our 22 patients (n=7) did not receive daily OCS before biologic initiation, and symptoms were independent of OCS tapering in five patients. Moreover, 46% had previously received omalizumab without such symptoms, despite good response and similar OCS weaning. Regardless of 15 years of omalizumab use worldwide, rheumatic adverse events have been rarely described, even in OCS-dependent patients [13]. Steroid-induced adrenal insufficiency, which can also induce muscle and joint pains, was diagnosed in only one patient, 11 months after onset of articular symptoms, ruling out a potential differential diagnosis. In the data obtained from the French pharmacovigilance database, hydrocortisone use was reported for two patients (one treated with mepolizumab, one with benralizumab), but no diagnosis of adrenal insufficiency was reported.

Recent observations support the role of anti-IL-5 drugs in the development of these various types of inflammatory rheumatisms such as systemic autoimmune diseases and rheumatism involving the innate immune system (*i.e.* CPPD). First, a dual role of eosinophils in a combined murine model of arthritis and asthma has been described: a subpopulation of eosinophils, named regulatory eosinophils (rEOS), was found to play a protective role in the joint compartment, *via* the production of pro-resolving mediators [5]. These rEOS differed from the inflammatory subpopulation isolated in the lung and expanded on systemic upregulation of IL-5 released by lung type 2 innate lymphoid cells. In mice, mepolizumab increased inflammation and bone erosion. rEOS were also identified in the blood and the synovial membrane in patients with rheumatoid arthritis in remission, but not in the active stage [5]. Lastly, inactive rheumatoid arthritis patients with concomitant asthma developed a flare of disease after mepolizumab treatment, which might be explained by the depletion of synovial anti-inflammatory rEOS, thus leading to deregulation of the local anti-inflammation balance [5]. Second, the use of dupilumab, an anti-IL-4/-13R biologic, in patients with atopic dermatitis, has also been associated with the occurrence of articular manifestations, mainly seronegative arthritis and enthesopathy, but not with polygenic humoral-mediated autoimmune diseases such as rheumatoid arthritis [14]. The main hypothesis to explain this observation is a polarisation toward T-helper and type 17 T-helper pathways induced by blocking the IL-3/-4 pathway.

Altogether, these data support the role of a blockade of type-2 inflammation in the occurrence of articular manifestations in anti-IL-5/-5R-treated patients. The role of underlying disease, asthma or atopic dermatitis, in directing articular manifestations toward a specific rheumatic phenotype remains to be elucidated.

The main limitations of this study are related to its retrospective design. Despite the collaboration of a large network of French pulmonologists and the analysis of the French pharmacovigilance database, we were unable to evaluate the true incidence of these adverse events. Further analysis of larger populations is needed to provide a more comprehensive evaluation of the association of anti-IL-5 blockade and articular manifestations.

Whether the IL-5-targeting biologics played a causal role in the flares of such rheumatisms, and the exact mechanisms leading to an immune imbalance in rheumatisms involving either adaptive or innate immune system remain unknown. Rigorous multidisciplinary team discussion should be carried out to assess the risk–benefit balance of withholding effective biologic treatment in these severe asthma patients in light of high morbidity. Nonetheless, expert rheumatologic evaluation and management is essential, as these articular manifestations may have an important functional impact, a potential progression to joint destruction and may require the use of DMARDs. As already reported, dual biologic therapy for treating rheumatic diseases and severe asthma was safe and well tolerated [15, 16].

To conclude, rheumatic conditions should be screened, and if present, monitored, before and during anti-IL-5/-5R therapies. Whether discontinuation of anti-IL-5/-5R therapy may improve rheumatic manifestations remains to be evaluated in larger series.

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