

Resolution of ocular and mediastinal sarcoidosis after Janus kinase inhibitor therapy for concomitant rheumatoid arthritis

Sirs,
Hospital-based series suggest that 2 to 15% of diagnosed uveitis are due to sarcoidosis (1). Treatment is mainly based on corticosteroids. Immunosuppressive therapy (methotrexate, TNF- α antagonists) are mostly indicated in cases of steroid side-effects (1). Paradoxically, cases of sarcoidosis after anti-TNF- α therapy have been described, including uveitis (2).
Tofacitinib, a small molecule inhibiting JAK1 and JAK3, has been approved by the FDA and the EMA for the treatment of rheumatoid arthritis (RA) (3). Six reports of

patients with refractory sarcoidosis successfully treated with JAK inhibitors (tofacitinib or ruxolitinib) are currently available in the literature but none of these patients had ocular involvement (4-8) (Table I).
We report of a case of a 62-year-old Caucasian woman diagnosed with RA in 2014, who was referred in May 2019 to our internal medicine department for a mediastinal and ocular sarcoidosis that occurred during adalimumab therapy. Blood tests showed high levels of rheumatoid factor and anti-citrullinated protein antibodies. In September 2015, the patient was treated with oral sulfasalazine at 2 g/day. Oral methotrexate (at 15 mg/week) was started in December 2015 because of sulfasalazine inefficacy. Methotrexate route was switched to subcutaneous in May 2015 because of poor digestive tolerance. In August 2016, due to persistent RA activ-

ity, she has been started on adalimumab 40 mg every two weeks plus methotrexate 10 mg a week.
In February 2018, the patient was diagnosed with granulomatous, hypertensive, bilateral panuveitis. Adalimumab was stopped. Chest computed tomography revealed mediastinal and hilar lymphadenopathy. Biopsy samples from mediastinoscopy showed non-caseating epithelioid granulomas. Prednisone therapy was started and methotrexate was continued at 15 mg per week. In September 2018, uveitis was still active with slight improvement of the vasculitis. There was no regression of the vitritis with snowballs. In October 2018, while prednisone was decreased under 10 mg a day, the patient experienced recurrence of joint pain due to RA. Echography showed active synovitis. Joint corticosteroid injection and increased dosage of prednisone were necessary. Because

Table I. Known case reports on JAK kinase inhibitors in sarcoidosis.

Reference	Age in years	Sex	Diagnosis	Disease duration in years	Prior therapies	JAK Kinase inhibitor efficiency
Damsky <i>et al.</i> 2018 (3)	48	F	Sarcoidosis: -cutaneous -pulmonary	8	Topical glucocorticoids Minocycline Hydroxychloroquine Methotrexate Adalimumab Tacrolimus (oral) Apremilast	Tofacitinib 5mg twice daily Complete cutaneous remission Persistence of asymptomatic pulmonary involvement (limited fibrotic lung disease)
Damsky <i>et al.</i> 2020 (4)	34	M	Sarcoidosis: -cutaneous -pulmonary	6	Prednisone Hydroxychloroquine Adalimumab + methotrexate	Tofacitinib 5mg twice daily Near-complete cutaneous remission
	68	F	Sarcoidosis: -cutaneous	25	Hydroxychloroquine Minocycline Methotrexate	Tofacitinib 5mg twice daily Complete cutaneous remission
Levraut <i>et al.</i> 2019 (5)	51	F	Multivisceral sarcoidosis-like systemic granulomatosis: -peripheral lymphadenopathy, hepatomegaly and splenomegaly -recurrent fever, elevated CRP -pulmonary -hypercalcaemia -bone -peritoneal and pleural effusion -cutaneous	5	Prednisone Doxycycline Antituberculosis therapy Hydroxychloroquine Azathioprine Mycophenolate mofetil Cyclophosphamide Infliximab Methotrexate Adalimumab Anakinra	Ruxolitinib 20 to 30mg daily Clinical and biological remission with permanent steroid discontinuation
Wei <i>et al.</i> 2019 (6)	60	F	Sarcoidosis: -cutaneous -pulmonary	1	Intralesional steroid injections	Ruxolitinib 10mg twice daily Complete cutaneous remission Improvement of lung nodules and mediastinal lymphadenopathy Remission of polycythemia vera
			Polycythemia vera	ND		
Rotenberg <i>et al.</i> 2018 (7)	60	F	Sarcoidosis: -cutaneous -pulmonary (moderate pulmonary fibrosis)	18	Prednisone Hydroxychloroquine Methotrexate Azathioprine Leflunomide Adalimumab Infliximab	Ruxolitinib 5mg twice daily Complete cutaneous remission Improvement of lung infiltration and vital capacity Remission of polycythemia vera
			Polycythemia vera	1		
Our case 2020	62	F	Sarcoidosis-like: -uveitis -pulmonary	1	Adalimumab discontinuation Prednisone Methotrexate	Tofacitinib 5mg twice daily Improvement of ocular inflammation Decrease of mediastinal lymphadenopathy hypermetabolism Remission of rheumatoid arthritis
			Rheumatoid arthritis	6		

of the high dose steroid dependency, additional therapy was considered.

In May 2019, while the patient was still receiving methotrexate at 15 mg per week and prednisone at 10 mg a day, ophthalmological examination, performed at our institution, showed a best-corrected visual acuity at 20/32 for the right eye and 20/25 for the left eye. There was no inflammation in the anterior chamber. At fundus examination, there was vitritis and typical snowballs, associated with active retinal vasculitis. OCT showed bilateral macular oedema. Angiography showed 360° venous occlusive retinal vasculitis at the periphery with several ischaemic areas. The positron emission tomography (PET) showed mediastinal lymphadenopathy hypermetabolism (SUV 6).

In this context, the patient was started on tofacitinib at 5 mg twice a day. In September 2019, whereas prednisone and methotrexate had been stopped, the PET showed a decrease of mediastinal lymphadenopathy hypermetabolism (SUV 4). In February 2020, ophthalmological examination revealed a best corrected visual acuity of 20/50 for the right eye and 20/32 for the left eye. Fundus examination showed a complete resolution of vitritis and disappearance of snowballs. There was no more macular oedema on OCT and angiography showed the disappearance of vasculitis. Lower visual acuity was explained by progression of the cataract in both eyes. Joint pain or synovitis were no longer present. No significant adverse effects of tofacitinib were reported.

To our knowledge, this is the first report of a JAK inhibitor efficacy on sarcoidosis-related uveitis. The pathogenesis of sarcoidosis involves several cytokines (IL-12/23, IL-17, IL-22, INF- γ), which signal through the JAK-STAT pathway. Transcriptome analyses have revealed *STAT1* gene upregulation

as a characteristic of mononuclear cells and tissues in sarcoidosis patients. To date, there are six reports of sarcoidosis, especially with cutaneous involvement, effectively treated with JAK inhibitors (4-8). Although, the very promising findings in these reports need to be evaluated in larger studies, which are underway (NCT03910543, NCT03793439) (9-10). Confirmation/identification of the critical targets of tofacitinib/ruxolitinib in sarcoidosis may allow further refinement of therapy.

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