Comparison of the treatment guidelines for sarcoidosis: common sense in the search for evidence

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To the Editor:

We congratulate the authors of the highly anticipated European Respiratory Society (ERS) clinical practice guidelines on treatment of sarcoidosis [1]. The ERS clinical practice guidelines are an update of the guideline developed by the American Thoracic Society, ERS and World Association of Sarcoidosis and Other Granulomatous Disorders in 1999. The current task force committee has put more emphasis on patient tailored choice than the 1999 guideline. They used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to develop 12 specific treatment recommendations for management of sarcoidosis. All recommendations were based on very low to low quality of evidence. As such, an important message of the 2021 guideline is that high or even moderate quality evidence for optimal management of sarcoidosis is lacking [2]. Although knowledge of the pathogenesis of sarcoidosis has improved, this has not yet translated into better evidence-based first- and second-line therapies for patients with pulmonary sarcoidosis. For refractory sarcoidosis, third-line therapies such as infliximab and adalimumab have become available. In addition to the ERS clinical practice guidelines, the British Thoracic Society (BTS) recently published a clinical statement on pulmonary sarcoidosis, which covers both diagnosis and management [3]. The BTS statement did not use the GRADE methodology to rate the level of evidence; instead, they chose to provide clinical practice points, predominantly based on expert opinion and clinical experience, due to the weak available evidence.

Interestingly, the ERS and BTS documents provide slightly different recommendations, especially regarding medication dosages and treatment schedules [1, 3]. The ERS guideline advises to initiate prednisone treatment at a dose of 20 mg per day, whereas the BTS statement advises to start with 20–40 mg per day. Both the ERS guideline and BTS statement suggest addition of methotrexate in patients who have continued disease or unacceptable side-effects of glucocorticoids. The ERS guideline advises a dosage of 10–15 mg per week and suggests (in the supplement) that there are guidelines underpinning this recommendation, which to our knowledge do not exist. The BTS statement advises to start with a dose of 5–10 mg per week and increase until a maintenance dose of 15–20 mg per week. No recommendations about duration and tapering of methotrexate treatment are made. To highlight differences and similarities in the existing guidelines and changes from the previous guideline, we have provided an overview of recommendations focused on pulmonary sarcoidosis in table 1.

As shown in the guideline recommendations, evidence for first- and second-line treatment options is still limited. Optimal prednisone treatment schedules are unknown and it remains unclear whether this treatment prevents disease progression in the long-term [4]. Most studies in the past decade focused on novel third-line treatment options in patients with refractory pulmonary sarcoidosis, often glucocorticoid dependent, and several studies are ongoing [5]. Some clinical studies based on a strong pathophysiological rationale showed disappointing results [6]. This could be due to several reasons. The heterogeneity of sarcoidosis and variable disease course make a good study design challenging, particularly regarding patient selection and relevant outcome measures. Studies focusing on patients with refractory sarcoidosis are biased, as those patients may have a distinct immunological profile compared to treatment-naïve patients and could respond differently to medication [7, 8]. Choosing relevant end-points in sarcoidosis remains challenging, as disease phase, amount of irreversible lung disease, variable physiological impairment (obstructive and restrictive) and differences in burden of disease should be taken into account

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TABLE 1 Comparison of the treatment guidelines for pulmonary sarcoidosis[#]

	ERS guidelines 2021	BTS statement 2020	ATS/ERS/WASOG guideline 1999
Methodology	Task force formulated PICO questions and used the GRADE methodology to rate the level of evidence	Clinical statement group (pulmonologists, nurses, radiologist and patients) provided clinical practice points; the content was developed in accordance with the BTS Standards of Care Committee	Guideline written by sarcoidosis experts; level of evidence is largely based on expert opinion
When to start treatment	Patients with major involvement from pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis (strong recommendation, low quality of evidence)	Potential danger of a fatal outcome or permanent disability Unacceptable loss of QoL	No clear recommendation when to start treatment for pulmonary sarcoidosis Most healthcare providers prescribe corticosteroids in case of progressive symptomatic disease In asymptomatic patients treatment may be required in case of pulmonary function impairment or persistent pulmonary infiltrates
First-line treatment			
Prednisone	1) High risk: Initial treatment 20 mg per day Maintenance dose 5–10 mg per day to every other day Inhaled steroids not advised 2) Intermediate risk, but impaired QoL: 5 to 10 mg per day	1) Pulmonary sarcoidosis: Initial treatment 20–40 mg per day for 4 to 6 weeks Slow tapering to maintenance dose of 5–10 mg per day Inhaled steroids not advised 2) Loss of QoL: the choice and dose of agent should be negotiated with the patient	Initial treatment 20–40 mg per day Evaluation for response after 1–3 months In responders taper prednisone to 5–10 mg per day or every other day Continue treatment for at least 12 months
Second-line treatment			
General statement	Addition of MTX is advised for symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids and have continued disease or unacceptable side-effects from glucocorticoids (conditional recommendation, very low quality of evidence) AZA, mycophenolate and leflunomide are also effective in pulmonary sarcoidosis; chloroquine was mildly beneficial (not assessed per GRADE methodology)	Review diagnosis and treatment compliance before introducing second-line agents Indications for second-line therapy: 1) uncontrolled disease or unacceptable symptoms, 2) intolerable side-effects, 3) inability to taper prednisone below 10–15 mg per day, 4) presents comorbidities likely related to corticosteroids, and 5) strong patient aversion against steroids (can occasionally be used as first-line treatment)	Cytotoxic agents have been used to treat sarcoidosis It is not clear when cytotoxic agents should be used The evidence is based on case reports and small cohort studies MTX and AZA are the preferred agents Cyclophosphamide should be reserved for refractory cases (high toxicity profile)
MTX	10–15 mg once a week	Most frequently used Initiate at 5–10 mg per week and increase every two weeks to a target of 15–20mg	10–25 mg per week
AZA	50–250 mg per day	Initiate at 50 mg per week, increase by 25 mg every 2–3 weeks until the maintenance dose is reached (typically 2 mg per kg)	50–200 mg per day
Mycophenolate mofetil	500–1500 mg twice a day	In general: do not consider before MTX and AZA Usual dose between 1000–1500 mg twice a day	Not mentioned

Continued

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TABLE 1 Continued

	ERS guidelines 2021	BTS statement 2020	ATS/ERS/WASOG guideline 1999
Leflunomide	10–20 mg per day	No advice on treatment dose	Not mentioned
Cyclophosphamide	Not mentioned	Rarely used as second-line treatment due to its toxicity profile	50–150 mg per day or 500–2000 mg every 2 weeks intravenously
Hydroxychloroquine/ chloroquine	200–400 mg per day	Mainly advocated for use in fatigue, joint and skin sarcoidosis; might help reduce prednisone dose in pulmonary sarcoidosis Usual dose 200 mg once or twice per day	200–400 mg per day
Third-line treatment			
General statement	Infliximab is advised for symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease (conditional recommendation, very low quality of evidence) Adalimumab was also found to be effective (not assessed per GRADE methodology)	Biological agents are considered third-line therapeutic agents, to be initiated in pulmonary disease only after failure of second line treatment Screen for latent tuberculosis infection	TNF-α inhibitors were not available at the time the guideline was published Agents proposed based on response in selected cases: cyclosporine, melatonin, thalidomide, and pentoxifylline
Infliximab	Initiate at a dose of 3–5 mg per kg, second dose 2 weeks later, than once every 4–6 weeks	Improves disease control in combination with MTX and AZA Should initially be given every 2 weeks and then every 4–8 weeks as part of maintenance therapy No advice on treatment dose	Not mentioned
Adalimumab	40 mg every 1–2 weeks	Not mentioned	Not mentioned
Continued disease after third-line treatment			
General statement	To consider on a case by case basis (not assessed per GRADE methodology)	Not mentioned	Not mentioned
Rituximab	Small case series supports the use of rituximab 500–1000 mg every 1–6 months	Not mentioned	Not mentioned
Repository corticotropin injection	Retrospective studies showed a steroid sparing effect 40–80 units twice a week	Not mentioned	Not mentioned
JAK inhibitor	Response reported in small retrospective case series No advice on treatment dose	Not mentioned	Not mentioned
Antifibrotic therapy			
General statement	Future research: also the role of anti-fibrotic agents such as nintenanib and pirfinedone need to be further studied	At time of publication pirfenidone and nintedanib were only registered for idiopathic pulmonary fibrosis	Not mentioned

[#]: recommendations as stated in the guidelines. ERS: European Respiratory Society; BTS: British Thoracic Society; ATS: American Thoracic Society; WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders; PICO: Patients, Intervention, Comparison, Outcomes; GRADE: Grading of Recommendations Assessment, Development and Evaluation; QoL: quality of life; MTX: methotrexate; AZA: azathioprine; TNF: tumour necrosis factor.

to capture a meaningful treatment effect. Therefore, studies with new agents should ideally be performed in an unbiased cohort of treatment-naïve patients with sarcoidosis.

We believe that more studies should focus on better evidence-based first- and second-line treatment. First of all, better insights should be obtained on the effect of treatment on the natural course of sarcoidosis. Currently, it is often not clear which patients with pulmonary sarcoidosis we should treat. In the guideline from 1999, no recommendation was provided on when to start treatment, whereas the recent guideline mainly gives general recommendations (treatment is advised in patients with pulmonary involvement at risk of mortality or permanent disability). Secondly, as prednisone is often accompanied by side-effects and reduced quality of life, research into other first-line treatment options is needed. Recently, an observational study found that first-line treatment with methotrexate seems to have the same efficacy as prednisone [9]. A randomised controlled trial investigating the efficacy of methotrexate compared with prednisone as first-line treatment option for pulmonary sarcoidosis is currently ongoing [10]. This study combines clinical and fundamental research, which will hopefully provide new insights into the pathophysiology of sarcoidosis and the immunological profile of responders *versus* non-responders on treatment. Finally, optimal treatment schedules for first- and second-line treatment should be established, to avoid "under treatment" with the risk of organ damage and "over treatment" with the risk of debilitating or dangerous side-effects. At this moment an ongoing trial evaluates the efficacy and safety of prednisone 40 mg per day *versus* prednisone 20 mg per day in sarcoidosis (NCT03265405).

Hopefully, the new guidelines will not only stimulate patient engagement and common sense when making treatment decisions, but will also encourage the field to generate high-quality evidence to support those decisions.

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