Clinical phenotyping: role in treatment decisions in sarcoidosis

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Expert Delphi consensus recommendations on clinical phenotyping to guide therapy for pulmonary sarcoidosis – asymptomatic: no therapy; acute: corticosteroids; chronic: cytotoxics plus other second line; advanced: biologics plus other third line. http://bit.ly/38Lio7U

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ABSTRACT A variety of phenotypic categorisations have been developed for sarcoidosis. Phenotyping has been used for genetics studies and to guide treatment selection. The authors participated in a Delphi expert consensus panel to develop a proposed phenotype categorisation and treatment recommendations for pulmonary sarcoidosis patients. Panellists reached consensus that asymptomatic patients with normal pulmonary function and adenopathy alone or normal chest imaging do not require therapy, while symptomatic patients with impaired pulmonary function or infiltrates should be treated. The panel did not reach consensus on asymptomatic patients with abnormal chest imaging or reduced pulmonary function, or symptomatic patients with normal chest imaging and pulmonary function. The proposed phenotype categories and associated treatment recommendations are asymptomatic (no therapy), acute (disease duration <1–2 years, apparently self-limited, corticosteroids), chronic (antimetabolites and other second-line therapies) and advanced (biologics). Some clinical settings, such as dyspnoea/hypoxaemia at rest, severely impaired or rapidly decreasing pulmonary function tests, and severe cardiac, neurologic, ocular or renal involvement warrant immediate therapy.

Introduction

Sarcoidosis is a multi-organ disease with a variable clinical outcome [1]. Because of this, researchers and healthcare providers have developed phenotypic categories to help identify distinct populations of sarcoidosis patients [2]. These phenotypic categories have been employed by both researchers and clinicians. For example, Löfgren syndrome was originally described because it was a clinical phenotype associated with an excellent prognosis. However, genetic studies demonstrated a high frequency of certain human leukocyte antigen (HLA) genotypes associated with a good clinical prognosis in patients with Löfgren syndrome [3]. Phenotyping is a dynamic process that evolves as further disease characteristics, biomarkers and genetic information are discovered. As our understanding of phenotypes improves, the use of phenotyping for clinical and/or research purposes may prove increasingly useful for many aspects of sarcoidosis.

History of clinical phenotyping in sarcoidosis

One of the most widely used clinical phenotype categorisations was developed based on chest radiograph patterns of patients with pulmonary sarcoidosis. In 1960 and 1961, Dr Wurm in Germany [4] and

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Dr Scadding in Scotland [5] reported independently that different combinations of the presence or absence of hilar adenopathy and parenchymal infiltrates were associated with different outcomes in chest radiograph over time. Scadding [5] added a fourth pattern and the Scadding stages of the chest radiograph have been used in practice for years.

Around the same time, Dr Löfgren noted that disease often resolved within 3–6 months in patients who presented with erythema nodosum and hilar adenopathy. A modification of Löfgren syndrome was suggested by Grunewald and Ecklund [6]. They found that periarticular arthralgia had the same prognosis as the presence of erythema nodosum [6]. They also noted that the use of HLA genotyping to predict prognosis was the same for those who presented with erythema nodosum as with periarticular arthralgias [3].

Another early proposed clinical phenotype was based on duration and clinical outcome of disease. Neville *et al.* [7] studied the clinical course of over 800 sarcoidosis patients followed at their clinic for >2 years. They noted that some patients had resolution of their disease within 2 years (acute disease) *versus* others who had persistent disease beyond 2 years (chronic disease) [7]. This simple division of patients into acute and chronic phenotypes has been used for many years by clinicians as they decide which patients may require long-term therapy.

In the past decade, several other phenotypes have been proposed [2]. Many of these were developed for genetic studies, but in other cases phenotypic categorisation has been used to define populations for specific treatments. A comparison of phenotype scales for sarcoidosis reported in literature is presented in table 1. From table 1, we note three papers which examined genotype/phenotype relations. Two studies by Grunewald and co-workers [3, 8] investigated HLA-DR markers in sarcoidosis patients with Löfgren syndrome and were able to differentiate patients with an excellent prognosis *versus* those with a 50% chance of having chronic disease. The study by Schupp *et al.* [15] identified clustering of symptoms so that further studies of genetic markers could be done on those patients with different clusters of organ disease.

Phenotyping for genetic studies

As noted, clinical phenotyping can help better understand the genetics of a disease. For example, cystic fibrosis is the result of the mutation of one gene, cystic fibrosis transmembrane conductance regulator (CFTR). Over the past few years, thousands of mutations of this gene have been identified, and different mutations of CFTR have been shown to lead to different clinical outcomes. In addition, other genes may modify expression of CFTR [16]. Sarcoidosis is a condition in which multiple genes may be responsible for disease and prognosis [17]. Nevertheless, the first step would seem to be to define homogenous populations among sarcoidosis patients; then, certain genes may be identified which are associated with specific clinical presentations or outcomes.

One phenotype of sarcoidosis is Löfgren syndrome. Several groups found that Löfgren syndrome associated with HLA-DQB1*0201 had a good prognosis, especially in European patients [18, 19]. Further studies have shown that Swedish patients with Löfgren syndrome and another HLA marker, DRB1*0301, have a highly favourable prognosis and rarely require any therapy [3, 6]. This has led to the use of HLA phenotyping for treatment decisions in some clinics.

Two recent phenotypes have been specifically described to help with genetic studies. In the study by Schupp *et al.* [15], a large population of sarcoidosis patients from various clinics in Europe were evaluated. The authors grouped the clinical features of these patients and identified some associations. For example, they found that patients with eye disease often have neurologic disease. They also found that patients with neurologic disease had a higher frequency of cardiac disease, as noted by others [20]. These clusters may prove useful as researchers are trying to determine genotypes associated with phenotypes.

The Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis study developed a phenotype proposal predicting prognosis for patients in whom multiple specimens had been obtained [14]. This study promises to provide detailed genetic information regarding these different phenotypes.

Phenotyping for treatment decisions

Phenotyping patients may also prove useful for decisions about therapy. The authors participated in a Delphi expert consensus panel to develop consensus recommendations for phenotyping and appropriate therapies for different phenotypes. The design and results of the modified Delphi consensus process are presented elsewhere in this issue of the *European Respiratory Review* [21]. The Delphi group included 26 panellists. This panel size is typical for Delphi consensus studies and reflects a balance between the need to sample a wide range of expert opinion and the difficulty in recruiting experts and coordinating the panel. The Delphi process developed the proposed phenotype categorisation and treatment recommendations described here and shown in supplementary appendix 1.

TABLE 1 Phenotype scales reported in sarcoidosis

First author [ref.]	Phenotype	Description of developing phenotype	Patients n	Validation	Single *versus* multi-centre	Established association to genotype	Comments
Scadding [5]	Pulmonary	Chest radiograph stage	136	No	Single	No	Did not use computed tomography
Neville [7]	Acute *versus* chronic	Rate of resolution	818	No	Single	No	Did not account for more than one factor in patient
Grunewald [3, 8]	Löfgren *versus* non-Löfgren	Clinical outcome of Löfgren patients	754	Yes	Single	Yes	Series of studies, may not apply to other racial groups
Wasfi [9]	Severe *versus* non-severe	Backward regression based on clinical parameters	104	Two different groups of clinicians assessed same patients	Single	No	Based on expert opinion, no follow-up analysis
Prasse [10]	Acute *versus* chronic and duration of treatment	Evaluated patients seen within 1 year of presentation	225	No	Single	No	More useful for acute disease
Baughman [11]	Acute *versus* chronic including therapy	Developed criteria for long-term outcome	500	No	Multi-centre	No	Retrospective look based on expert opinion
Rodrigues [12]	Acute, relapse, fibrosis	Factor analysis	137	No	Multi-centre	No	Phenotypes were not distinct
Walsh [13]	Severe *versus* non-severe	Regression analysis of multiple factors	251	Yes (additional 252)	Single	No	Only focused on advanced pulmonary disease
Moller [14]	Various groups of patients	Expert opinion of grouping of patients	Not given	No	Multi-centre	Yes	Established criteria to be studied
Schupp [15]	Organ clustering	Multi-factor analysis based on gene expression	2163	No	Multi-centre	Yes	Used genetic profile to identify associated organ manifestations

The proposed phenotyping is based on clinical outcomes and is derived from the World Association of Sarcoidosis and other Granulomatous Disorders Clinical Outcome Status [11]. The Clinical Outcome Status evaluates patients 2–5 years after diagnosis and places them into nine general categories based on therapy and current status. Patients can be classified as having either no or minimal disease (<25% of maximal disease), persistent disease or worsening disease. The classifications for therapy include never, none in the prior year, on therapy and stable, or on therapy and increased in prior year.

The phenotype categorisation in supplementary appendix 1 is derived from prior reported categories. One phenotype is the asymptomatic group. These patients have no symptoms and do not require any systemic therapy. The definition of symptomatic disease was left to the individual expert. Most patients who present with no symptoms rarely require therapy over time. This group is similar to the asymptomatic acute patients described by Prasse *et al.* [10]. It is also equivalent to groups 1, 3 and 5 from the World Association of Sarcoidosis and other Granulomatous Disorders Clinical Outcome Status [11].

The acute patients who present with symptoms are those within the first 1–2 years after diagnosis who appear to have self-limited disease. These patients are usually initially treated with prednisone. For these patients, the initial decision to start therapy is based on a combination of factors, including symptoms, chest imaging and pulmonary function testing.

The Delphi expert panel reached consensus regarding treatment for patients based on pulmonary function, chest imaging and symptoms (figure 1). Specifically, for symptomatic patients, there was consensus that a patient with a forced vital capacity (FVC) or diffusing capacity of the lung for carbon monoxide (D_{LCO}) ⩽80% should be considered for therapy. For the asymptomatic patient, there was consensus that those with normal D_{LCO} or FVC did not need treatment. The panel did not reach consensus on asymptomatic

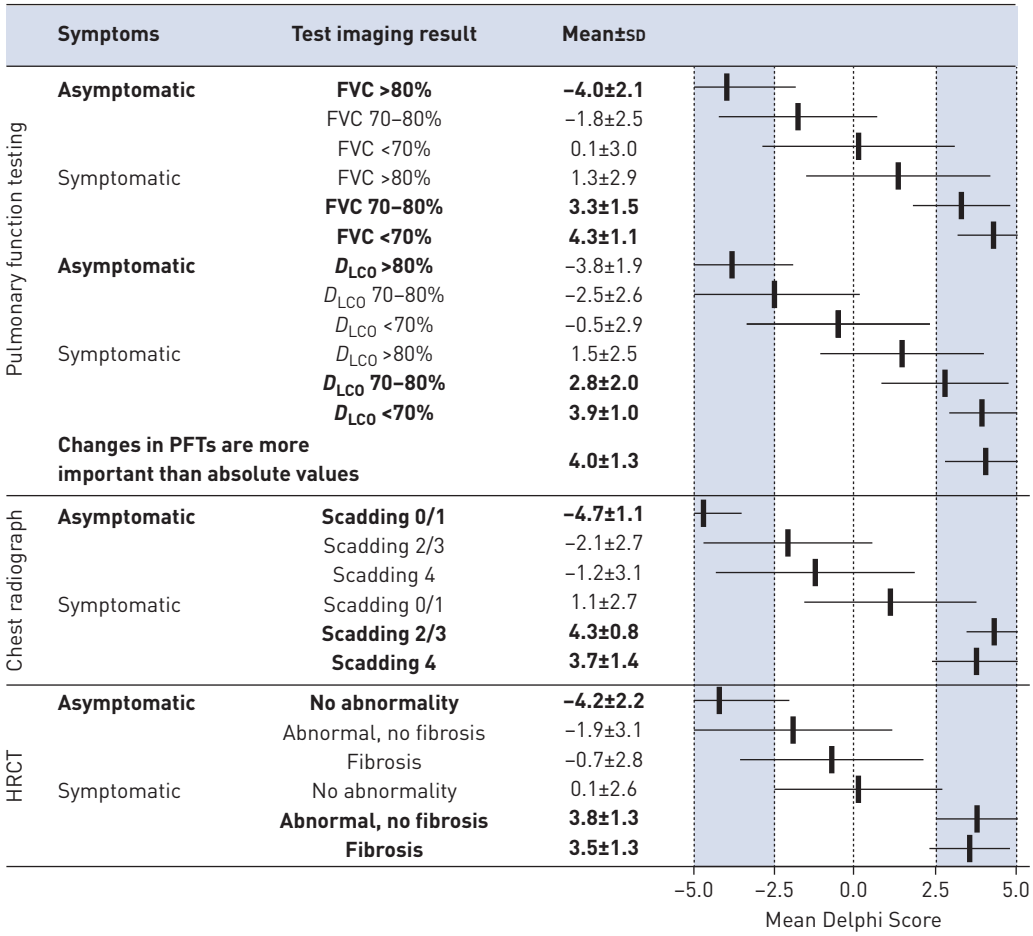

FIGURE 1 Delphi consensus on whether patients should be treated based on the presence of pulmonary symptoms, pulmonary function testing and imaging. Bold indicates consensus. HRCT: high-resolution computed tomography; PFT: pulmonary function test; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

patients with reduced pulmonary function or symptomatic patients with normal pulmonary function. Sarcoidosis patients should be evaluated initially and over time, and serial testing may indicate worsening disease. This was addressed in the Delphi and the experts felt that changes in pulmonary function testing were more important than the absolute value of the individual pulmonary function test.

With regard to imaging studies, there are no generally accepted criteria for an abnormal high-resolution computed tomography. Therefore, an abnormal high-resolution computed tomography was defined by the individual expert. The Delphi panel reached consensus that symptomatic patients with parenchymal infiltrates (Scadding stage 2 or 3) or fibrosis (Scadding stage 4) should be treated. Asymptomatic patients with adenopathy alone (Scadding stage 1) or normal chest radiograph do not require therapy. In evaluating the results of high-resolution computed tomography scans, the panel felt symptomatic patients with abnormal findings or fibrosis should be treated and asymptomatic patients with adenopathy alone do not require therapy. The panel did not reach consensus on asymptomatic patients with abnormal chest imaging or symptomatic patients with normal chest imaging. While we did explore criteria for moderate and severe individual findings in FVC, D_{LCO} and Scadding stage, we did not further explore what criteria would be considered severe disease. We left this definition to the individual expert. Future studies aimed at defining specific thresholds for these criteria would be useful.

For sarcoidosis patients, the clinician should consider several factors, including extrapulmonary disease. The Delphi panel reached consensus on several statements dealing with extrapulmonary disease, summarised in figure 2. In general, the panel agreed that treatment should be considered for patients with symptomatic extrapulmonary disease, and that extrapulmonary disease can be a useful marker of sarcoidosis activity. The panellists also agreed that not all extrapulmonary manifestations were created equal. Cardiac, neurologic, calcium, eye and renal involvement should be treated regardless of whether the

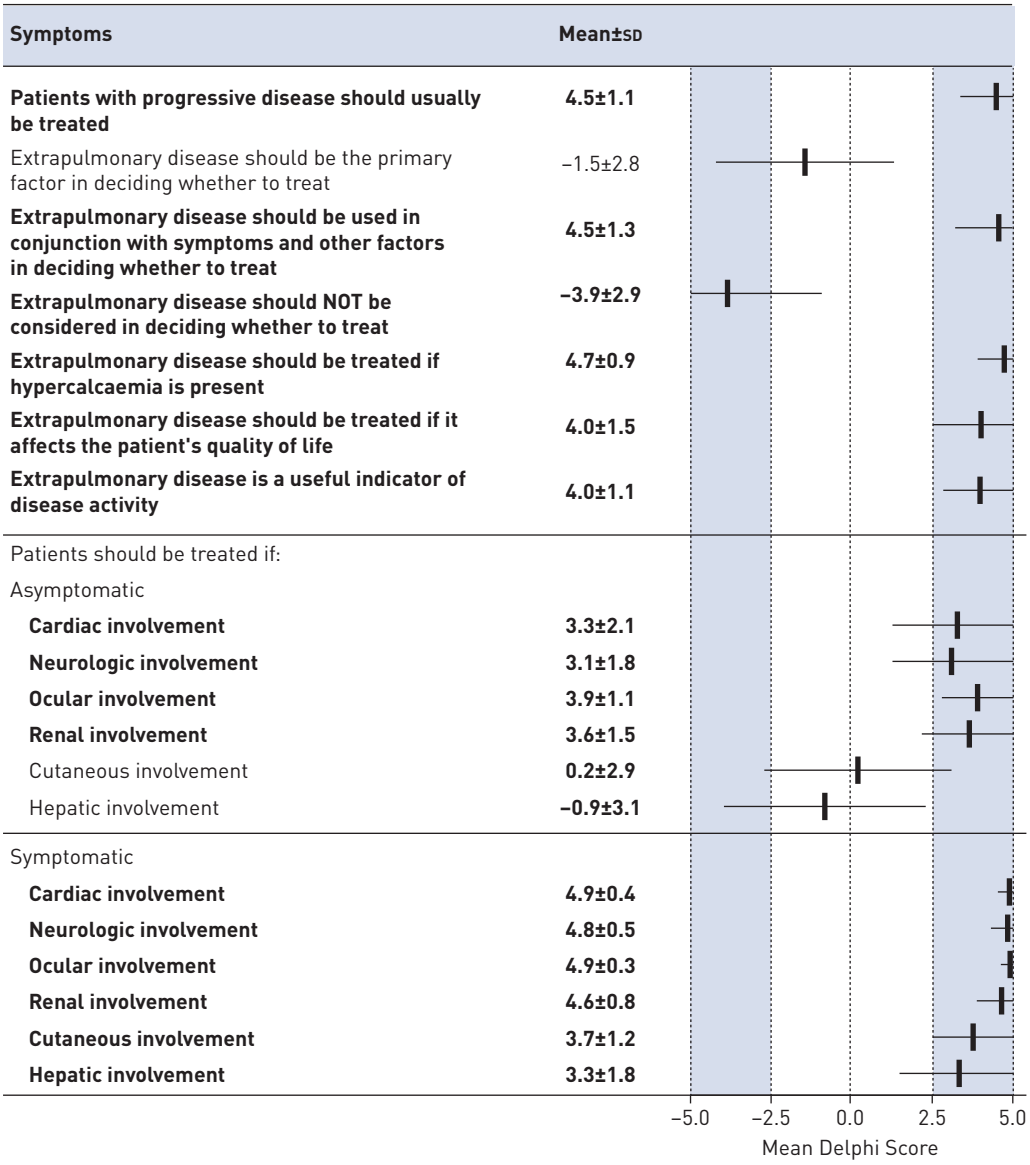

FIGURE 2 Delphi consensus on the role of extrapulmonary disease in treatment decisions. Bold indicates consensus.

patient is symptomatic. However, skin or liver involvement does not require treatment unless the patient is symptomatic. Hypercalcaemia, a common cause of renal dysfunction in sarcoidosis, should also be treated.

Appendix 2 summaries features which the panel felt were important factors that should influence the decision to initiate therapy. These include patient preference, symptom severity and quality of life impact, Imaging studies, pulmonary function tests, extrapulmonary disease, pulmonary hypertension, need for oxygen, progressive disease, stability of disease, cardiac magnetic resonance imaging and ophthalmologic examination. The panel also reached consensus on several factors that should be considered in decision to treat. These are summarised in supplementary appendix 2. These factors included pulmonary function testing, chest imaging, cardiac magnetic resonance imaging and results of the eye examination. Factors for which there was no consensus regarding decision to treat include the following: ACE levels, CBC/lymphocyte panel, comprehensive metabolic panel, ECG, Holter monitoring, echocardiography, erythrocyte sedimentation rate and C-reactive protein, liver function tests, long-duration disease, lysozyme, positron emission tomography scan, soluble interleukin-2, urinalysis/urinary calcium, and vitamin D and metabolites. Figure 3 shows clinical situations for which the panel agreed that immediate therapy is required.

Prolonged use of corticosteroids is associated with significant toxicity, including impaired quality of life [22]. Therefore, the decision to begin steroid-sparing agents is usually made when it becomes clear that a

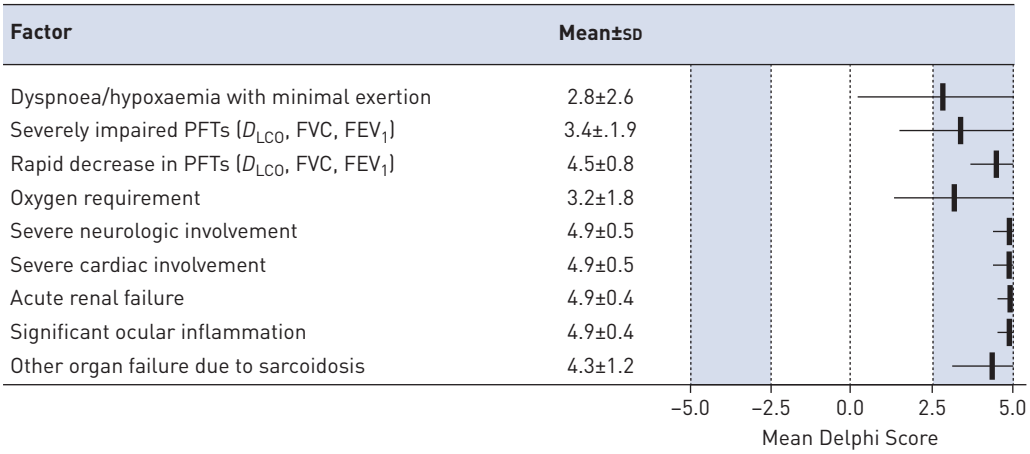

FIGURE 3 Delphi consensus on clinical situations in which immediate therapy is warranted. PFT: pulmonary function test; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s.

patient will have chronic disease. Several studies have attempted to characterise patients with chronic disease, including those by Neville *et al.* [7], Wasfi *et al.* [9] and Prasse *et al.* [10]. For example, patients who have been started on corticosteroids have a >50% chance of requiring long-term therapy [23, 24]. Clinical Outcome Status categories 2, 4 and 6 include both acute and chronic phenotypes. Patients in these categories who were treated for >2 years would be considered chronic. It has been shown that patients who present with certain features, such as neurosarcoidosis or FVC <80%, are more likely to have chronic disease [25].

The Delphi panel reached consensus on when the patient should be considered to have chronic disease and be considered for second-line therapy, typically non-biologic cytotoxic therapies such as methotrexate, azathioprine, leflunomide or mycophenolate (figure 4). The dose and duration of glucocorticoid use were major determinants of when to switch to non-biologics. While methotrexate and azathioprine were the

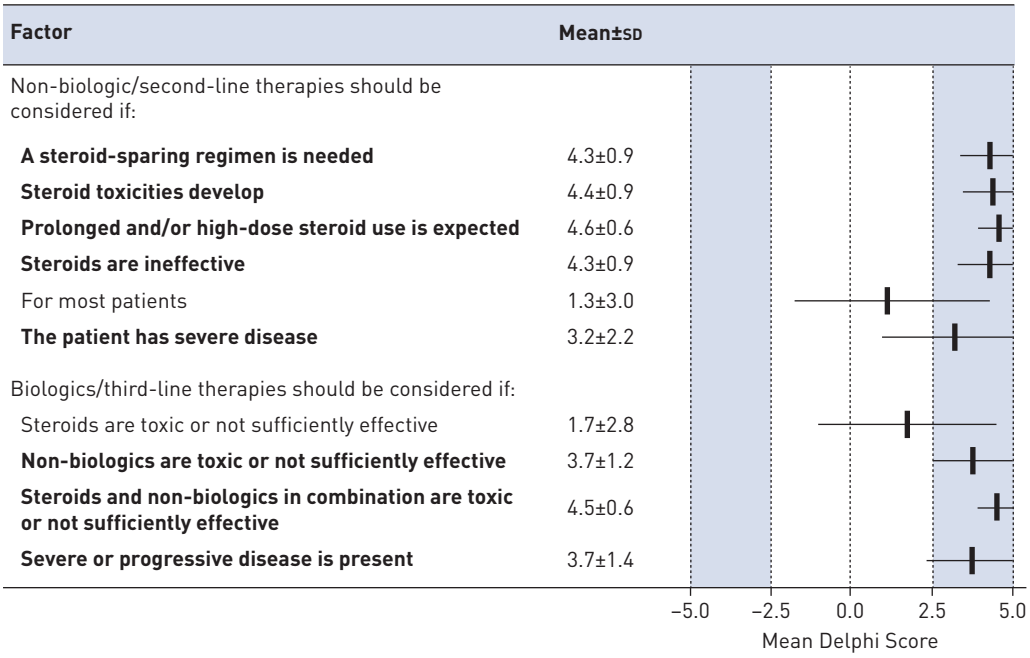

FIGURE 4 Delphi consensus on clinical situations in which second-line therapies (usually non-biologic cytotoxic agents) and third-line therapies (usually biologic agents) should be considered. Bold indicates consensus.

most commonly cited non-biologics, specific details regarding individual non-biologics are discussed elsewhere in this issue of the *European Respiratory Review* [26].

The final phenotypic category in supplementary appendix 1 is the patient with advanced disease. This group includes those who have stable disease but require ⩾10 mg of prednisone, often with other, non-biologic treatments as well as those refractory patients who required increasing treatment in the prior year, corresponding to Clinical Outcome Status groups 7, 8 and 9 [11]. For these patients, third-line treatments are often used, including infliximab, adalimumab, rituximab and repository corticotrophin injection. For the purpose of the Delphi consensus, all four of these agents were classified as biologics. Figure 4 shows those factors for which the panellists reached consensus about adding or switching to a biologic agent. Failure or toxicity of steroids with non-biologics was the major factor driving panellists to consider biologics.

Conclusion

Clinical phenotyping of sarcoidosis patients has many potential benefits in studying and treating sarcoidosis patients. In our Delphi study, we developed a clinical phenotype schema which can be used to help direct therapy. The Delphi participants reached consensus on when patients should be considered for different levels of treatment. These levels of therapy, including specific agents to be considered, are summarised in supplementary appendix 3.

Conflict of interest: R.P. Baughman reports grants and personal fees from Malllinckrodt, Novartis and Celgene, grants from Gilead, Genentech and Bayer, and personal fees from West Pharmaceutical, during the conduct of the study. M.B. Scholand reports other from Boehringer Ingelheim, Genentech, Fibrogen and Global Blood Therapeutics, outside the submitted work. In addition, M.B. Scholand has a patent Apparatus, Compositions and Methods for Assessment of Chronic Obstructive Pulmonary Disease Progression among Rapid and Slow Decline Conditions issued. F.F. Rahaghi reports grants and consulting fees from Mallinckrodt, during the conduct of the study.

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