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Definition of relapse criteria in patients with rapidly progressive systemic sclerosis treated with autologous haemopoietic stem cell transplantation

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Systemic sclerosis (SSc) is a rare systemic autoimmune disease characterized by the accumulation of extracellular collagen matrix in tissues and target organs, such as skin, lung, gut, and heart [1]. The clinical spectrum of SSc is largely heterogeneous, but usually two distinct forms are recognized., i.e., the limited cutaneous (lc) and the diffuse cutaneous (dc) SSc. The two variants strongly differ in the terms of skin extension, type and severity of internal organ involvement, and expected survival. Among patients with dcSSc, a subset may be characterized by a rapidly progressive course with early appearance and quick worsening of skin and internal organ involvement, and consequently a high mortality rate within the first five years after first non-Raynaud phenomenom symptoms [2]. In these cases of rapidly progressive dcSSc, autologous haematopoietic stem cell transplantation (AHSCT) has been recognized as a standard-of-care therapy option since 2017 [3–6]. This statement was the direct consequence of the consistent results obtained in three randomized controlled trials where this procedure had been shown to be superior to traditional immunosuppressive therapy in improving skin involvement, preserving lung function, and reducing mortality rates [6]. These results have been further confirmed in a recent retrospective study where AHSCT was shown to be superior to

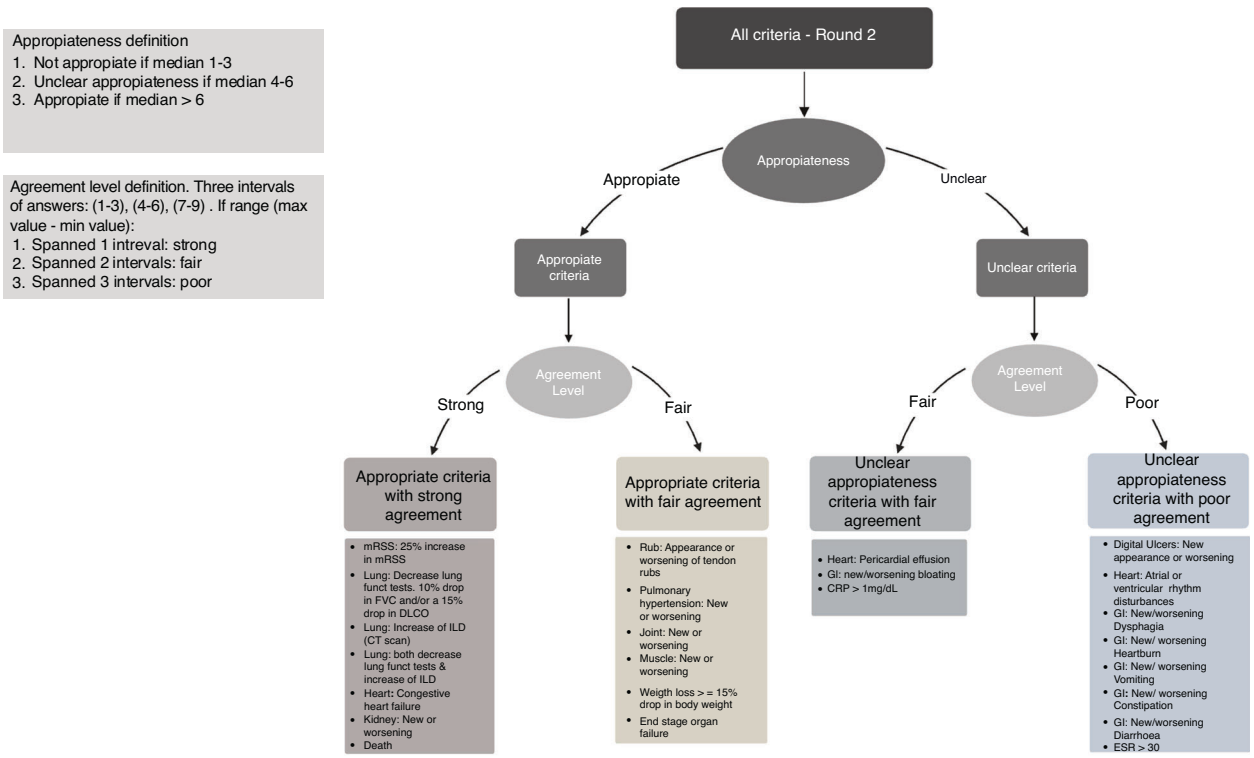

Fig. 1 Classification tree for Round 2 Delphi consensus on disease relapse after AHSCT in systemc sclerosis. Illustration of the hierarchical classification process of disease relapse after AHSCT in systemic sclerosis. Starting from all evaluated criteria, items were first categorized by their appropriateness level based on median scores, then further classified according to their agreement level determined by response range distribution. mRSS modified Rodnan Skin Score, ILD Interstitial Lung Disease, FVC Forced Vital Capacity, DLCO Diffusing Capacity for Carbon Monoxide, CT Computed Tomography, GI Gastrointestinal, CRP C-Reactive Protein, ESR Erythrocyte Sedimentation Rate.

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rituximab in improving all the above-mentioned outcomes [7]. Nevertheless, several aspects of AHSCT warrant further consideration. First, transplantation related mortality still exists, although it has been significantly reduced thanks to the important progress made, with better pretransplant evaluation of cardiac and pulmonary involvement and improved selection of patients at lower risk of complications [8]. Another question to be answered is how long the effects of AHSCT will last. Preliminary data indicate that the incidence of disease progression could happen between 4 and 6 years after transplantation and that disease response varied according to patients [9]. However, although the observed clinical response after AHSCT has been defined since the early pivotal trials (ASSIT, ASTIS, SCOT) and the absence of response or disease progression after AHSCT is easy to define as its counterpart, no dedicated and validated tools are currently available to precisely define the disease relapse after AHSCT. Acquiring the moment of relapse after prior response to AHSCT may make it easier to adopt therapeutic interventions that may allow to maintain the disease remission induced by AHSCT.

The present study was planned and carried out by the Autoimmune Disease Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT) to tentatively find a definition of disease relapse in patients with rapidly progressive dcSSc who underwent AHSCT.

A Delphi method was used for selecting the final list of disease relapse criteria after AHSCT [10].

In the first step, the steering committee composed by 6 EBMT experts from the ADWP were asked to list in a not restricted way all the clinical, biological, and instrumental items that were judged to be potentially relevant to a definition of a disease relapse. The

Table 1. Appropriate criteria for the definition of disease relapse in patients with rapidly progressive SSc treated with AHSCT.

Appropriate criteria for the definition of disease relapse[a]
A. With strong agreement
Skin
1. 25% increase in mRSS
Definition: Assessment of skin thickness on a scale from 0 (normal thickness) to 3 + (severe thickness) at 17 anatomic areas (values from 0–51).
Lung
2. Decrease of lung function tests: ≥10% in FVC and/or ≥15% in DLCO of the predicted values.
3. Increase of interstitial lung disease (assessed though HRCT) defined by an expert radiologist
4. Both decrease lung function tests and increase of interstitial lung disease.
Heart
5. Congestive heart failure
Definition: non-systemic sclerosis related causes must have been reasonably excluded by an experienced cardiologist
Kidney
6. New appearance or worsening of renal involvement
Definition: Urine analysis abnormalities (proteinuria, hematuria, casts), new/worsening of renal insufficiency (serum creatinine > upper limit of normal/ rise > 25%) with or without accelerated/ malignant hypertension.
Death
7. Related to the disease
B. With fair agreement
Tendons
1. New appearance or worsening of tendon rubs
Definition: Perception of leathery crepitus during motion of hands, wrists, elbows, shoulders, knees and ankles (both at anterior and posterior aspects)
Lung
2. New appearance of pulmonary hypertension
Definition: resting mean pulmonary artery pressure (mPAP) > 20 mmHg (by right heart catheterization)
Joints
3. New appearance or worsening of articular involvement
Definition: symmetric swelling and tenderness of the peripheral joints
Muscle
4. New or worsening in muscle involvement
Definition: as detected at physical examination associated with CK increase
Weight loss
5. ≥ 15% unvoluntary drop in body weight
Systemic
6. End stage organ failure

[a]The listed criteria should be strictly related to the course of SSc. The possibility that the appearance or worsening of any feature may be caused by other pathologic conditions should be excluded by an expert physician of the specific subspecialty.

mRSS modified Rodnan Skin Score, *FVC* Forced Vital Capacity, *DLCO* Diffusing capacity of the Lungs for Carbon monoxide, *HRCT* High-Resolution Computed Tomography, *mPAP* mean Pulmonary Artery Pressure, *CK* Creatine Kinase.

standardized clinical chart drawn up by the group contained all the symptoms, laboratory and other diagnostic parameters most widely used by clinicians treating this disease carefully defined according to the most authoritative sources available [11]. As a result, 24 items were selected. Subsequently, the Delphi method was performed by a panel of 34 clinical experts in the field of SSc to determine both the appropriateness of each criterion and the level of agreement among experts. The experts were internationally recognised as specialists in SSc with several years of experience in diagnosing and treating patients with this disease. The starting point for the Delphi method was the preliminary list of 24 items. The experts scored each criterion on a scale from 1 (not appropriate for relapse definition) to 9 (extremely appropriate) through 5 (appropriateness unclear). Each item was considered as appropriate to define disease relapse when the median score was above 6, unclear appropriate when the median was 4 to 6, not appropriate when the median score less than 4. The level of agreement among experts was assessed as follows: when all answers fell within a single interval (7–9, 4–6, or 1–3), agreement was strong; when answers spanned two intervals, agreement was fair; and when answers spanned all three intervals, agreement was poor. In the second Delphi round, the range of answers was presented to the experts, who were then asked to reassess their opinion about criteria for which agreement was fair or poor in the first round. The level of agreement was assessed based on all answers except outliers (Supplemetary Fig. 1).

The Delphi exercise was completed until July 2024. All 34 experts completed the 2 rounds.

After the second round of Delphi voting, 13 criteria coded as appropriate were finally selected for defining disease relapse, 7 with strong agreement and 6 with fair agreement (Fig. 1).

As expected, this final core set of 13 items includes the same clinical, radiological, and instrumental features whose early appearance and rapid worsening characterize the patient candidate for AHSCT (Table 1). Most of these items are also included in the set of revised EUSTAR disease activity criteria [12]. This is an expected finding since the AHSCT procedure is usually adopted to induce a drastic decrease of the disease activity, and recent data confirm that it can obtain this achievement [7]. Then, the relapse can be considered a resumption of disease activity.

In summary, the 13 selected items may constitute the first core set of criteria potentially indicative of disease relapse in the follow-up of AHSCT-treated patients with dcSSc. This study forms the basis for validating these preliminary criteria with a view to developing a gauged tool to define and capture the moment of disease relapse in AHSCT-treated patients with rapidly progressive dcSSc with accuracy and precision across multiple sites, supporting clinical trials, other studies, routine data registry reporting, and clinical care.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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