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Health-related quality of life in systemic sclerosis before and after autologous haematopoietic stem cell transplant—a systematic review

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Abstract

Objectives. In severe rapidly progressive SSc, autologous haematopoietic stem cell transplantation (AHSCT) allows significant improvements in overall and event-free survival. We undertook this study to identify, appraise and synthesize the evidence on health-related quality of life (HRQoL) before and after AHSCT for SSc.

Methods. We performed a systematic review of the literature, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, in PubMed and ScienceDirect from database inception to 1 February 2019. All articles with original HRQoL data were selected.

Results. The search identified 1080 articles, of which 8 were selected: 3 unblinded randomized controlled trials [American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST), Autologous Stem Cell Transplantation International Scleroderma, Scleroderma: Cyclophosphamide or Transplantation), 3 uncontrolled phase I or II trials and 2 cohort studies. HRQoL data from 289 SSc patients treated with AHSCT and 125 treated with intravenous CYC as a comparator with median 1.25–4.5 years follow-up were included. HRQoL was evaluated with the HAQ Disability Index (HAQ-DI; 275 patients), the 36-item Short Form Health Survey (SF-36; 249 patients) and the European Quality of Life 5-Dimensions questionnaire (EQ-5D; 138 patients). The quality of the studies was moderate to low. AHSCT was associated with significant improvement in the HAQ-DI (P = 0.02–<0.001), SF-36 Physical Component Summary score (P = 0.02–<0.0001) and EQ-5D index-based utility score ($P < 0.001$). The SF-36 Mental Component Summary score improved in the ASSIST ($n = 19$) and one small retrospective cohort ($n = 30$ patients, $P = 0.005$) but did not improve significantly in 2 randomized controlled trials ($n = 200$ patients, P = 0.1–0.91).

Conclusion. AHSCT in severe SSc patients is associated with significant and durable improvement in physical HRQoL.

Key words: autologous haematopoietic stem cell transplantation, quality of life, systemic sclerosis

Rheumatology key messages

- AHSCT in severe SSc is associated with significant and durable improvement in physical HRQoL.
- The evidence concerning the impact of AHSCT on mental HRQoL remains inconsistent.
- Further research will be required to understand the causal associations between AHSCT for SSc and HRQoL.

Introduction

SSc is a chronic autoimmune multi-organ disease characterized by progressive fibrosis of the skin and internal organs [1]. In rapidly progressive dcSSc, the 5 year mortality rate reaches 30%, depending on the extent of lung, heart and kidney involvement [2, 3]. In addition to reduced

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survival and major organ dysfunction, SSc is associated with significant morbidity, including skin thickening [4], RP, digital ulcers [5], dyspnoea [6], gastroesophageal reflux disease [7] and anal incontinence [8], among other complaints. In turn, these contribute to limitations in physical mobility and function, pain, fatigue [9], disfigurement [1], sleep disturbance [10] and depression [11]. We previously showed that physical health-related quality of life (HRQoL) in SSc was on average 1.5 S.D.s below that of the general population [12]. This magnitude of impairment is comparable to or worse than patients with other common chronic conditions, including heart and lung disease, diabetes and depression [12].

SSc is a rare disease with high unmet therapeutic needs. All conventional immunosuppressive drugs tested so far have had, at best, modest effects aimed at stabilizing disease and little effect on survival [13]. The only treatment shown to have sustained disease-modifying properties is autologous haematopoietic stem cell transplantation (AHSCT). Indeed, in severe SSc, early European and North American phase I and II studies [14–18] followed by three randomized controlled trials (RCTs) {namely American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST) [19], Autologous Stem Cell Transplantation International Scleroderma (ASTIS) [20] and Scleroderma: Cyclophosphamide or Transplantation (SCOT) [21]} showed that AHSCT allowed rapid and durable regression of skin and lung fibrosis and better long-term overall survival and event-free survival (EFS) for at least 5 years when compared with intravenous CYC. Today, with ~1000 SSc patients transplanted worldwide, AHSCT has become the best treatment option for severe SSc [22, 23]. With the publication of three favourable RCTs [19–21] and current European and North American guidelines [24–26], the demand for ASHCT is increasing worldwide.

In the context of early rapidly progressive SSc, AHSCT is an effective but aggressive treatment where the benefit of therapy must be weighed against the risk of serious toxicities and treatment-related mortality. This provides rationale for studying HRQoL in this setting [27]. The aim of the present study was therefore to identify, appraise and synthesize the evidence on HRQoL before and after AHSCT for SSc.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [28]. We searched the PubMed and ScienceDirect databases for all articles using the following search strategy: ('Scleroderma, Systemic'[Mesh]) AND 'Haematopoietic Stem Cell Transplantation'[Mesh]) from database inception to 1 February 2019 and without any restriction to language. One investigator (MP) screened titles and abstracts to select papers for full-length review. Only studies reporting original HRQoL data on more than five SSc patients undergoing AHSCT were selected. The reference lists of selected articles were also screened for any other potentially relevant article. In the selected papers, HRQoL was measured using three different tools.

HAQ Disability Index (HAQ-DI)

The HAQ-DI is a self-administered questionnaire specifically validated for functional assessment in SSc [29, 30]. It includes 20 questions in eight categories (dressing and grooming, standing, eating, walking, hygiene, reach, grip and performing activities). The patient is asked to rate his/her difficulty over the past week in performing the specific tasks in each category on a scale of 0–3 (without difficulty = 0, with some difficulty = 1, with much difficulty or with assistance = 2, unable = 3). The highest scores in each category are added and the total is divided by 8. Scores range from 0 (no disability) to 3 (severe disability). The French version of the HAQ-DI has been validated in SSc [31]. A minimal clinically important difference (MCID) in the HAQ-DI score in SSc is 0.14 point [32].

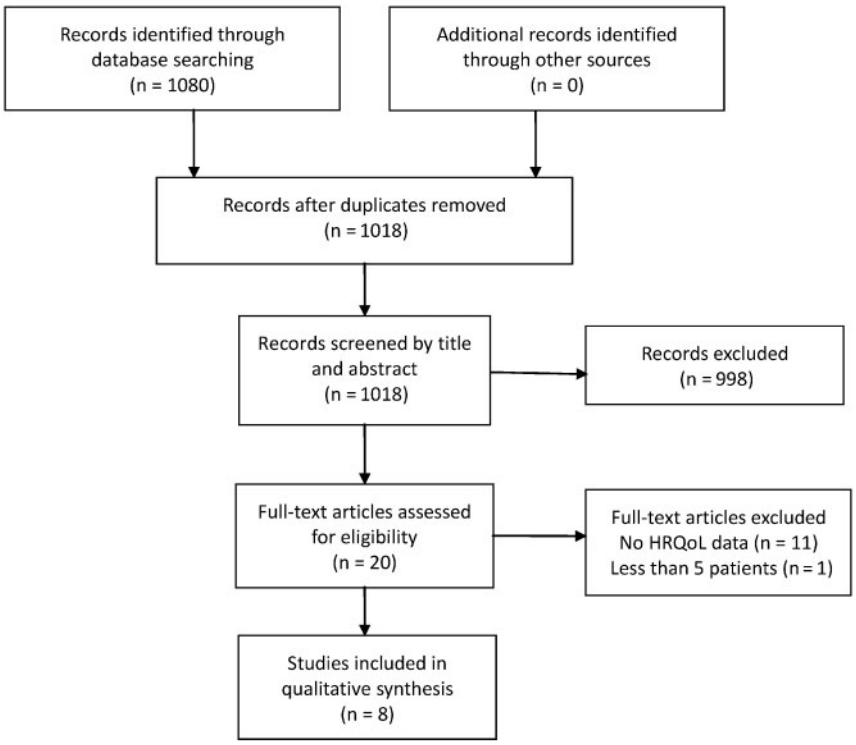
36-item Short Form Health Survey (SF-36)

The SF-36 is a generic HRQoL instrument that consists of 36 questions in eight domains: physical functioning, bodily pain, role physical, general health, social functioning, mental health, vitality and role emotional. Each domain can be scored separately, with scores ranging from 0, indicating the worst health state, to 100, indicating the best health state. Domain scores can also be summarized into a Physical Component Summary (PCS) score and a Mental Component Summary (MCS) score. The PCS and MCS are scored using norm-based scoring based on a general population sample to produce T scores for each patient [mean 50 (S.D. 10)]. Therefore, for the two summary scores, HRQoL is worse than average if it is <50 and better than average if it is >50, and each point is 0.1 S.D.. This tool has been translated into French and used in studies of SSc [33]. The MCID of the PCS and MCS scores in SSc range from 2.5 to 5 points [32].

European Quality of Life 5-Dimensions questionnaire (EQ-5D)

The EQ-5D is a generic tool consisting of five questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with either three (1 = no problem, 2 = moderate problem, 3 = severe problem) [34] or five (1 = no problem, 2 = slight problem, 3 = moderate problem, 4 = severe problem, 5 = unable to do) [35] potential answers for each item. Both versions of the EQ-5D had been validated and can be used in clinical practice [34]. A summary index (utility) can be derived from these five dimensions. The maximum score of 1 indicates the best health state and higher scores indicate more severe or frequent problems. In addition, there is a visual analogue scale (VAS) that measures the patient's self-rated general health status, with anchors at 0 ('worst imaginable health state') and 100 ('best imaginable health state'). The EQ-5D has been translated into French and used in studies of SSc [36]. The MCID of the summary index in SSc has been reported to be 0.08 for improvement and -0.13 for deterioration [37].

Fig. 1 Flow chart



Data extraction and quality assessment

The following data were extracted from the selected papers: study design; date of publication; country or World Health Organization (WHO) region where the study was conducted; eligibility criteria; clinical, biological and immunological characteristics of the patients[age; sex; modified Rodnan skin score (mRSS); presence of heart, lung or kidney involvement; presence of specific SSc antibodies], mobilization regimen for stem cell collection; type of conditioning for the AHSCT procedure and duration of follow-up. When RCTs were selected, the treatment in the comparator group was extracted.

Bias was assessed using the Cochrane risk of bias tool for RCT [38] and the Newcastle–Ottawa Scale (NOS) [39] for non-interventional studies. Publication bias was evaluated by searching for unpublished studies registered at ClinicalTrials.gov [40] or in the WHO International Clinical Trials Registry Platform [41].

Data were summarized in tabular form and synthesized qualitatively. Paucity, heterogeneity and poor quality of the data did not allow us to perform any pooled, sensitivity or subgroups quantitative analysis.

Results

Study selection and characteristics

The search strategy identified 196 records in PubMed and 884 in ScienceDirect, of which 62 were duplicates and 998 were excluded after title and abstract review (Fig. 1). Of the 20 articles selected for full-text review, 11 were excluded because they did not report any HRQoL data after AHSCT and 1 was excluded because HRQoL data were reported on fewer than five patients. Eight studies reporting on a total of 289 SSc patients treated with AHSCT and 125 treated with intravenous CYC as a comparator were included in this review (Tables 1–3). HRQoL data were available for 203 SSc patients treated with AHSCT and 121 treated with CYC.

The three RCTs included one European phase III (ASTIS [20], $n = 156$) and two North American phase II (ASSIST [19], $n = 19$; SCOT [21], $n = 75$) studies. ASTIS was a multicentre trial that randomly assigned patients to AHSCT ($n = 79$ patients) or CYC ($n = 77$ patients) and allowed crossover after 2 years. The primary endpoint was EFS (death or persistent major organ failure). After a median follow-up of 5.8 years (95% CI 4.1–7.8), both EFS and overall survival were significantly better in the AHSCT arm compared with the CYC arm. ASSIST [19] was a single-centre study conducted at Northwestern Memorial Hospital (Chicago, IL, USA) originally designed to enrol 60 patients, allowing crossover plus an interim analysis. The primary outcome was improvement at 12 months of follow-up, defined as a decrease in mRSS (>25%) or an increase (>10%) in forced vital capacity (FVC). After 19 patients were randomized, all 10 allocated to AHSCT improved *vs* none of nine in the comparator group ($P < 0.00001$). The trial was therefore stopped due to 'failure to reach equipoise'. Seven patients in the CYC

Table 1 Setting, design, inclusion and exclusion criteria of selected studies

			Inclusion criteria								Main exclusion criteria			
Study	Setting	Design	Age (years)	Disease duration	mRSS	Lung	Heart	Kidney	GI	Other	Previous CYC	Lung	Heart	Kidney
Farge *et al.*, 2002 [16]	France	Cohort (phase I/II)	No	⩽4	No	DLCO <70%	2nd or 3rd AV block, ventricular arrhythmia, LVEF <55%, PAP >40 mmHg	Proteinuria >0.5 g/24 h or creatinine >120 μmol/L	Yes	No	Yes	DLCO <45%	LVEF <30%, PAH	GFR <20 mL/min
McSweeney *et al.*, 2002 [15]	USA	Cohort (phase I/II)	<65	⩽3	⩾16[a]	FVC or DLCO <75% or decrease of 15% of FVC or DLCO in the previous 6 months, active interstitial lung disease (chest CT scan or BAL)[b]	Myocardial disease[c]	Proteinuria >0.5 g/24 h or creatinine >ULN	No	No	No	DLCO <45%	Congestive heart failure, uncontrolled malignant arrhythmia	GFR <40 mL/min
Nash *et al.*, 2007 [17]	USA	Cohort (phase II)	<65	⩽3	⩾16[a]	FVC or DLCO <75% or decrease of 15% of FVC or DLCO in the previous 6 months, active interstitial lung disease (chest CT scan or BAL)[b]	Myocardial disease[c]	Proteinuria >0.5 g/24 h or serum creatinine >ULN	No	No	No	No	No	No
Burt *et al.*, 2011 [19]	USA	Randomized (phase II)	<60	⩽4	⩾14[a]	DLCO <80% or decrease of >0% FVC in the previous year, pulmonary fibrosis or ground glass on chest CT scan[b]	Abnormal ECG	No	Yes	No	Yes	TLC <45%	LVEF <40%, symptomatic cardiac disease, PAH	Creatinine >177 μmol/L
Moore *et al.*, 2012 [42]	Australia	Cohort	<65	⩽3	No	Yes	Myocarditis[c]	No	No	CYC failure	No	No	No	No
Burt *et al.*, 2013 [41]	USA, Brazil	Cohort	No	No	⩾14[a]	Pulmonary fibrosis or ground glass on chest CT scan[b]	Abnormal ECG	No	Yes	No	No	TLC <45%	LVEF <40%, PAH	No
van Laar *et al.*, 2014 [20]	Europe	Randomized (phase III)	18–65	⩽4	⩾15[a]	Yes	Yes	Yes	No	No	Yes	Yes	PAH >50 mmHg	Yes
Sullivan *et al.*, 2018 [21]	USA	Randomized (phase II)	18–69	⩽5	No	Active interstitial lung disease (chest CT scan or BAL) and FVC <70% or DLCO <70%	No	Previous SSc-related renal disease	No	No	Yes	DLCO <40%, FVC <45%	LVEF <50%	GFR <40 mL/min

[a]Required skin involvement with at least one other organ involvement. [b]Lung involvement alone was an inclusion criteria. [c]Not defined. AV: atrio-ventricular; BAL: bronchoalveolar lavage; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; GI: gastro-intestinal; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; mRss: modified Rodnan skin score; PAH: pulmonary arterial hypertension; TLC: total lung capacity; ULN: upper limit normal; USA: United States of America.

Table 2 Mobilization, graft manipulation and conditioning regimens used in selected studies

Study	Mobilization	CD34$^+$ selection	Conditioning regimen
Farge *et al.*, 2002 [16]	CYC 4 g/m^2	Yes	CYC 200 mg/kg (9 patients) CYC 200 mg/kg + rATG 4000 mg (1patient) Melphalan 140 mg/m^2 + rATG 4000 mg (1patient)
McSweeney *et al.*, 2002 [15]	G-CSF only	Yes	TBI 800 cGy + CYC 120 mg/kg + eATG 90 mg/kg
Nash *et al.*, 2007 [17]	G-CSF only	Yes	TBI 800 cGy + CYC 120 mg/kg + eATG 90 mg/kg
Burt *et al.*, 2011 [19]	CYC 2 g/m^2	No	CYC 200 mg/kg + rATG 6.5 mg/kg
Moore *et al.*, 2012 [42]	CYC 2 g/m^2	Yes	CYC 200 mg/kg + eATG dose unknown
Burt *et al.*, 2013 [41]	CYC 2 g/m^2	No	CYC 200 mg/kg + rATG 6.5 mg/kg
van Laar *et al.*, 2014 [20]	CYC 4 g/m^2	Yes	CYC 200 mg/kg + rATG 7.5 mg/kg
Sullivan *et al.*, 2018 [21]	G-CSF only	Yes	TBI 800 cGy + CYC 120 mg/kg + eATG 90 mg/kg

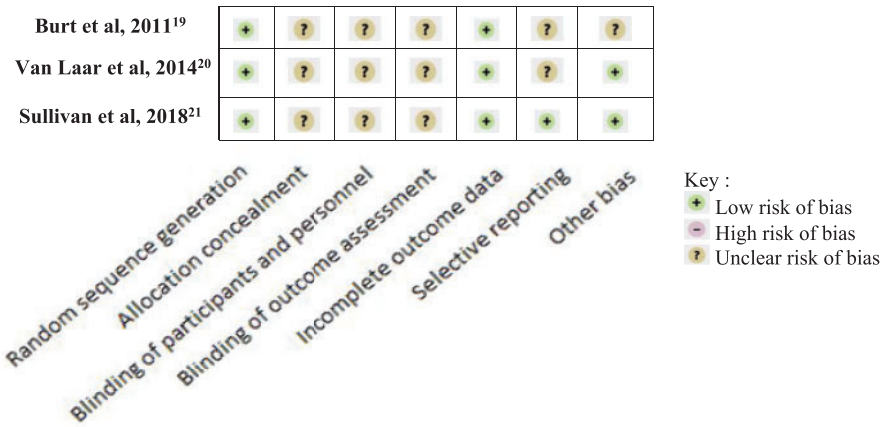
cGy: centigray; eATG: equine anti-thymocyte globulin; G-CSF: granulocyte colony stimulating factor; rATG: rabbit anti-thymocyte globulin; TBI: total body irradiation.

Table 3 Baseline characteristics of patients in selected studies

Study	Median age (range), years	Female, %	Disease duration before treatment, median (range) years	mRSS, median (range)	Lung involvement, %	Heart involvement, %	Kidney involvement, %	Anti-topoisomerase antibody, %
Farge *et al.*, 2002 [16]	43 (17–54)	64	2.5 (0.6–3.6)	32 (9–41)	91	27	0	67
McSweeney *et al.*, 2002 [15]	40 (23–61)	84	1.7 (0.3–3.2)	31 (3–50)	95	Unknown	5	53
Nash *et al.*, 2007 [17]	41 (23–61)	76	1.8 (0.3–4.3)	30 (3–48)	100	26	6	32
Burt *et al.*, 2011 [19]	45 (26–54)	89	1.3 (0.2–3.0)	23 (4–48)	79	53	0	63
Moore *et al.*, 2012 [42]	43 (23–46)	80	1.3 (0.8–2.9)	25 (15–40)	60	Unknown	Unknown	Unknown
Burt *et al.*, 2013 [41]	42 (16–71)	81	2.1 (0.2–13.0)	24 (3–47)	81	49	1	48
van Laar *et al.*, 2014 [20]	44 (11)[a]	59	1.4 (1.3)[a]	25 (8)[a]	87	8	3	74
Sullivan *et al.*, 2018 [21]	46 (11)[a]	64	2.3 (1.2)[a]	30 (10)[a]	97	0	Unknown	39

[a]Expressed as mean (S.D.).

Fig. 2 Risk of bias of RCTs assessed with the Cochrane risk of bias tool



group subsequently switched to HSCT. The multicentre SCOT [21] trial was initially started as a phase III trial with 226 patients planned to be enrolled, but was subsequently modified into a phase II trial due to low accrual. A total of 75 patients were finally randomized to AHSCT ($n = 36$ patients) or CYC ($n = 39$ patients). The primary endpoint was the global rank composite score (GRCS) comparing patients as pairs on the basis of a hierarchy the following features: death, EFS (survival without respiratory, renal or cardiac failure), FVC, HAQ and mRSS. In the intention-to-treat analysis, the GRCS at 54 months showed the superiority of AHSCT *vs* CYC ($P = 0.01$). Five non-randomized studies were also included in the present review: one phase I/II study [15] ($n = 19$ patients) conducted in the USA, two phase II studies ($n = 34$ patients in the USA [17] and $n = 11$ patients in France [16]) and two cohort studies ($n = 90$ patients in the USA and Brazil but HRQoL data available only on $n = 30$ [42] and $n = 10$ patients in Australia [43]). All reported beneficial effects of AHSCT on standard biomedical outcome measures.

Study and patient characteristics, inclusion and exclusion criteria, mobilization, graft manipulation, conditioning regimen and patients in the selected studies are presented respectively in Table 1, 2 and 3. There was considerable heterogeneity in all of these parameters among the studies.

Quality assessment

Overall, the risk of bias was moderate in the three RCTs [19–21] (Fig. 2), most importantly because patients were not blinded to their treatment and this may have influenced their HRQoL assessments. In addition, although the median follow-up in ASTIS [20] was close to 6 years, HRQoL was reported only at 2 years. There was similar selective reporting in ASSIST [19]. The risk of bias was moderate to high in the non-randomized study [15–17, 42, 43] (Table 4). In addition to the fact that patients were not blinded to their treatment, none of those studies included a comparator group and some patients were lost during follow-up.

One unpublished phase I trial was registered at ClinicalTrials.gov (number NCT00058578). We did not identify any other relevant studies in the WHO International Clinical Trials Registry Platform.

Impact of AHSCT on HRQoL

HRQoL was analysed as a secondary outcome in all selected studies.

HAQ-DI

The HAQ-DI results were reported in different ways (absolute scores, differences and percentage of subjects with improvement) among 275 patients in six studies [15–17, 20, 21, 43] (Table 5), complicating data interpretation. Nevertheless, all studies reported improved scores in association with AHSCT. In ASTIS [20], HAQ-DI scores at 2 years fell by 0.58 points compared with baseline in the AHSCT arm, whereas they fell by 0.19 in the CYC group ($P = 0.02$). In SCOT, 53% of subjects in the AHSCT arm had

Table 4 Quality assessment of selected studies

Bias in	Representiveness	None exposed	Ascertainment exposure	Outcome of interest present	Comparability of the cohorts	Assessment of outcomes	Follow-up duration	Adequacy of follow-up	Total
Farge *et al.*, 2002 [16]	*	–	*	*	–	–	–	*	4
McSweeney *et al.*, 2002 [15]	*	–	*	*	–	–	*	–	3
Nash *et al.*, 2007 [17]	*	–	*	*	–	–	*	–	4
Moore *et al.*, 2012 [42]	*	–	*	*	–	–	*	*	5
Burt *et al.*, 2013 [41]	*	–	*	*	–	–	*	*	5

Table 5 Associations between HRQoL and AHSTC in SSc: results of the HAQ-DI

Study	No. of patients with data *vs* no. of patients in the study	Follow-up at time data collected, years	HAQ-DI					
			Baseline	After treatment				
				Absolute score Difference				
			Mean (S.D.)	Mean (range)	Mean (IC95)	% improved	*P*-value	Reported or calculated differences in scores
RCTs								
van Laar *et al.*, 2014 [20]	AHSCT (*n*=68/79)	2	1.3 (0.7)		−0.6 (1.1)[a]		0.02	−0.6
	CYC (*n*=73/77)		1.4 (0.8)		−0.2 (0.8)[a]			−0.2
Sullivan *et al.*, 2018 [21]	AHSCT (*n*=36/36)	4.8 (4.5–6.0)[b]	1.2 (0.6)			53%[c]	0.01	Unknown
	CYC (*n*=39/39)		1.4 (0.9)			16%[c]		
Non-randomized studies								
Farge *et al.*, 2002 [16]	AHSCT (*n*=9/11)	1 (*n*=7)	1.8 (0.0–0.8)[b]	0.4 (0.0, 1.6)				−1.4
McSweeney *et al.*, 2002 [15]	AHSCT (*n*=14/19)	1 (*n*=10)	2.1 (0.8–2.5)[d]		−1.7 (−2.3, 0.0)		0.002	−1.7
Nash *et al.*, 2007 [17]	AHSCT (*n*=26/34)	1.5 (*n*=23)	1.9 (0.3–2.9)[d]		−1.3 (−1.6, −0.9)		<0.001	−1.3
		4 (*n*=26)			−1.0 (−1.4, −0.7)		<0.001	−1.0
		7.5 (*n*=11)			−1.5 (−1.9, −1.1)		<0.001	−1.5
Moore *et al.*, 2012 [42]	AHSCT (*n*=10/10)	1 (*n*=8)	2.0 (1.8, 2.3)[b]	1.4 (1.1, 1.7)			<0.05	−0.6

After-treatment HAQ-DI scores are presented as absolute scores, difference in scores or percentage of patients improved, depending on the data reported in the individual studies. Differences were extrapolated for the Farge *et al.* 2002 and Moore *et al.* 2012 studies in an attempt to present the data in a comparable format in the last column. [a]Adjusted difference in multivariate analysis comparing follow-up and baseline scores, expressed as mean (S.D.). [b]Expressed as median (range). [c]Percentage of patients improved defined as a decrease in HAQ-DI of ⩾0.4 points. [d]Expressed as median (95% CI).

an improvement of ⩾0.4 points compared with 16% in the CYC arm after a follow-up time of 4.8 years ($P = 0.01$). The magnitude of improvement in HAQ-DI scores in the uncontrolled studies [15–17, 43] were generally even larger and sustained over time (up to 7.5 years), although the long-term results were based on few observations.

SF-36

The SF-36 results were also reported heterogeneously (absolute scores, differences and percentage of subjects with improvements) among 249 patients in four studies [19–21, 42] (Table 6). The difference in the PCS between the AHSCT and CYC groups in the three RCTs strongly favoured AHSCT: the PCS improved by 10 points in the AHSCT arm *vs* only 4 points in the CYC arm at 2 years in ASTIS [20] ($P = 0.01$) and by 20 points in the AHSCT arm, whereas it deteriorated by 6 points at 1 year in ASSIST [19]. In SCOT [21], 56% of patients in the AHSCT arm improved by ⩾10 points *vs* only 15% in the CYC arm after 4.8 years of follow-up ($P = 0.02$). One uncontrolled study ($n = 30$) also reported a large improvement of 20 points in the PCS after AHSCT [42].

The results of the MCS were inconsistent across studies. ASTIS [20] ($n = 125$) reported modest improvement in MCS (∼3 points) in both the AHSCT and CYC groups (and no difference between the two arms, $P = 0.91$) at 2 years. SCOT [21] ($n = 75$) reported that 31% of patients in the AHSCT arm improved by at least 10 points *vs* 8% in the CYC arm, although this difference was not statistically significant ($P = 0.1$). On the other hand, ASSIST [19] ($n = 19$) reported that the MCS improved by 12 points in the AHSCT arm and deteriorated by 14 points in the CYC arm. One uncontrolled study ($n = 30$) also reported a large improvement of 13 points in the MCS after AHSCT [42].

EQ-5D

The EQ-5D was reported in 138 subjects in one trial [20] (Table 7). Only the EQ-5D version with three levels of responses was used. At 2 years, the index-based utility score improved in the AHSCT group by 0.31 points, whereas it only improved by 0.03 points in the CYC arm ($P < 0.001$). The VAS of general health improved by 16.9 points in the AHSCT arm compared with 10.2 points in the CYC arm, although the difference was not statistically significant ($P = 0.36$).

Discussion

This systematic review of the literature analysed HRQoL data from a total of 203 SSc patients treated with AHSCT

Table 6 Associations between HRQoL and AHSTC in SSc: results of the SF-36 PCS and MCS

Author	No. of patients with data *vs* no. of patients in the study	Follow-up at time data collected, years		SF-36					
				PCS	*P*-value	Reported or calculated differences in scores	MCS	*P*-value	Reported or calculated differences in scores
Randomized controlled trials									
Burt *et al.*, 2011 [19]	AHSCT (*n*=10/10)	1	Pre-/post-treatment scores	30/50	0.007	20	46/58	0.076	12
	CYC (*n*=9/9)			38/32	0.32	−6	56/42	0.043	−14
van Laar *et al.*, 2014 [20]	AHSCT (*n*=59/79)	2	Baseline (S.D.)/difference between post- and pre-treatment scores (S.D.)[a]	32.2 (10.4)/10.1 (15.8)	0.01	10[a]	41.2 (10.7)/3.1 (16.0)	0.91	3[a]
	CYC (*n*=66/77)			32.2 (9.6)/4.0 (11.2)		4[a]	42.6 (12.0)/3.4 (17.1)		3[a]
Sullivan *et al.*, 2018 [21]	AHSCT (*n*=36/36)	4.8 (4.5–6.0)[b]	Baseline (S.D.) scores/% improved[b]	29.5 (9.2)/56%[b]	0.02	Unknown	44.7 (10.7)/31%[b]	0.1	Unknown
	CYC (*n*=39/39)			28.9 (9.5)/15%[b]			44.6 (9.9)/8%[b]		
Non-randomized studies									
Burt *et al.*, 2013 [41]	AHSCT (*n*=30/30)	Unknown	Pre-/post-treatment scores	35/55	<0.0001	20	51/64	0.005	13

Scores are presented as absolute mean scores, difference in mean scores or percentage of patients improved, depending on the data reported in the individual studies. Differences were extrapolated for the Burt *et al.* 2011 and Burt *et al.* 2013 studies, in an attempt to present the data in a comparable format in columns 7 and 10. [a]Adjusted difference in multivariate analysis comparing follow-up and baseline scores. [b]Percentage of patients improved defined as an increase in the score of $\geqslant$10 points.

Table 7 Associations between HRQoL and AHSTC in SSc: results of the EQ-5D

Study	No. of patients with data *vs* no. of patients in the study	Follow-up at time data collected, years	EQ-5D					
			IBUS pre-treatment	IBUS difference post-treatment[a]	*P* value	VAS pre-treatment	VAS difference post-treatment[a]	*P* value
van Laar *et al.*, 2014 [20]	AHSCT (*n* = 65/79) CYC (*n* = 73/77)	2	0.46 (0.32) 0.47 (0.32)	0.31 (0.50) 0.03 (0.44)	<0.001	53.4 (22.1) 50.7 (21.1)	16.9 (44.5) 10.2 (39.7)	0.36

[a]Adjusted difference in multivariate analysis comparing follow-up and baseline scores.

and 121 treated with CYC. There was evidence of improvement in physical HRQoL using HAQ-DI scores and the SF-36 PCS. The magnitude of improvement with AHSCT was considerably larger than the MCID in SSc. The improvements appeared to be sustained over time, although these results were reported in only two studies: one uncontrolled study with 11 patients at 7.5 years after AHSCT and the SCOT trial at 54 months. However, the SCOT trial only reported the proportion of patients who improved without providing absolute HRQoL scores. The impact of AHSCT on mental HRQoL remains uncertain. The improvements appeared to be sustained over time, although those results were reported in the SCOT trial [21], which only provided the proportion of patients who improved rather than actual scores, and in one small uncontrolled study with results of only 11 patients at 7.5 years [17]. The impact of AHSCT on mental HRQoL remains uncertain. The two large randomized trials, ASTIS and SCOT [21], reported only modest improvement just at the limit of the MCID. On the other hand, the small randomized single-centre study ASSIST reported that the MCS improved more than MCID in the AHSCT arm and deteriorated in the CYC arm and another small ($n = 30$) uncontrolled study also reported a large improvement in MCS after AHSCT. Results of the EQ-5D were reported at 2 years only in the ASTIS trial, where the improvement in the index-based utility score was larger than the MCID after AHSCT. However, there was no improvement in the VAS. These results need to be interpreted with caution since there was at least a moderate risk of bias, even in the trials where patients were not blinded to their treatment.

We hypothesize that in SSc, improvement in physical HRQoL after AHSCT is related to the regression of skin and lung fibrosis after transplant, translating into better function and exercise tolerance. On the other hand, the absence of a strong signal for improvement in mental HRQoL remains to be elucidated. The fact that patients may have residual damage and therefore not feel 'cured' of their SSc may contribute to this. Other possible explanations include residual fatigue, disfigurement, fear of relapse, fear of social stigmatization and uncertainty about the future, including personal life and work. Further research will be required to understand the causal associations between AHSCT for SSc and HRQoL.

The findings in this study suggesting only modest improvement in physical HRQoL with CYC are consistent with those reported with the use of conventional immunosuppressive treatment in SSc. In the European Scleroderma Observational Study [43], with a large, prospective, observational cohort of 326 early dcSSc patients who were assessed every 3 months for 12–24 months under either MTX, MMF, CYC or 'no immunosuppressant', changes over time for the HAQ-DI did not differ between protocols ($P = 0.130$ and 0.073), regardless of adjustments for confounding variables. The HAQ-DI was associated with, among other parameters, mRSS, FVC and diffusing capacity of the lung for carbon monoxide (DLCO) and worsening HAQ-DI was related to increasing mRSS score [9].

Although promising, the data on HRQoL in the setting of AHSCT for SSc remains limited. Data were only available for 203 patients treated with AHSCT, of which approximately one-third came from small, uncontrolled studies [15–17, 42, 43]. The duration of follow-up overall was short. There was considerable heterogeneity in the way data were reported (absolute scores, differences in scores, proportion of patients with improvement), thereby precluding the pooling of results. Non-random missing data (due to death, for example) may have biased estimates, and the magnitude and direction of this bias is difficult to determine. There were inconsistencies in some of the results, most notably the SF-36 MCS. Finally, all three HRQoL measures studied lack specificity with respect to the protean features of SSc, including dyspnoea, pruritus, gastroesophageal disease, sleep disturbances and anal incontinence, among others. Another study limitation was the fact that the title and abstract review was performed by a single investigator. However, the study was performed under the supervision of two experts in the field (DF for AHSCT and MH for HRQoL data analysis and interpretation) with in-depth knowledge of the literature. As the number of AHSCTs for SSc continues to grow, there is strong rationale and an opportunity to undertake further HRQoL research in this setting.

In early, rapidly progressive severe SSc, three RCTs have now demonstrated improved outcomes with AHSCT as compared with CYC, with better overall and event-free survival up to 10 years in ASTIS [20] and 5 years in SCOT [21], and significant improvements in

skin involvement and lung function. In these studies, which have established the superiority of AHSCT *vs* CYC with grade A–level evidence, AHSCT was also associated with clinically meaningful and durable improvements in physical HRQoL. The HRQoL data reported in non-randomized studies showed similar results. No other conventional therapy in early, rapidly progressive severe SSc has shown results of the same magnitude. On the other hand, the impact of AHSCT on mental AHSCT remains uncertain. Future research is needed to measure the impact of AHSCT on HRQoL in SSc patients treated outside of clinical trials and to clarify its impact on mental HRQoL.

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