nature reviews rheumatology

https://doi.org/10.1038/s41584-023-00909-5

Review article

Check for updates

State-of-the-art evidence in the treatment of systemic sclerosis

In the format provided by the authors and unedited

Supplementary Table 1. Randomized clinical trials in diffuse cutaneous systemic sclerosis (dcSSc) reporting modified Rodnan skin score (mRSS)

Trial Intervention Phase N	Inclusion Criteria	Outcome	Mean disease duration	Antibody profile	Mean mRSS at baseline	ΔmRSS
Randomized trials of autologous haematopoetic stem cell transplantation (AHSCT) in dcSSc						
"Cardiac Safe AHSCT" (2020)[1] Fludarabine-based regimen±RTX± IVIG Phase 2/3 N=42	i. dcSSc, mRSS >14, lung or gastrointestinal disease OR ii. lcSSc with mRSS <14 AND lung disease AND iii. scleroderma heart disease	Flu/CYC/ATG vs Flu/CYC/ATG/RT X ± IVIG: ΔmRSS at 12 months (secondary) Flu/CYC/ATG/RT X 1000 mg vs Flu/CYC/ATG/RT X 500 mg/IVIG: ΔmRSS at 6 months (secondary)	Flu/CYC/ATG 69 months Flu/CYC/ATG/RT X ± IVIG 71 months	Flu/CYC/ATG Scl70+ 8/14 RNAPIII 2/14 Flu/CYC/ATG/RT X ± IVIG ATA 11/28 RNAP 9/28	Flu/CYC/ATG 18 Flu/CYC/ATG/RT X 1000 mg 16 Flu/CYC/ATG/RT X 500 mg/IVIG 20	At 12 months: Flu/CYC/ATG -11.7 vs Flu/CYC/ATG/RT X ± IVIG -9.4 At 6 months: Flu/CYC/ATG/RT X 1000 mg -5.4 vs Flu/CYC/ATG/RT X 500 mg/IVIG -8.5
ASTIS (2014)[2] Non-myeloablative AHSCT vs CYC Phase 3 N=156	dcSSc, minimum mRSS ≥15, <4 years of disease and heart, lung, kidney disease; or mRSS ≥20 and <2 years of disease	ΔmRSS at 24 months (secondary)	AHSCT 1.4 years CYC 1.5 years	AHSCT ATA 67% CYC ATA 81%	AHSCT 25 CYC 26	AHSCT -20 CYC -9
ASSIST (2011)[3] Non-myeloablative AHSCT vs CYC Phase 2 N=19	i. dcSSc, mRSS >14, lung or gastrointestinal disease OR ii. lcSSc with mRSS <14 AND lung disease	Secondary: ΔmRSS at 12 months (secondary)	AHSCT 14 months CYC 18 months	AHSCT ATA 5/10 CYC ATA 7/9	AHSCT 28 CYC 19	AHSCT -13 CYC +3
SCOT (2018) [4] Myeloablative CD34+ AHSCT vs CYC Phase 2 N=75	SSc ≤5 years Renal or lung (active ILD by HRCT or BAL PLUS FVC (or DLCO)<70%) involvement	Primary: Global rank composite score (death, event free survival (EFS), FVC, mRSS, HAQ-DI score) at 54mo Secondary: mRSS	AHSCT 25 months CYC 29 months	AHSCT ATA 13/36 (36%) RNAPIII 2/15 (6%) ACA 2/36 (6%) CYC ATA 16/39 (41%) aRNAPIII 6/17 (15%) ACA 2/39 (5%)	AHSCT 29 CYC 31	AHSCT vs CYC mRSS improvement (≥25 change from baseline or ≥5 if baseline mRSS≤20): 100% vs 82%, p=0.03 (among event-free survivors) 71% vs 29%, p=0.1(among those dead or with organ failure)
Randomized trials of standard immunosuppression in dcSSc						
SLS II (2016)[5] MMF vs oral CYC	ILD	ΔFVC at 24 months	MMF 2.6 years CYC 2.5 years	ATA 46% RNAPIII 13%	MMF 15 CYC 14	Change at 24 months (including dcSSc and lcSSc):

Phase 2 N=142 (randomized 1:1)				ACA 2%		MMF - 4.90 CYC -5.35 Difference 0.45 (95% CI -1.7, 2.6)
SLS I (2006)[6] Oral CYC vs Placebo Phase 3 N=158 (randomized 1:1)	ILD	∆FVC at 12 months	CYC 3.2 years Placebo 3.1 years		CYC 16 Placebo 14	Difference at 12 months in dcSSc: -3.06 (95% CI -3.54, -0.52, p=0.008)
Methotrexate (2001)[7] MTX vs Placebo Phase NA N=71 (randomized 1:1)	dcSSc <3 years duration	∆mRSS (0-78) at 12 months	MTX 6.3 months Placebo 7.3 months		MTX 28 Placebo 27	Difference at 12 months: Complete case analysis: MTX – 6.3 Placebo – 1.1 p <0.17 ITT analysis: MTX -4.3 Placebo 1.8 p<0.009
Methotrexate (1996)[8] MTX vs Placebo Phase NA N=29 (randomized 1:1)	Disease duration <3 years	∆Total skin score (0-104) at 24 weeks	MTX 3.2 years Placebo 3.2 years	ATA MTX 53% Placebo 58%	MTX 20.2 Placebo 20.7	MTX -0.7 Placebo 1.2 p=0.06
Randomized trials of targeted therapies and biologics with skin as primary endpoint						
RISE-SSc (2020)[9] Riociguat vs Placebo Phase 2b N=121 (randomized 1:1)	dcSSc Duration ≤18 months mRSS 10–22	∆mRSS at 12 months	Riociguat 9.5 months Placebo 8.6 months	ATA 41% RNAP 22%	17	Mean ∆mRSS at week 52: Riociguat: -2.09 Placebo: –0.77 LSM difference 2.34 (95% CI 4.99, 0.30; p=0.08)
ASSET (2020)[10] Abatacept vs Placebo Phase 2 N=88 (randomized 1:1)	dcSSc and Duration ≤18 months with mRSS 10–35 or Duration 18–36 months with mRSS 15–45 and either progressive skin disease or tendon friction rubs	∆mRSS at 12 months	Abatacept 20 months Placebo:18 months		Abatacept 23 Placebo 22	Adjusted mean ∆mRSS at week 52: Abatacept: -6.24 Placebo: -4.49 Adjusted mean treatment difference −1.75 (p=0.28)
FocuSSced (2020)[11] Tocilizumab vs Placebo Phase 3	dcSSc Duration ≤5 years mRSS 10–35 units “Active” disease	∆mRSS at week 48	Tocilizumab 23.1 months Placebo 22.2 months	ATA 50.5% RNAP 17.5% ACA 8.5%	Tocilizumab 20.3 Placebo 20.4	LSM ∆mRSS at week 48: Tocilizumab: -6.14 Placebo: - 4.41 Adjusted difference –1.73

N=210 (randomized 1:1)						(95% CI 3.78, 0.32; p=0·10)
Romilkimab (2020)[12] Romilkimab vs Placebo Phase 2 N=97 (randomized 1:1)	dcSSc	∆mRSS at week 24	Romilkimab 19 months Placebo 22 months		Romilkimab 21 Placebo 21	LSM ∆mRSS at week 24: Romilkimab: –4.8 Placebo: –2.5 Mean difference –2.31 (90% CI –4.32, –0.31; p=0.0291, one-sided)
NOVESA (2020) (abstract only)[13] Ziritaxestat vs Placebo Phase 2a N=33 (randomized 2:1)	dcSSc mRSS >10	∆mRSS at week 24	Ziritaxestat 18 months Placebo 31 months		Ziritaxestat 27 Placebo 23	LSM difference (95% CI) was –2.8 (–5.6, –0.1; p=0.04) in favour of Ziritaxestat
Belimumab (2018)[14] Belimumab vs Placebo Phase 2 N=20 (randomized 1:1)	Duration <3 years mRSS ≥16	∆median mRSS at week 52	Belimumab 11.7 months Placebo 9 months	Scl70 25% RNAP 50%	Belimumab 27 Placebo 28	∆median mRSS at week 52: Belimumab: - 10 Placebo: - 3 p-value 0.41
Recent randomized trials in which skin was secondary outcome						
Lenabasum (2020)[15] Lenabasum vs Placebo Phase 2 N=42 (randomized 1:1)	DcSSc Duration ≤3 years or 3–6 years with elevated inflammatory markers, mRSS ≥16 progressive skin disease	Safety CRISS	Mean: Lenabasum 34 months Placebo 34 months		Lenabasum 24 Placebo 26	Lenabasum -4.6 Placebo -2.0 Mean difference −2.6 at week 16 (p=0.09, on-sided, and p=0.17, two-sided)
SENSCIS (2019)[16] Nintedanib vs Placebo Phase 3 N=576	ILD Duration <7 years	∆FVC at week 52	Median: Nintedanib 3.4 years Placebo 3.5 years	ATA 61%	dcSSc: Nintedanib 17 Placebo 16 lcSSc: Nintedanib 5 Placebo 5	Adjusted mean ∆mRSS at week 52: Nintedanib −2.17 Placebo −1.96 in Difference −0.21, 95% CI −0.94 to 0.53

ACA; anti-centromere antibody positive; ATG, anti-thymocyte globulin; CYC, cyclophosphamide; DLCO, diffusion capacity of the lungs for carbon monoxide; EFS, event-free survival; Flu, fludarabine; FVC, forced vital capacity; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; lcSSc, limited cutaneous systemic sclerosis; LSM, least square mean; MTX, methotrexate; RTX, rituximab; RNAPIII, anti-RNA polymerase III antibody positive; ∆, change.

Supplementary Table 2: Disease modification in randomized trials of autologous haematopoetic stem cell transplantation (AHSCT)

Trial Phase N	Mobilization	Conditioning	Global outcome	Results	Treatment-related deaths	Incidence of cancer
"Cardiac Safe AHSCT" (2021)[1] Phase 2/3 N=42	CYC 2 g/m^2	Flu/CYC/ATG Flu/CYC/ATG/RTX 1000 mg Flu/CYC/ATG/RTX 500 mg/IVIG	Primary: Overall survival at 1 year	Flu/CYC/ATG 86% vs Flu/CYC/ATG/RTX ± IVIG 96% p=0.25 Flu/CYC/ATG/RTX 1000 mg 93% vs Flu/CYC/ATG/RTX 500 mg/IVIG 100% p=NS	Flu/CYC/ATG 0 vs Flu/CYC/ATG/RTX ± IVIG 4% p=0.99	
SCOT (2018)[4] Phase 2 N=75	G-CSF only CD34+ selected	Treatment: Myeloablative AHSCT • TBI 800cGy • CYC 120 mg/kg • eATG 90 mg/kg Comparator: CYC 500-750 mg IV monthly x 12 months	Primary: Global rank composite score (GRCS; higher scores better) Secondary: Overall survival Event-free survival	Median GRCS (ITT) at 54 months: AHSCT 17 CYC -6 P=0.01 Overall survival (per-protocol) at 72 months: AHSCT 86% CYC 51% p=0.02 EFS (per-protocol) at 54 months: AHSCT 79% CYC 50% p=0.02	6% (both late, from myelodysplastic syndrome)	AHSCT 8% (including 2 late occurrences of myelodysplastic syndrome) CYC 3%
ASTIS (2014)[2] Phase 3 N=156	CYC 4 g/m^2 CD34+ selected	Treatment: Non-myeloablative AHSCT • CYC 200 mg/kg • rATG 7.5 mg/kg Comparator: CYC 750 mg/m^2 IV monthly x 12 months	Primary: Event-free survival Secondary: Overall survival	Event-free survival at 4 years: AHSCT 81% CYC 74% (hazard ratio 0.34, 95% CI, 0.16-0.74; p=0.006) Overall survival at 4 years: AHSCT 83.5% CYC 74% (hazard ratio 0.29, 95%CI, 0.13-0.64; p=0.002)	10% (within 1 year, in AHSCT group; predominantly from cardiac dysfunction)	AHSCT 0 CYC 4%
ASSIST (2011)[3] Phase 2 N=19	CYC 2 g/m^2 No selection	Treatment: Non-myeloablative AHSCT: • CYC 200 mg/kg • rATG 6.5 mg/kg Comparator: CYC 1 g/m² IV x 6 months	Secondary: Overall survival	No deaths in either group at mean 2.6 years follow up		

ATG, anti-thymocyte globulin; CYC, cyclophosphamide; EFS, event-free survival; Flu, fludarabine; G-CSF, granulocyte colony-stimulating factor; GRCS, global rank composite score; IVIG, intravenous immunoglobulin; rATG, rabbit anti-thymocyte globulin; RTX, rituximab; TBI, total body irradiation.

References

1. Burt, R.K., et al., *Cardiac safe hematopoietic stem cell transplantation for systemic sclerosis with poor cardiac function: a pilot safety study that decreases neutropenic interval to 5 days.* Bone Marrow Transplant, 2021. **56**(1): p. 50-59.
2. van Laar, J.M., et al., *Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial.* JAMA, 2014. **311**(24): p. 2490-8.
3. Burt, R.K., et al., *Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial.* Lancet, 2011. **378**(9790): p. 498-506.
4. Sullivan, K.M., et al., *Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma.* N Engl J Med, 2018. **378**(1): p. 35-47.
5. Tashkin, D.P., et al., *Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial.* Lancet Respir Med, 2016. **4**(9): p. 708-719.
6. Tashkin, D.P., et al., *Cyclophosphamide versus placebo in scleroderma lung disease.* N Engl J Med, 2006. **354**(25): p. 2655-66.
7. Pope, J.E., et al., *A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma.* Arthritis Rheum, 2001. **44**(6): p. 1351-8.
8. van den Hoogen, F.H., et al., *Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial.* Br J Rheumatol, 1996. **35**(4): p. 364-72.
9. Khanna, D., et al., *Riociguat in patients with early diffuse cutaneous systemic sclerosis (RISE-SSc): randomised, double-blind, placebo-controlled multicentre trial.* Ann Rheum Dis, 2020. **79**(5): p. 618-625.
10. Khanna, D., et al., *Abatacept in Early Diffuse Cutaneous Systemic Sclerosis: Results of a Phase II Investigator-Initiated, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial.* Arthritis Rheumatol, 2020. **72**(1): p. 125-136.
11. Khanna, D., et al., *Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet Respir Med, 2020. **8**(10): p. 963-974.
12. Allanore, Y., et al., *A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis.* Ann Rheum Dis, 2020. **79**(12): p. 1600-1607.
13. Khanna, D., et al., *A Phase 2a Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA) [abstract]. Arthritis Rheumatol. 2020; 72 (suppl 10).* https://acrabstracts.org/abstract/a-phase-2a-randomized-double-blind-placebo-controlled-study-of-ziritaxestat-in-early-diffuse-cutaneous-systemic-sclerosis-novesa/. *Accessed May 18, 2021.*
14. Gordon, J.K., et al., *Belimumab for the Treatment of Early Diffuse Systemic Sclerosis: Results of a Randomized, Double-Blind, Placebo-Controlled, Pilot Trial.* Arthritis Rheumatol, 2018. **70**(2): p. 308-316.
15. Spiera, R., et al., *Safety and Efficacy of Lenabasum in a Phase II, Randomized, Placebo-Controlled Trial in Adults With Systemic Sclerosis.* Arthritis Rheumatol, 2020. **72**(8): p. 1350-1360.
16. Distler, O., et al., *Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease.* N Engl J Med, 2019. **380**(26): p. 2518-2528.