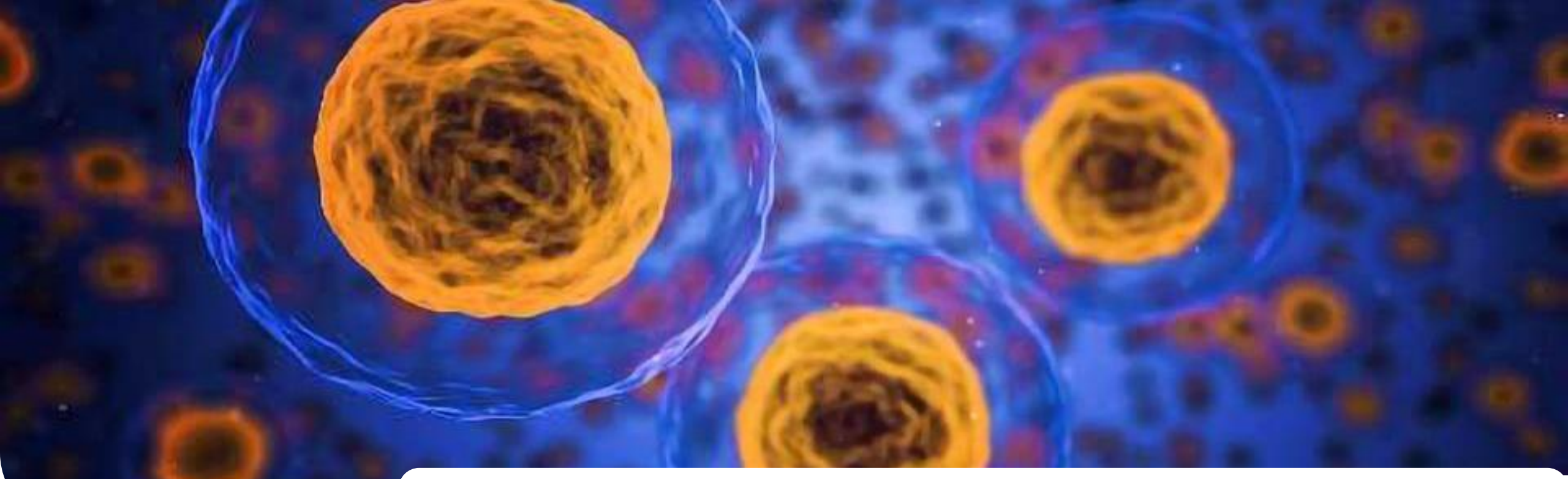


Stamceltransplantatie bij systemic sclerosis

Julia Spierings MD PhD

UMC Utrecht

Utrecht Rheumatology & Clinical Immunology

Inhoud

- Casus
- Autologe stamceltransplantatie
- Optimale selectie
- UPSIDE studie

- Kennisagenda

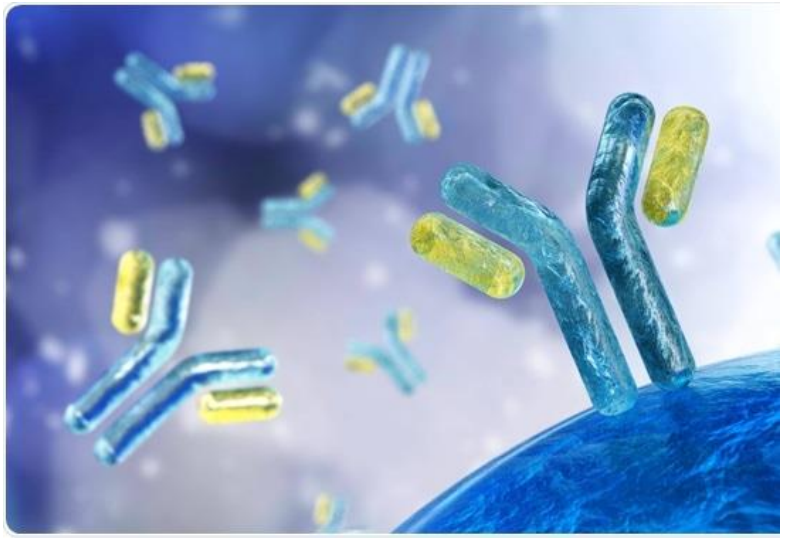
Casus

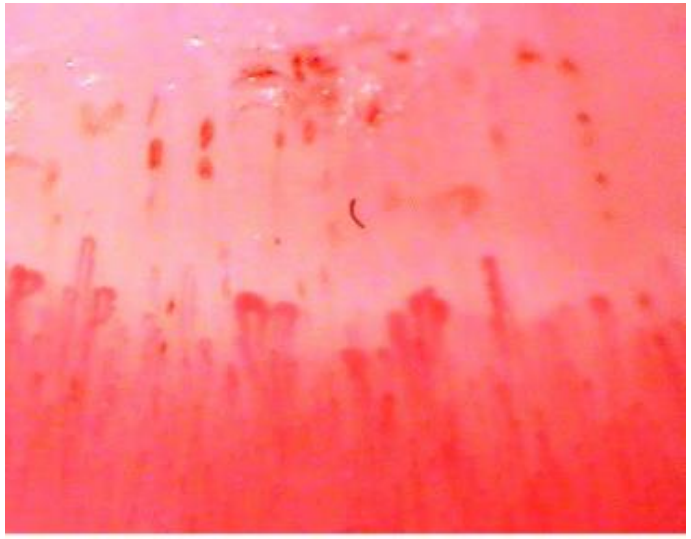
Dhr. D

- 38 jaar
- Roker
- Bouwvakker

>> KOUDE HANDEN

5 maanden





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Casus Systemische sclerose

Puffy hands, mRSS 4

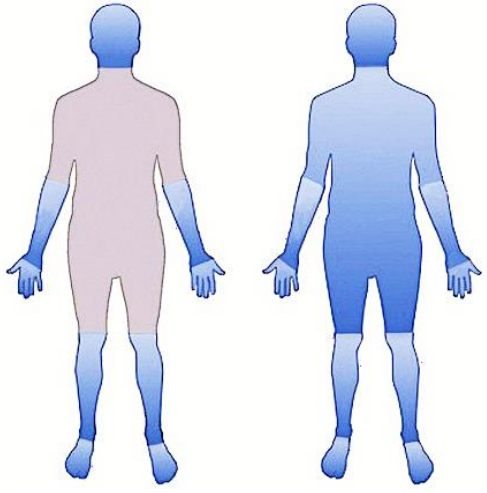
Pitting scars

Behandeling

- MMF 2 gram
- Nifedipine 30mg

MacFarlane et al. Rheumatology 2018

Pathofysiologie & kliniek



Gelimiteerd cutaan Diffuus cutaan

Vasculopathy
Endothelial damage
Vasoconstriction
Hypoxemia, ↑ ROS
Angiogenesis

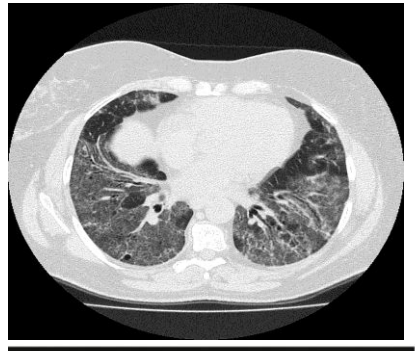
Endothelin 1
IL-4
IL-6

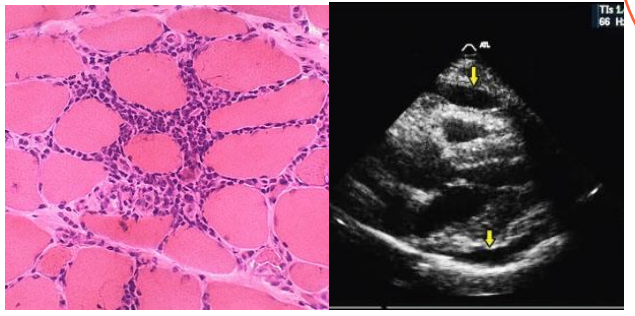
IL-4, cellular toxicity, anti-EC bodies

Inflammation
↓ M1 ↑M2
↑mest cell activation
↑ cytokines
↓ Th1 ↑Th2
↑B -cells

TGF-B
IL-6
IL-4, MCP-1, IL-1

Fibrosis
↑Fibroblasts
↑ Extracell. matrix
↓MMP-1
↑ IL-1ra

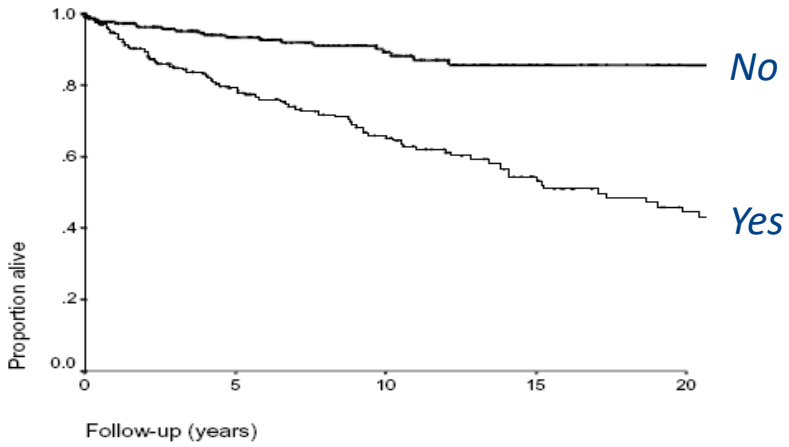




- 3000 - 4000 patiënten in Nederland
- Incidentie: 1-5 per 100.000 per jaar
- Heterogene manifestaties en beloop

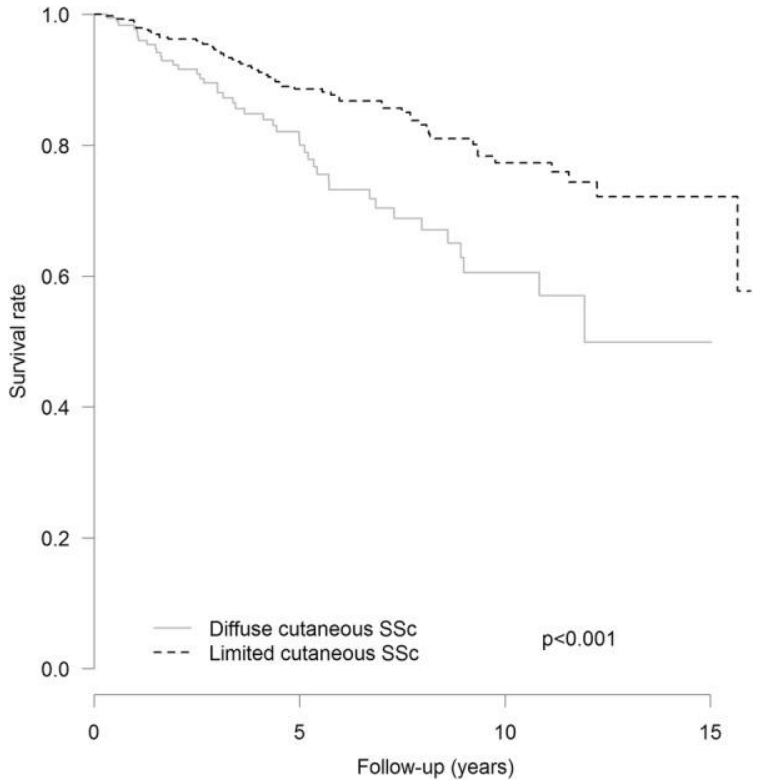
Ioannidis et al. Am J Med ***2005***

Organ involvement?



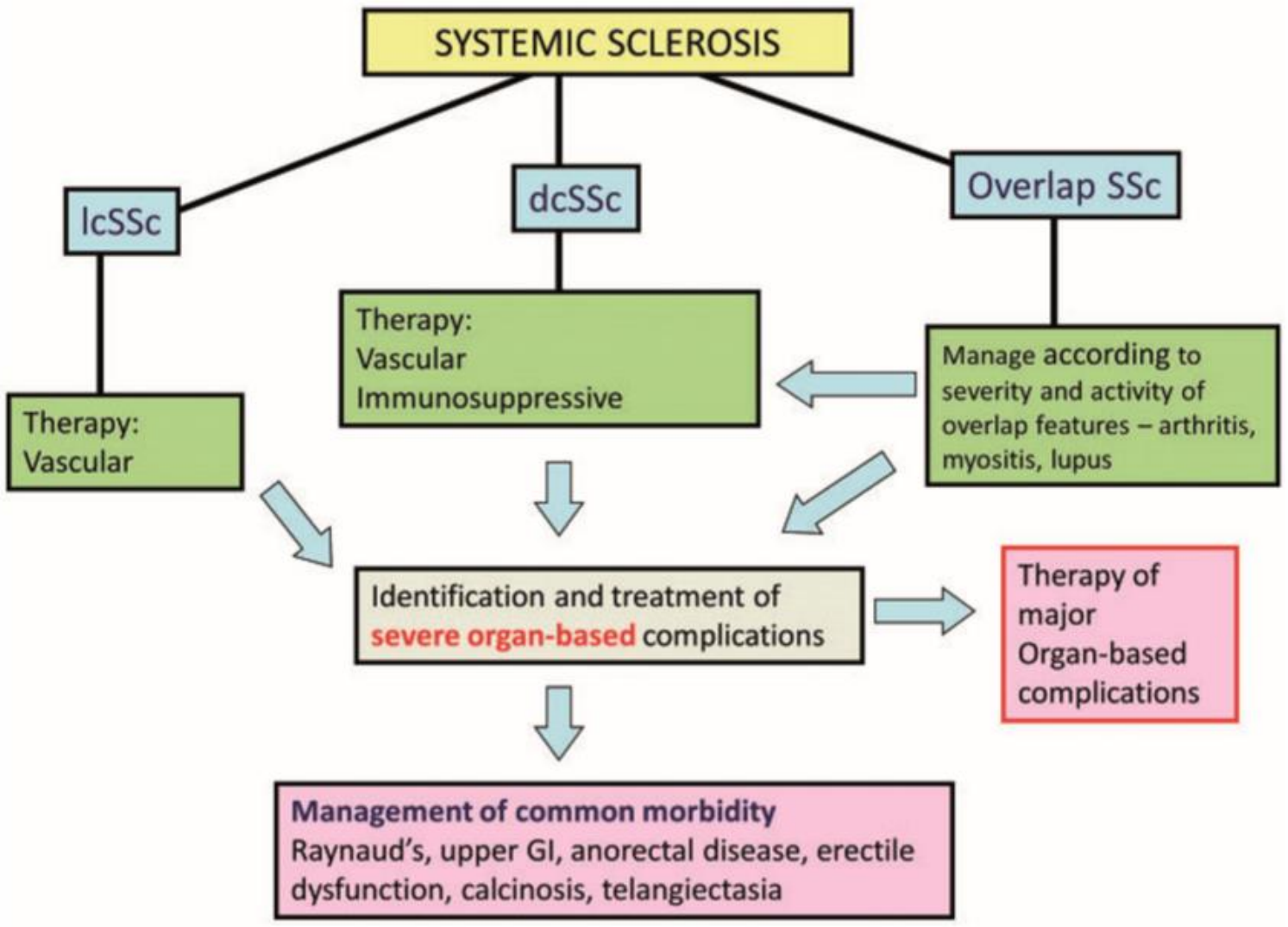
Organ involvement					
Yes	237	131	87	49	31
No	234	137	90	50	32

Pokeerbux et al. Arthritis Res Ther. ***2019***



Denton et al. Rheumatology 2016

Behandelrichtlijn



Casus

Na 8 weken:

- mRSS 15 (diffuus patroon)
- Artralgie/myalgie
- Vermoeidheid
- Sterk verhoogd hs troponine

→ MMF 3 gram/dag

→ **Volgende stap?**

Vroege progressieve diffuse cutane SSc

a window of opportunity

MTX

MMF

Cyclofosfamide

Rituximab

Tocilizumab

Fibroseremmers

Autologe stamceltransplantatie

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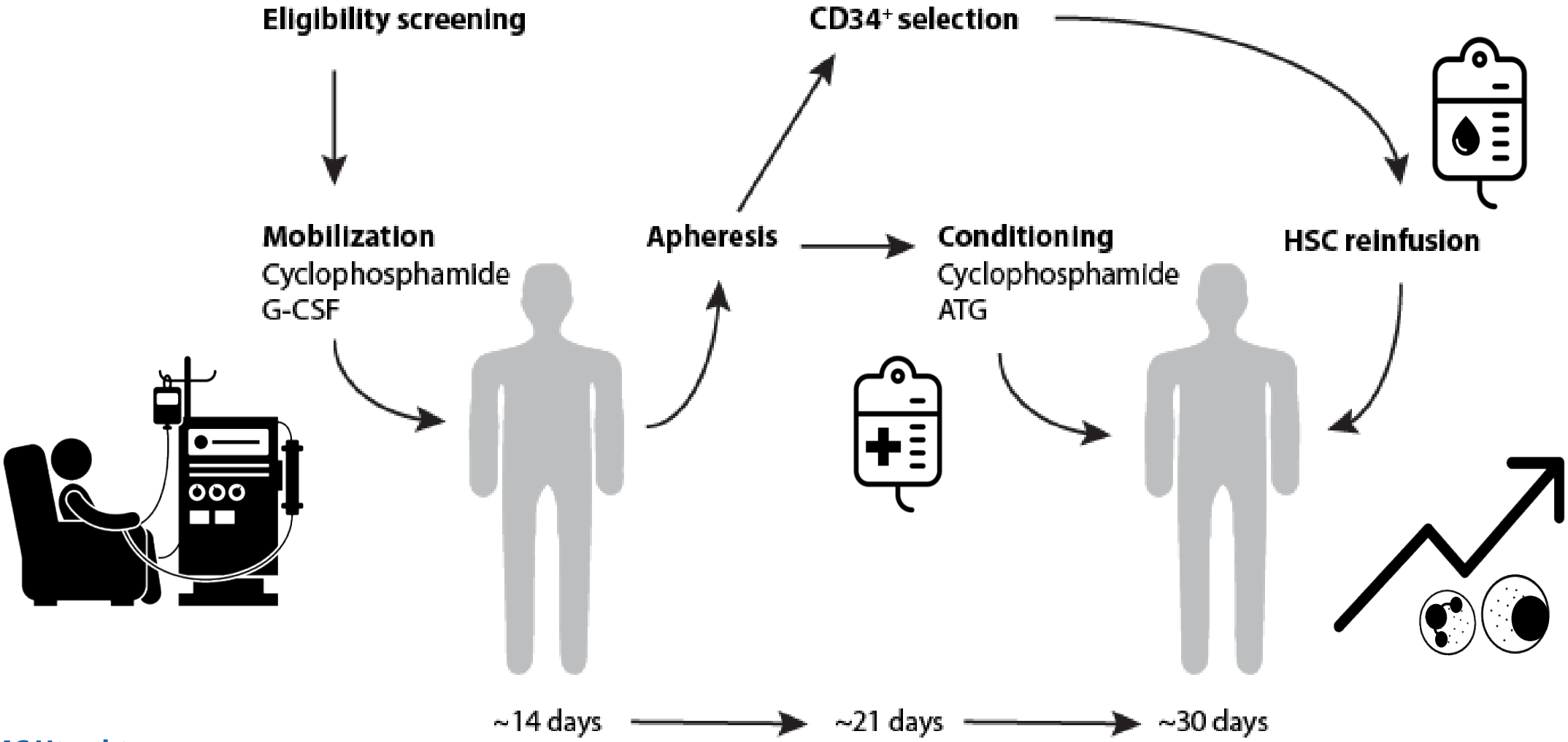
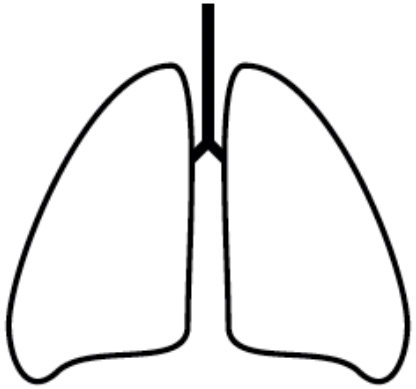
KEEP CALM
AND PRESS
CTRL-ALT
DELETE

Procedure

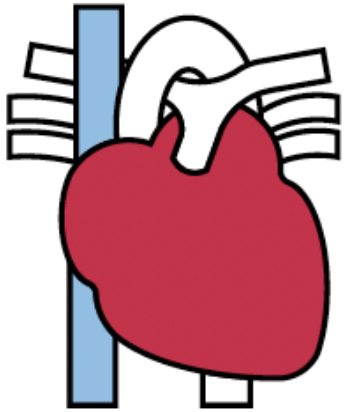

Eligibility screening
CD34+ selection
Mobilization
Cyclophosphamide
G-CSF
Apheresis
Conditioning
Cyclophosphamide
ATG
HSC reinfusion
~14 days
~21 days
~30 days

Screening

Bloedonderzoek:
bloedbeeld, nierfunctie, leverfunctie, virusserologie, urine

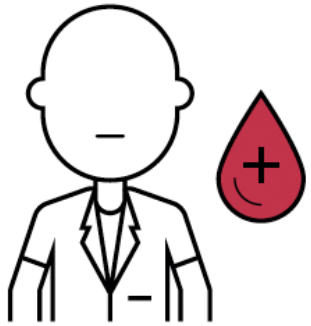


Longen:
longfunctie en longscan



Hart:
echo, holter (recorder voor hartritme), MRI en rechts katheterisatie

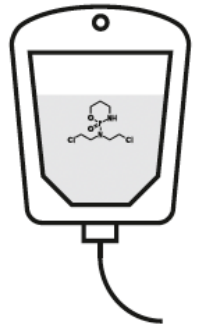
Mobilisatie



Afspraak bij de hematoloog

Opname op afdeling hematologie.

Ongeveer 2 weken

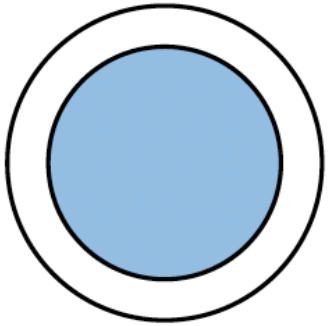


Cyclofosfamide infuus

1 dag

Dagelijkse injectie groeifactoren

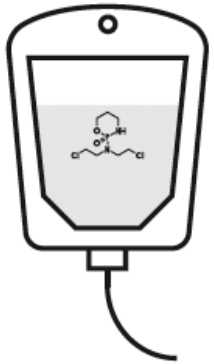
5 dagen – 11 spuitjes



Oogsten van stamcellen

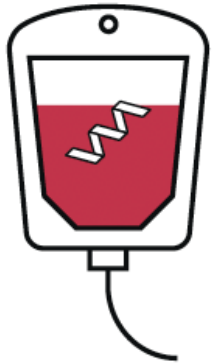
1-2 dagen

Conditionering



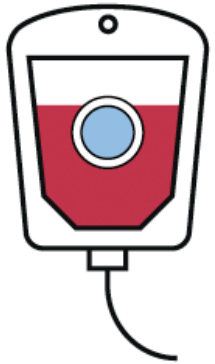
Cyclofosfamide infuus

4 dagen



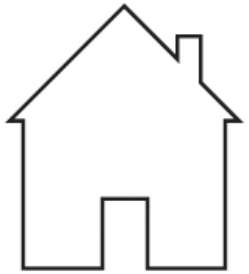
ATG infuus

3 dagen



Infuus met stamcellen

1 dag



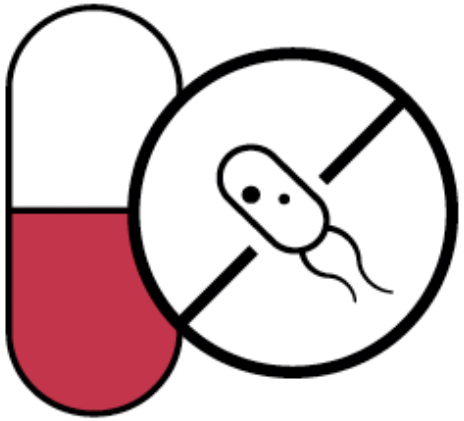
Na uitrijping van de stamcellen naar huis

2 weken na toediening

Herstel

Bloedonderzoek

2-wekelijks de eerste 3 maanden, daarna maandelijks



Antibiotica

Gemiddeld een jaar

Spierings et al. Curr Opin Rheumatol 2018

Werkt het?

2 RCTs en verschillende cohort studies

AHSCT in patiënten met **diffuse cutane** systemische sclerose

- Betere lange termijnsoverleving
- Preventie progressie orgaanbetrokkenheid
- Verbetering huid

❌ **Hoger risico op ernstige complicaties t.o.v. andere behandelingen**

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Original Investigation

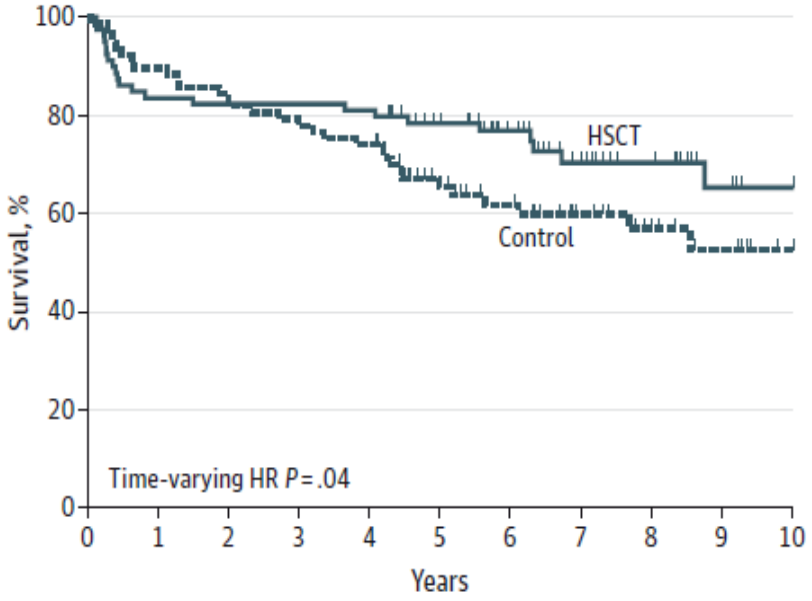
Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

A Randomized Clinical Trial

van Laar et al, JAMA 2014

Event-free survival & overall survival beter na AHSCT tov cyclofosfamide

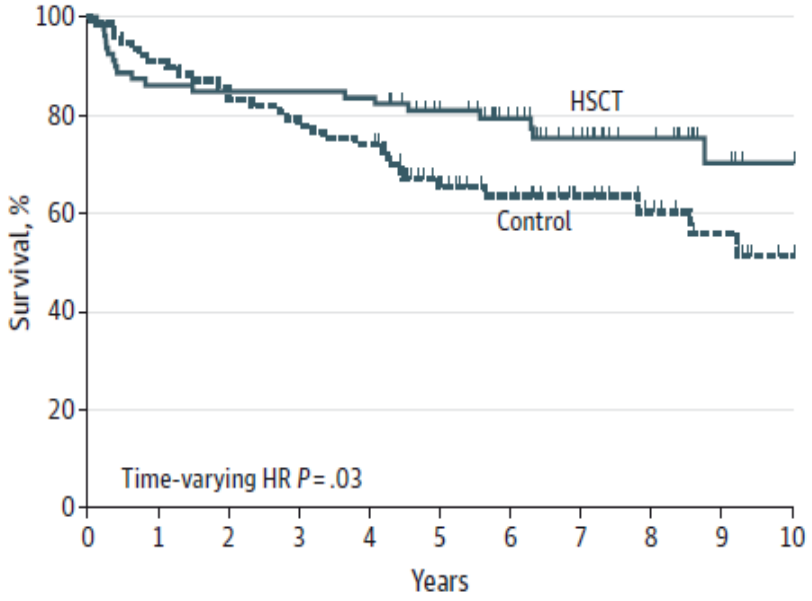
A Event-free survival



No. at risk

HSCT	79	66	65	65	64	53	41	29	21	13	10
Control	77	69	63	60	57	40	33	23	17	11	6

B Overall survival



No. at risk

HSCT	79	68	67	67	66	55	43	32	23	14	11
Control	77	70	64	60	57	40	34	25	18	12	6

TRM 10%

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URCI

The NEW ENGLAND JOURNAL of MEDICINE

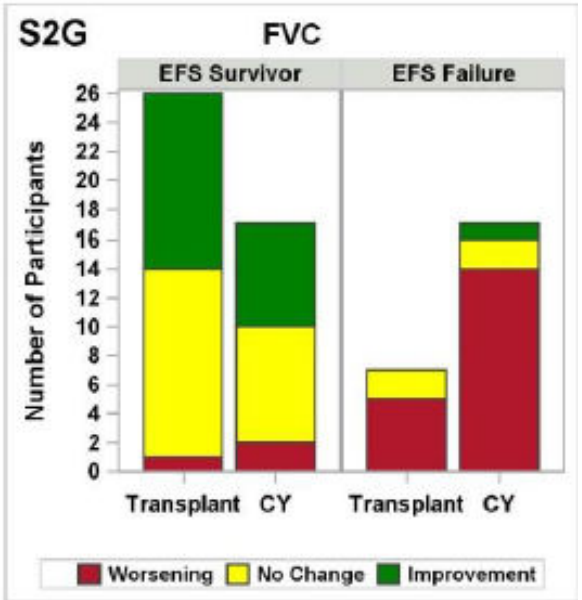
Sullivan et al, NEJM 2018

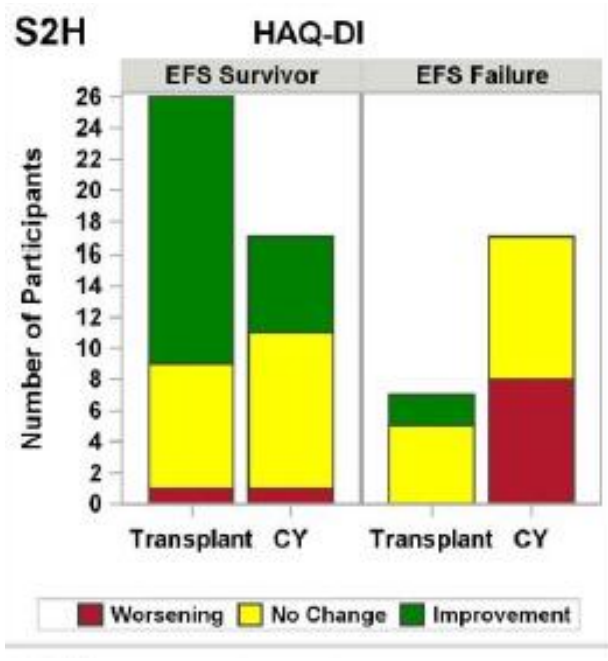
ORIGINAL ARTICLE

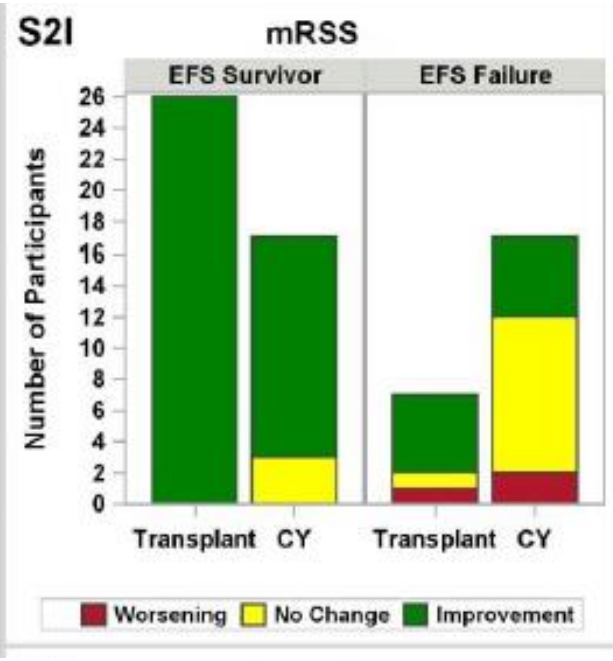
Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

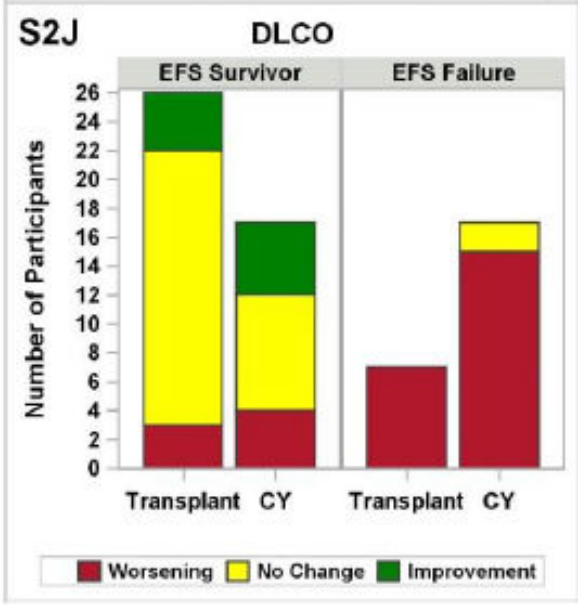
SCOT trial bevestigt voordelen van AHSCT

TRM 6%









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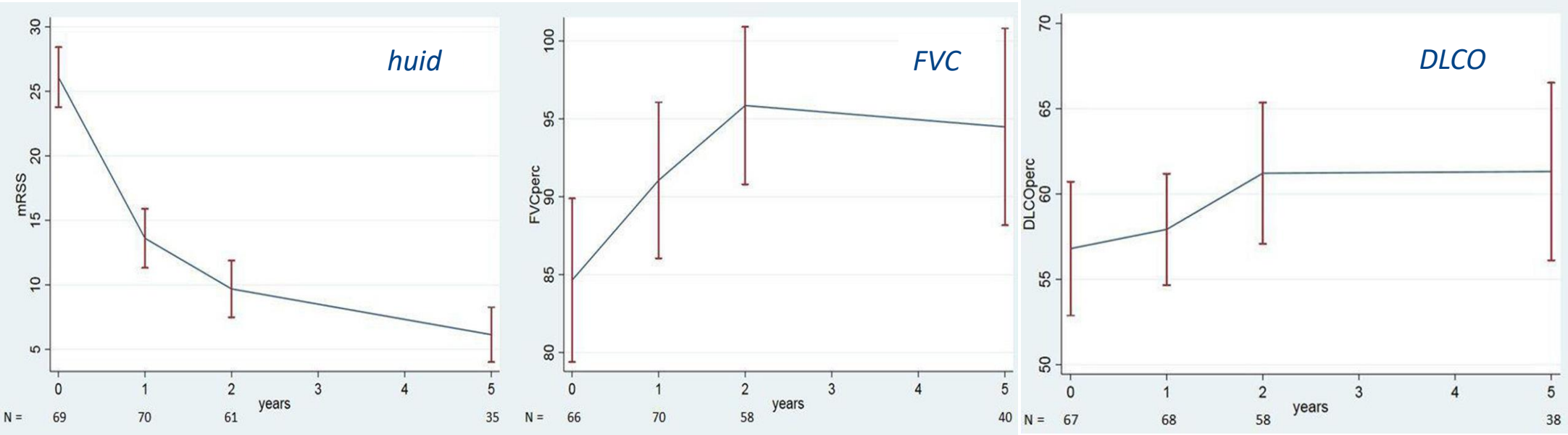
van Bijnen et al. Ann Rheum Dis 2020

Nederlands AHSCT cohort

n=92

Even free survival op 15 jaar follow-up: 66%

Treatment related mortality beter over de tijd: 13.7% >> 7.3%



Verbetering kwaliteit van leven na AHSCT

doi:10.1093/rheumatology/kez300

Original article

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

Mathieu Puyade [1,2,*] Nancy Maltez [3,*], Pauline Lansiaux [4,5], Grégory Pugnet [6,7], Pascal Roblot [1,8], Ines Colmegna [9,10], Marie Hudson [10,11,*] and Dominique Farge [4,5,10,*]

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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Submitted 8 March 2019; accepted 10 June 2019

*Mathieu Puyade, Nancy Maltez, Marie Hudson and Dominique Farge contributed equally to this article.

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CLINICAL SCIENCE

Systematic review:

- 8 studies (N=289 AHSCT, N=125 CYC)
- Median 1.25-4.5 jaar follow-up
- HAQ-DI, SF-36, EQ5D

Hoe werkt het?

Stamceltransplantatie

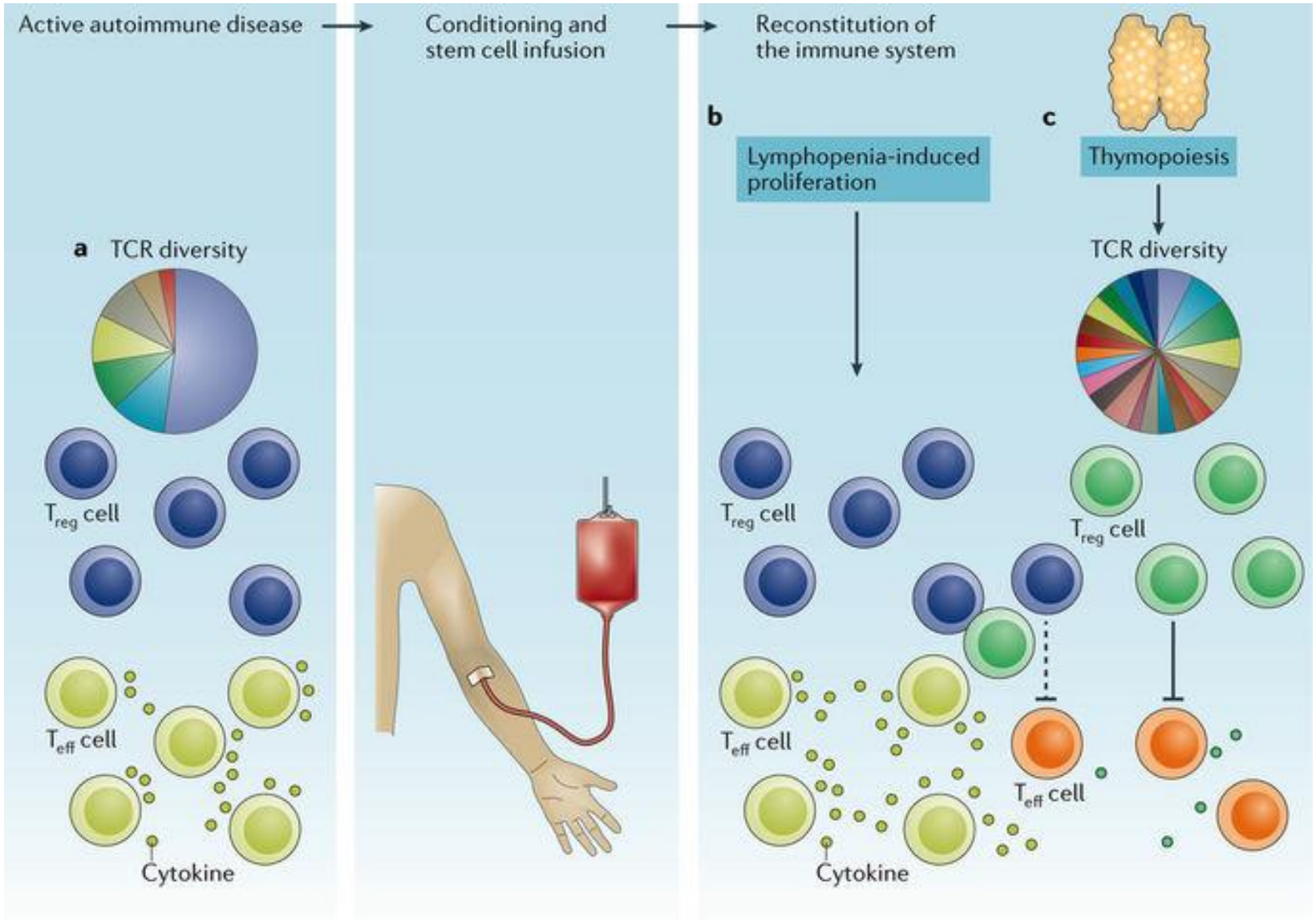
Immuun balans

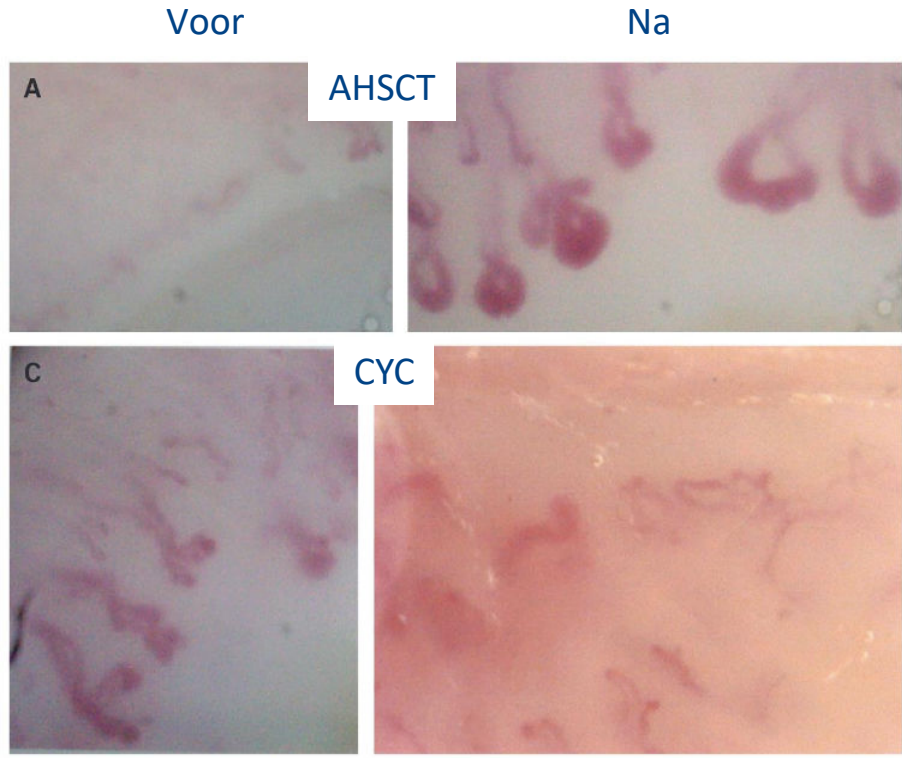
vs

Immuunsuppressiva

Onderdrukken immuunsysteem

Regeneratie van immuunsysteem & microcirculatie





Miniati et al. Ann Rheum Dis 2009

Swart et al. Nat Rev Rheumatol 2017

Patiënt **selectie**

Which patients benefit most?

Who has high risk of complications?

How to support decision making?

Welke patiënten hebben het meest effect?

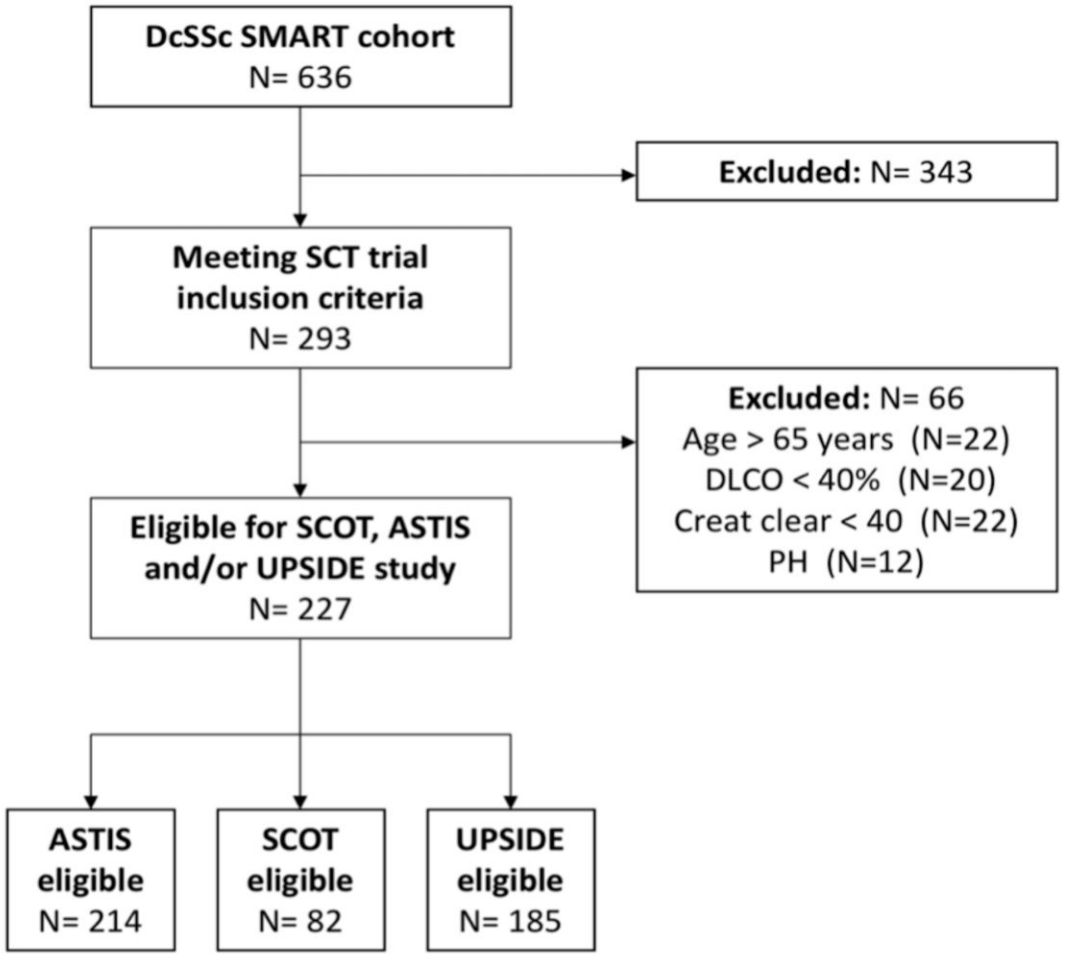
INCLUSION CRITERIA		
	ASTIS	**SCOT**
Age	18 - 65	18 - 69
Early disease	≤ 4 yrs	≤ 4 yrs
mRSS	≥15	≥16
Organ involvement	lung, kidney, heart	lung, kidney
Prognostic factors	ESR >25mm/h, Hb <11g/dl	

Spierings et al. Rheumatology 2022.

Trial criteria selecteren hoog risico patiënten

- Analyse Royal Free Hospital SSc cohort
- N=227 patiënten voldeden aan studiecriteria, maar anders behandeld.

	2 yrs	5 yrs	10 yrs	15 yrs
Event free survival	78%	66%	51%	37%
Overall survival	96%	88%	73%	61%



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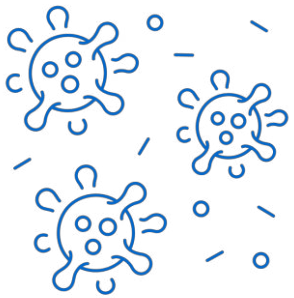
Patiënt selectie

Which patients benefit most?

Who has high risk of complications?

How to support decision making?

Ernstige complicaties



Infecties

EBV, CMV

opportunistische infecties

Cytokine storm (ATG)

ARDS

Neurologische symptomen

Cardiaal

CYC toxiciteit

Sepsis

volume overbelasting

Maligniteit

Lymphoproliferatief

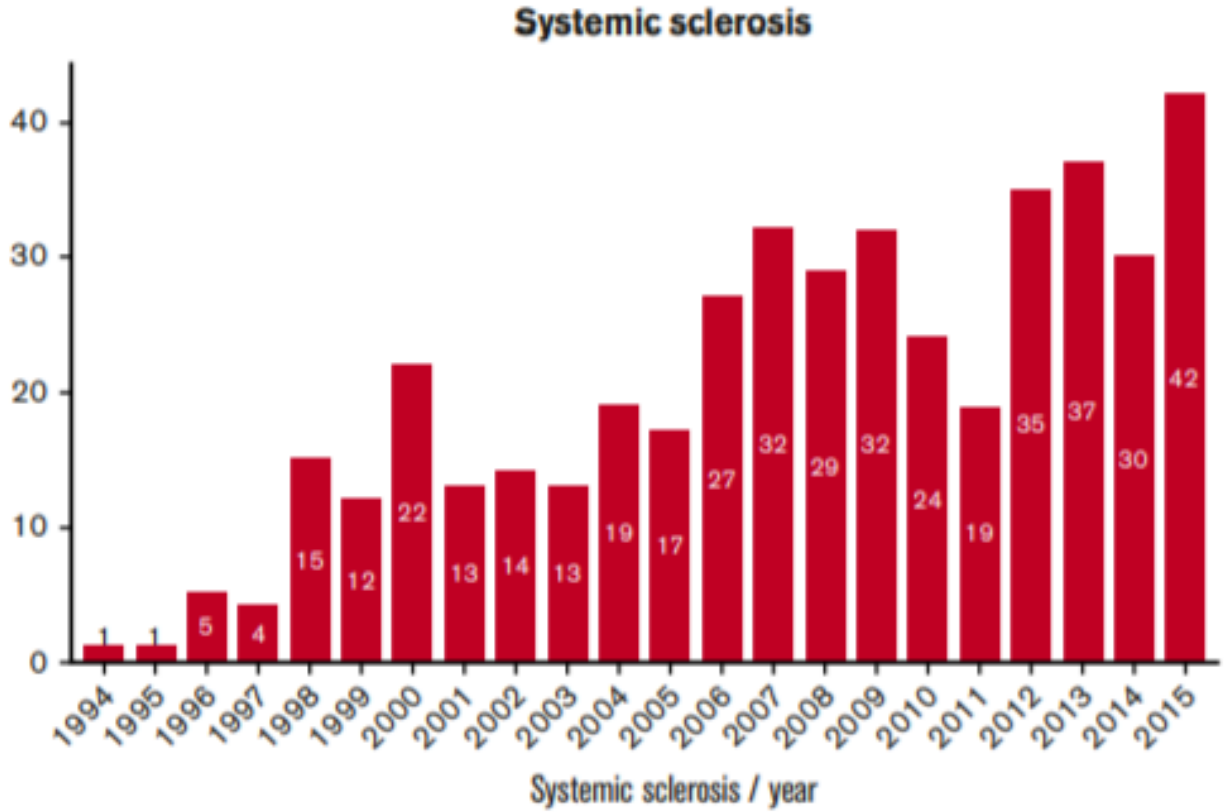
Leukemie / MDS

Blaascarcinoom

Welke patiënten hebben hoog risico op complicaties?

EXCLUSION CRITERIA	ASTIS	SCOT
Age	>65 yrs	>70 yrs
Pulmonary hypertension	mPAP >50mmHg	mPAP>30mmHg
Cardiac function	<45%	<50%
Lung function	DLCO<40%	FVC <45% DLCO<40%
Kidney function	Creat clearance < 40ml/min	
Infection	Any infection	
CYC history	> 5gr iv	> 6 iv courses

Meer ervaring en betere selectie = betere uitkomsten



Pre-transplant screening & supportive care

Patiënt selectie

Which patients benefit most?

Who has high risk of complications?

How to support decision making?

Educatie & begeleiding

- Keuzehulp
- Peer support
- Post transplantatie

Spierings et al. Rheumatology 2020
Spierings et al. J Scleroderma Relat Disord. 2020

Treatments for systemic sclerosis

In systemic sclerosis, four immunosuppressive treatments aiming to stop disease progression are commonly used. The choice of treatment depends on your personal situation and preferences. This leaflet can be used to support the decision making process with your doctor.

1. Methotrexate
Once a week tablets or subcutaneous injections

Don't use in case of: infection, moderate or severe liver kidney disease, bone marrow disease or extensive lung fibrosis. Don't use during pregnancy.

Expected effect after 3 months.

2. Mycophenolate mofetil (Cellcept)
Three to six tablets daily

Don't use in case of: infection or bone marrow disease. Don't use during pregnancy.

Expected effect after 3 months.

3. Cyclophosphamide (Endoxan)
Monthly infusion on daycare unit

Don't use in case of: infection, moderate or severe liver or kidney disease, bone marrow disease or heart failure. Don't use during pregnancy. *Please discuss family planning with your doctor prior to start of this therapy.*

Expected effect after 3 to 6 months

4. Autologous stem cell transplantation
Approximately 6 weeks hospital admission

Don't use: when older than 65 years or if there is: infection, moderate or severe liver or kidney disease, bone marrow disease, extensive lung fibrosis or heart failure. Don't use during pregnancy. *Please discuss family planning with your doctor prior to start of this therapy.*

Expected effect in weeks to months

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Wat is de beste timing van stamceltransplantatie?

Vroeg of als laatste redmiddel?

> Complicaties?

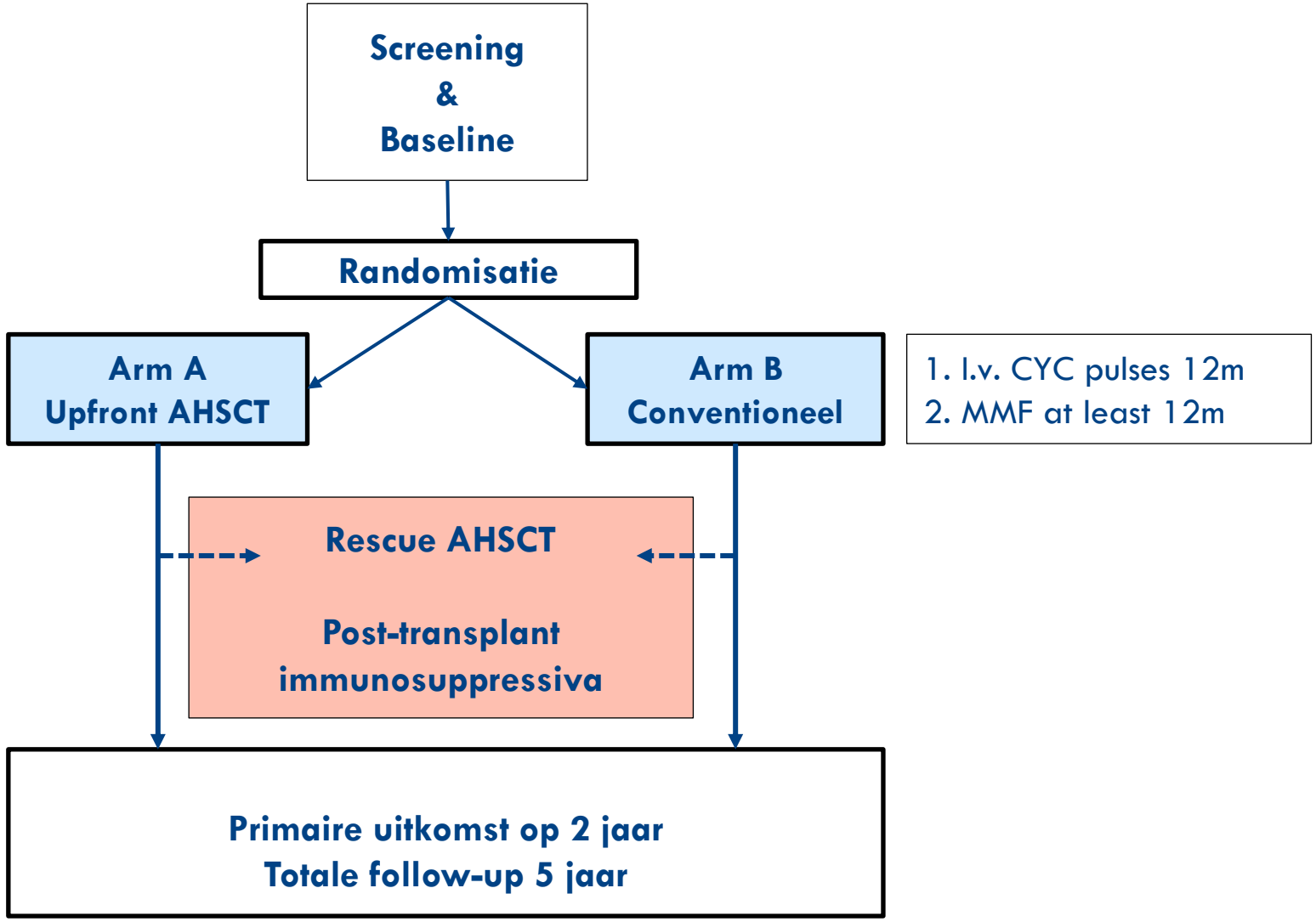
> Effect?

> Kosten?

> Overbehandeling?

Spierings et al. BMJ Open 2021

UPSIDE trial
2019-004718-32



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ZonMw

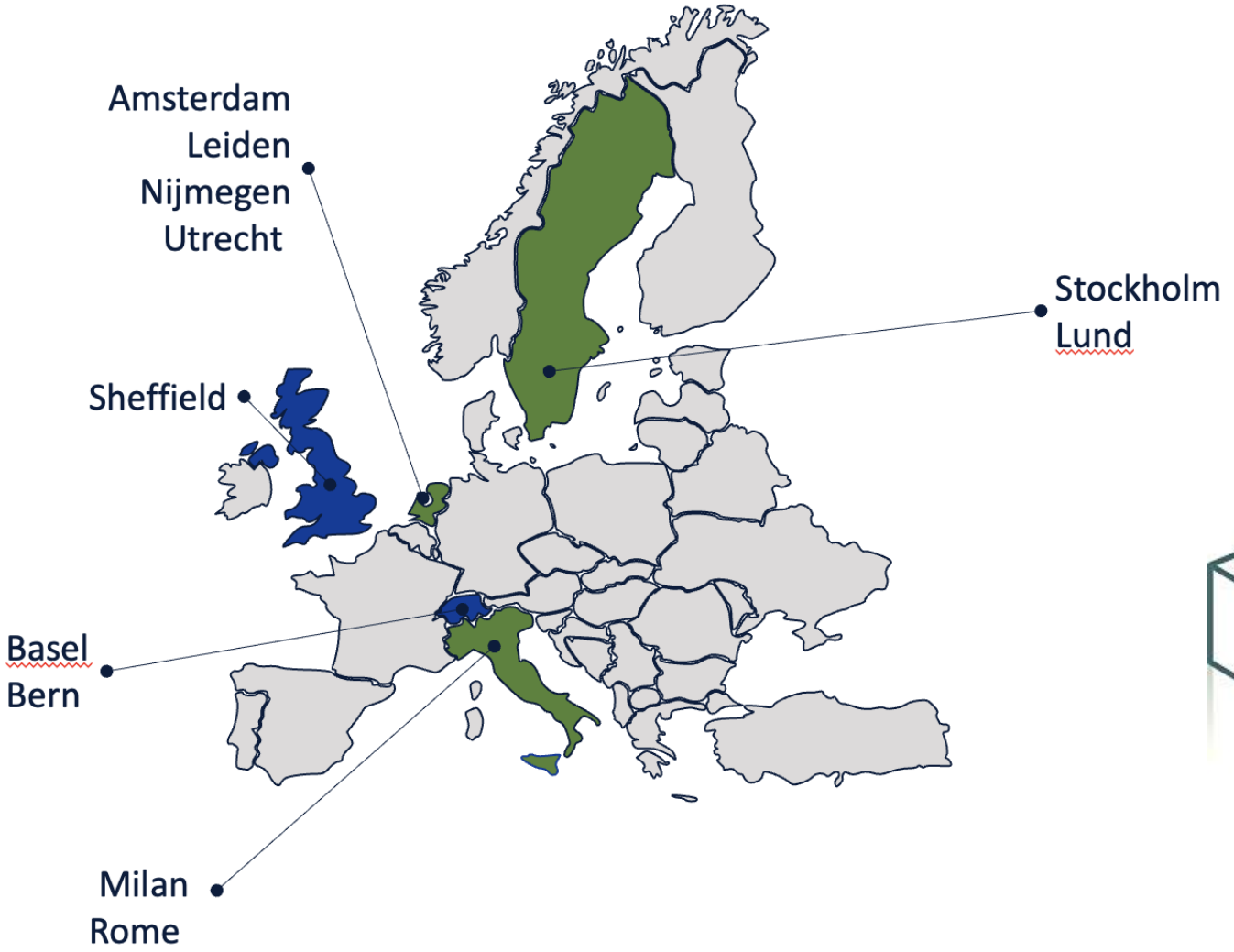
UPSIDE trial
2019-004718-32

DOEL: 50 deelnemers

Inclusie criteria

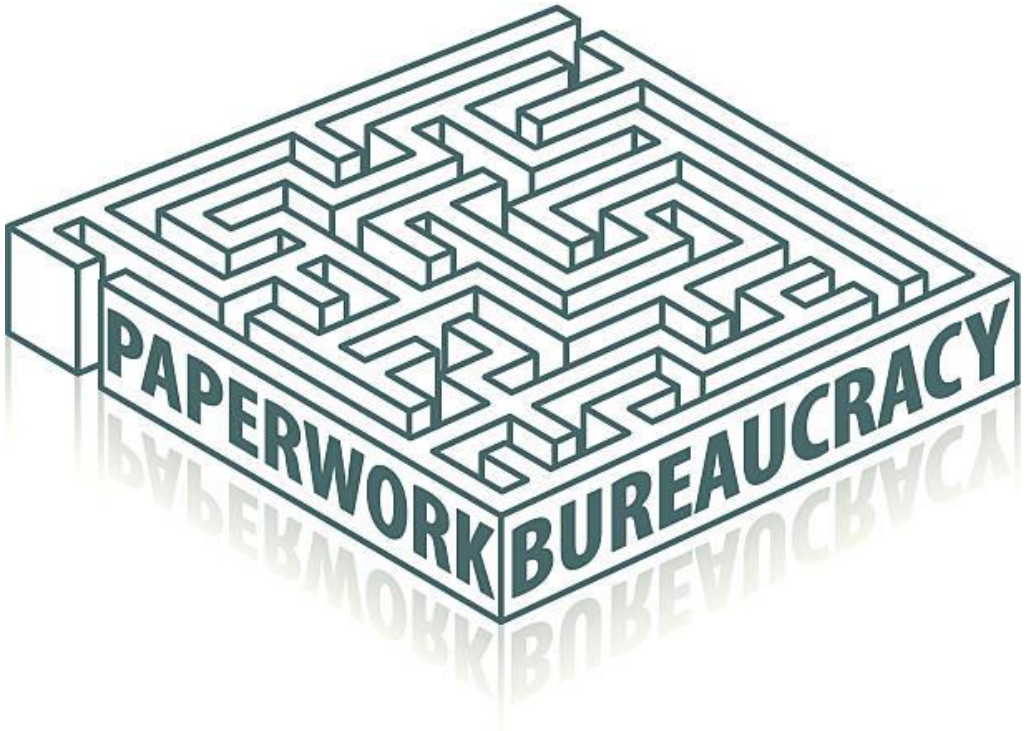
- Leeftijd ≤ 65 jaar
- Diffuse cutane systemische sclerose
- Ziekteduur ≤ 3 jaar
  - mRSS ≤ 15 **OF** orgaanbetrokkenheid
  - mRSS ≤ 10 **EN** ATA/ARA+ **OF** CRP/BSR++
- CYC naïef / ≤ 12 maanden DMARDs

Internationale samenwerking



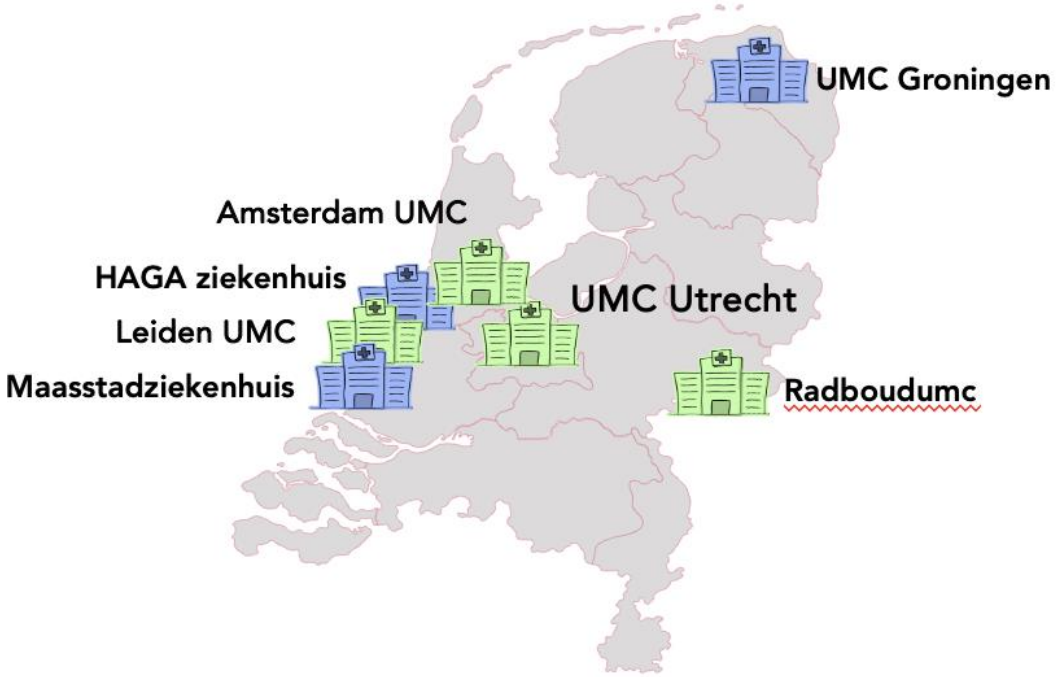
Huidig consortium

- 5 landen
- 11 centra



Nationale samenwerking

- Maandelijks online studiemeeting met casusbespreking
- Door nieuwe regelgeving kan behandeling arm B in eigen ziekenhuis
- Aandacht voor studie tijdens ARCH (regio) overleg

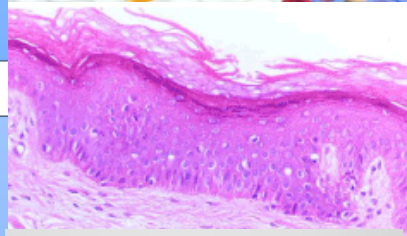


Substudies

- **Werkingsmechanisme**
- **Farmacokinetiek**
- **Voorspellers voor respons**
- **Effect dagelijks leven**

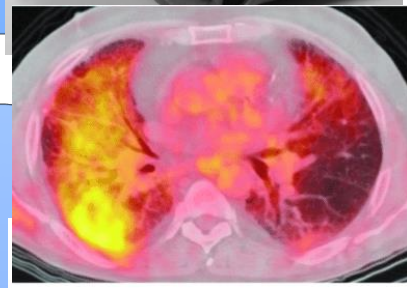
Mechanismen

- Autoantilichamen/celsubsets
- Farmacokinetiek ATG
- Huid
- Urine
- Microbioom



Orgaansystemen

- Longen
- Hart
- Microcirculatie

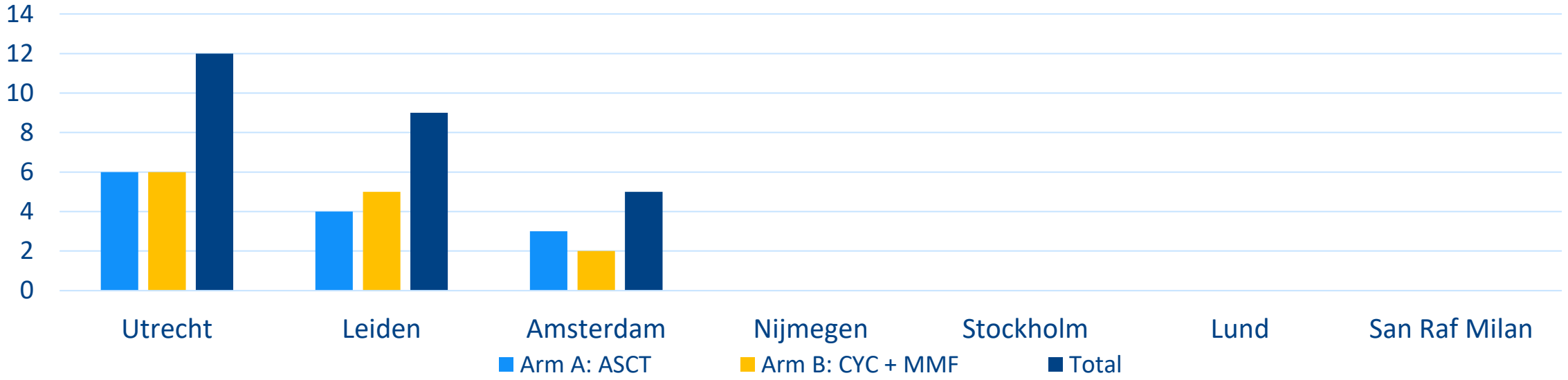


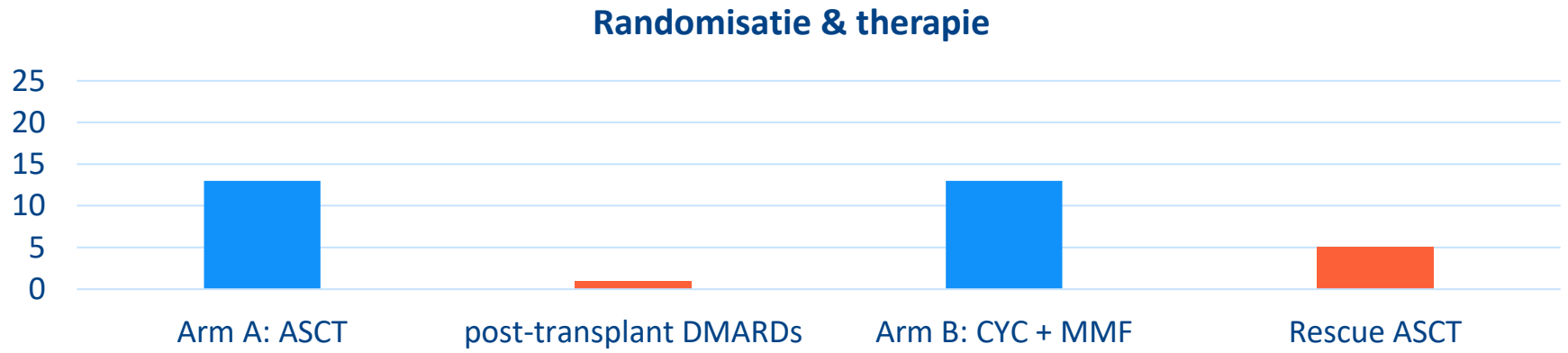
Dagelijks leven

- Handmobiliteit
- Seksuele gezondheid
- Werk
- Vermoeidheid

ReumaNederland

Hoe gaat het?





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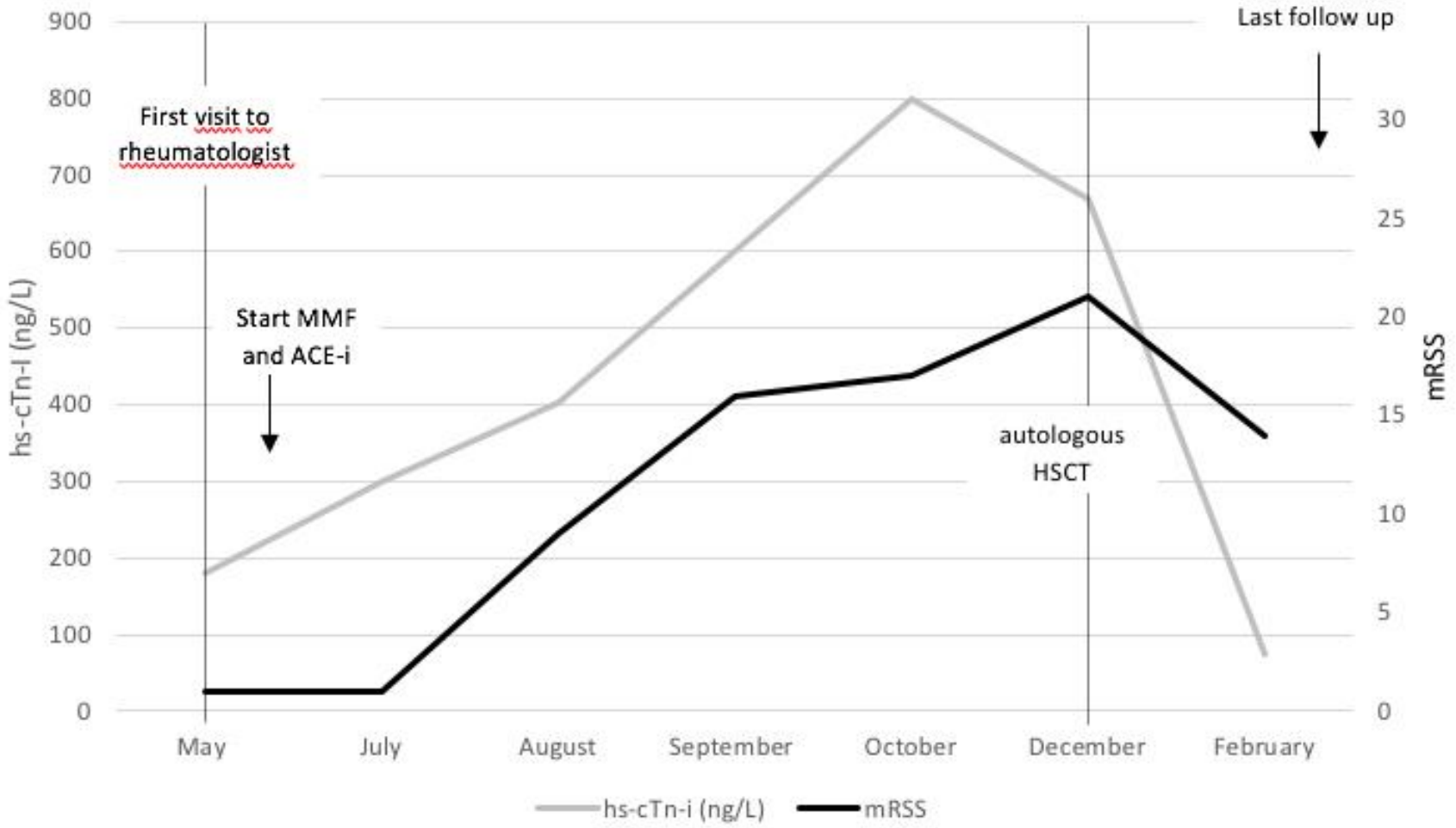
CASUS



Eerste 12m na ASCT

- EBV > PTLD > Rituximab
- Aspergillus longen

Na 3 jaar:

- mRSS 2
- Raynaud+
- Geen andere klachten
- Volledig terug aan het werk

SSc team care & research

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DANK!

Patienten

SSc team UMC Utrecht

(Inter)nationale partners

Financiers

Royal Free London NHS
NHS Foundation Trust

eular
EUROPEAN LEAGUE AGAINST RHEUMATISM

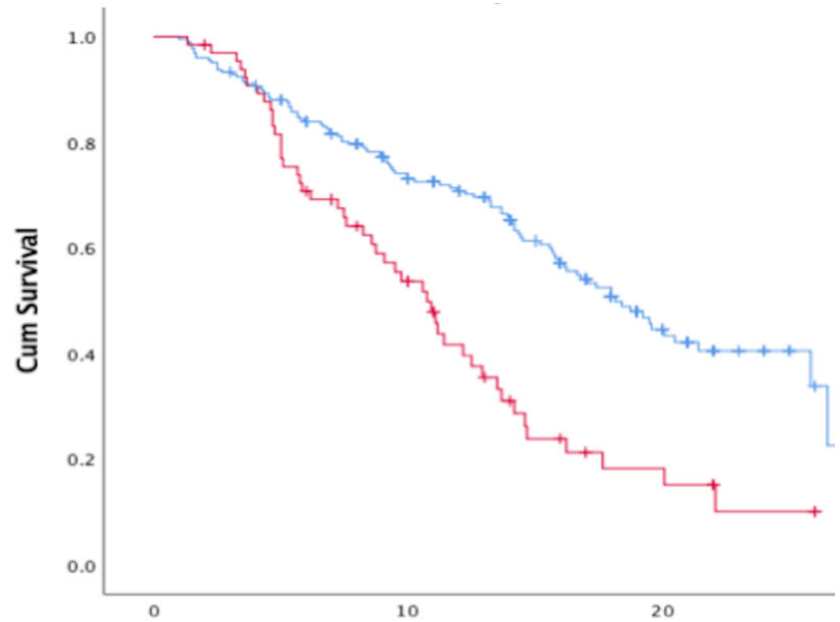

How a
3 Day Fast
Resets the
Immune
System
DrJockers.com
SUPERCHARGE YOUR HEALTH

Patienten uitgesloten voor AHSCT hebben slechtste prognose

- Royal Free Hospital SSc cohort
- Exclusie (n=66) obv leeftijd (>65), DLCO (<40%) of pulmonale hypertensie

Event Free Survival

Kaplan-Meier estimated survival curve



Numbers at risk

Follow-up (yrs)	0	2	5	10	15	20	25
Excluded	65	63	49	27	9	5	1
Eligible	226	217	192	135	88	35	6

NVR KENNISAGENDA 2023

Hoe kunnen patiënten
met **progressieve diffuse cutane systemische sclerose**
die **niet** in aanmerking komen
voor stamceltransplantatie
optimaal worden behandeld?

TOP 10 KENNISHIATEN

Nederlandse Vereniging *voor* Reumatologie

1. Welk algoritme van testen is van toegevoegde waarde op de huidige praktijkvoering voor het vaststellen van de diagnose reuscelarteriitis en monitoring van ziekteactiviteit bij patiënten met deze ziekte?

2. Welke voor andere ziekten bestaande behandelingen zijn effectief en veilig bij artrose en is er een relatie tussen de mate van effectiviteit van deze behandeling en de verschillende fenotypes?

3. Welke klinische en biologische markers voorspellen de behandelrespons in reumatoïde artritis?

4. Wat is de plaats van patient-reported outcome measures bij de behandeling van patiënten met reumatische aandoeningen in de spreekkamer?

5. Welk instrument is het meest geschikt om in de klinische praktijk ziekteactiviteit bij spondyloartritis te meten?

6. Hoe kunnen patiënten met progressieve diffuse cutane systemische sclerose die niet in aanmerking komen voor stamceltransplantatie optimaal worden behandeld?

7. Wat is de plaats van gecombineerde leefstijl interventies bij reumatische aandoening?

8. Wat is de optimale behandelstrategie (medicamenteus en niet-medicamenteus) van axiale en perifere spondyloartritis?

9. Is het zinvol om patiënten met artralgie (zonder artritis) die at risk zijn om reumatoïde artritis te ontwikkelen, te behandelen met DMARDs? En zo ja, bij welke patiënten is dit zo en met welke DMARD ga je dan behandelen?

10. Wat is de optimale interdisciplinaire stepped care benadering van pijn en/of vermoeidheid bij patiënten met reumatische ziekten?

Kennisagenda 2023 Reumatologie (NVR)

Scan bovenstaande QR-code om de Kennisagenda te downloaden.

Subsidies

Samenwerken is een voorwaarde

Uitdagingen

- Systemische auto-immuunziekten zijn zeldzaam
- Kostenbesparing aantonen

Relevantiecriteria (1)

Doelmatigheidswinst
- Gezondheidswinst
- Volume
- Potentiele kostenbesparing

Wegen het zwaarste in de beoordeling

Urgentie
- Toegevoegde waarde
- Praktijkvariatie

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