Εαρινές ημέρες Ρευματολογίας
13-15 Μαΐου 2022
Xenia Poros Image Hotel
ΠΟΡΟΣ

Σύγχρονη αντιμετώπιση φ.Raynaud

Θεοδώρα Σιμοπούλου
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Σύγκρουση συμφερόντων

- Καμία για τη συγκεκριμένη ομιλία

Την τελευταία διετία:

Amgen, Boehringer, Genesis, Elpen, Janssen, Pfizer

Raynaud

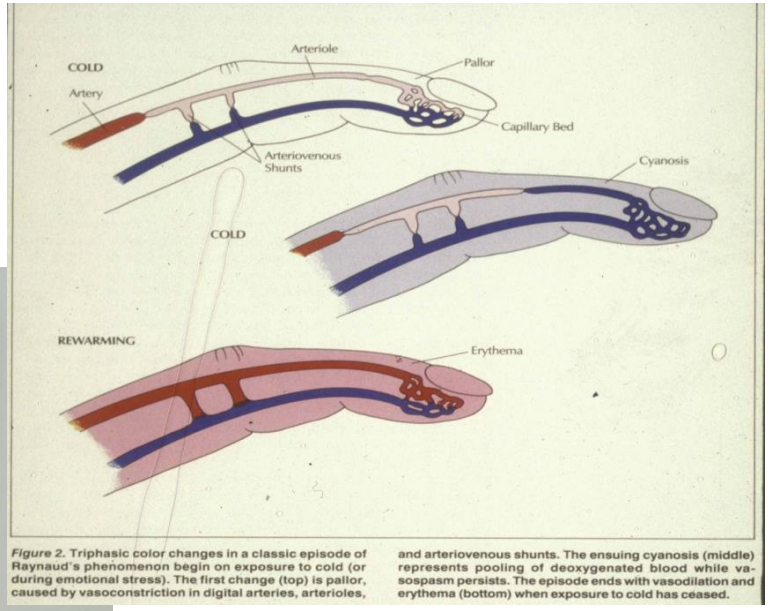


Figure 2. Triphasic color changes in a classic episode of Raynaud's phenomenon begin on exposure to cold (or during emotional stress). The first change (top) is pallor, caused by vasoconstriction in digital arteries, arterioles, and arteriovenous shunts. The ensuing cyanosis (middle) represents pooling of deoxygenated blood while vasospasm persists. The episode ends with vasodilation and erythema (bottom) when exposure to cold has ceased.

- Μεταβολή του χρώματος των δακτύλων (ωχρότητα – κυάνωση - ερυθρότητα), μετά από έκθεση στο κρύο ή συγκινησιακή φόρτιση.
- Συχνά συνοδεύεται με αιμωδίες και πόνο των δακτύλων

Αιτιολογία

Table 1. Main differential diagnosis of (and associations with) Raynaud's phenomenon.

Primary (idiopathic)
Secondary causes:
Connective tissue diseases:
Systemic sclerosis
Mixed connective tissue disease, undifferentiated connective tissue disease and other overlap syndromes
Inflammatory muscle disease
Systemic lupus erythematosus
Sjögren's syndrome
Vasculitis
Hand–arm vibration syndrome ('vibration white finger').
Extrinsic vascular compression (e.g. cervical rib).
Large vessel disease [e.g. atherosclerosis, thromboangiitis obliterans (Buerger's disease)], consider this possibility especially if symptoms are asymmetrical
'Intravascular' diseases associated with increased viscosity and impaired digital microvascular perfusion (e.g. paraproteinaemia, underlying malignancy)
Certain drugs, chemicals or other occupational exposures (e.g. β blockers, ergotamine, clonidine, vinyl chloride)
Other causes or associations (e.g. hypothyroidism)

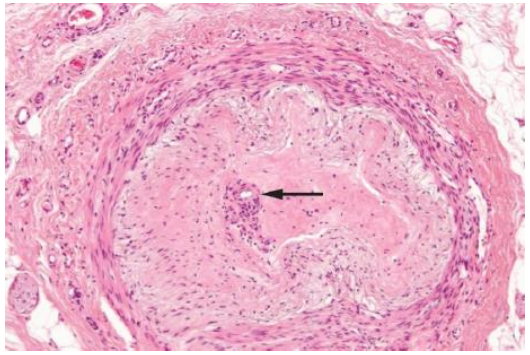
Herrick A. Ther Adv Musculoskel Dis 2017; 9(12): 317–329

Παθογένεια

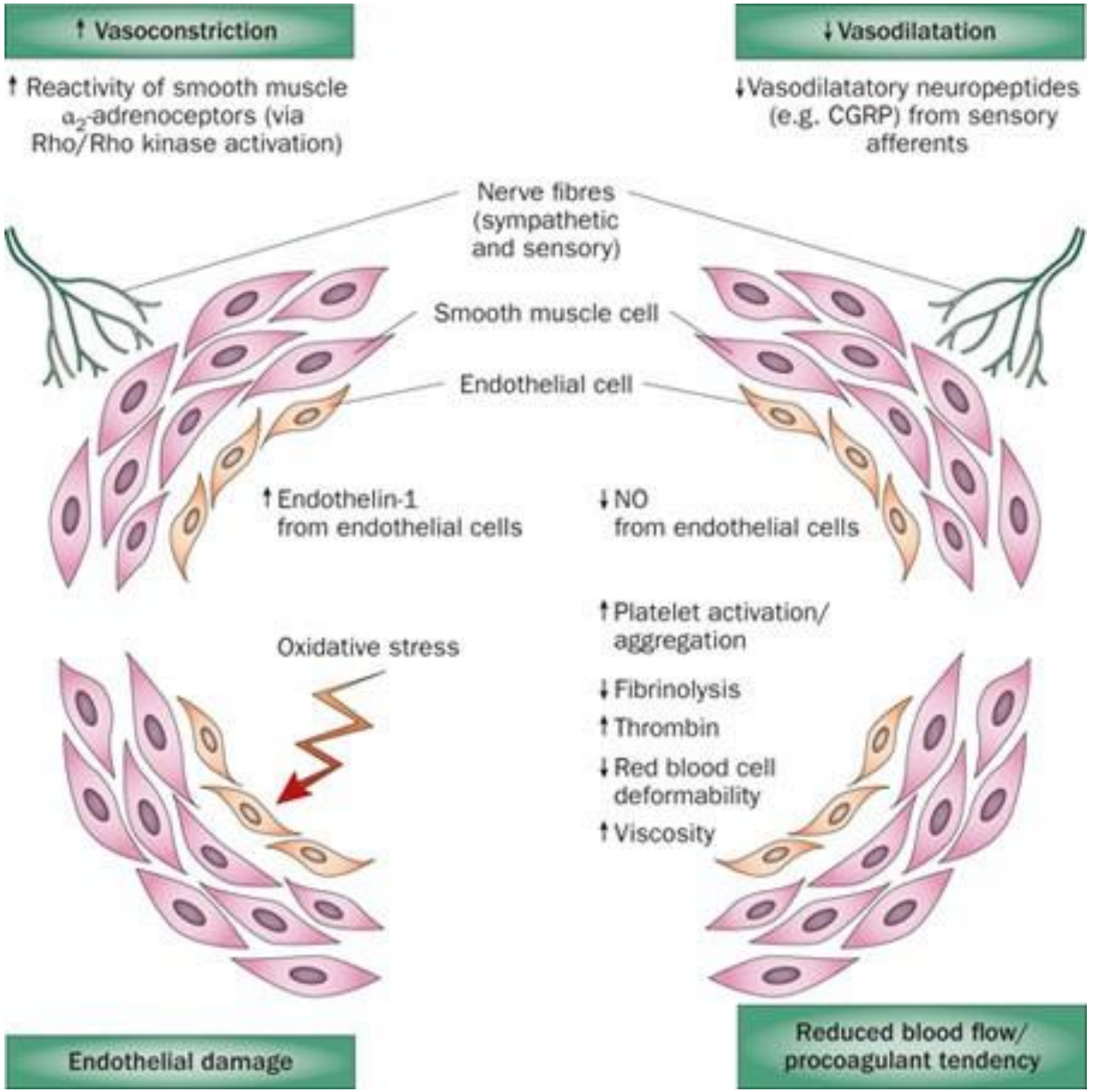
Το πρωτοπαθές Raynaud θεωρείται αμιγώς αγγειοσυσπαστικό φαινόμενο

Το σχετιζόμενο με SSc φαίνεται ότι σχετίζεται με:

- **Δομικές αγγειακές ανωμαλίες**, τόσο στα μικρά τριχοειδικά αγγεία όσο και στο επίπεδο των δακτυλικών αρτηριών



Schematic representation of some of the key elements and mechanisms contributing to the pathogenesis of Raynaud phenomenon.



Herrick A. Nat Rev Rheum 2012; 8: 469-479

Αντιμετώπιση

- Εκπαίδευση ασθενών
- Αποφυγή έκθεσης στο ψύχος και επαφής με παγωμένα αντικείμενα
- Διακοπή καπνίσματος
- Αποφυγή αγγειοσυσπαστικών ουσιών (καφεΐνη, φάρμακα)

- Μη φαρμακευτικά μέτρα
  - Μπορεί να είναι επαρκή για το πρωτοπαθές Raynaud

- Φαρμακευτική θεραπεία
  - Τοπική
  - Από του στόματος
  - Ενδοφλέβια

Μη επιπλεγμένο

Επιπλεγμένο –δακτυλικά έλκη, γάγγραινα

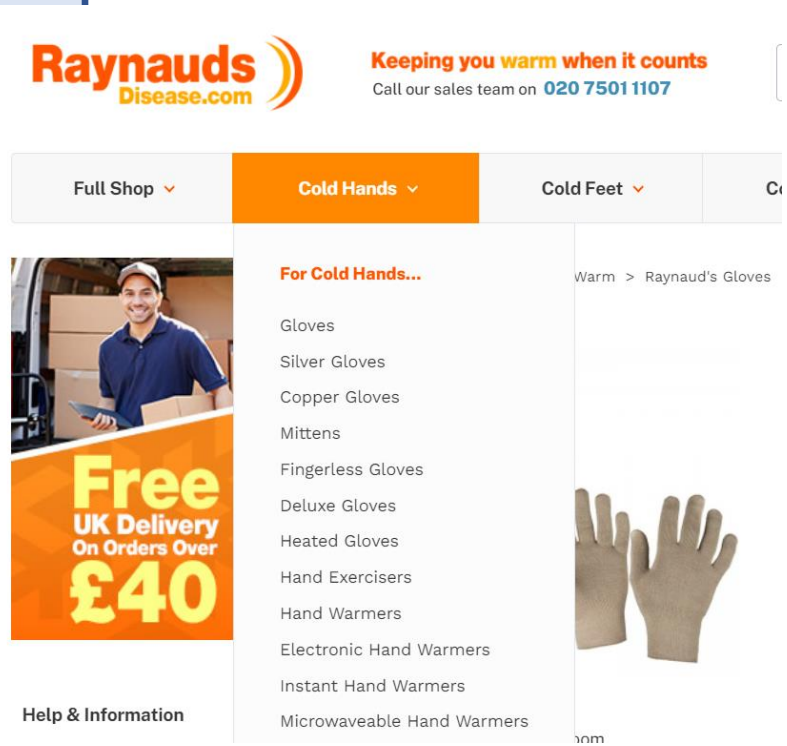


Table 1. Examples of oral drugs most widely used in the treatment of complicated and uncomplicated RP.

Drug or group of drugs	Main mechanism of action/other points to highlight	Examples	Usual dose range
Calcium channel blockers	Act on smooth muscle to cause vasodilation	Nifedipine (sustained release) Amlodipine	10 mg twice daily to 40 mg twice daily 5 mg once daily to 10 mg once daily
Phosphodiesterase type 5 inhibitors	Inhibit degradation of cyclic guanosine monophosphate (and therefore increase nitric oxide effect)	Sildenafil Tadalafil	20 mg/25 mg three times daily to 50 mg three times daily 20 mg alternate days to 20 mg once daily
Angiotensin II receptor blockers	Block action of angiotensin II on vascular smooth muscle	Losartan	25 mg once daily to 100 mg once daily
Alpha-adrenergic blockers	Block vasoconstriction	Prazosin	500 µg twice daily to 2 mg twice daily
Selective serotonin reuptake inhibitors	Block uptake of serotonin, a vasoconstrictor	Fluoxetine	20 mg once daily
Endothelin-1 receptor antagonists	Block action of endothelin-1 on smooth muscle cells. For prevention of recurrent digital ulcers in patients with SSc	Bosentan	62.5 mg twice daily increasing to 125 mg twice daily

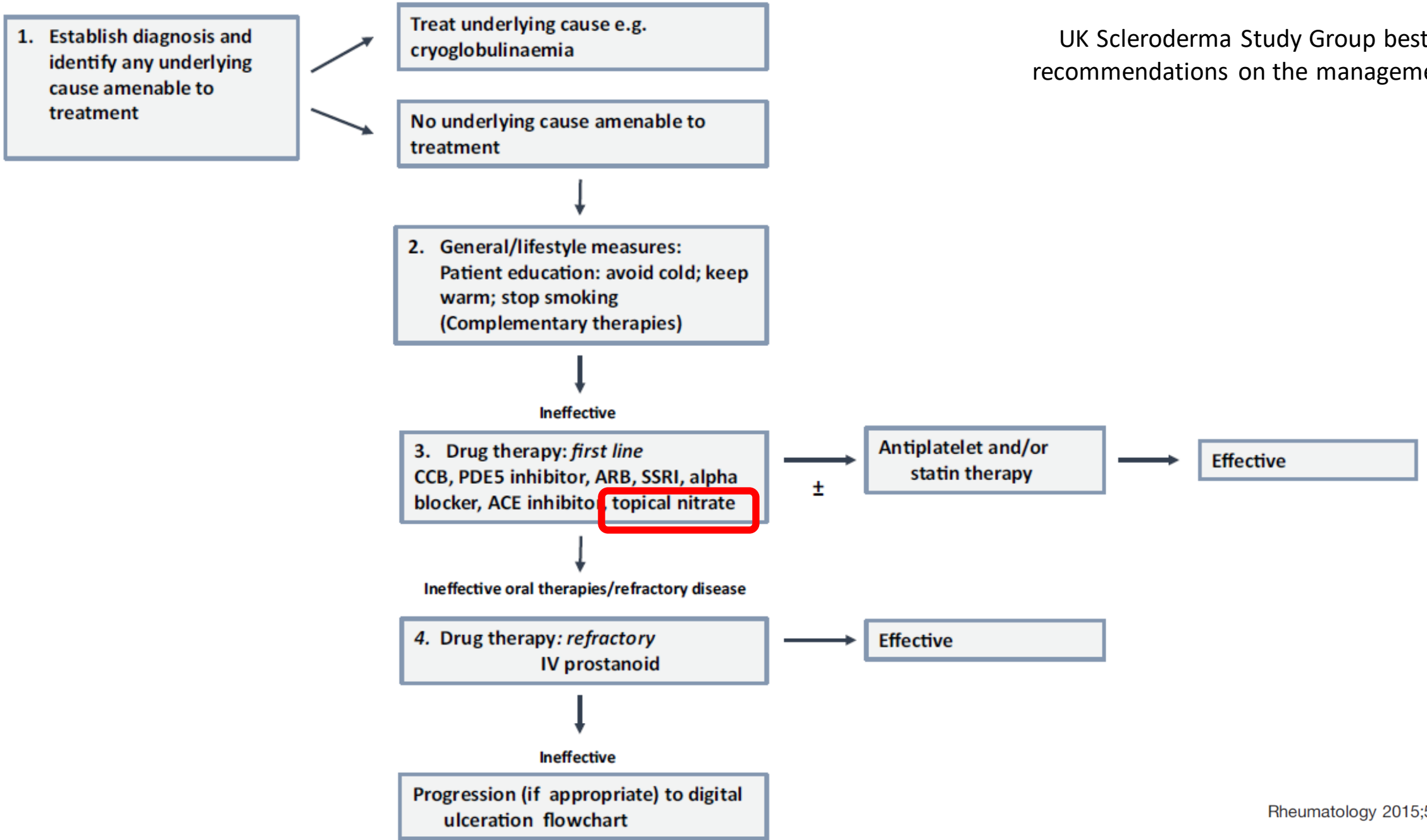
Herrick A. JSRD 2019; 4(2): 89-101

Table 1 The updated EULAR recommendations for treatment of systemic sclerosis, according to the organ involvement, including strength of the recommendations and the results of internal evaluation within the task force group

Organ involvement	Recommendation	Strength of recommendation	Results of internal evaluation
I. SSc-RP	A meta-analysis of RCTs on *dihydropyridine-type calcium antagonists* indicates that nifedipine reduces the frequency and severity of SSc-RP attacks. A meta-analysis of RCTs indicates that *PDE-5 inhibitors* reduce the frequency and severity of SSc-RP attacks. Dihydropyridine-type calcium antagonists, usually oral nifedipine, should be considered as first-line therapy for SSc-RP. PDE-5 inhibitors should also be considered in treatment of SSc-RP.	A	8.19
	A meta-analysis of RCTs on *prostanoids* indicates that *intravenous iloprost* reduces the frequency and severity of SSc-RP attacks. Intravenous iloprost should be considered for severe SSc-RP. Experts recommend that intravenous iloprost should be used for treatment of SSc-RP attacks after oral therapy.	A	8.29
	One small study indicates that *fluoxetine* might improve SSc-RP attacks. Fluoxetine might be considered in treatment of SSc-RP attacks.	C	6.06

Kowal-Bielecka O, *et al*. *Ann Rheum Dis* 2017;**76**:1327–1339.

Management of Raynaud's phenomenon



UK Scleroderma Study Group best practice recommendations on the management of RP

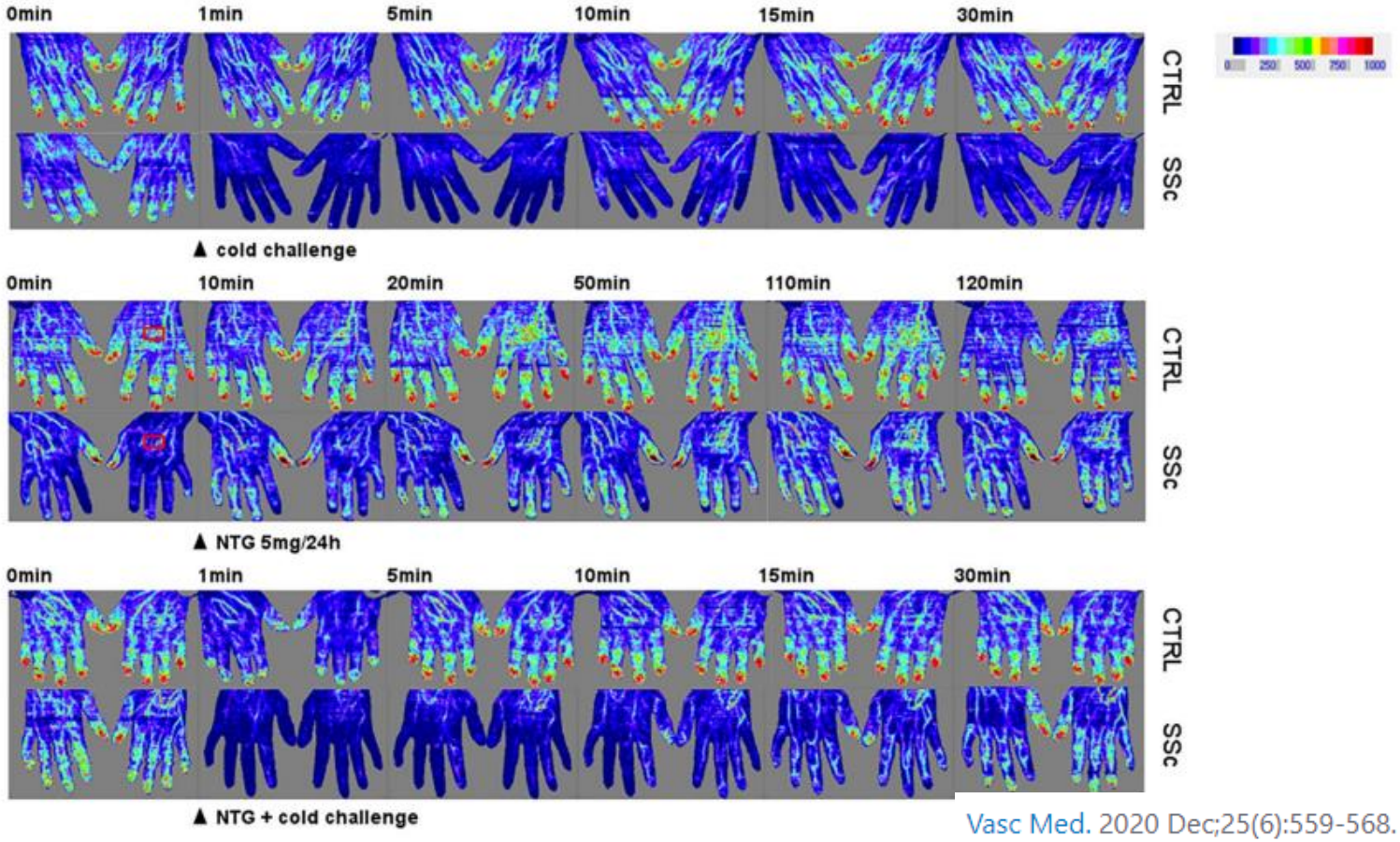
Rheumatology 2015;54:2015–2024

Τοπική θεραπεία σε ασθενείς με SSc

- 21 **ασθενείς με SSc** και 13 εθελοντές
- **NTG patch** (Trinipatch® 5 mg/24 h) εφαρμόστηκε στον καρπό

Εφαρμογή επιθέματος NTG οδήγησε σε **αύξηση της αιματικής ροής** και στη **θερμοκρασία του χεριού** στον ασθενείς με SSc.

Εφαρμογή του NTG οδήγησε σε **ταχύτερη επαναιμάτωση μετά από έκθεση στο ψύχος**.



Vasc Med. 2020 Dec;25(6):559-568.

Τοπική θεραπεία σε ασθενείς με SSc

Χρήση αλοιφής νιτρογλυκερίνης (1-2%) για την αντιμετώπιση πρωτοπαθούς και δευτεροπαθούς φαινομένου Raynaud

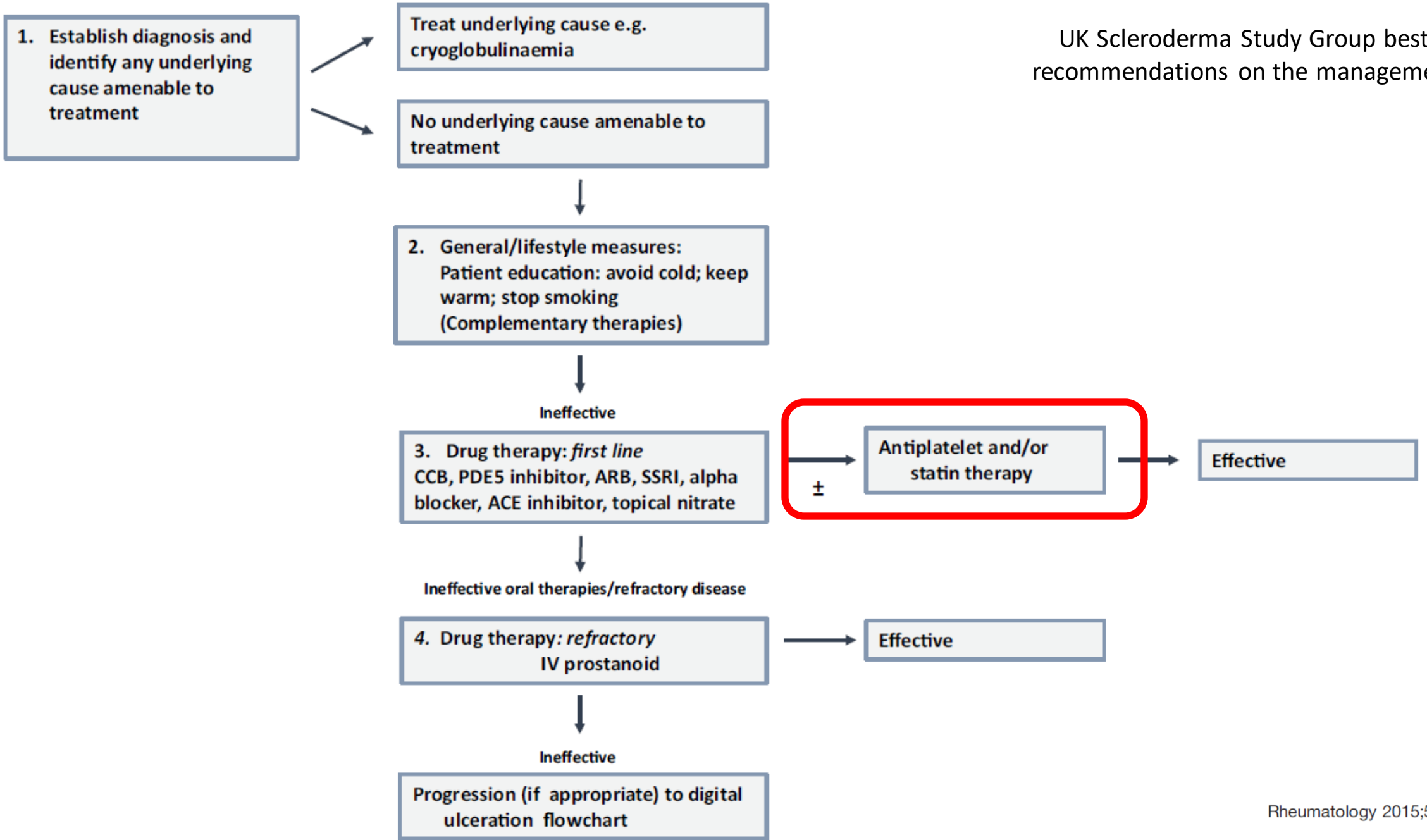
Συστηματική βιβλιογραφική ανασκόπηση

- 7 μελέτες (6 small placebo-controlled clinical trials and one case series)

- Although the included studies used different measures of efficacy, the majority reported **positive responses to nitroglycerin ointment**.

Rheumatol Int. 2018 Dec;38(12):2209-2216.

Management of Raynaud's phenomenon



UK Scleroderma Study Group best practice recommendations on the management of RP

Rheumatology 2015;54:2015–2024

Σιλοσταζόλη

- Εκλεκτικός αναστολέας της φωσφοδιεστεράσης-ΙΙΙ
- Ένδειξη: διαλείπουσα χωλότητα
- Ανασταλτική δράση στη συσσώρευση των αιμοπεταλίων & Αγγειοδιασταλτική δράση

Efficacy of **cilostazol** for the treatment of **Raynaud's** phenomenon in systemic sclerosis patients.

Negrini S, Spanò F, Penza E, Rollando D, Indiveri F, Filaci G, Puppo F.

Clin Exp Med. 2016 Aug;16(3):407-12. doi: 10.1007/s10238-015-0370-5. Epub 2015 Jun 19.

- 21 ασθενείς με SSc (open-label study)
- Cilostazol 100mg x2 για 12 μήνες
- Η χρονική διάρκεια των επεισοδίων καθώς και ο ημερήσιος αριθμός αυτών μειώθηκαν σημαντικά στην ομάδα της σιλοσταζόλης (p = 0.0049 και p = 0.0067, αντιστοίχως).
- Βελτίωση VAS και HAQ
- Έξι ασθενείς δεν ολοκλήρωσαν τη μελέτη λόγω ανεπιθύμητων ενεργειών (κεφαλαλγία 1, αίσθημα παλμών 1, υπόταση 1, ναυτία 1 και ζάλη 2)

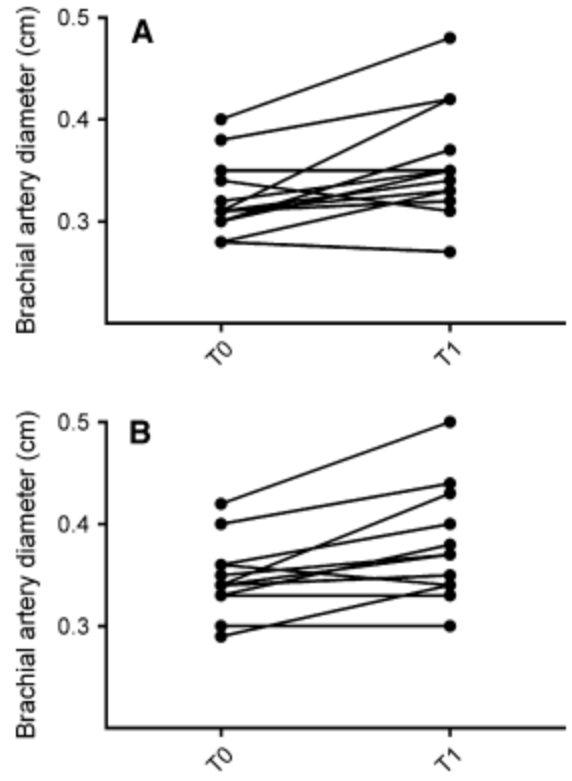


Fig. 3 Effect of cilostazol treatment on brachial artery diameter. Pre-ischemic (*panel A*) and post-ischemic (*panel B*) diameter of brachial artery before (T0) and after (T1) cilostazol treatment (respectively, $p = 0.0119$ and $p = 0.0076$)

Στατίνες

Statins: Potentially Useful in Therapy of Systemic Sclerosis-related Raynaud's Phenomenon and Digital Ulcers

- 84 ασθενείς με SSc; μια ομάδα (n = 56) έλαβε 40 mg/day ατορβαστατίνης για 4 μήνες; οι υπόλοιποι (n = 28) έλαβαν placebo
- Ο συνολικός αριθμός δακτυλικών ελκών ήταν σημαντικά μειωμένος στην ομάδα που έλαβε στατίνη (2.5 νέα έλκη/ασθενή στο εικονικό φάρμακο, 1.6 στην ομάδα της στατίνης
- Στατιστικά σημαντική βελτίωση στο SHAQ-DI, στην κλίμακα του πόνου και στη βαρύτητα των δακτυλικών ελκών (statin vs placebo).

J Rheumatol. 2008 Sep;35(9):1801-8.

Review > Semin Arthritis Rheum. 2016 Jun;45(6):698-705. doi: 10.1016/j.semarthrit.2015.10.013. Epub 2015 Nov 2.

A review of the effects of statins in systemic sclerosis

Karim Ladak [1], Janet E Pope [2]

Βιβλιογραφική ανασκόπηση (18/404 σχετικές μελέτες)
Κλινική βελτίωση στις σχετιζόμενες με SSc αγγειακές επιπλοκές .
Σχετική ασφάλεια και καλή ανοχή στους ασθενείς με SSc.

Box 1 Research agenda

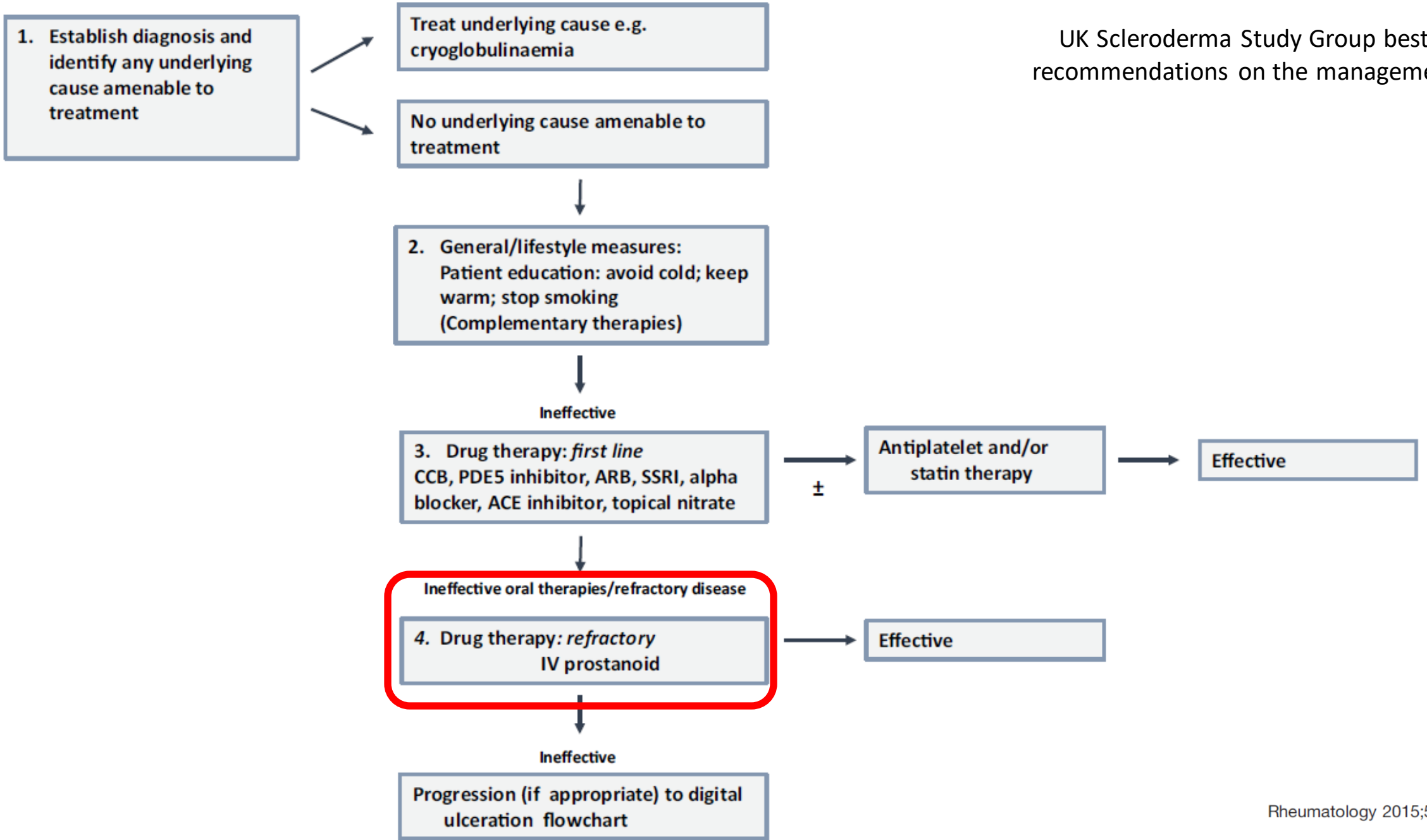
1. Evaluation of the efficacy and safety of cyclophosphamide in the treatment of early diffuse SSc
2. Evaluation of the efficacy and safety of mycophenolate mofetil and azathioprine in the treatment of SSc
3. Evaluation of the efficacy and safety of anti-CD20 therapies in the treatment of SSc
4. Evaluation of calcium antagonists in the prevention of SSc-PAH
5. Evaluation of calcium antagonists in the treatment of digital ulcers in SSc
6. Evaluation of statins in the treatment of digital ulcers in SSc
7. Evaluation of the efficacy and safety of ACE inhibitors in the prevention of SRC
8. Evaluation of the efficacy of non-pharmacological treatments in SSc

PAH, pulmonary arterial hypertension; SRC, scleroderma renal crisis; SSc, systemic sclerosis.

Kowal-Bielecka O, *et al*. *Ann Rheum Dis* 2017;**76**:1327–1339.

- Αντιμετώπιση ανθεκτικού & επιπλεγμένου Raynaud
  - Δακτυλικά έλκη
  - Ιστική νέκρωση

Management of Raynaud's phenomenon



UK Scleroderma Study Group best practice recommendations on the management of RP

Rheumatology 2015;54:2015–2024

Table 1 The updated EULAR recommendations for treatment of systemic sclerosis, according to the organ involvement, including strength of the recommendations and the results of internal evaluation within the task force group

Organ involvement	Recommendation	Strength of recommendation	Results of internal evaluation
II. Digital ulcers in patients with SSc	Two RCTs indicate that *intravenous iloprost* is efficacious in healing digital ulcers in patients with SSc. Intravenous iloprost should be considered in the treatment of digital ulcers in patients with SSc.	A	8.39
	A meta-analysis of RCTs and results of an independent RCT indicate that *PDE-5 inhibitors* improve healing of digital ulcers in patients with SSc. Moreover, the results of one small RCT indicate that PDE-5 inhibitors may prevent development of new digital ulcers in SSc. PDE-5 inhibitors should be considered in treatment of digital ulcers in patients with SSc.	A	8.03
	Bosentan has confirmed efficacy in two high-quality RCTs to reduce the number of new digital ulcers in patients with SSc. Bosentan should be considered for reduction of the number of new digital ulcers in SSc, especially in patients with multiple digital ulcers despite use of calcium channel blockers, PDE-5 inhibitors or iloprost therapy.	A	8.19

Kowal-Bielecka O, *et al*. *Ann Rheum Dis* 2017;**76**:1327–1339.

Semin Arthritis Rheum. 2019 Feb;48(4):686-693. doi: 10.1016/j.semarthrit.2018.03.019.
Epub 2018 Apr 4.

Practical suggestions on intravenous iloprost in Raynaud's phenomenon and digital ulcer secondary to systemic sclerosis: Systematic literature review and expert consensus

Francesca Ingegnoli [1], Tommaso Schioppo [2], Yannick Allanore [3], Roberto Caporali [4], Michele Colaci [5], Oliver Distler [6], Daniel E Furst [7], Nicolas Hunzelmann [8], Florenzo Iannone [9], Dinesh Khanna [10], Marco Matucci-Cerinic [11]

- IV ILO is most commonly administered at a dosage between 0.5 and 2 ng/kg/min for 6-8 hours
- Data about IV ILO duration and frequency are less clear.

Digital ulcers healing

- Therapy should be administered for 1-3 days every month.

Digital ulcers prevention

- iv ILO should be administered one day every month.

Raynaud's phenomenon

- IV ILO can be useful in severe RP or RP refractory to CCB and PDE-5i. To control RP symptoms, it should be administered 1-3 days every month.

Locoregional Treatments for Digital Ulcers in Systemic Sclerosis: A Systematic Review

- A total of 58 studies were included

- Promising results:
  - Botulinum toxin
  - Injections of fat-derived cells

- Disappointing results:
  - Sympathectomy

- Conflicting results:
  - hyperbaric oxygen therapy
  - phototherapy (ultraviolet A)
  - low-level light therapy
  - intermittent compression
  - Waon therapy
  - extracorporeal shockwave
  - vitamin E gel
  - topical dimethyl sulphoxide

Acta Derm Venereol. 2021 Jun 22;101(6):adv00478.

What's new?

Warming Cold Hands: A New Treatment for Raynaud's Syndrome

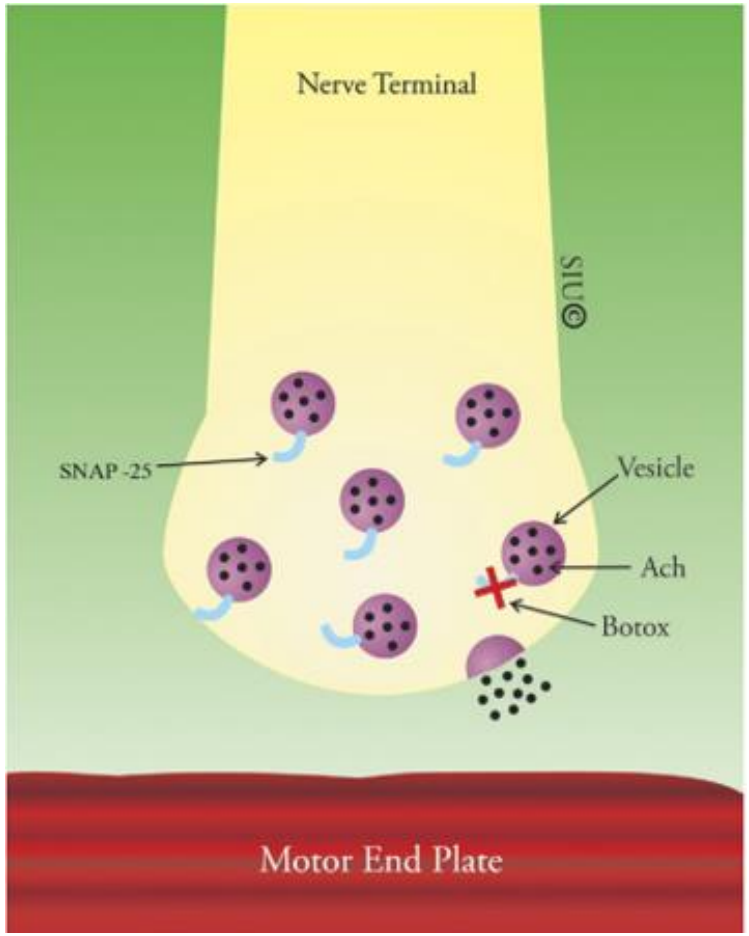
UVA Health is one of the first hospitals in the country to offer a revolutionary treatment technique for severe Raynaud's syndrome. *Image-guided botox injections performed by radiologists can help fight against the symptoms of Raynaud's disease for up to 6 months.*

Treat Your Cold Fingers and Toes at UVA Health

If you or a loved one is dealing with severe symptoms of known or suspected Raynaud's Disease, ask you care provider about image-guided Botox injections performed by UVA Radiologists. Contact the **UVA Hand Center** at 434.982.4263 to schedule a consultation with Dr. Brent DeGeorge. Or contact UVA Musculoskeletal Radiology directly at 434.243.0391.

Botulinum toxin – μηχανισμός δράσης

- Η δράση της αλλαντοτοξίνης έγκειται στην αποτροπή της απελευθέρωσης ακετυλοχολίνης μέσω της αναστολής του πεπτιδίου SNAP-25 (synaptosomal-associated protein, 25kDa).
- Η απουσία ακετυλοχολίνης έχει ως αποτέλεσμα την παράλυση των μυών, συμπεριλαμβανομένων και των λείων μυικών ινών των δακτυλικών αρτηριών.
- Η έναρξη της παράλυσης τυπικά εμφανίζεται 1 – 4 ημέρες μετά την έκθεση στην τοξίνη και παραμένει για 2-4 μήνες, όσος είναι και ο χρόνος που απαιτείται για την επανασύνθεση του απενεργοποιημένου SNAP-25



The toxin's interaction with skeletal muscle involves the binding of SNAP-25 proteins responsible for acetylcholine vesicular transport and release at the presynaptic end of the neuromuscular junction, resulting in temporary muscular paralysis

Table III. Toxin botulinum injection for treatment of digital ulcers (DUs) in systemic sclerosis (SSc)

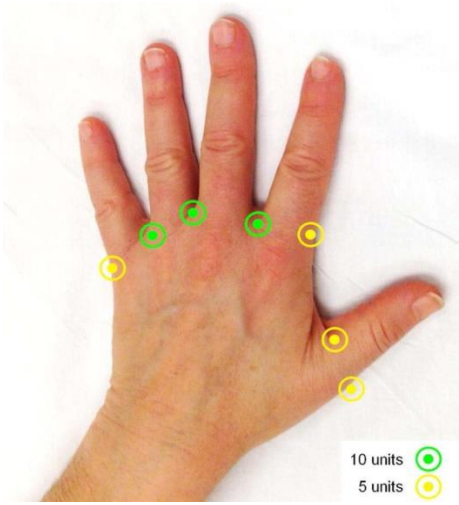
Reference	Patients *n*	Study design	Results
Bello et al. 2017 (9)	40	Double-blind RCT	Placebo-controlled trial, 50 IU of BT-A No significant reduction in DUs at 1 month ($p=0.697$) and 4 months ($p=0.572$), likewise or VAS ($p=0.121$ and $p=0.585$, respectively
Motegi et al. 2017 (10)	45	Single-blind RCT	Control group, and 3 treatment groups, using 250, 1,000 or 2,000 IU of BT-B Significant reduction in DUs and VAS at week 16 ($p<0.01$)
Serri et al.2013 (26)	18	Uncontrolled cohort	100 IU of BT-A Complete healing at 3 months Reduction in VAS: mean 6 at baseline, 2 at month 3
Uppal et al. 2014 (27)	20	Uncontrolled cohort	100 IU of BT-A Complete healing among 3 patients in 4 in 60 days No significant reduction in VAS
Fregene et al. 2009 (29)	7 SSc/MCTD among 26 patients	Retrospective cohort	100 IU of BT-A Complete healing among 11 patients in 60 days Follow-up between 1 and 45 months
Medina et al. 2018 (28)	9 SSc among 15 patients	Retrospective cohort	24 to 48 IU of BT-A Significant reduction in VAS ($p<0.005$)
Motegi et al. 2016 (30)	10	Case series	10 IU of BT-A Complete healing in all patients with at month 12 Iloprost as additional treatment Decrease of VAS from a mean of 10 to 2
Van Beek et al. 2006 (31)	10 SSc/MCTD among 11 patients	Case series	40 to 50 IU of BT-A Complete healing of all small DUs Iloprost as additional treatment Reduction in VAS
Souk et al. 2019 (33)	2	Case report	10 IU of BT-A Complete healing in 5weeks for the 1st patient and 7 for the 2nd one
Motegi et al. 2018 (32)	2	Case report	1,600 IU of BT-B Complete healing in 16 and 24 weeks Reduction in VAS from 10 in both patients to 1 and 2
Blaise et al. 2017 (35)	1	Case report	20 IU of BT-A Complete healing in 16 weeks Reduction in VAS
Berk-Krauss et al. 2018 (34)	1	Case report	100 IU of BT-A Partial healing

RCT: randomized controlled trial; VAS: visual analogue scale; MCTD: mixed connective tissue disease; BT: botulinum toxin; IU: International Unit.

Randomized Controlled Trial > Arthritis Rheumatol. 2017 Aug;69(8):1661-1669.
doi: 10.1002/art.40123. Epub 2017 Jun 26.

The Therapeutic Efficacy of Botulinum Toxin in Treating Scleroderma-Associated Raynaud's Phenomenon: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

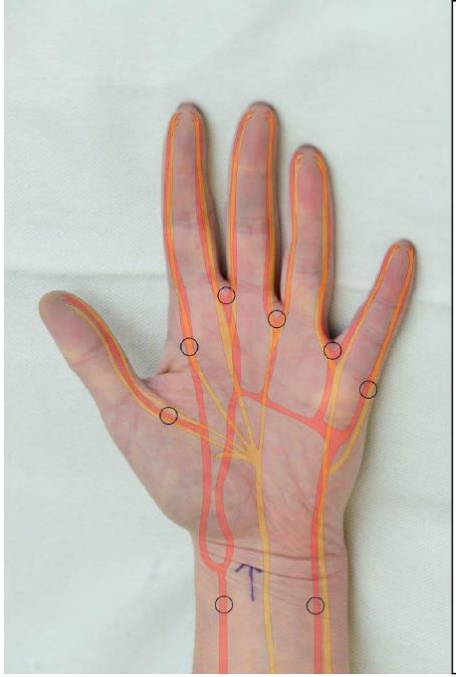
Ricardo J Bello [1], Carisa M Cooney [1], Eitan Melamed [1], Keith Follmar [1], Gayane Yenokyan [1], Gwendolyn Leatherman [1], Ami A Shah [1], Fredrick M Wigley [1], Laura K Hummers [1], Scott D Lifchez [1]



- 40 patients (25 limited SSc, 15 diffuse)
- Btx-A (50 units in 2.5 ml sterile saline) in one randomly selected hand and sterile saline (2.5 ml) in the opposite hand.
- From baseline to 1-month follow-up, there was a greater reduction in average blood flow in Btx-A-treated hands compared to placebo-treated hands.
  - The model estimated that this difference was statistically significant (average difference -30.08 flux units [95% confidence interval -56.19, -3.98], P for interaction = 0.024).
  - This difference was mainly influenced by patients with longstanding RP and diffuse scleroderma.
- Change in blood flow at 4-month follow-up was not significantly different between groups.
- Clinical measures (QuickDASH, McCabe Cold Sensitivity Score, pain on a visual analog scale, and Raynaud's Condition Score) improved slightly for Btx-A-treated hands.

Conclusion: Our data do **not** support using Btx-A to treat RP in all scleroderma patients. The secondary clinical outcomes suggest some positive effect, but its clinical meaningfulness is questionable. The role of Btx-A in treating RP should be further studied with more homogeneous patient populations and in unique clinical situations such as acute digital ischemia.

Targeted high concentration botulinum toxin A injections in patients with Raynaud's phenomenon: a retrospective single-centre experience



1. Patient's hand showing signs of Raynaud's phenomenon.

2. Neurovascular structures of the hand illustrated.

3. Black Circles indicate the standard BTX-A Injection sites used.

4. Additional injection sites at the wrist level, in the vicinity of radial and ulnar artery in patients with severe vasospastic symptoms.

- Botox 100 units in 2.0 mL of sterile normal saline
- 11 patients, 3 primary RP, 8 secondary RP (SSc)
- 30 treatment episodes, over a period of 7½ years
- The primary site of BTX-A injection was at the base of the digit around the palmar digital neurovascular bundle.

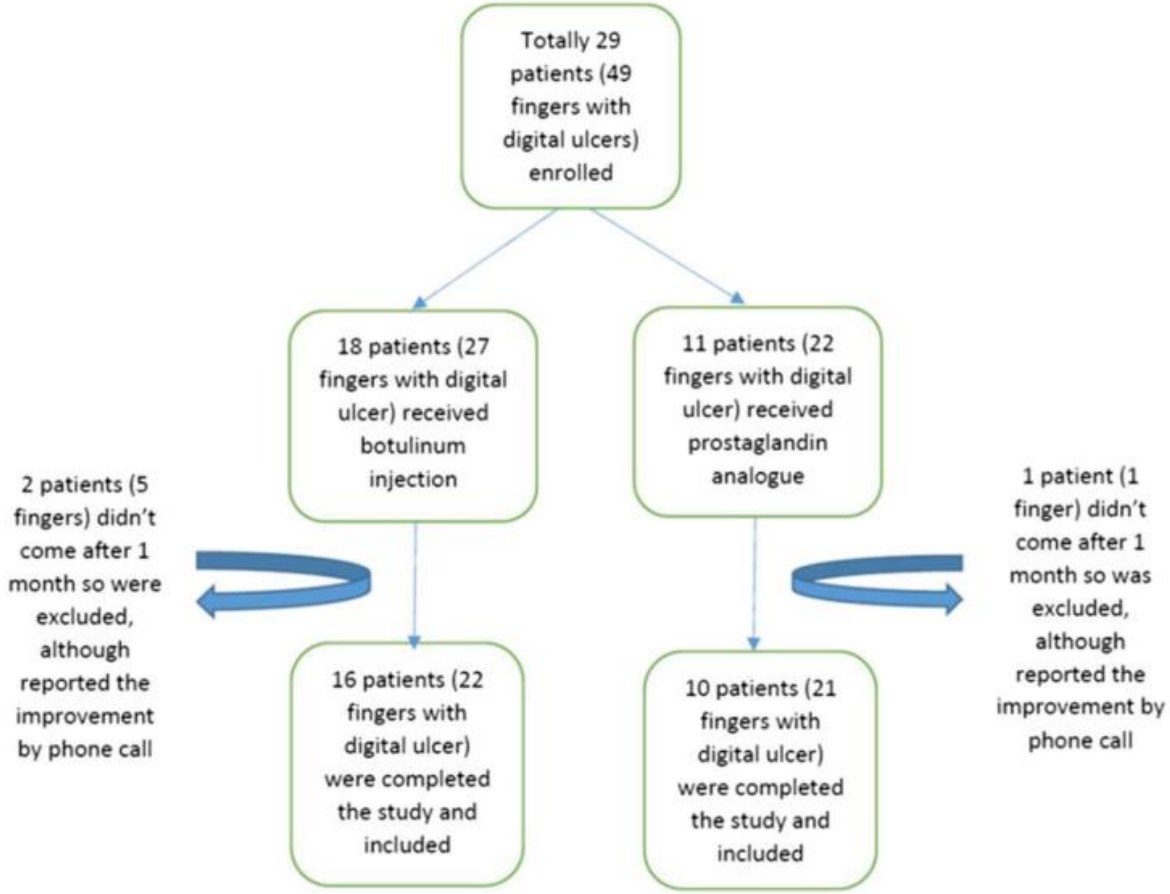
- All patients reported an improvement in symptoms and healing of digital ulcers.
- One patient reported a temporary muscle weakness.
- SSc patients had an average of 6-month interval between treatment episodes.

Clinical Rheumatology (2022) 41:95–104
https://doi.org/10.1007/s10067-021-05900-7

ORIGINAL ARTICLE

A 4-week comparison of capillaroscopy changes, healing effect, and cost-effectiveness of botulinum toxin-A vs prostaglandin analog infusion in refractory digital ulcers in systemic sclerosis

- 20 units BTX-A, στη βάση κάθε δακτύλου.
- 20 μg iloprost (3d).



Clinical Rheumatology (2022) 41:95–104
https://doi.org/10.1007/s10067-021-05900-7

ORIGINAL ARTICLE

A 4-week comparison of capillaroscopy changes, healing effect, and cost-effectiveness of botulinum toxin-A vs prostaglandin analog infusion in refractory digital ulcers in systemic sclerosis

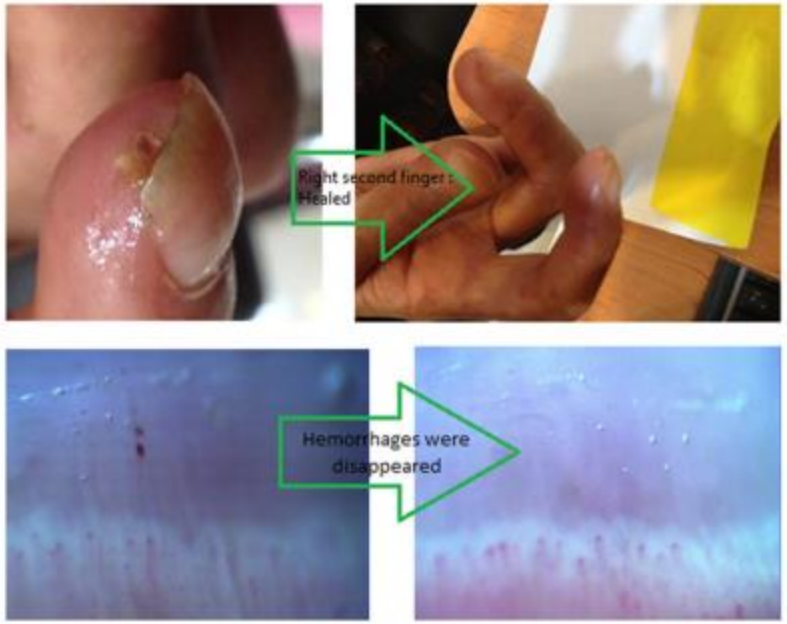


Fig. 2 Sample digital ulcer healing effect of botulinum toxin-A in a patient with scleroderma and capillaroscopy changes in another patient before and after 1 month

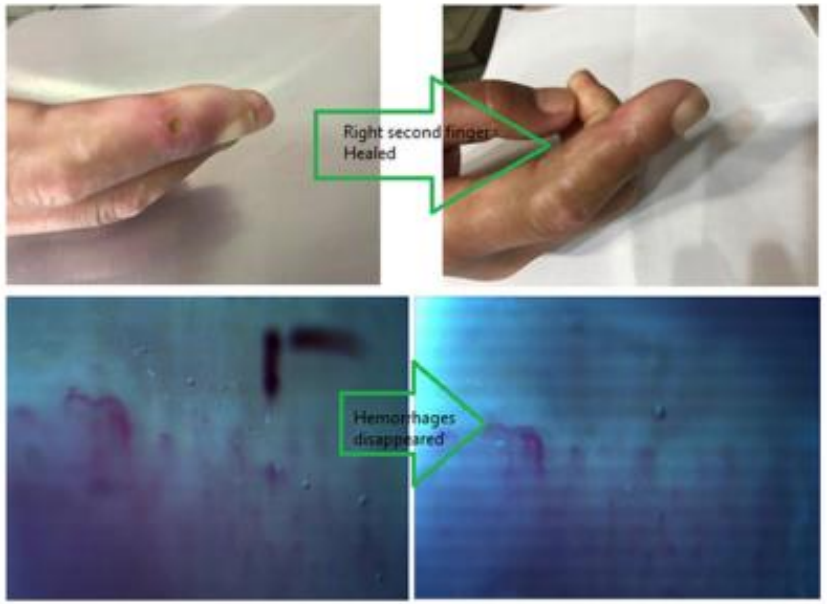
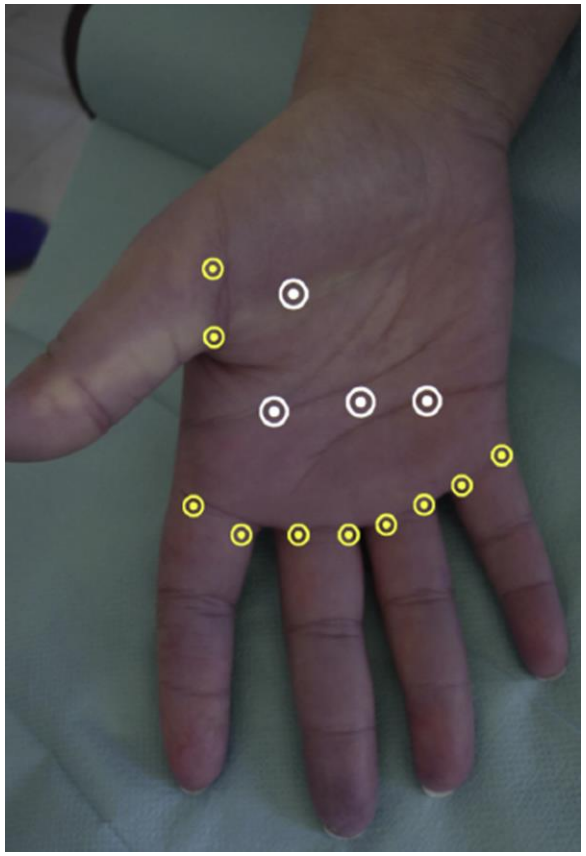


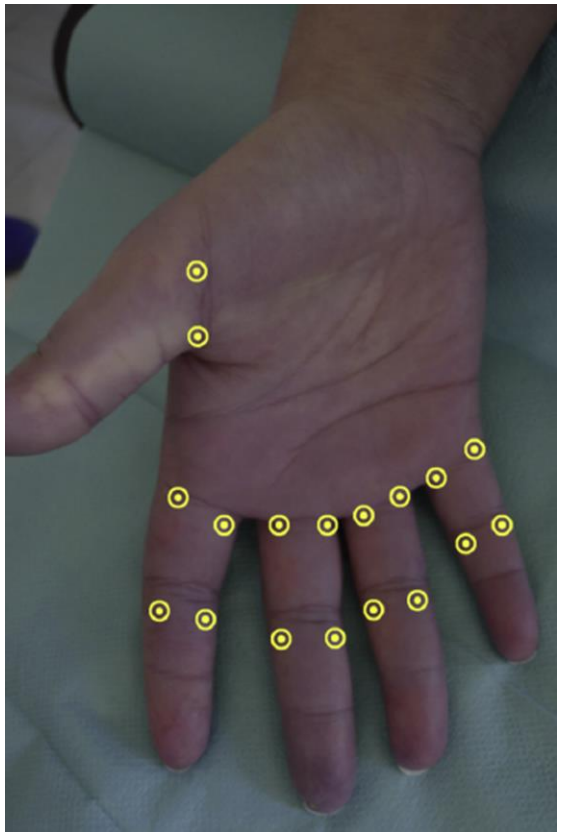
Fig. 3 Sample digital ulcer healing effect of prostanoid infusions in a patient with scleroderma and capillaroscopy changes in another patient 1 month after treatment

- Both BTX-A and prostaglandin analogs contributed to healing of digital tip ulcers and improving the pain
- In capillaroscopy, microhemorrhages were significantly decreased or disappeared after treatment
- No significant side effect in both groups
- In the BTX-A group, the cost was significantly lower when performed on an outpatient treatment and was more time-saving.

Injection protocol

- Digital
- Palmar
  - palmar injections are painful and may require sedation
  - intrinsic muscle paralysis in some patients





Journal of the American Academy of Dermatology 2020 83e409-e410DOI: (10.1016/j.jaad.2020.02.085)

Αντενδείξεις

TABLE 2. Contraindications to Treatment of RP With Botulinum Toxin*

Contraindications
Allergy to botulinum toxin A
Pregnancy or breastfeeding
Active infection
Coadministration with medications that decrease neuromuscular transmission (penicillamine, aminoglycosides, licoamides, polymixins, magnesium, anticholinesterases, succinylcholine, quinidine)

*Myasthenia gravis is described as a relative contraindication.

Περιοχική μεταμόσχευση αυτόλογου λιπώδους ιστού

- Ο λιπώδης ιστός αποτελεί τον συχνότερα χρησιμοποιούμενο ιστό ως filler για την αντιμετώπιση ιστικών ελλειμμάτων.

- Οι θεραπευτικές δράσεις του αυτόλογου μοσχεύματος λίπους επεκτείνονται και σε επουλωτικές ικανότητες και αγγειογενετικές δράσεις

- Αυτές αποδίδονται στα αδιαφοροποίητα προγονικά κύτταρα (undifferentiated adipose-derived stem cells, ADSCs).

Table II. Loco-regional implantation of adipose tissue-derived cells for treatment of digital ulcers (DUs) in systemic sclerosis

Reference	Patients *n*	Study design	Results
Bene et al. 2014 (25)	9 (15 DUs)	Uncontrolled cohort	Reduction in pain (allowing a reduction in analgesics) in 7 of 9 patients Complete healing of 10//15 DUs at 3 months
Del Papa et al. 2015 (22)	15 (15 DUs)	Uncontrolled cohort	Reduction in the VAS score at 1 month and 6 months ($p < 0.001$) Complete healing of 15/15 DUs and no recurrence at 6 months Increased number of capillaries at 1 month ($p < 0.0002$) and 6 months ($p < 0.0001$)
Faggioli et al. 2015 (24)	9 (10 DUs)	Uncontrolled cohort (*congress abstract*)	Complete healing of 6/10 DUs at 1 month
Bank et al. 2014 (23)	11 (14 DUs)[a]	Uncontrolled cohort	Pain results not interpretable because 2 patients with primary RP were included. Complete healing of 14/27 DUs (the healing assessment date is not specified in the article)
Granel et al. 2015 (20)	12 (15 DUs)	Uncontrolled cohort	Decrease in the VAS of 41.7% from the baseline at 6 months ($p = 0.001$) Complete healing of 8/15 DUs at 6 months Capillaroscopy evaluation showed no significant change in the number of nail-fold capillary loops from baseline to 6 months
Daumas et al. 2017 (21)	12 (15 DUs)[b]	Uncontrolled cohort	At 24 months, a 33.1% decrease in the VAS score from baseline Complete healing of 9/15 DUs at last visit (>24 months)
Del Papa et al. 2019 (8)	38 (38 DUs)	RCT	Placebo controlled-trial Reduction in the VAS score after 4 and 8 weeks ($p < 0.0001$) Complete healing of 23/25 DUs after fat graft and 1/13 after the same procedure at 8 weeks ($p < 0.0001$). Increase in capillary numbers in the affected finger after 4 and 8 weeks ($p < 0.0001$)

[a]Exclusion of patients with primary Raynaud phenomenon (RP). [b]Patients included in Granel's study → long-term follow-up (22–30 months after treatment)
RCT: randomized controlled trial; VAS: visual analogue scale.

Autologous Fat Grafting for Scleroderma-Induced Digital Ulcers. An Effective Technique in Patients with Systemic Sclerosis

Autologe Fettransplantation für Skleroderma verursachte Finger Ulzera. Eine effektive Technik für Patienten mit Systemische Sklerodermie

- 9 patients (15ulcers)
- Complete healing occurred in 10 DUs and size reduction ≥50% in 2, within 8-12 weeks.

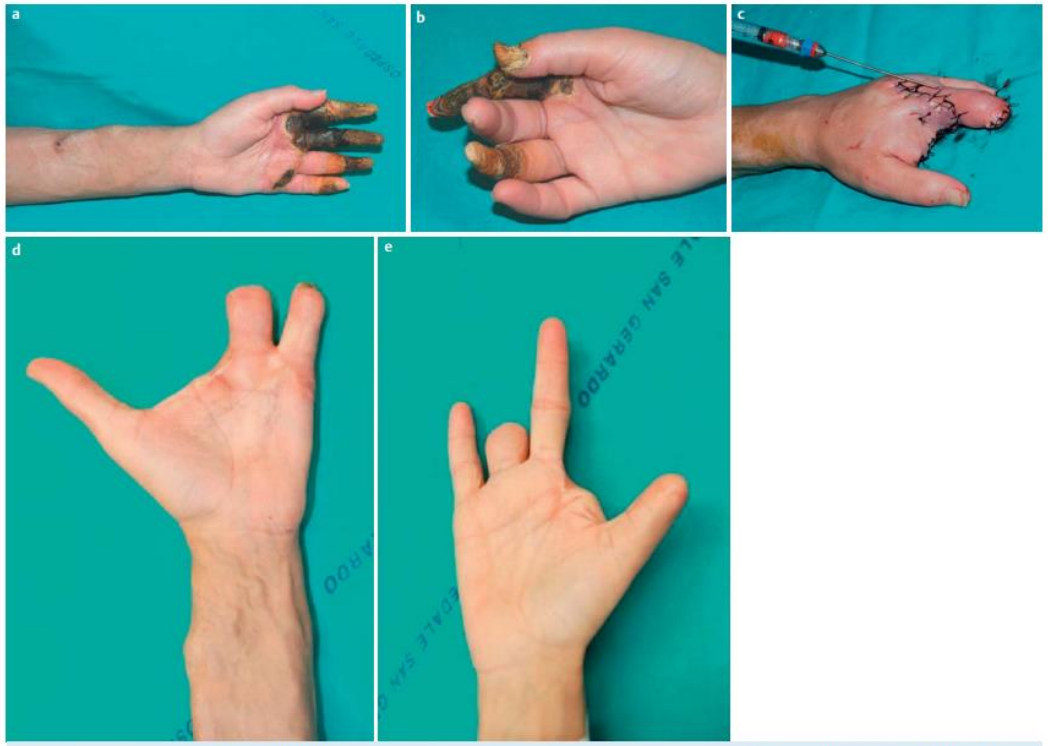


Fig. 1 Appearance of digital ulcers on both hands in patient with systemic sclerosis (SSc) with severe necrosis **a**, **b**. Intra- and postoperative pictures show the result after autologous fat grafting and finger amputation **c–e**.

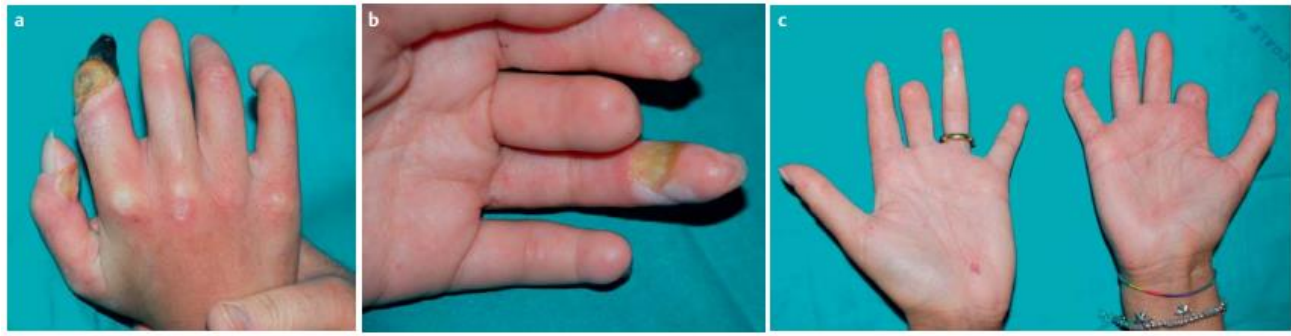


Fig. 2 Changes in appearance of a digital ulcer in a patient with SSc before **a**, **b** and after fat grafting **c**-

Handchir Mikrochir Plast Chir. 2014 Aug;46(4):242-7.

Fat Grafting to the Hand in Patients with Raynaud Phenomenon: A Novel Therapeutic Modality

- 13 patients were treated (21 hands).
  - 12 patients had undergone prior botulinum toxin injection, and 11 patients had prior sympathectomies.

- reduced pain (average reduction, 6.86 of 10 to 2.38 of 10),
- fewer cold attacks
- improved skin and soft-tissue texture
- decrease in ulcerations
- patient-reported improved function
- Three patients had no changes.
- There were no major complications.

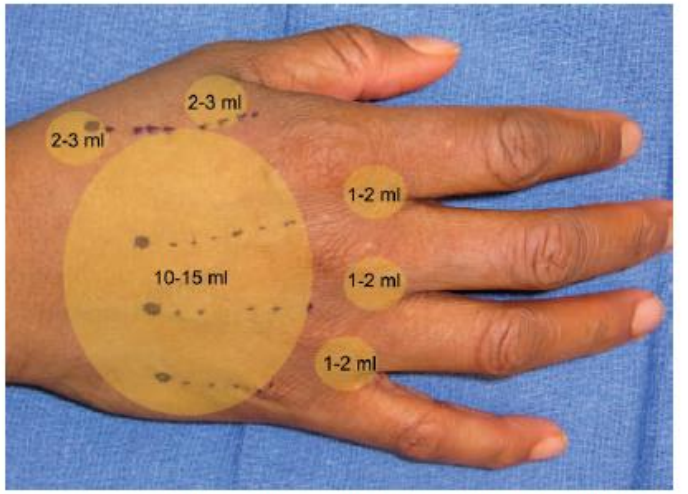


Fig. 1. Fat grafting to the dorsum of the hand. Stab incisions are made, and blunt cannulae are used to introduce small aliquots of fat for a total of 10 to 15 ml in the dorsum of the hand; 2 to 3 ml in the snuffbox; 1 to 2 ml in each dorsal webspace.

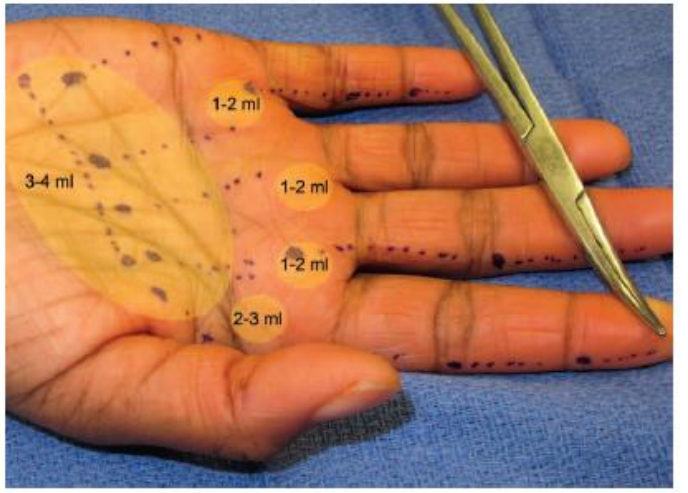


Fig. 2. Fat grafting to the palm of the hand. Using a technique similar to that used for the dorsum of the hand, fat is grafted for a total of 3 to 4 ml along the superficial palmar arch; 1 to 2 ml in volar webspaces 2 to 4; and 2 to 3 ml in the first webspace.

Plast Reconstr Surg. 2014 May;133(5):1109-1118.

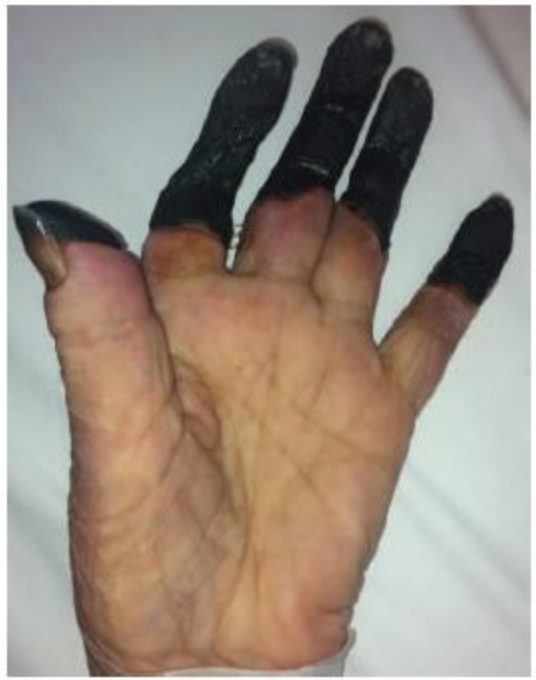
Fat grafting to the hand in patients with raynaud phenomenon: a novel therapeutic modality

Leonidas Pavlidis [1], Stamatis Sapountzis, Georgia Alexandra Spyropoulou, Efterpi Demiri

- An 84-year-old female patient presented with bilateral, 10-digit ischemia, with no ulceration.
- She had a history of scleroderma and was on endothelin-1 receptor antagonists and two injection sessions of neuromodulators (botulinum toxin) 6 months before first consultation.

- The patient was injected with 28 ml of decanted fat in the left hand and 27 ml in the right.

- She presented 10-digit ischemia 36 hours postoperatively that did not respond to neuromodulators or intravenous prostanoids.
- Interestingly, the patient also developed nose tip necrosis simultaneously, which was also treated surgically.



Five-digit necrosis of the left hand.

Five-digit necrosis of the right hand.

Plast Reconstr Surg. 2015 Jan;135(1):229e-230e.

Regional grafting of autologous adipose tissue is effective in inducing prompt healing of indolent digital ulcers in patients with systemic sclerosis: results of a monocentric randomized controlled study

Nicoletta Del Papa[1*], Gabriele Di Luca[2], Romina Andracco[1], Eleonora Zaccara[1], Wanda Maglione[1], Francesca Pignataro[1], Antonina Minniti[1] and Claudio Vitali[3]

- blindly treated with adipose tissue (AT) grafting (G) (0.5–1 ml AT after centrifugation of fat aspirate) or a sham procedure (SP) (false liposuction and local injection of saline solution).
- primary endpoint - the cumulative prevalence of healed DUs within the following 8w

- DU healing was observed in 23/25 and 1/13 patients treated with AT-G and the SP respectively ($p < 0.0001$).
- significant reduction of pain intensity after 4 and 8 weeks ($p < 0.0001$ in all cases).
- significant increase of capillary numbers in the affected finger was recorded by nailfold videocapillaroscopy after 4 and 8 weeks ($p < 0.0001$ in both cases).

- The 12 patients who received the unsuccessful SP underwent a rescue AT-G. In all of them, IDU healing was observed after 8 weeks of observation.

Arthritis Res Ther. 2019 Jan 7;21(1):7.

What's new?

Regional grafting of autologous adipose tissue is effective in inducing prompt healing of indolent digital ulcers in patients with systemic sclerosis: results of a monocentric randomized controlled study

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Fig. 3 Digital ulcer progressive healing of patient 2 (**a**) and patient 8 (**b**) after autologous AT-G

Arthritis Res Ther. 2019 Jan 7;21(1):7.

› Joint Bone Spine. 2022 Jan 20;89(4):105348. doi: 10.1016/j.jbspin.2022.105348.
Online ahead of print.

G- CSF treatment for refractory digital ulcers in systemic sclerosis

Shiri Keret [1], Gleb Slobodin [1], Abid Awisat [1], Lisa Kaly [1], Itzhak Rosner [1], Michael Rozenbaum [1], Nina Boulman [1], Aniela Shouval [1], Doron Rimar [2]

Why G-CSF?

- Stimulates neutrophil production and mobilization from bone marrow
- Inhibits neutrophil apoptosis
- Primes neutrophils, augmenting their responses to chemotactic factors
- Neutrophils promote tissue restoration, angiogenesis and cell proliferation
- Mobilization of bone marrow stem cells of all lineages including mesenchymal stem cells with regenerative and angiogenetic properties

Phillipson M, Kubes P. **The Healing Power of Neutrophils**. Trends Immunol. 2019 Jul;40(7):635-647.

Clinical Trial > Reumatismo. Jan-Mar 2006;58(1):26-30. doi: 10.4081/reumatismo.2006.26.

[The treatment of skin ulcers in systemic sclerosis: use of granulocyte-colony stimulating factor (G-CSF) in 26 patients]

[Article in Italian]

Dilia Giuggioli [1], Rocco Magistro, Michele Colaci, Umberto Franciosi, Andrea Caruso, Clodoveo Ferri

- 26 ασθενείς με SSc και χρόνια εμμένοντα έλκη
- 19/26 έλκη κάτω άκρων
- 12/26 επιμολυσμένα (θετικές καλλιέργειες)

- G-CSF, 5 microg/kg, υποδορίως, για 5 ημέρες

- Βελτίωση στα δερματικά έλκη στους 24/26 ασθενείς
  - 22/26 πλήρης επούλωση
  - 2/26 μερική επούλωση
  - 2 ασθενείς αμετάβλητα έλκη μετά από 6μήνες
- Βελτίωση στην ποιότητα ζωής [VAS (from 88+/-13 to 55+/-28; p<.0001) and HAQ (from 2.12 +/-0.45 to 1.28+/-0.30; p<.0001)]. Μείωση πόνου
- Εκρίζωση παθογόνων (12/12)
- Χωρίς ανεπιθύμητες ενέργειες

What's new?

Joint Bone Spine. 2022 Jan 20;89(4):105348. doi: 10.1016/j.jbspin.2022.105348.
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- 10 ασθενείς με δακτυλικά έλκη παρά τη μέγιστη ανεκτή θεραπεία με τρία αγγειοδιασταλτικά
- Filgrastim 300mcg άπαξ ημερησίως για 3 συνεχόμενες ημέρες
- WBC>30.000 διακοπή

DU subtype: (N, %)	
Chronic	8 (80%)
Recurrent	2 (20%)
Episodic	0 (0%)
Mean DU duration before G-CSF (months)±SD	15.07 ± 8.10

Parameter	SSc (n=10)
Mean age at DU onset (years) ±SD	53 ± 11
Female gender (N, %)	9, 90%
Mean duration of SSc (years)	15.4 ±8
Antibodies	
ATA (N, %)	3, 30%
ACA (N, %)	5, 50%
ANA + only	2, 20%
Diffuse SSc subtype (N, %)	5, 50%
Treatment (N, %)	
iloprost	10, 100%
bosentan	10, 100%
Sildenafil	6, 60%
CCB	2, 20%
Smoking (N, %)	2, 20%
Peripheral artery disease (N, %)	1, 10%

› Joint Bone Spine. 2022 Jan 20;89(4):105348. doi: 10.1016/j.jbspin.2022.105348.
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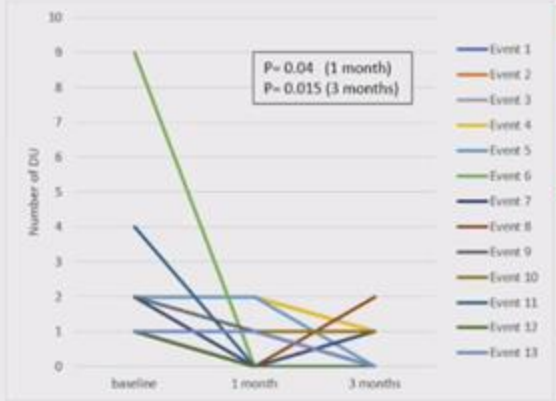
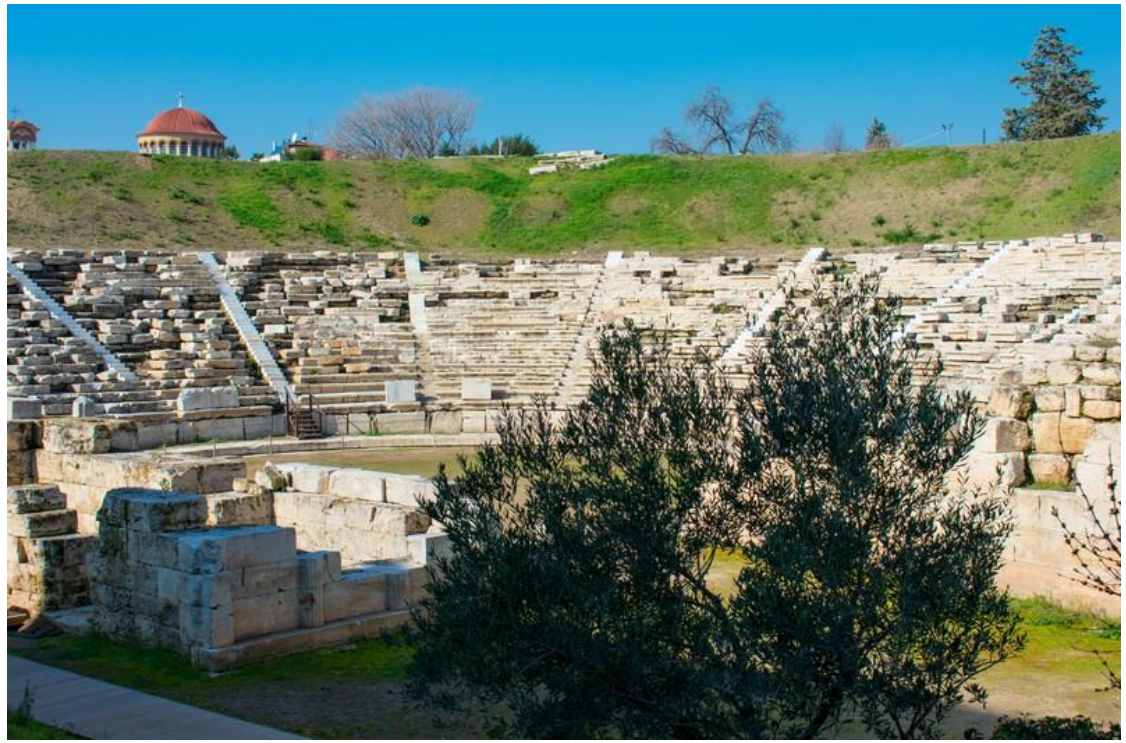
figure 2a: Mean digital ulcers number at baseline, after one month, and after three months:

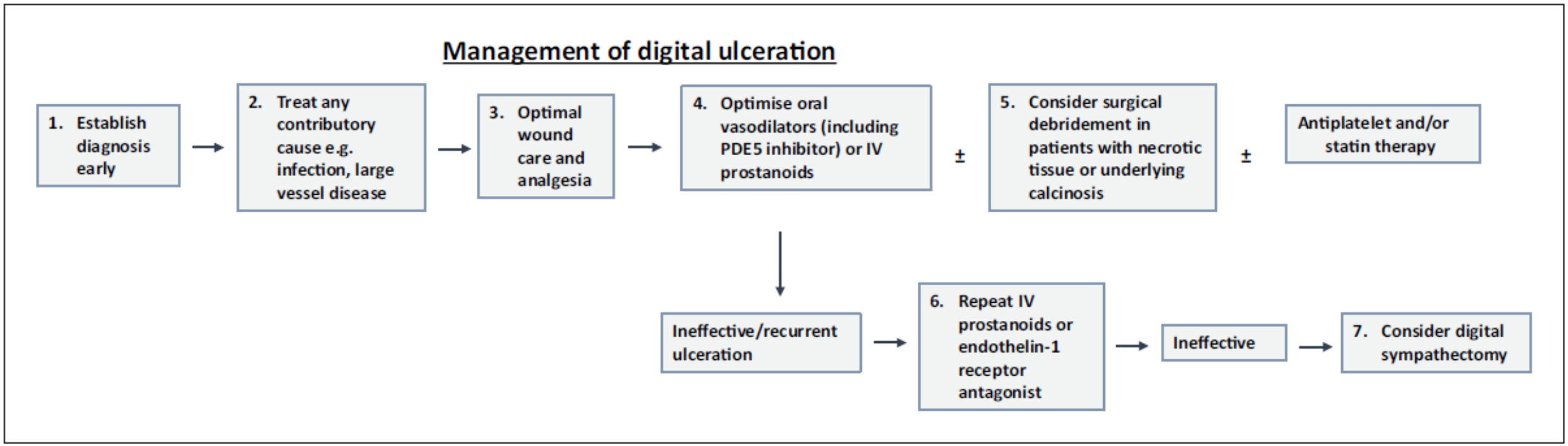


Mean Number of DU- baseline	2.23±2.20
Mean Number of DU – 1m	0.84±0.80
Mean Number of DU- 3m	0.50±0.67
Mean time to heal- (months)±SD	1.57 ± 0.75

Mean WBC number at baseline	6.59±1.50 10^9/L
Mean maximal WBC number	26.02±5.73 109/L
Antibiotics (N, %)	5, 50%
Adverse reactions (N, %)	0, 0%
Death cases (N, %)	0, 0%

Ευχαριστώ




Management of digital ulceration
1. Establish diagnosis early
2. Treat any contributory cause e.g. infection, large vessel disease
3. Optimal wound care and analgesia
4. Optimise oral vasodilators (including PDE5 inhibitor) or IV prostanoids
±
5. Consider surgical debridement in patients with necrotic tissue or underlying calcinosis
±
Antiplatelet and/or statin therapy
Ineffective/recurrent ulceration
6. Repeat IV prostanoids or endothelin-1 receptor antagonist
Ineffective
7. Consider digital sympathectomy

Συμπαθεκτομή

- Αναδρομική μελέτη σε 17 ασθενείς με SSc (εφαρμογή σε 26 χέρια) ανέφεραν συμπτωματική ανακούφιση από τον πόνο στο 92.3% των χεριών και επούλωση δακτυλικών ελκών (100%).

Microsurgery. 2015 Sep;35(6):441-6.

Periarterial sympathectomy and arterial bypass are microsurgical techniques which the literature suggests can provide improvement in digital pain and ulceration in patients with systemic sclerosis who have persistent symptoms despite medication management.

J Scleroderma Relat Disord. 2020 Jun 1;5(2):130-136.

Figure 4.

Sympathectomy can be performed through three incisions—longitudinal incisions proximal to the distal wrist crease to expose the radial (white arrow) and ulnar (black arrow) arteries and an oblique incision over the palm to expose the superficial palmar arch (circle) and common digital arteries (asterisks).

Συμπαθεκτομή

- Αναδρομική μελέτη σε 17 ασθενείς με SSc (εφαρμογή σε 26 χέρια) ανέφεραν συμπτωματική ανακούφιση από τον πόνο στο 92.3% των χεριών και επούλωση δακτυλικών ελκών (100%).

Microsurgery. 2015 Sep;35(6):441-6.

Figure 1. Access incisions for peripheral sympathectomy overlying the radial and ulnar arteries as well as transversely in the palm for exposure of the superficial palmar arch and common digital arteries.

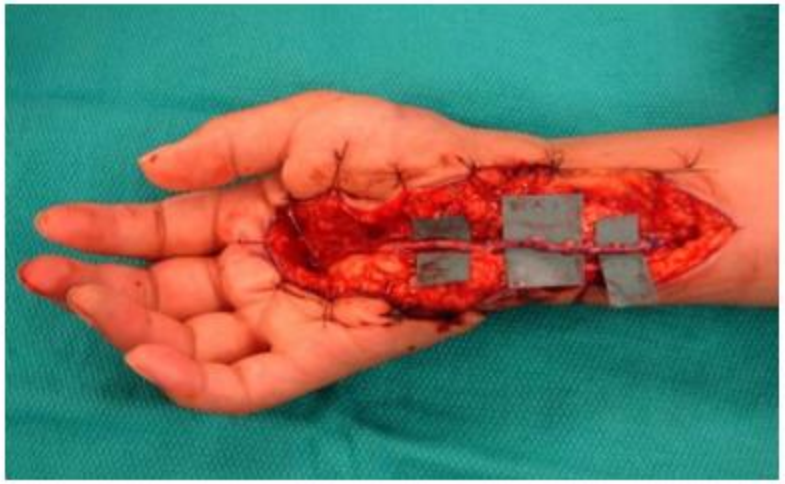


Figure 2. Revascularization by means of a vein graft was only possible given the presence of distal targets.

Table V. Sympathectomy for treatment of digital ulcers (DUs) in systemic sclerosis (SSc)

Reference	Patients *n*	Study design	Results
Ruch et al. 2002 (45)	22	Uncontrolled cohort	Mean follow-up: 46 months Complete healing in 6/22 patients 4 amputations in 3 patients Reduction in pain in 18 patients
Tham et al. 1997 (52)	6	Uncontrolled cohort	Complete healing in 2/3 DUs Mean of healing time for 27 days No recurrence during follow-up (12–29 weeks)
Ward et al. 1995 (50)	7	Uncontrolled cohort	Complete healing in 6 weeks Recurrence in 2 patients (3 hands) Persistent pain in 3 patients
O'Brien et al. 1992 (51)	11 SSc among 13 patients	Uncontrolled cohort	Complete healing in all patients Recurrence in 4 patients
Momeni et al. 2015 (47)	16	Retrospective cohort	Complete healing in all patients Recurrence in 2 patients at month 6 and year 4, respectively 3 wound infections, 2 wound openings, 2 stitch abscesses
Hartzell et al. 2009 (46)	17 SSc/3MCTD	Retrospective cohort	Complete healing in 28/42 DUs 11 digital amputations Mean follow-up: 90 months
Agarwal et al. 2005 (59)	6	Retrospective cohort	Complete healing in 9 of 11 DUs at month 20 Relief of pain
Tomaino et al.2001 (49)	6	Retrospective cohort	Decrease of VAS from a mean of 9 to1 at month 6 7 digital amputations 2 wound delay healing
McCall et al. 1999 (54)	4 SSc among 7 patients	Retrospective cohort	Complete healing in all patients, recurrence in 2 patients Mean healing time: 14 weeks Recurrent infection in 1 patient
Stratton et al. 1997 (48)	13	Retrospective cohort	No reduction in number of DUs. Mean follow-up: 19 months Pain reduction from 3.9 to 3.2 (scale from 0 to 4)
Koman et al. 1995 (61)	6	Retrospective cohort	Complete healing in 6/7 DUs at month 6 Pain relief in all patients
Jones et al. 1987 (53)	5	Retrospective cohort	Data on DU or pain not available. 2 partial amputations in 1 patient
Gahhos et al. 1984 (44)	59 (8 operations)	Retrospective cohort	No symptomatic relief in 3 patients No healing, appearance of new DUs
Flatt et al. 1980 (55)	2 SSc/MCTD among 8 patients	Retrospective cohort	Partial healing Pain relief, raised local temperature
Wasserman et al. 2010 (57)	1	Case report	Complete healing in 3 months No recurrence within 1 year
Volchok et al. 2005 (43)	1	Case report	Complete healing at 1 year, no recurrence
Greengrass et al. 2003 (42)	1	Case report	Nerve block of ropivacaine, no recurrence
Tomaino et al. 2002 (62)	2	Case report	Complete healing in 6 weeks for patient 1, 14 for patient 2 Patient 1: wound haematoma and dehiscence
Hafner et al. 1997 (58)	2	Case report	Patient 1: pain relief, recovery of digital systolic pressure, no follow-up Patient 2: pain relief, complete healing in 4 weeks, no recurrence at year 2
Van Den Broecke et al. 1997 (56)	1	Case report	Recurrence in 2 fingertips, 1 phalangeal amputation
El Gammal et al. 1991 (60)	1	Case report	No healing or pain reduction 1 finger amputation

RCT: randomized controlled trial; VAS: visual analogue scale; MCTD: mixed connective tissue disease.

Table IV. Hyperbaric oxygen therapy for treatment of digital ulcers (DUs) in systemic sclerosis (SSc)

Reference	Patients, *n*	Study design	Results
Hassanien et al. 2018 (11)	50	RCT	All patients treated by calcium channel blockers Higher rate of complete healing at day 20 ($p=0.032$) No effect on VAS ($p=0.16$) Follow-up <1 month
Mirasoglu et al. 2017 (36)	6	Case series	1 session per day, 5 days a week Complete healing in 4 patients after 40 mean sessions Partial healing for 2 patients after 42 mean sessions
Ueno et al. 2014 (38)	1 SSc (among 29 patients)	Case series	30% reduction in DUs size
Dowling et al. 1967 (41)	6	Case series	2 sessions per day 4 patients with DUs Complete healing for 2 patients in 3 weeks, relapse for another one, amputation for the last one
Poirier et al. 2017 (37)	1	Case report	DU healing at month 8
Gerodimos et al. 2013 (39)	1	Case report	DUs healing in 1 month No relapse at month 6
Markus et al. 2006 (40)	1	Case report	Complete healing for 1 DU, partial for the second one at the end of treatment Persistence of 1 DU at month 6

RCT: randomized controlled trial; VAS: visual analogue scale.

Vascular. 2021 Jul 14;17085381211032854. doi: 10.1177/17085381211032854. Online ahead of print.

Outcomes of periarterial sympathectomy in patients with digital ischemia

Ahmed A Elshabrawy [1], Mohammed Elkassaby [1 2], Mohamed S Abdelgawad [1], Ehab Atif [3], Abdelsalam Megahed [1], Samer Regal [1]

Affiliations + expand

PMID: 34256627 DOI: 10.1177/17085381211032854

Abstract

Introduction: Digital ischemia with subsequent severe pain and tissue loss is often difficult to treat, with no obvious guidelines or strong evidence in the literature to support a specific treatment modality. Patients who fail medical treatment remain with very limited surgical options due to the difficulty of any intervention in this "no man's land" area of the hand, as described since 1918. Extended distal periarterial sympathectomy is reported as an effective treatment option since the eighties of last century. The procedure entails large incisions and major technical difficulties. In this study, we describe a less invasive approach with very promising results and equally high success rates.

Materials and methods: This was a prospective study. All patients with severe digital ischemia manifesting with bluish discoloration, ulceration, and/or dry gangrene who failed medical treatment underwent distal periarterial sympathectomy for the radial and ulnar arteries, with added digital sympathectomy in very severe cases. Primary endpoints were ulcer healing and improvement in pain scores assessed by Visual Analog Scale pain scoring system. Secondary endpoints included complications and amputation rates.

Results: This study recruited 17 patients between January 2019 and January 2020. The mean follow-up was 14.6 months. The mean age was 33.71 (±SD 13.14) years. 41% were males. 59% suffered from vasculitis, 35% of patients had dry gangrene, and 71% had ulcers. Periarterial radial and ulnar sympathectomy was performed for all cases, with digital sympathectomy for 12 fingers. We had 50% complete ulcer healing within 1 month ($p = 0.031$), and 100% were completely healed at 6 months ($p < 0.001$). Pain scores showed significant reductions at 1 ($p = 0.001$) and 6 months ($p < 0.001$) of follow-up.

Study Protocol: A Randomized Controlled Prospective Single-Center Feasibility Study of Rheopheresis for Raynaud's Syndrome and Digital Ulcers in Systemic Sclerosis (RHEACT Study)

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- The presence of DU is associated with increased whole blood viscosity (WBV).
- Rheopheresis (RheoP) is an extracorporeal apheresis technique used to treat microcirculatory disorders by improving blood viscosity.

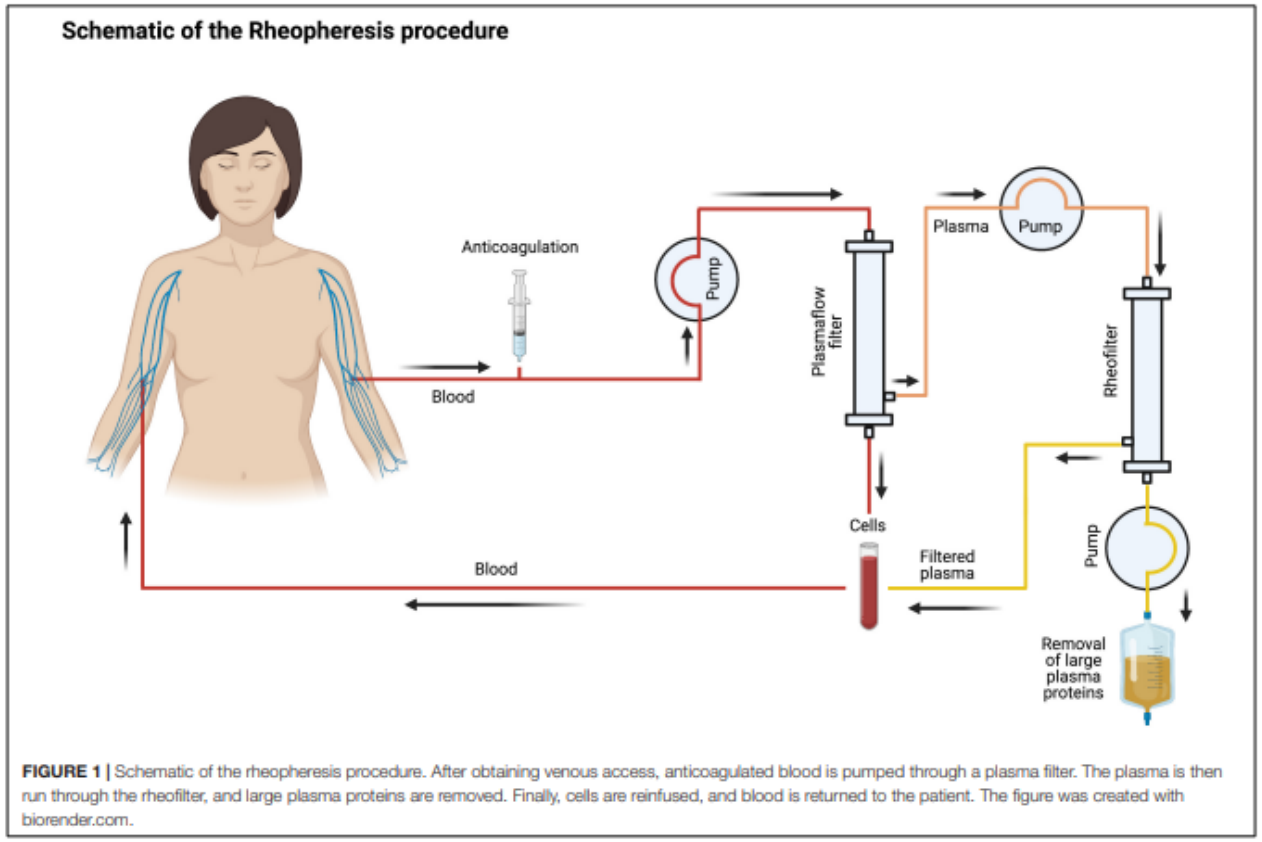

FIGURE 1 | Schematic of the rheopheresis procedure. After obtaining venous access, anticoagulated blood is pumped through a plasma filter. The plasma is then run through the rheofilter, and large plasma proteins are removed. Finally, cells are reinfused, and blood is returned to the patient. The figure was created with biorender.com.

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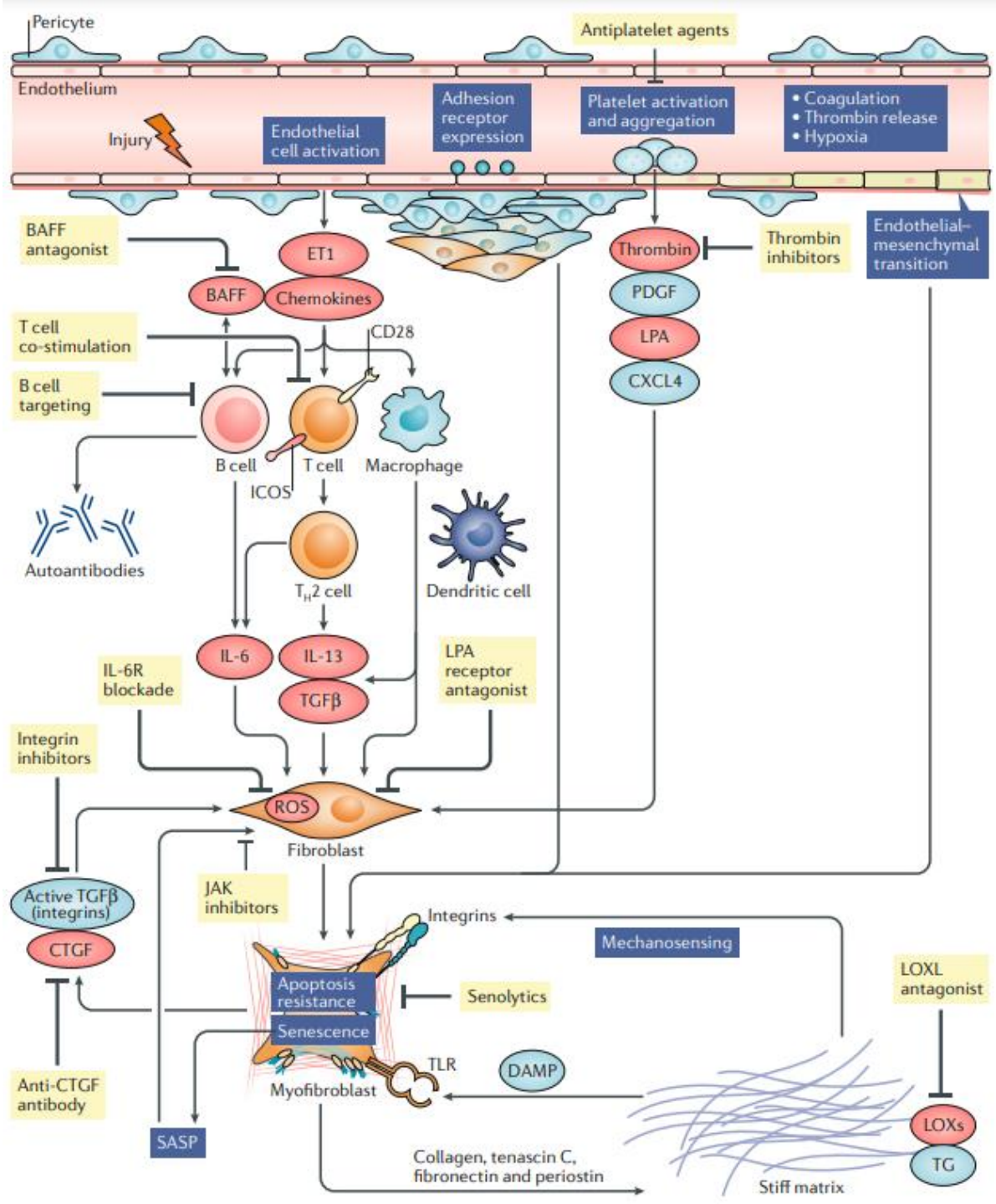
Pericyte
Antiplatelet agents
Endothelium
Injury
Endothelial cell activation
Adhesion receptor expression
Platelet activation and aggregation
• Coagulation
• Thrombin release
• Hypoxia
Endothelial–mesenchymal transition
BAFF antagonist
ET1
BAFF
Chemokines
Thrombin
Thrombin inhibitors
PDGF
LPA
CXCL4
T cell co-stimulation
CD28
B cell targeting
B cell
T cell
Macrophage
ICOS
Autoantibodies
T_H2 cell
Dendritic cell
IL-6
IL-13
TGFβ
IL-6R blockade
LPA receptor antagonist
Integrin inhibitors
ROS
Fibroblast
Active TGFβ (integrins)
CTGF
JAK inhibitors
Integrins
Mechanosensing
Apoptosis resistance
Senescence
Senolytics
LOXL antagonist
TLR
DAMP
Myofibroblast
Anti-CTGF antibody
SASP
LOXs
TG
Collagen, tenascin C, fibronectin and periostin
Stiff matrix