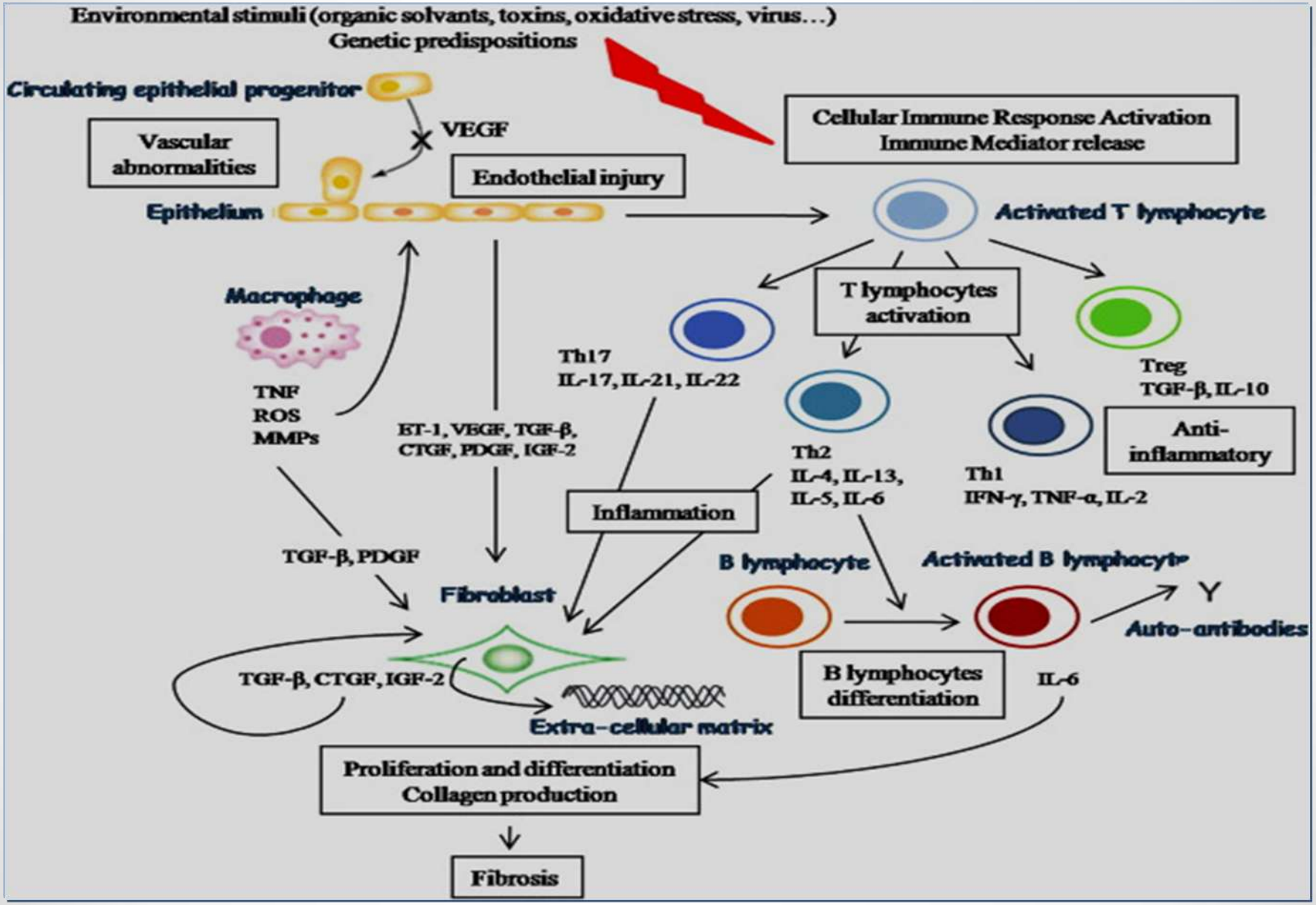
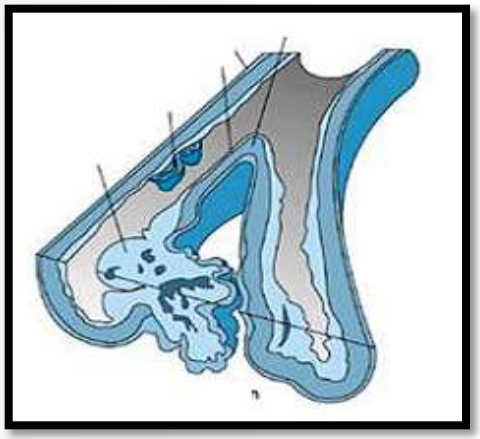
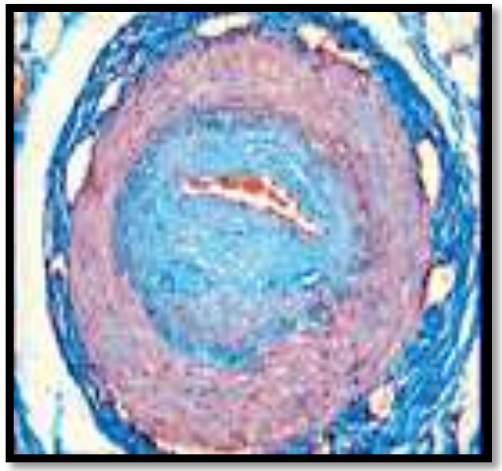
Vasculopatía Periférica en la Esclerosis sistémica: Tipos de úlceras i abordaje terapéutico

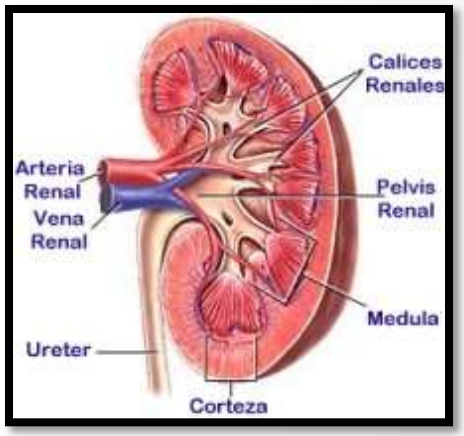
II Curs de malalties autoinmunes de la SCR

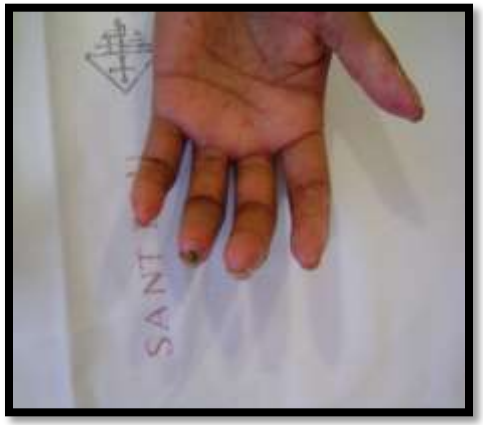
Ivan Castellví Barranco
Hospital de la Santa Creu i Sant Pau
Hospital Comarcal de l'Alt Penedès
Universitat Autònoma de Barcelona


Environmental stimuli (organic solvants, toxins, oxidative stress, virus…)
Genetic predispositions
Circulating epithelial progenitor
VEGF
Vascular abnormalities
Endothelial injury
Epithelium
Cellular Immune Response Activation
Immune Mediator release
Activated T lymphocyte
T lymphocytes activation
Macrophage
TNF
ROS
MMPs
ET-1, VEGF, TGF-β, CTGF, PDGF, IGF-2
Th17
IL-17, IL-21, IL-22
Th2
IL-4, IL-13, IL-5, IL-6
Th1
IFN-γ, TNF-α, IL-2
Treg
TGF-β, IL-10
Anti-inflammatory
Inflammation
TGF-β, PDGF
Fibroblast
B lymphocyte
Activated B lymphocyte
Y
Auto-antibodies
B lymphocytes differentiation
IL-6
TGF-β, CTGF, IGF-2
Extra-cellular matrix
Proliferation and differentiation
Collagen production
Fibrosis






Calices Renales
Arteria Renal
Vena Renal
Pelvis Renal
Medula
Ureter
Corteza



FACULTÉ DE MÉDECINE DE PARIS.

THÈSE

POUR

LE DOCTORAT EN MÉDECINE,

Présentée et soutenue le 25 février 1862,

Par A.-G.-Maurice RAYNAUD,

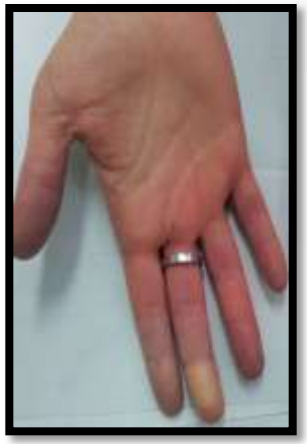
né à Paris,

Licencié ès Lettres, Licencié ès Sciences;
Interne en Médecine et en Chirurgie des Hôpitaux et Hospices civils de Paris;
Lauréat des Hôpitaux (*Médaille d'Argent*, 1858; *Médaille d'Or*, 1860);
Lauréat de la Faculté de Médecine (grand Prix de l'École Pratique, *Médaille d'Or*, 1861);
ex-Médecin traitant aux Hôpitaux de l'Armée d'Italie, 1859 (*Médaille d'Argent de 1re Classe*);
Membre de la Société Anatomique.

DE L'ASPHYXIE LOCALE

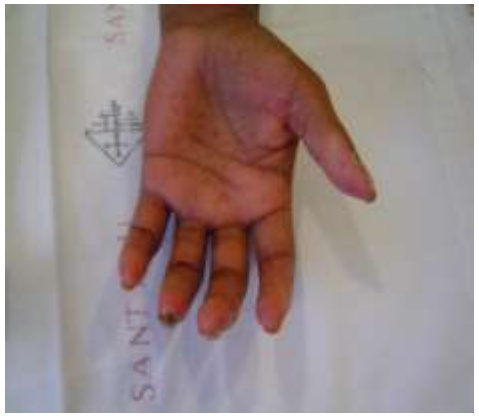
ET

DE LA GANGRÈNE SYMÉTRIQUE DES EXTRÉMITÉS.



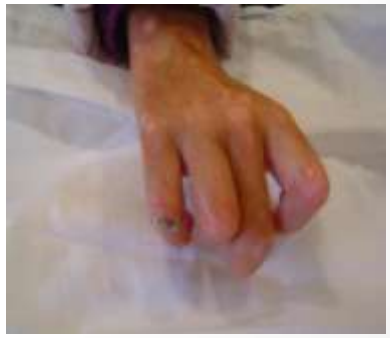
Úlceras Digitales

- Prevalencia 17-58%.
- Incidencia 30% pac-año.
- 1-11% amputación.
- Hospitalización: 38% (6 d).
- 46% antibioterapia.
- 73% casos en 5 primeros años.



Consensus opinion of a North American Working Group regarding the classification of digital ulcers in systemic sclerosis

Murray Baron · Lorinda Chung · Geneviève Gyger · Laura Hummers · Dinesh Khanna · Maureen D. Mayes · Janet E. Pope · Ami A. Shah · Virginia D. Steen · Russell Steele · Solène Tatibouet · Ariane Herrick · Ulf Müller-Ladner · Marie Hudson



Ingraham KM et al. Arthritis Rheum 2006.
Nihtyanova SI et al. Ann Rheum Dis 2008.
Steen V et al. Rheumatology 2009.
Hachulla E et al. J Rheumatol 2007.
Herrick AL et al. Arthritis Rheum 2009.
Baron M et al. Clin Rheumatol 2014.

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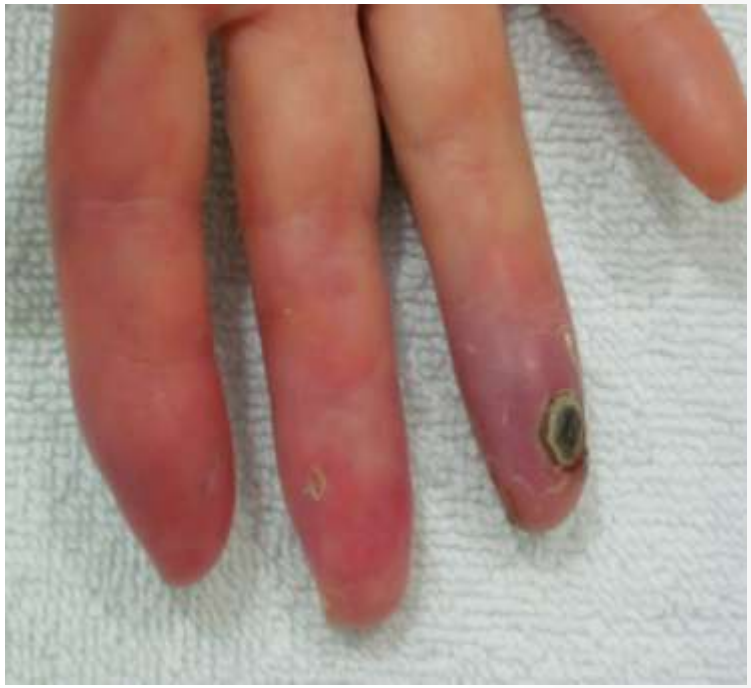
Digital ulcers: A digital ulcer is a lesion with visually discernable depth and a loss of continuity of epithelial coverage, which could be denuded or covered by a scab or necrotic tissue. A scab, or crust, is a hardened covering of dried secretions (as blood, plasma, or pus) that forms over an ulcer. Necrotic tissue is black or very dark brown and is the remnant of normal tissue that has become necrotic because of the ischemia to that area of the digit. The DUs that are usually studied in therapeutic trials are those that are thought to be ischemic in origin. Digital ulcers do not include fissures, paronychia, extrusion of calcium, ulcers over calcium (Fig. 1a–c), or ulcers over the metacarpophalangeal joints or elbows. If the examiner suspects calcium but is not certain, then an X-ray of the area should be obtained. Only digital ulcers at or distal to the proximal interphalangeal joints and without bone infection or calcinosis are to be assessed.



Baron M et al. Clin Rheumatol 2014.

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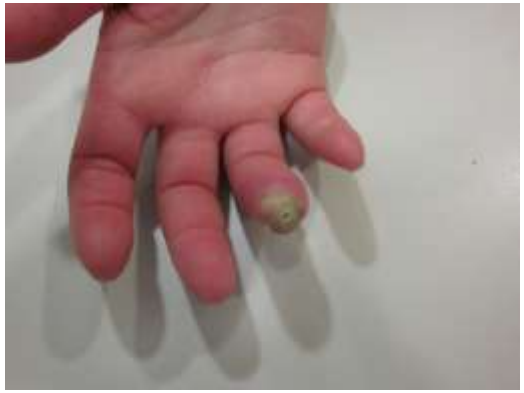
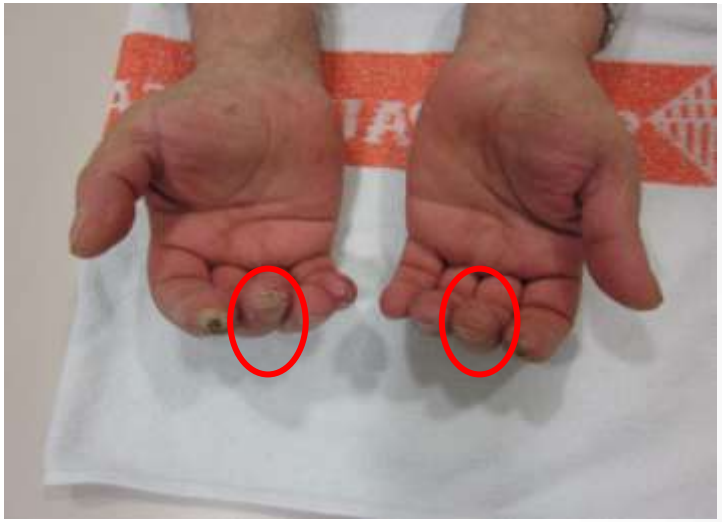
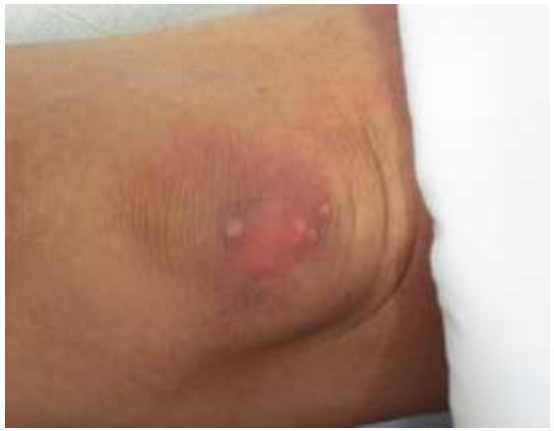
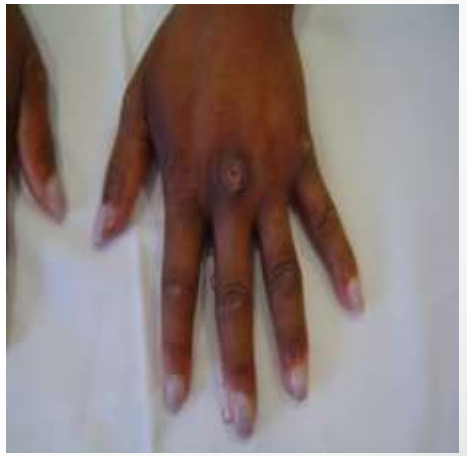
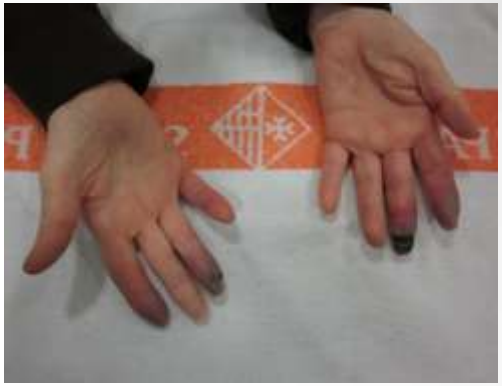
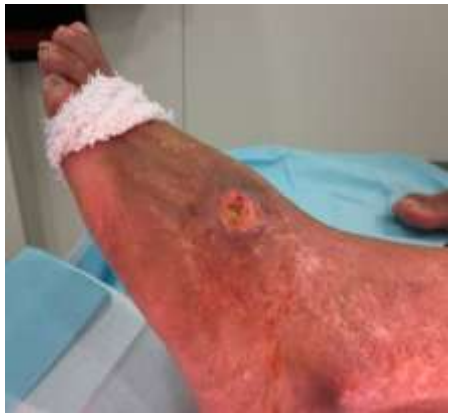


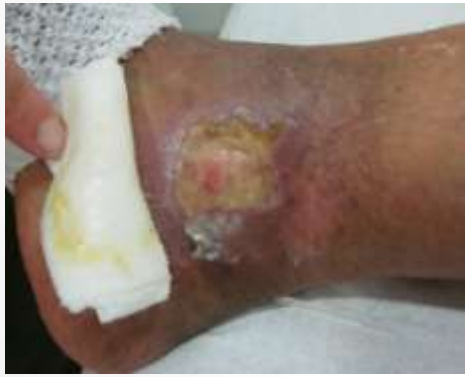


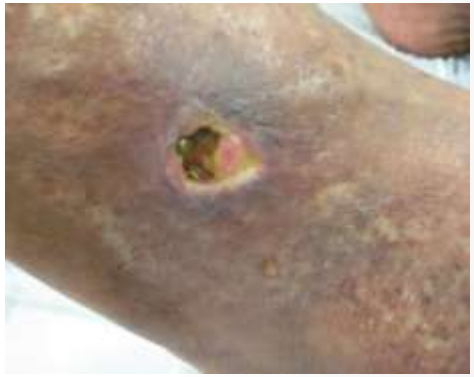


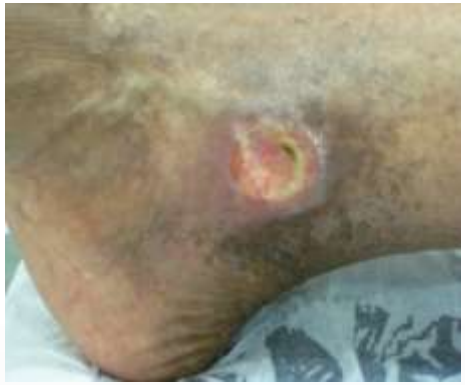








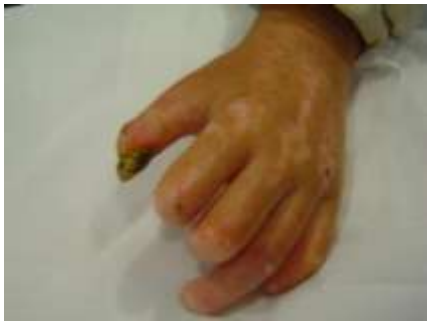




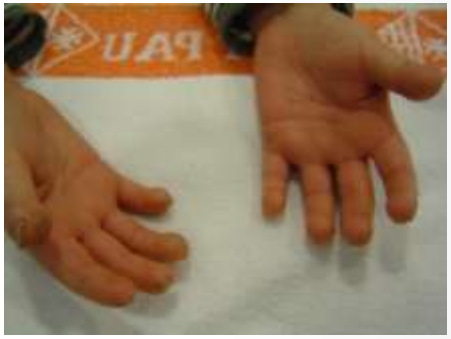
Tratamiento de la vasculopatia digital (y periférica): Objetivos

Disminución de clinica (FRaynaud)

Tratamiento específico complicación

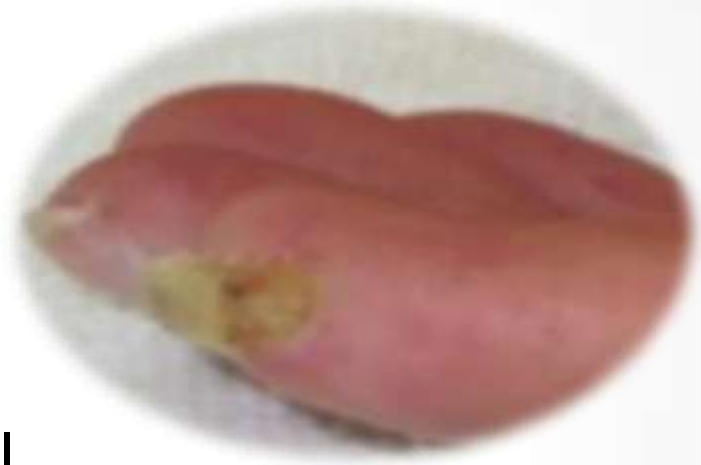


Prevención de complicacion



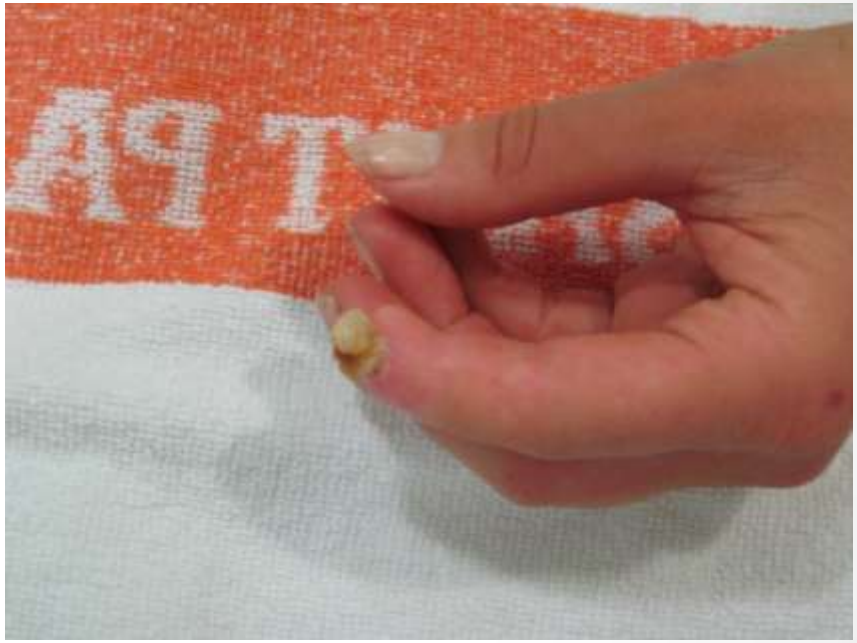
Vasculopatia Digital (UD)

- Presencia previa de UD.
- Afectación cutanea
- < DLCO
- VSG, IL-6
- Relación con autoAc
- Marcadores de daño endotelial
- sCD40L
- VCP: areas avasculares.



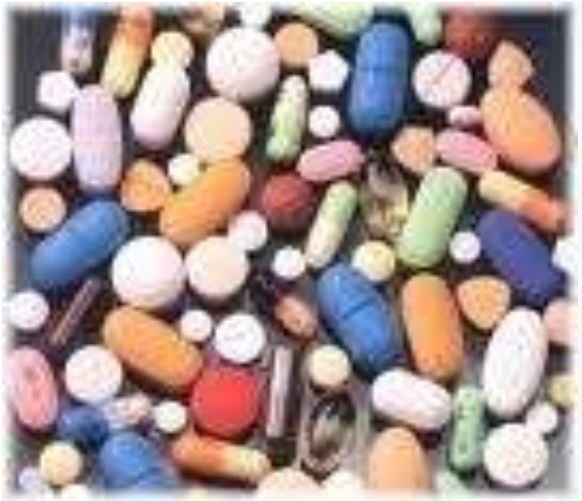
Hachulla E et al. J Rheumatol 2007.
Maricq HR et al. Arthritis Rheum 1981.
Kabasakal Y et al. Ann Rheum Dis 1996.
Khidmas S et al. Arthritis Care Res 2011.
Avouac J, et al. Ann Rheum Dis 2011.
Alivernini S et al. J Am Acad Dermatol 2008.
Allanore Y et al. Ann Rheum Dis 2005.

Manejo de las complicaciones



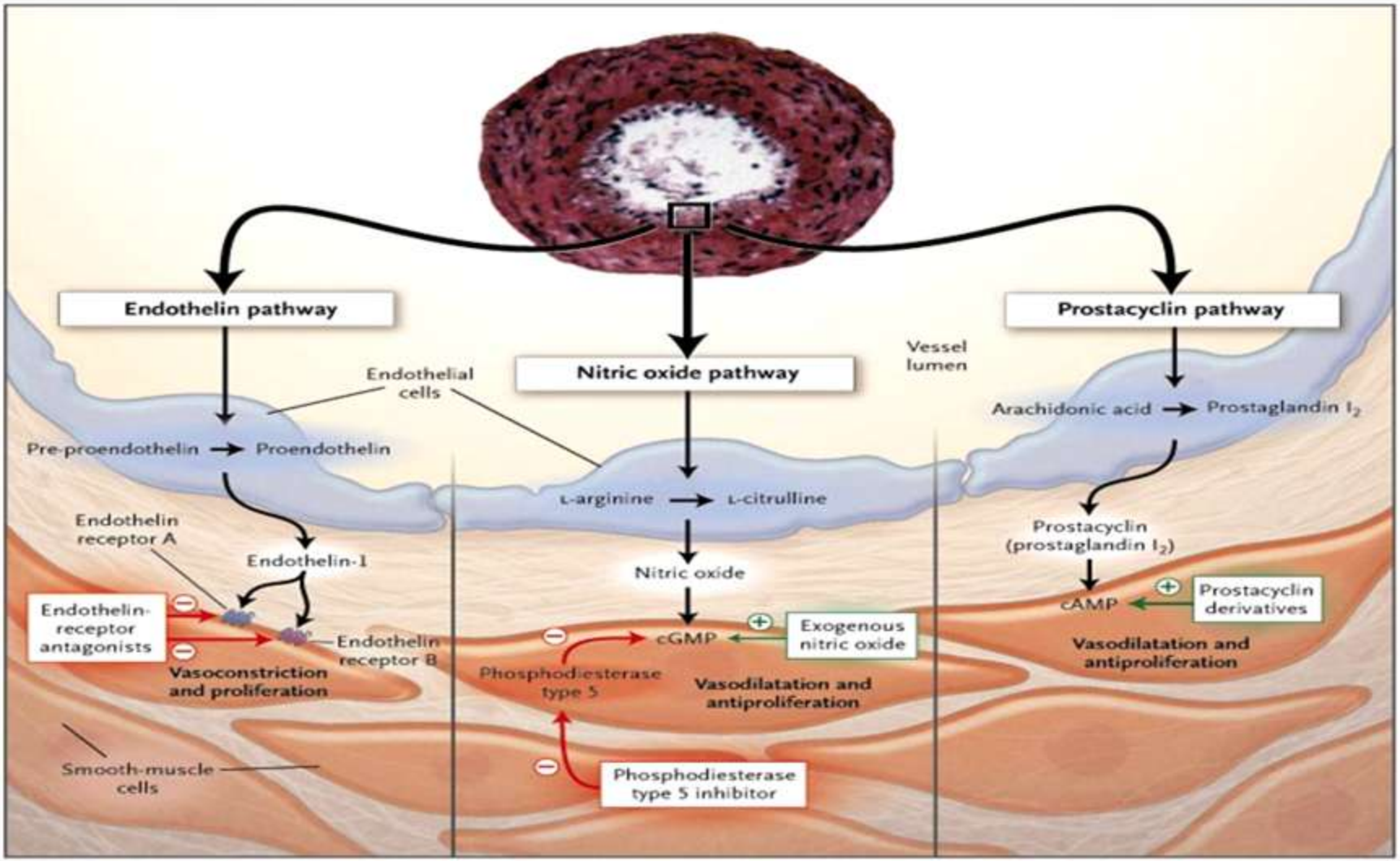
Terápias habituales

- Calcioantagonistas (nifedipino, amlodipino)
- Diltiazem
- IECA (Captopril)
- ARA-II (Losartán)
- Bloqueo α- adrenérgico (prazosin)
- Fluoxetina
- Nitratos tópicos
- *Atorvastatina*
- *Pentoxifilina*
- *AAS/Clopidogrel*
- *N-Acetil cisteína ev*
- *Vitamina E tópica*
- HBPM



Thompson AE, et al. Rheumatology 2005.
Dziadzio M et al. Arthritis Rheum 1999.
Pope J et al. Cochrane Database Sys Rev 2000.
Coleiro B et al. Rheumatology 2001.
Franks Jr AJ et al. Lancet 1982.
Abou-Raya et al. J Rheumatol 2008.
Kuwama M et al. Arthritis Rheum 2009.
Sambo P et al. J Rheumatol 2001.
Denton CP et al, Clin Exp Rheumatol 2000.

Terápias avanzadas



Humbert M et al. New Engl J Med 2004

Análogos de Prostanoides

- Tratamiento de isquemia distal /UD.
- Múltiples efectos
- Eficacia de endovenosos
  - Iloprost
  - Alprostadil
- EA/administración.

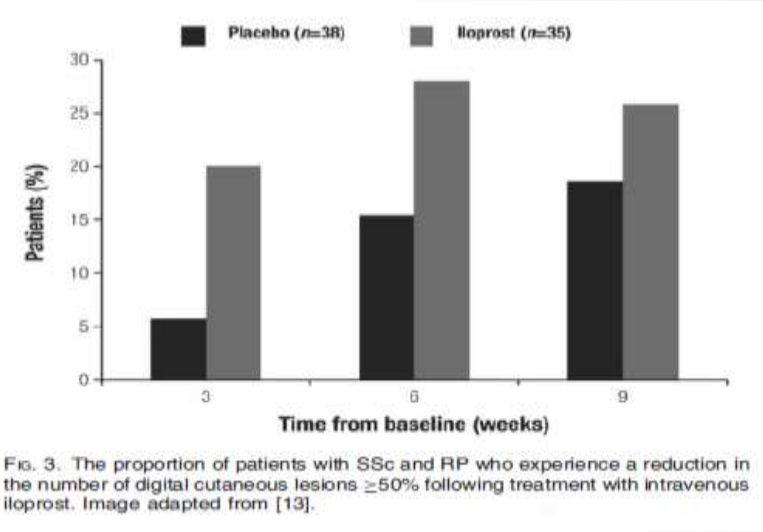
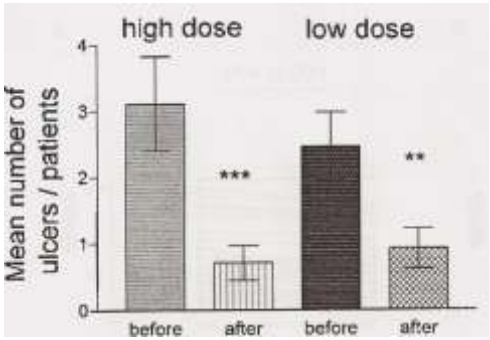


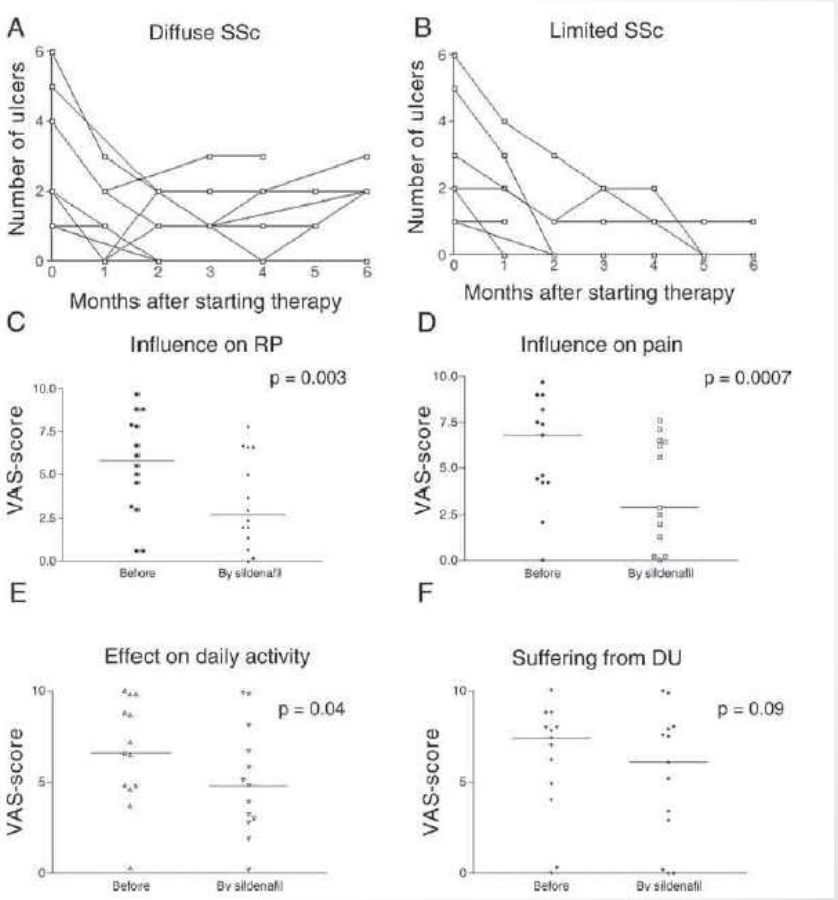
FIG. 3. The proportion of patients with SSc and RP who experience a reduction in the number of digital cutaneous lesions ≥50% following treatment with intravenous iloprost. Image adapted from [13].



Mittag M et al. Acta Derm Venereol. 2001
Kahaleh MB et al. Arthritis Rheum. 2000
Pope J et al. Cochrane Database Sys Rev. 2005
Wigley FM et al. Ann Intern Med 1994
Kawald A , et al. J Rheumatol. 2008

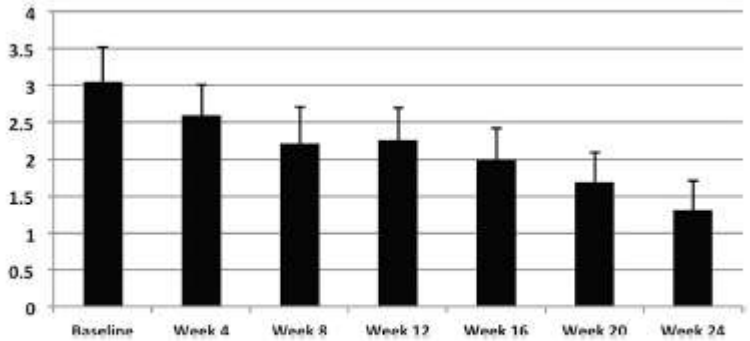
Inhibidores de la PDE-5

- Sildenafilo, Vardenafilo, tadalafilo
- Disminucion de crisis de FR en ES.
- Curación de UD.
- No prevencion de UD.
- Ausencia de ECA.



Herrick AL , et al. Arthritis Rheum 2009.
Brueckner CS, et al. Ann Rheum Dis 2010.
Shenoy PD et al. Rheumatology 2010.

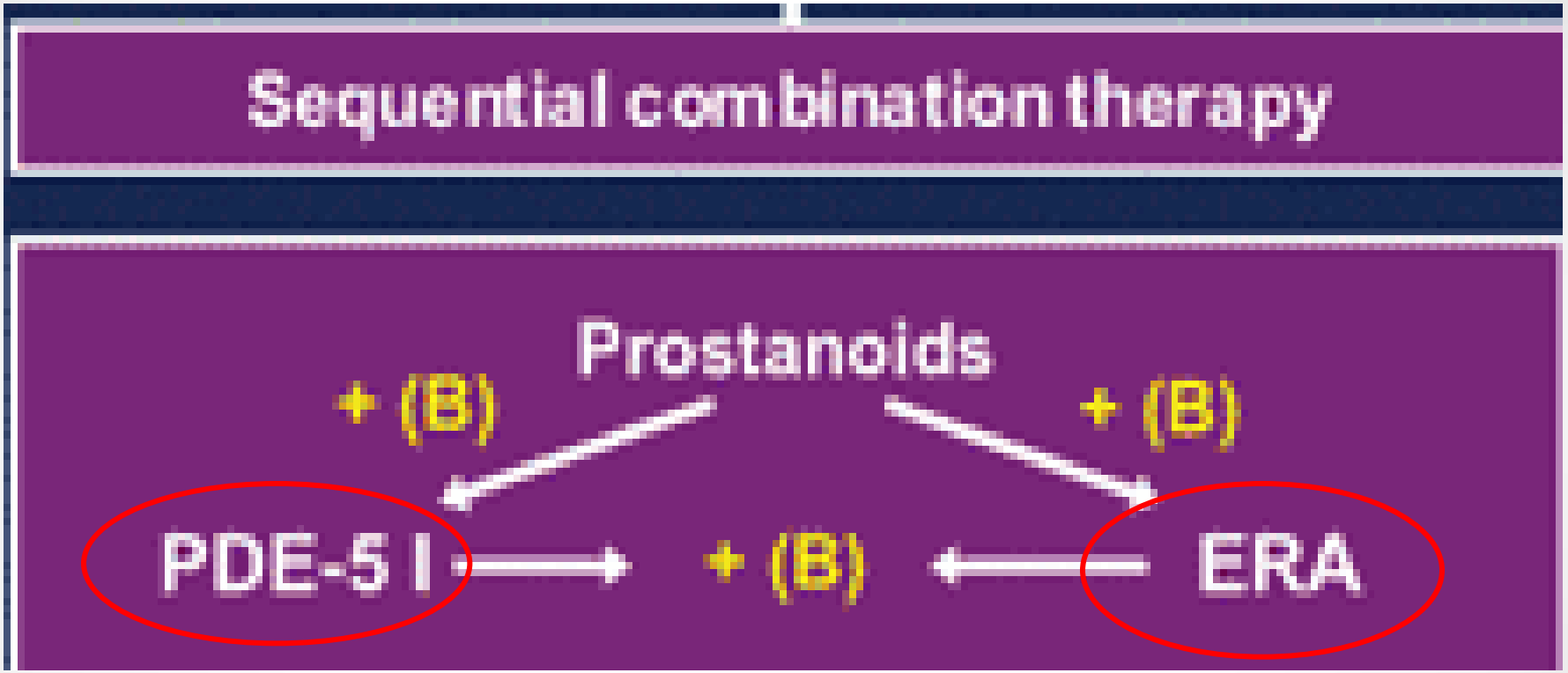
Antagonistas Receptores de la Endotelina

- Bosentan
  - Menor probabilidad de desarrollar múltiples UD en pacientes tratados con Bosentan.
  - 

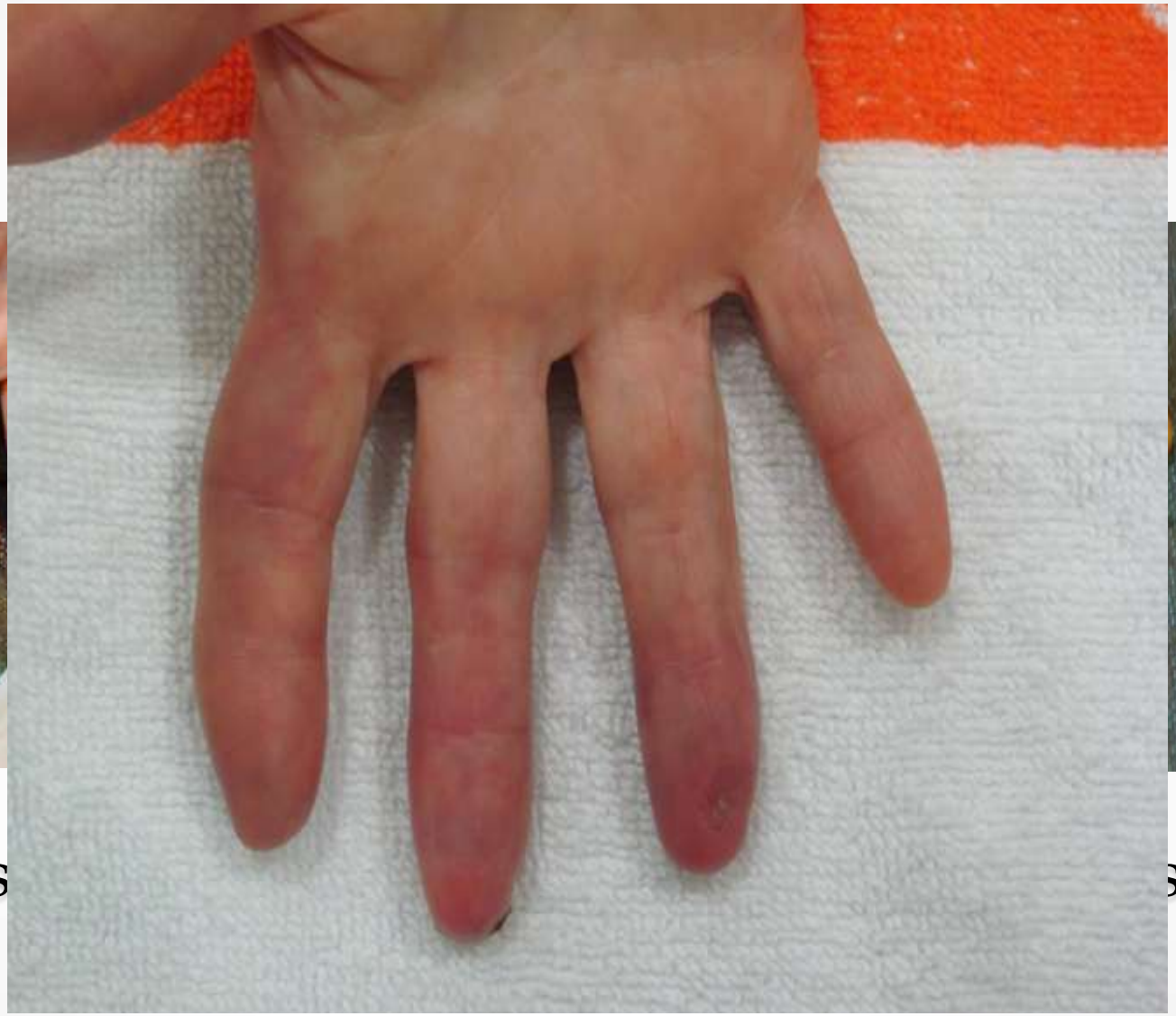
con
  - ión.
- Ambrisentan
  - Curación 4/6 pacientes con UD rebeldes a Pgs y Bosentan.
  - 20 pacientes con AMB 24s.

Fig 2. The mean number of total digital ulcers per patient was lower at week 12 (2.3 ± 1.9; $P = .07$) and significantly lower at week 24 (1.3 ± 1.6; $P = .004$) compared to baseline (3.1 ± 2.1).

Korn et al. Arthritis Rheum 2004 .
Tsifetaki et al. J Rheumatol 2009.
Matucci-Cerinic et al. Ann Rheum Dis 2011.
Román-Ivorra JA, Simeon CP, Fonollosa V et al. J Rheumatol 2011.
Parisi S et al. Rheumatology 2013.
Chung L et al. J Am Acad Dermatol 2014



Ambach A et al. JDDG 2009.
Moinzadeh P et al. J Am Acad Dermatol 2011.



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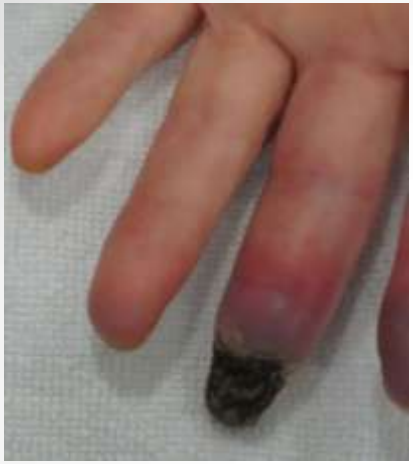
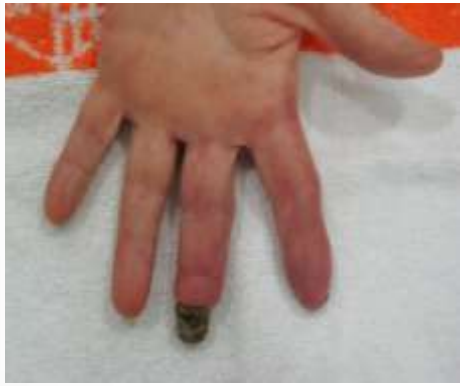
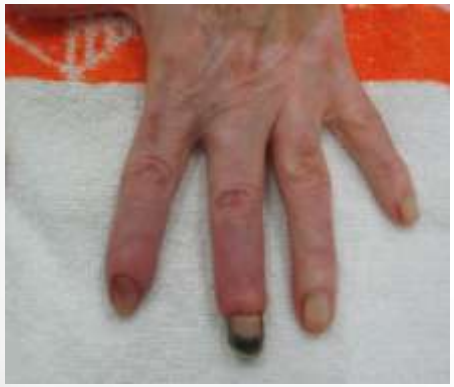
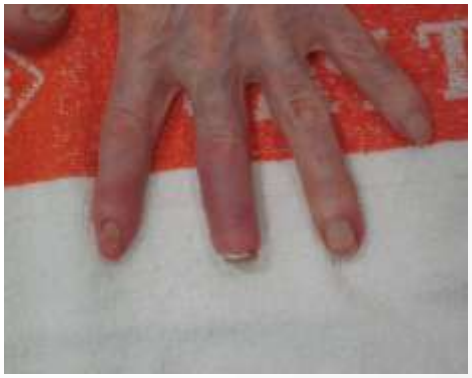
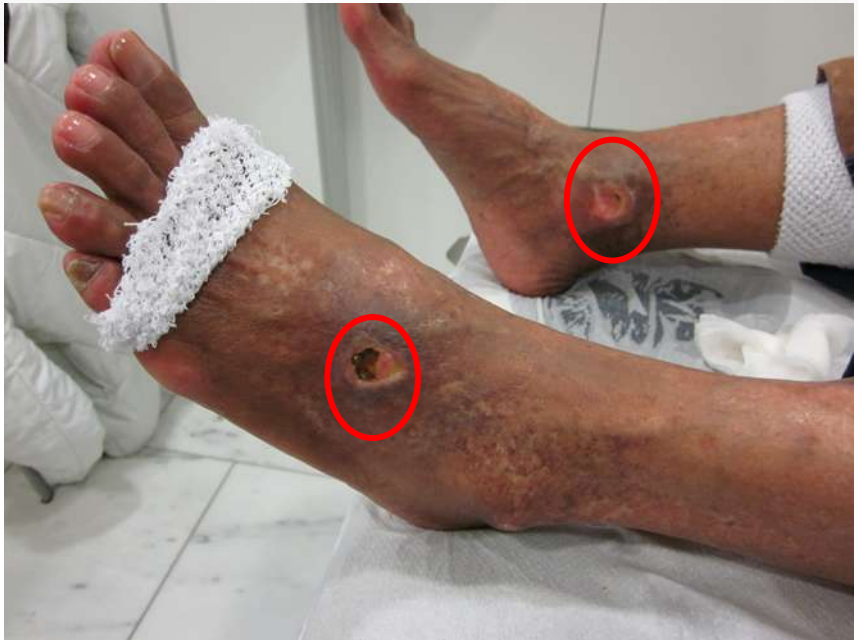


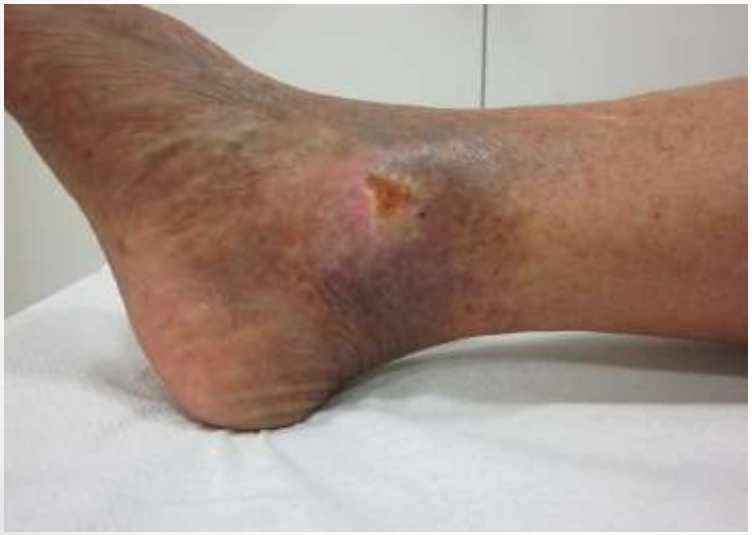
- Prostanoides Iv
- HBPM
- Analgesia / AINE (!!)
- *Estatinas*
- *Pentoxifilina*
- CUIDADO CON LAS DERIVACIONES A C. VASCULAR!!! (excepto sospecha de infección severa)

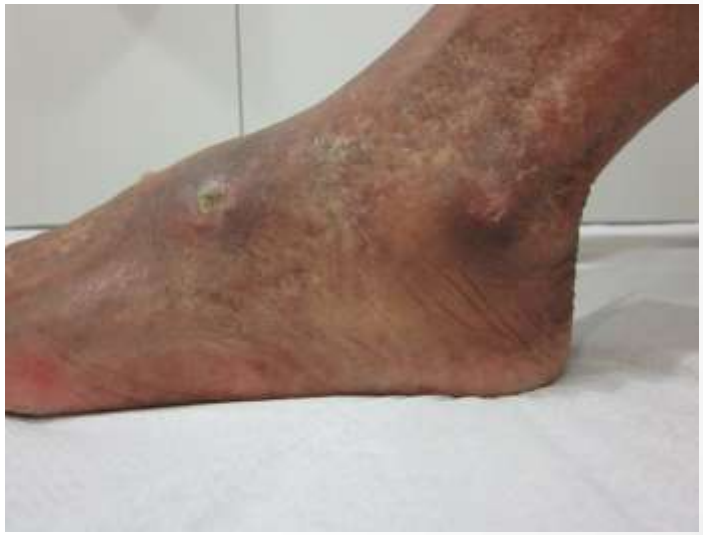












CASE BASED REVIEW

Rituximab for refractory digital infarcts and ulcers in systemic sclerosis

Chiew-Gek Khor · Xena Lung-Fang Chen · Ting-Syuan Lin · Cheng-Hsun Lu · Song-Chou Hsieh

Mod Rheumatol
DOI 10.1007/s10165-010-0274-x

ORIGINAL ARTICLE

Therapeutic angiogenesis in patients with systemic sclerosis by autologous transplantation of bone-marrow-derived cells

Yoshiaki Ishigatsubo · Atsushi Ihata · Hiroshi Kobayashi · Maasa Hama · Yohei Kirino · Atsuhisa Ueda · Mitsuhiro Takeno · Akira Shirai · Shigeru Ohno

Recombinant human erythropoietin stimulates vasculogenesis and wound healing in a patient with systemic sclerosis complicated by severe skin ulcers

C. Ferri, D. Giuggioli, A. Manfredi, N. Quirici,* C. Scavullo,* M. Colaci, U. Gianelli,† G. Lambertenghi Deliliers‡ and N. Del Papa§

Effect of Clonazepam on Raynaud's Phenomenon and Fingertip Ulcers in Scleroderma

Murat Colakoğlu, Veli Cobankara, and Tekin Akpolat

The Journal of Rheumatology Volume 33, no. 8

Ischemic scleroderma wounds successfully treated with hyperbaric oxygen therapy.

Y Michael Markus, Mary J Bell and A Wayne Evans

LETTER TO THE EDITOR

Digital ulcer in systemic sclerosis successfully treated with Waon therapy

Concise Report

Local implantation of autologous mononuclear cells from bone marrow and peripheral blood for treatment of ischaemic digits in patients with connective tissue diseases

Y. Kamata[1], Y. Takahashi[1], M. Iwamoto[1], K. Matsui[2], Y. Murakami[2], K. Muroi[3], U. Ikeda[2], K. Shimada[2], T. Yoshio[1], H. Okazaki[1] and S. Minota[1]

ARTICLE ORIGINAL

Intérêt de la toxine botulinique de type A dans le traitement des syndromes de Raynaud sévères secondaires à la sclérodermie systémique

Botulinum toxin type A contribution in the treatment of Raynaud's phenomenon due to systemic sclerosis

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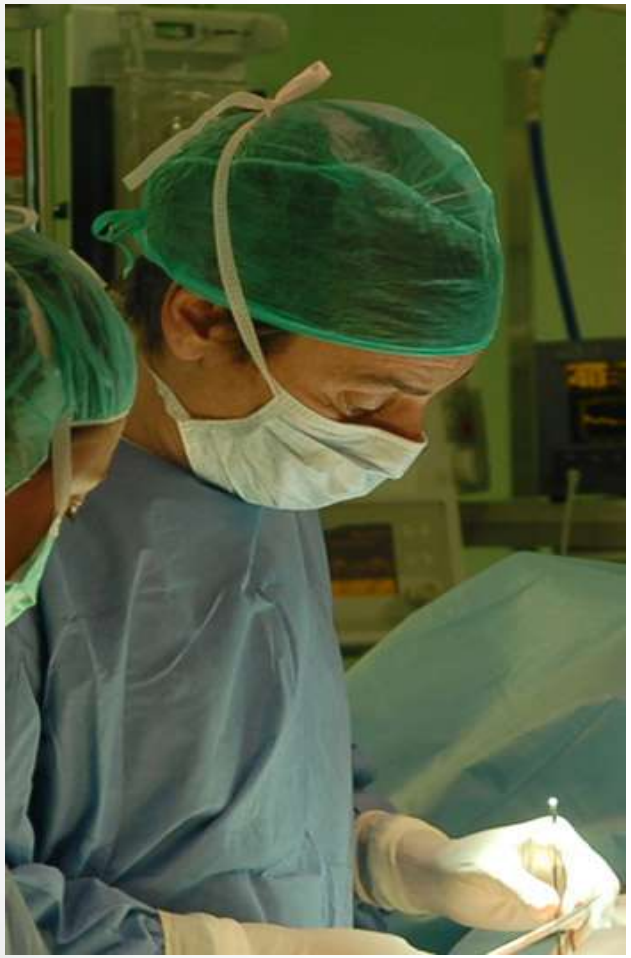
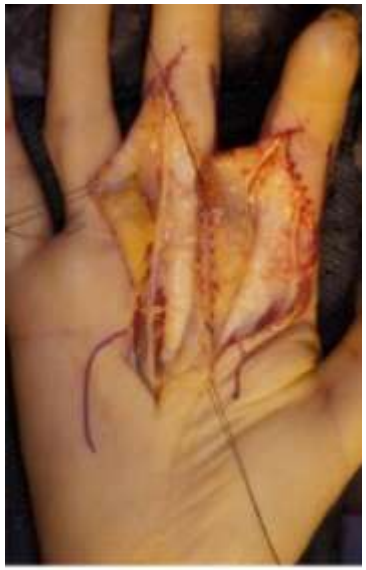
Tratamiento quirúrgico





Kotsis S et al. J Rheumatol 2003.
Bogoch ER et al. J Rheumatol 2005.

Conclusiones

- La vasculopatía periférica y sobretodo la vasculopatía digital (UD) son una complicación frecuente de la Esclerosis Sistémica.
- La vasculopatía digital traduce clínicamente la lesión primordial vascular de la Esclerosis Sistémica.
- En los pacientes con Esclerosis Sistémica las lesiones vasculares periféricas diferentes a la vasculopatia digital también traducen el compromiso vascular de la enfermedad (en parte).
- El tratamiento de la vasculopatía se fundamente en prevención primaria , tratamiento de la complicación y prevención secundaria de la complicación.

Conclusiones

- El tratamiento con prostanoides intravenosos es fundamental en los casos de vasculopatia digital grave.
- El uso de los ARE y IPDE5 (o la combinación de éstos) también es útil para el tratamiento de la vasculopatía digital.
- El tratamiento local (desbridaje / limpieza) es básico en algunas circunstancias.
- La anticoagulación (HBPM) puede ser útil en los casos de necrosis digital.
- La necrosis digital puede presentar buena evolución con tratamiento no quirúrgico.

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