Vall d'Hebron Hospital

UAB Universitat Autònoma de Barcelona

SOCIETAT CATALANOBALEAR MEDICINA INTERNA

TRACTAMENT EN LES MALALTIES AUTOIMMUNES

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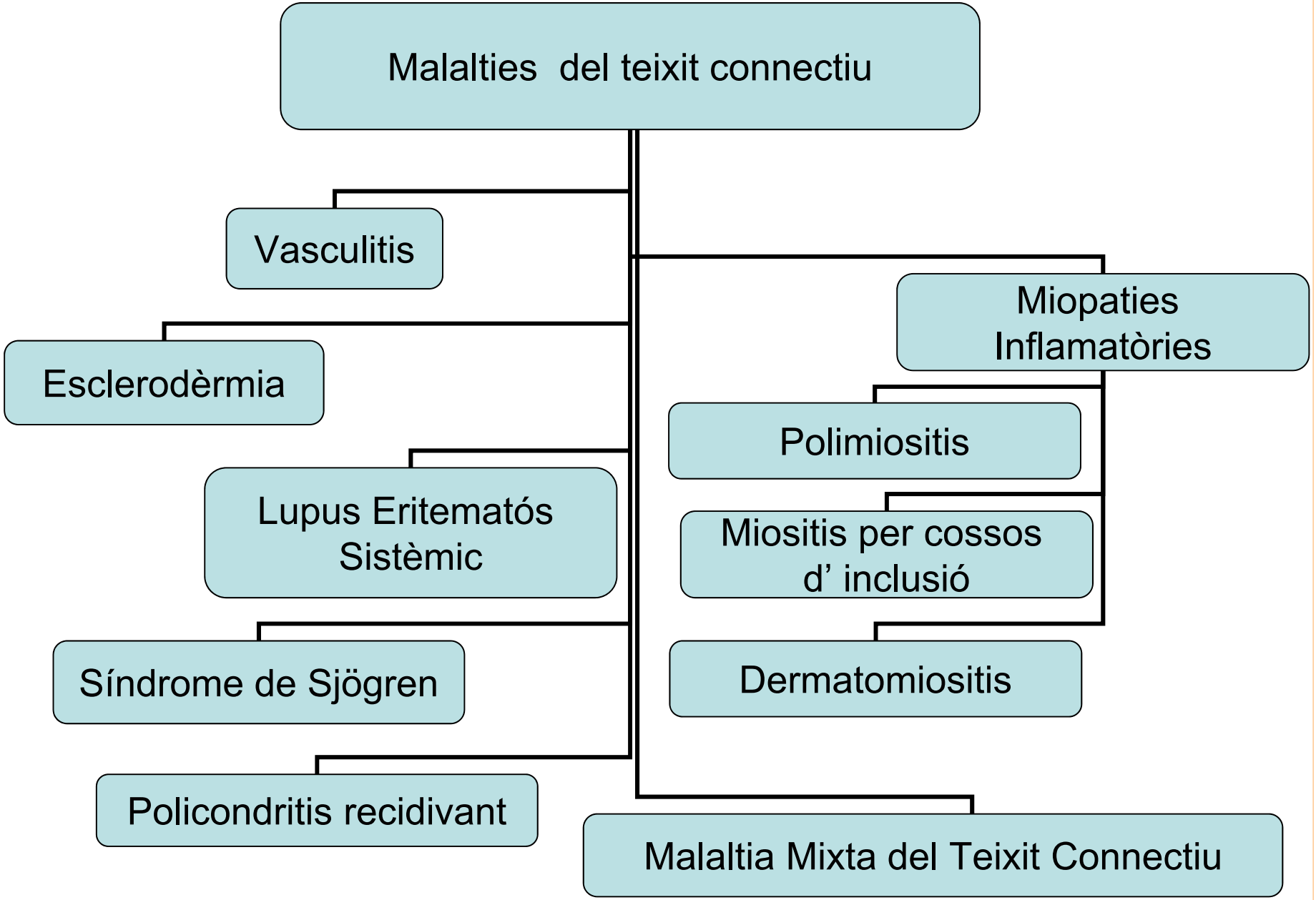

Malalties del teixit connectiu
Vasculitis
Esclerodèrmia
Lupus Eritematós Sistèmic
Síndrome de Sjögren
Policondritis recidivant
Miopaties Inflamatòries
Polimiositis
Miositis per cossos d' inclusió
Dermatomiositis
Malaltia Mixta del Teixit Connectiu

Principis Generals

- totes les malalties autoimmunes no son iguals
- no existeix un tractament ideal (seguretat, tolerància, eficàcia, cost, efectes adversos)
- diferents mecanismes d'acció dels fàrmacs, de vegades complementaris
- necessari utilitzar el fàrmac menys tòxic en funció de les manifestacions clíniques: estratificació del tractament

Tractament en les malalties autoimmunes

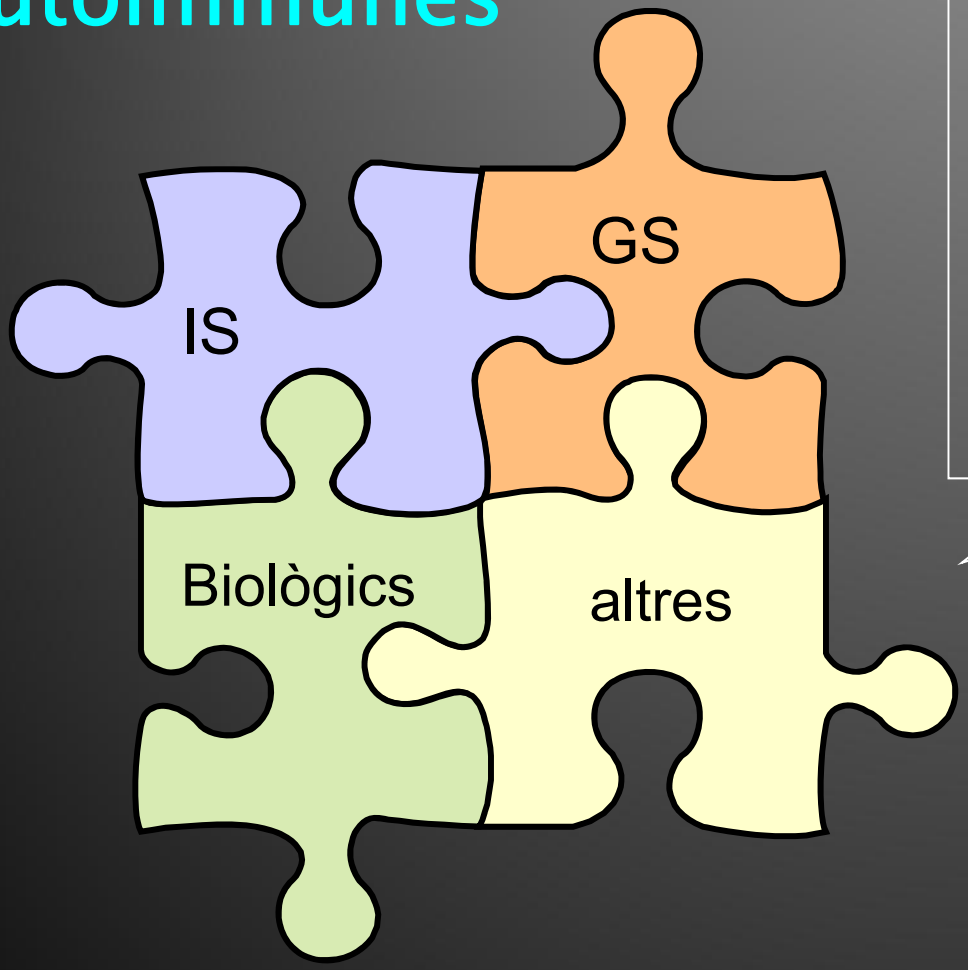
Glucocorticoides

- Fàrmacs IS:
  - Ciclofosfamida
  - Azatioprina
  - Metotrexate
  - Micofenolat
  - Ciclosporina
  - Tacrolimus

- Fàrmacs no IS
  - Bosentan
  - Sildenafilo
  - Prostaglandinas
  - Colchicina
  - Hidroxicloroquina
  - Talidomida
  - AINEs
  - IECAs

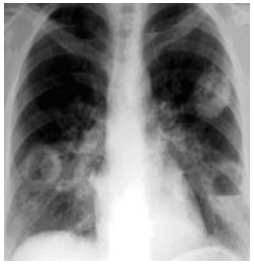
➢ Teràpies biològiques
- Anti-TNF
- Anti-CD20

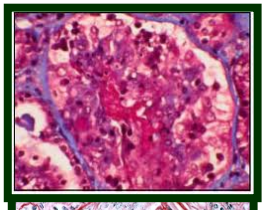
Tractament en les malalties autoimmunes

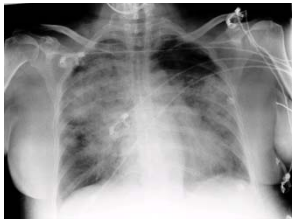


¿quins utilitzar?
¿quan temps?
¿quins es poden utilitzar durant l'embaràs?

RECOMENACIONS TERAPÈUTIQUES VASCULITIS ASSOCIADES A ANCA







EULAR Recommendations for the management of primary small and medium vessel vasculitis

Chetan Mukhtyar, Loic Guillevin, Maria C Cid, Bhaskar Dasgupta, Kirsten de Groot, Wolfgang Gross, Thomas Hauser, Bernhard Hellmich, David Jayne, Cees GM Kallenberg, Peter A Merkel, Heiner Raspe, Carlo Salvarani, David GI Scott, Coen Stegeman, Richard Watts, Kerstin Westman, James Witter, Hasan Yazici and Raashid Luqmani

Ann Rheum Dis 2009;**68**:310–317.

KDIGO Clinical Practice Guideline

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

for Glomerulonephritis

Kidney International Supplements (2012) **2,** 233–239

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

N Engl J Med 2010;363:221-32.

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

N Engl J Med 2010;363:211-20.

Estratificació tractament

Table 1 | Management of antineutrophil cytoplasmic antibody-associated vasculitides

Disease severity	European Vasculitis Study Group definition	Induction therapy	Maintenance therapy
Localized disease	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms	Methotrexate and steroids	Low-dose steroids plus azathioprine or leflunomide or methotrexate (and trimethoprim–sulfamethoxazole)
Early systemic disease	Disease that is neither organ-threatening nor life-threatening	Methotrexate or cyclophosphamide and steroids	Low-dose steroids plus azathioprine
Generalized disease	Renal or other organ-threatening disease; serum creatinine level <500 μmol/l	Cyclophosphamide and steroids	Low-dose steroids plus azathioprine or mycophenolate mofetil
Severe disease	Renal or other vital organ failure; serum creatinine level >500 μmol/l	Cyclophosphamide and steroids plus plasma exchange	Low-dose steroids plus azathioprine or mycophenolate mofetil
Refractory disease	Progressive disease unresponsive to glucocorticoids and cyclophosphamide	Deoxyspergualin, mycophenolate mofetil, antithymocyte globulin or rituximab	No consensus

EULAR recomanacions

6. We recommend a combination of cyclophosphamide (intravenous or oral) and glucocorticoids for remission-induction of generalised primary small and medium vessel vasculitis.

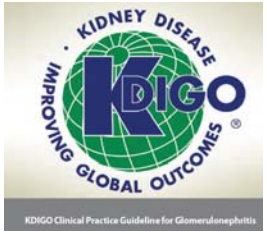
[Level of evidence 1A for WG and MPA, Grade of recommendation A]

[Level of evidence 1B for PAN and CSS, Grade of recommendation A]

13.1: Initial treatment of pauci-immune focal and segmental necrotizing GN

13.1.1: We recommend that cyclophosphamide and corticosteroids be used as initial treatment. (*1A*)

13.1.2: We recommend that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (*1B*)



Tractament d'inducció de remissió

es recomana

Ciclofosfamida +Corticoides (1A)

o

Rituximab 375 mg/m2 x 4 + Corticoides (1B)

+

Plasmafèresis (si requereix diàlisis o deterior ràpid) (2C)

En malalts amb contraindicació CF o malaltia no severa

es suggereix

Afegir plasmafèresis si hemorràgia pulmonar difusa (2C)

Plasmafèresis en malalts anti-MBG+ANCAS (2D)

Discontinuar el tractament amb ciclofosfamida després de 3 mesos si el malalt segueix requerint diàlisis (2C)

Règim recomanat de tractament

Table 30 | Recommended treatment regimens for ANCA vasculitis with GN

Agent	Route	Initial dose
Cyclophosphamide[a]	i.v.	0.75 g/m^2 q 3-4 weeks. Decrease initial dose to 0.5 g/m^2 if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust subsequent doses to achieve a 2-week nadir leukocyte count >3000/mm^3.
Cyclophosphamide[b]	p.o.	1.5–2 mg/kg/d, reduce if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust the daily dose to keep leucocyte count >3000/mm^3.
Corticosteroids	i.v.	Pulse methylprednisolone: 500 mg i.v. daily × 3 days.
Corticosteroids	p.o.	Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60 mg daily. Taper down over 3-4 months.
Rituximab[c]	i.v.	375 mg/m^2 weekly × 4.
Plasmapheresis[d]		60 ml/kg volume replacement. *Vasculitis*: Seven treatments over 14 days If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments. *Vasculitis in association with anti-GBM antibodies*: Daily for 14 days or until anti-GBM antibodies are undetectable.

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; i.v., intravenous; p.o., orally.

[a]Given with pulse and oral steroids. An alternative i.v. cyclophosphamide dosing schema is 15 mg/kg given every 2 weeks for three pulses, followed by 15 mg/kg given every 3 weeks for 3 months beyond remission, with reductions for age and estimated GFR.[705]

[b]Given with pulse and oral steroids.

[c]Given with pulse and oral steroids.

[d]Not given with pulse methylprednisolone. Replacement fluid is 5% albumin. Add 150-300 ml fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.

Tractament de manteniment de remissió

es recomana

mantenir tractament en malalts que han assolit remissió (1B), excepte si requereixen diàlisis > 3 mesos i no presenten cap manifestació extra-renal (1C)

AZA 1-2 mg/kg/dia (1B)

10. We recommend remission-maintenance therapy with a combination of low dose glucocorticoid therapy and, either azathioprine, leflunomide or methotrexate.

[Level of evidence 1B for Azathioprine, Grade of recommendation A]
[Level of evidence 1B for Leflunomide, Grade of recommendation B]
[Level of evidence 2B for Methotrexate, Grade of recommendation B]

mantenir tractament de manteniment al menys 18 mesos en malalts que estan en remissió complerta (2D)

TMT-SX en malalts amb afecció de via respiratòria alta (2B)

REMAIN trial (AVERT project BIOMED-2: BMH-CT93-1078), EUVAS

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.D., Robert Spiera, M.D., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., and John H. Stone, M.D., M.P.H., for the RAVE-ITN Research Group*

N Engl J Med 2013;369:417-27.
AUGUST 1, 2013

- Estudi RAVE: RTX *versus* CF + AZA
- RC als 6 mesos en 64% RTX *versus* 53% CF
- RTX mes eficaç en pacients amb malaltia recidivant a la entrada en l'estudi
- No diferencia en quant a la duració de la remissió, ni freqüència i gravetat de recidives, ni en quant a efectes adversos excepte menor freqüència leucopènia y pneumònia en grup RTX

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

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N Engl J Med 2013;369:417-27.
AUGUST 1, 2013

- major risc de recaiguda:
  - pacients PR3 + ($p < 0.001$)
  - pacients con GPA
  - [illegible]ada en l'

Desconeixem quan temps hem de donar RTX per mantenir la remissió, quina dosis hem d'utilitzar i cada quan l'hem d'administrar

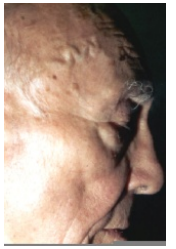
- CD20 reconstituïts en 88% pacients tractats amb RTX i 55% de tractats amb CF + AZA, que van presentar recidiva (no relació amb ANCA)

Recomanacions

- CF i RTX son igual de eficaços en la inducció de remissió en les VAA, però es recomana administració de RTX en:
  - malalts que han presentat múltiples recidives
  - quan la CF no es eficaç
  - malalts joves en edat fèrtil
  - malalts que han rebut altes dosis de CF
- no es recomana la administració conjunta de RTX i altres immunosupressors a dosis completa, si be s'ha d'avaluar el se us conjunt en dosis mes baixes
- no es recomana readministraciò de RTX en malats que han presentat citopènies (neutropènia, pneumònia)

Does glucocorticosteroid-resistant large-vessel vasculitis (giant cell arteritis and Takayasu arteritis) exist and how can remission be achieved? A critical review of the literature

I. Kötter[1], J.C. Henes[1], A.D. Wagner[2], J. Loock[3,4], W.L. Gross[4]



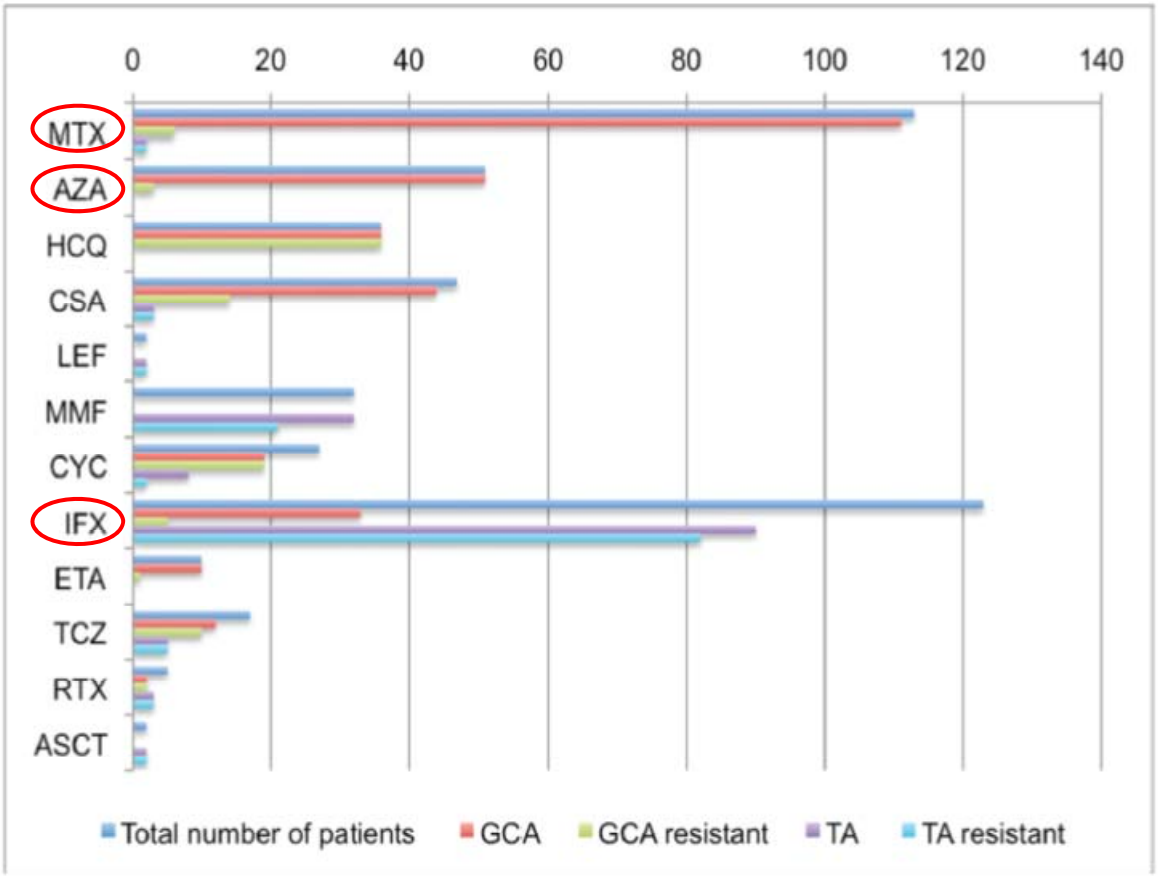


Fig. 1. Distribution of patients on medications. Columns show total number of patients for GCA and TA as well as the number of patients regarded as resistant to GC treatment, respectively.

- No hi han estudis prospectius randomitzats que comparin GC *versus* GS + IS
- No hi ha criteris ben definits de remissió de la malaltia, de recaiguda, ni de malaltia refractària
- No existeix un "índex d'activitat" estandarditzat
- No existeixen recomanacions basades en la evidencia

Clin Exp Rheumatol 2012; 30 (Suppl. 70): S114-S129.

Treatment of Refractory Polymyalgia Rheumatica with Infliximab: a Pilot Study

CARLO SALVARANI, FABRIZIO CANTINI, LAURA NICCOLI, MARIA GRAZIA CATANOSO, PIERLUIGI MACCHIONI, LIA PULSATELLI, ANGELA PADULA, IGNAZIO OLIVIERI, and LUIGI BOIARDI

(J Rheumatol 2003;30:760–3)

Annals of Internal Medicine ARTICLE

Infliximab plus Prednisone or Placebo plus Prednisone for the Initial Treatment of Polymyalgia Rheumatica

A Randomized Trial

Carlo Salvarani, MD; PierLuigi Macchioni, MD; Carlo Manzini, MD; Giuseppe Paolazzi, MD; Aldo Trotta, MD; Paolo Manganelli, MD; Marco Cimmino, MD; Roberto Gerli, MD; Maria Grazia Catanoso, MD; Luigi Boiardi, MD; Fabrizio Cantini, MD; Catherine Klersy, MD; and Gene G. Hunder, MD

Ann Intern Med. 2007;146:631-639.

EDITORIAL Annals of Internal Medicine

Treatment of Polymyalgia Rheumatica and Giant Cell Arteritis: Are We Any Further Forward?

Ann Intern Med. 2007;146:621-630.

Annals of Internal Medicine ARTICLE

Infliximab for Maintenance of Glucocorticosteroid-Induced Remission of Giant Cell Arteritis

A Randomized Trial

Gary S. Hoffman, MD; Maria C. Cid, MD; Karen E. Rendt-Zagar, MD; Peter A. Merkel, MD, MPH; Cornelia M. Weyand, MD; John H. Stone, MD, MPH; Carlo Salvarani, MD; Weichun Xu, PhD; Sudha Visvanathan, PhD; and Mahboob U. Rahman, MD, PhD, for the Infliximab-GCA Study Group*

Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents

N. Pipitone[1], I. Olivieri[2], C. Salvarani[1]

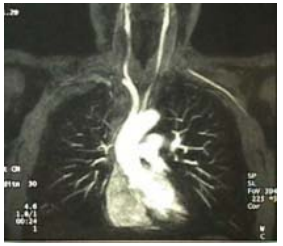
Clin Exp Rheumatol 2012; 30 (Suppl. 70): S139-S161.

- No se recomienda el uso de anti-TNF (Infliximab, Etanercept) en monoterapia ni como tratamiento adyuvante, en el tratamiento inicial de la ACG.
- Sólo se recomienda el uso de anti-TNF en pacientes con ACG y ≥ 2 brotes a pesar de tratamiento adecuado con GC y ≥ 1fármaco inmunosupresor (MTX o AZA) (nivel de evidencia 4 C)
- No se recomienda la administración de Tocilizumab (anti-IL6) como monoterapia ni como tratamiento adyuvante en la ACG. Sólo se aconseja en pacientes con ACG y afección de grandes vasos refractaria a GC y ≥ 1 fármaco inmunosupresor (nivel de evidencia 4C)
- No existe evidencia que avale el uso de Rituximab (2 casos)
- Si no existe mejoría a los 4 meses de la administración de terapia biológica, se aconseja discontinuarla

Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents

N. Pipitone[1], I. Olivieri[2], C. Salvarani[1]

Clin Exp Rheumatol 2012; 30 (Suppl. 70): S139-S161.



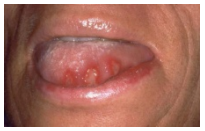
- No existe evidencia que avale el uso de anti-TNF en monoterapia en el tratamiento de TAK. Tampoco existe evidencia que avale el uso de Tocilizumab en monoterapia.

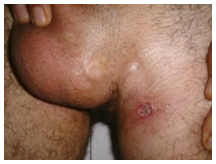
- No existe evidencia que avale el uso de anti-TNF ni de Tocilizumab como fármacos de primera línea en el tratamiento del TAK de reciente diagnóstico.

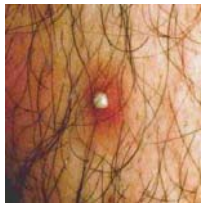
- Los fármacos anti-TNF y el Tocilizumab pueden administrarse en pacientes afectos de TAK de ≥ 6 meses de evolución, con actividad persistente o que hayan presentado ≥ 2 brotes, a pesar de tratamiento con GC y ≥ 1 fármaco inmunosupresor (MTX, AZA, MMF) (nivel de evidencia 4 C)

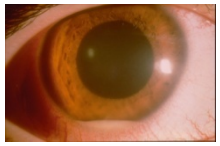
- Si no existe mejoría a los 4 meses de la administración de terapia biológica, se aconseja discontinuarla

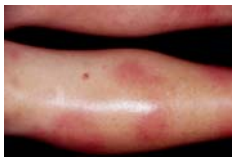
Glucocorticoides, azatioprina, MMF, anti-TNF











Immunosuppressants Reduce Venous Thrombosis Relapse in Behçet's Disease

A. C. Desbois,[1] B. Wechsler,[1] M. Resche-Rigon,[2] J. C. Piette,[1] D. Le Thi Huong,[1] Z. Amoura,[1] F. Koskas,[3] K. Desseaux,[2] P. Cacoub,[1] and D. Saadoun[1]

807 pacients

ARTHRITIS & RHEUMATISM
Vol. 64, No. 8, August 2012, pp 2753–2760

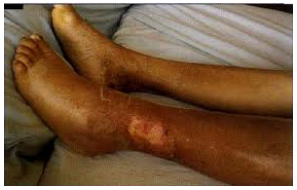
Table 1. Comparison of the patients with Behçet's disease according to the presence or absence of venous involvement*

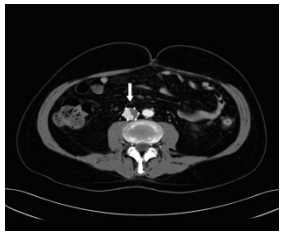
	With venous involvement (n = 296)	Without venous involvement (n = 511)	*P*
Demographic features			
Male sex	217 (73.3)	317 (62)	0.0009
Age, median (IQR) years	30 (24–36)	30 (24–37)	0.91
Geographic origin			
Europe	140 (47.3)	238 (46.6)	–
North Africa	126 (42.6)	221 (43.2)	–
Africa	17 (5.7)	20 (3.9)	–
Clinical features			
Oral ulcerations	294 (99.3)	497 (97.3)	1
Genital ulcerations	177 (59.8)	309 (60.5)	1
Articular involvement	114 (38.5)	258 (50.5)	0.0006
Ocular involvement	163 (55.1)	348 (68.1)	0.0002
Cardiac involvement	29 (9.8)	18 (3.5)	0.0005
Arterial involvement	55 (18.6)	30 (5.9)	<0.0001
Neurologic involvement	114 (38.5)	144 (28.2)	0.005
HLA–B51 positive	98/219 (44.7)	211/380 (55.5)	0.014
Death	19 (6.4)	21 (4.1)	–

Colchicina, glucocorticoides, azatioprina, ciclosporina A, anti-TNF (Infliximab, Adalimubab)

807 pacients BÇ

296 (37%): trombosis venosa (24-36 anys), 73% ♂





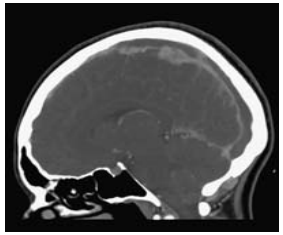
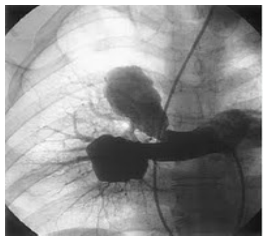


Table 2. Characteristics of venous involvement in the BD patients*

Superficial	26 (4.4)
Deep	560 (95.6)
Multiple	207 (35.3)
Location/type of venous lesions	
Lower limbs	306 (52.2)
Cerebral veins	77 (13.1)
Pulmonary embolism	57 (9.7)
Inferior vena cava	44 (7.5)
Superior vena cava	19 (3.2)
Upper limbs	17 (2.9)
Budd-Chiari syndrome	14 (2.4)
Cervical veins	13 (2.2)
Right ventricle	6 (1)
Right atrium	5 (0.9)
Other thrombosis	28 (4.8)
Retinal	14 (0.50)
Renal	4 (0.14)
Temporal	4 (0.14)
Ophthalmic	2 (0.07)
Nasal	2 (0.07)
Hypogastric	1 (0.04)
Portal	1 (0.04)

* Values are the number (%) of events. There were 586 thrombosis events overall in the 296 patients with Behçet's disease (BD) who had venous involvement.



Anticoagulació 98.6% malalts, 10 mesos (4-24)

IS 46.8% malalts, 3.1 anys (1-5):

- 34% CF polsos
- 69% AZA
- 8.5% MTX
- 14.6% CL
- 5.8% CyA
- 5.1% talidomida
- 1.5% IFX
- 2.9% α-IFN

GS 68.7% malalts

Treatment strategies. Medical treatments included anticoagulants, immunosuppressive agents, and glucocorticoids. Anticoagulation consisted of heparin followed by oral anticoagulants. Anticoagulants did not include aspirin or clopidogrel. Main indications for the use of immunosuppressive agents included large-vessel thrombosis, severe cardiac lesions and/or arterial lesions, and severe uveitis and/or neurologic involvement. Immunosuppressive agents were prescribed in 53% of cases of large-vessel thrombosis, 63% of cases of neurologic involvement, 75% of cases of arterial involvement, 61% of cases of cardiac lesions, and 51% of cases of ocular involvement.

A l'anàlisi multivariant l'ús de immunosupressors es va relacionar significativament amb la prevenció de recidives de trombosis venoses (HR 0.27, 95% CI 0.14-0.52), $p<0.0001$.

Es va observar una tendència a la prevenció de recidiva de trombosis amb l'ús de corticosteroides (HR 0.62, 95%IC 0.4-0.97), p= 0.058

REVIEWS

Systemic sclerosis—challenges for clinical practice

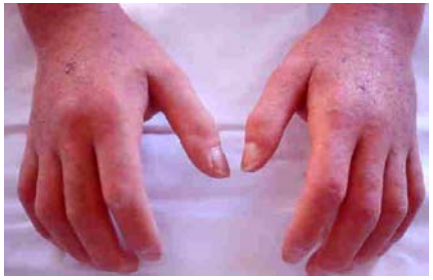
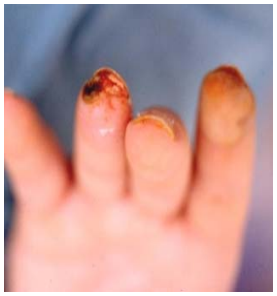
McMahan, Z. H. & Hummers, L. K. *Nat. Rev. Rheumatol.* advance online publication 13 November 2012;

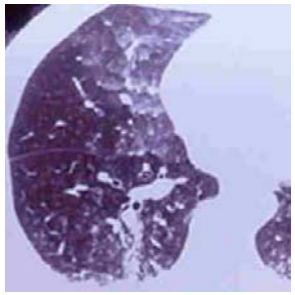
Review

Clinical trial design in scleroderma: where are we and where do we go next?

L. Chung[1], C.P. Denton[2], O. Distler[3], D.E. Furst[4], D. Khanna[5], P.A. Merkel[6]
for the Scleroderma Clinical Trials Consortium

Clin Exp Rheumatol 2012; 30 (Suppl. 71)




Estratificació tractament

Diagnosis and Classification of Systemic Sclerosis

Eric Hachulla · David Launay

Clinic Rev Allerg Immunol (2011) 40:78–83

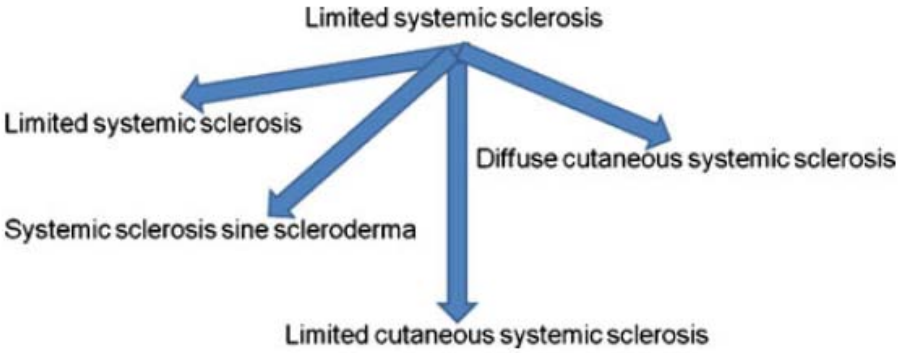
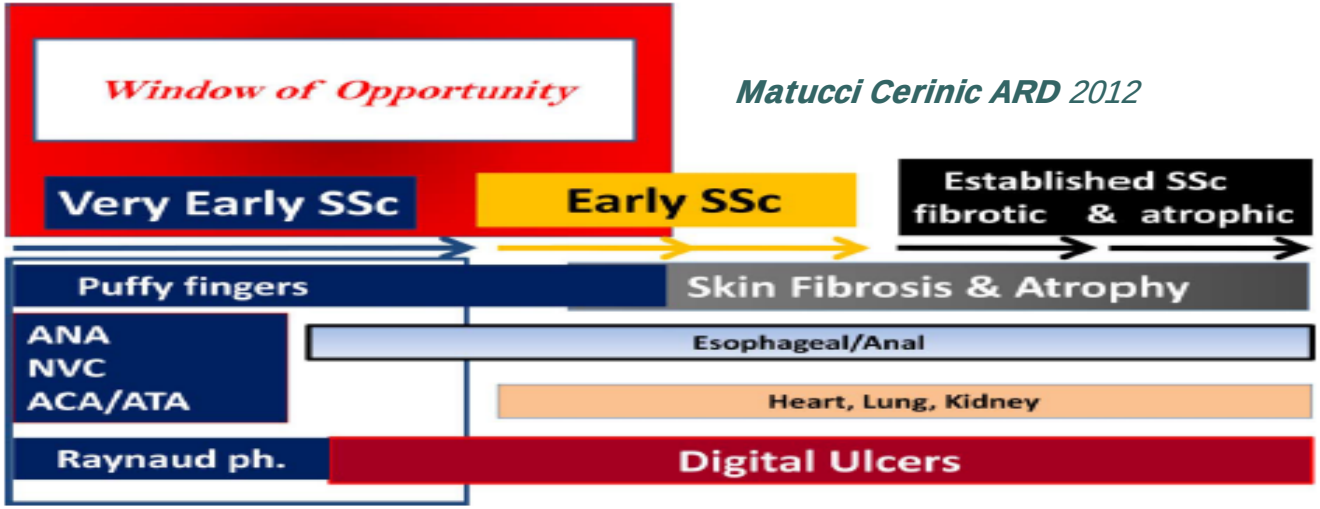


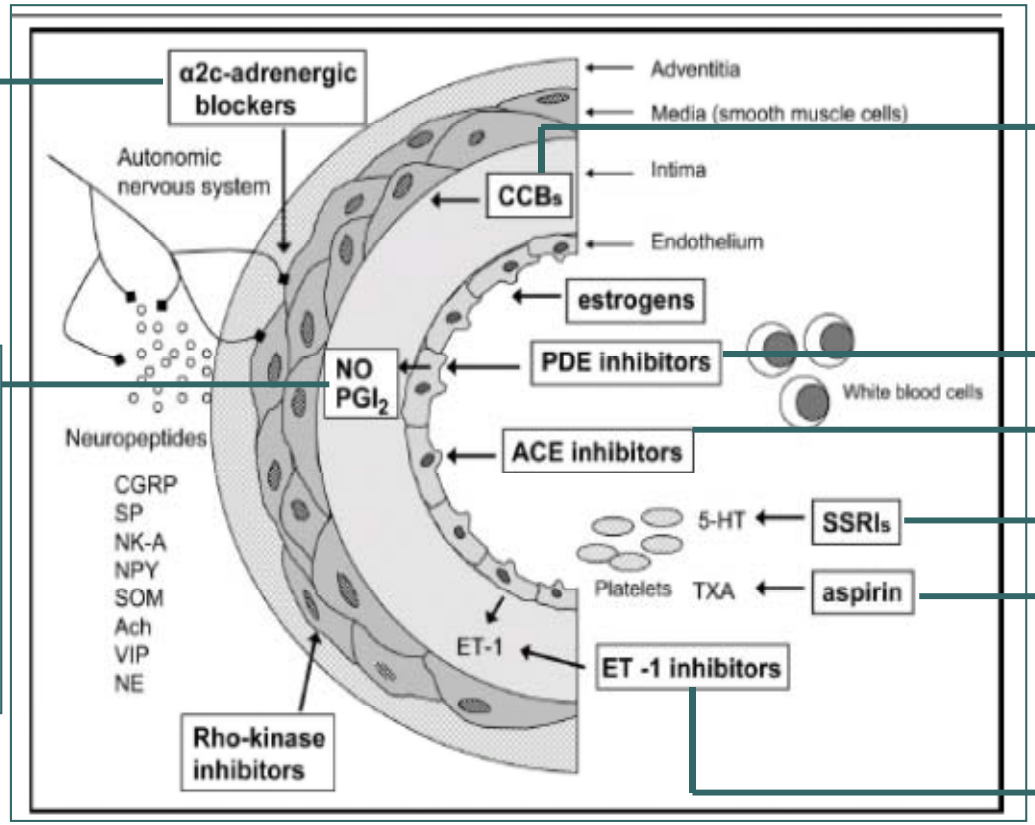
Fig. 1 The four possible evolutions of limited systemic sclerosis



***Matucci Cerinic ARD** 2012*

ESCLERODÈRMIA: Tractament Úlceres digitals

OC-28326



Prostaciclina
Epoprostenol iv
Alprostadil iv
Iloprost iv
Treprostinil sc
Tópica

Calciantagonistes
Nifedipi
Amlodipi
Diltiazem

Sildenafil

IECAs – ARA II

Fluoxetina

Á. acetilsalicílic
Clopidogrel
Anticoagulació

Bosentan

Mesures generals
Antibioteràpia
Cures tòpiques
Analgèsia

Tractament quirúrgic
Simpatectomia cervical
Simpatectomia digital
Desbridament

ESCLERODÈRMIA: Tractament Úlceres digitals

Medidas generales

Evitar: . exposición al frio y stress
. fármacos/tóxicos vasoconstrictores
. Heridas, golpes
Hidratación correcta,
Hb normal, Estado nutricional correcto

Efectivo → Seguir igual

Inefectivo → **Antagonistas del calcio** (Diltiazem o Amlodipino) + **+ AAS 100 mg/d** o clopidrogel 75 mg/d → **Efectivo** → Seguir igual

Inefectivo → **+ ARA II** (losartan 25-100 mg/d) **+/- nitratos tópicos** **+/- ISRS** (fluoxetina 20-40 mg/d) → **Efectivo** → Seguir igual

Inefectivo → **Úlcera digital** (regresión?) ? → **Bosentan** y/o sildenafilo → **Efectivo** → Seguir igual

Bosentan y/o sildenafilo → Inefectivo → **IQ:** Simpatectomia digital / Amputación

Inefectivo → **Úlcera/s digital/es** Complicadas (isquemia severa) → **Prostaglandinas ev** Iloprost / Alprostadil

Desbridamiento? / HBPM? Antibiótico? / Analgesia

Atorvastatina 40 mg/d Vitamina E gel /N.A.C

Rheumatology 2009;48:iii25–iii31 doi:10.1093/rheumatology/kep107

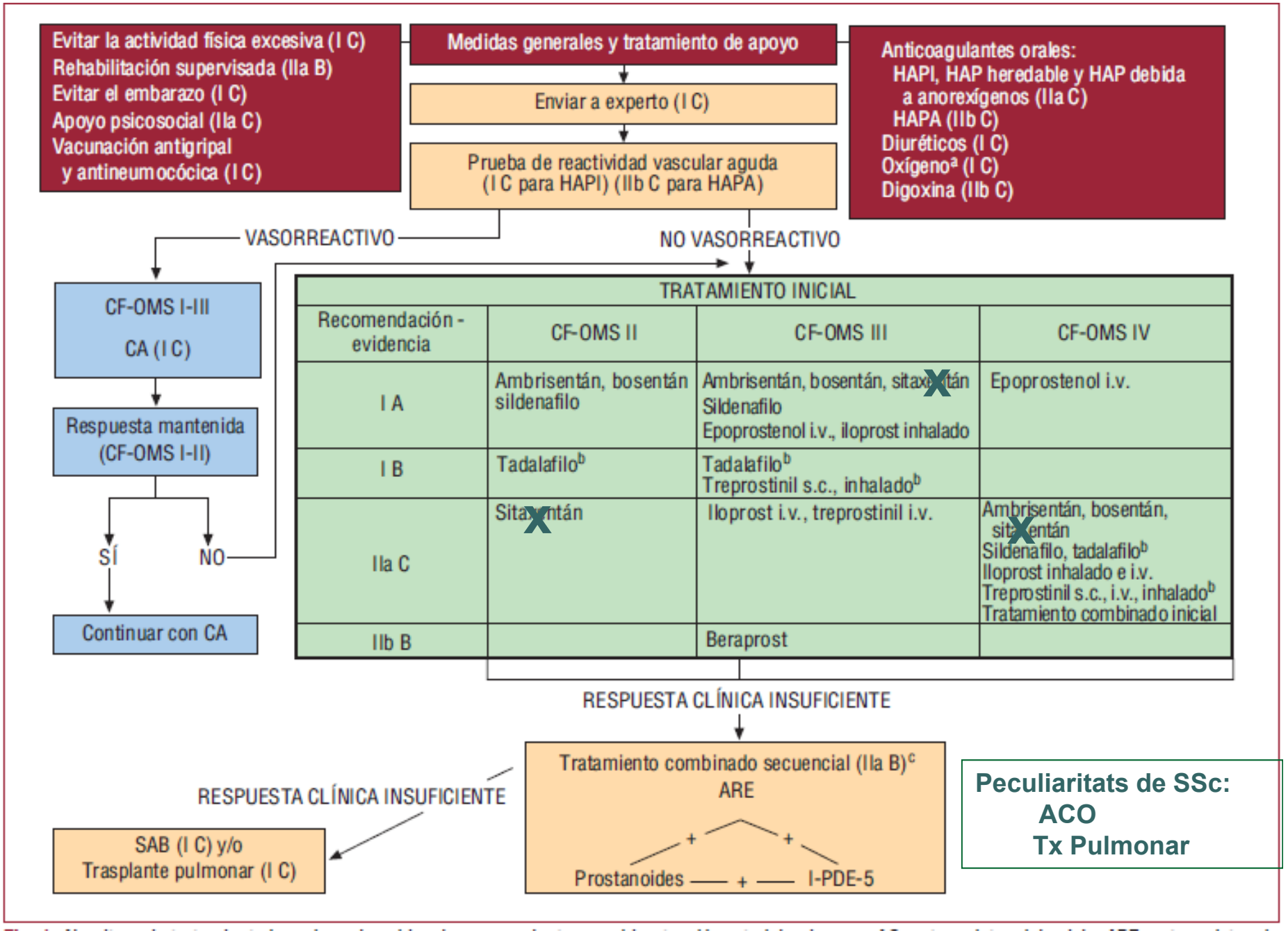
Pulmonary arterial hypertension: the most devastating vascular complication of systemic sclerosis

V. McLaughlin[1], M. Humbert[2], G. Coghlan[3], P. Nash[4] and V. Steen[5]

TABLE 2 Survival in systemic sclerosis-associated pulmonary arterial hypertension

Survival %					
1-yr	2-yr	3-yr	5-yr	Median	
Not reported	60	Not reported	Not reported	Not reported	1986
50	44	40	4	12 months	1996
Not reported	50	Not reported	10	Not reported	2003
81	63	56	Not reported	3 yrs	2003
81	71	NR	Not reported	Not reported	2006
78	58	47	Not reported	Not reported	2009
86	68	56	Not reported	Not reported	2009
85	72	67	36	4 yrs	2010
80	56	51	Not reported	Not reported	2010
82	Not reported	Not reported	Not reported	Not reported	2010
81	72	64	49	4.9 yrs *	2000
Not reported	72	Not reported	48	Not reported	2011

Eur Respir Rev 2011; 20: 122, 277–286



Galié, European Heart Journal 2009

Effect of mycophenolate sodium in scleroderma-related interstitial lung disease

Carmen Pilar Simeón-Aznar • Vicent Fonollosa-Plá •
Carles Tolosa-Vilella • Albert Selva-O'Callaghan •
Roser Solans-Laqué • Miquel Vilardell-Tarrés

Clin Rheumatol.2011;11:1383-8

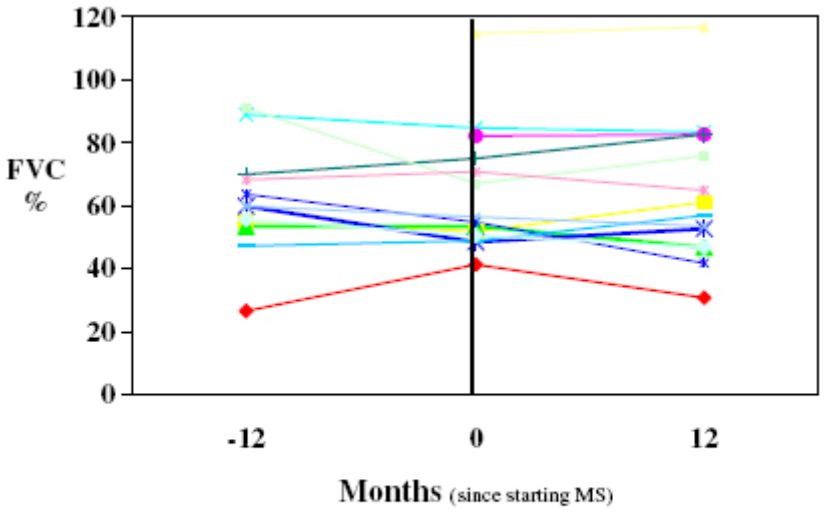


Fig. 1 FVC (percentage of predicted) over time in SSc-ILD patients. Each *line* represents measurements made in each single subject. A time of 0 month indicates when MS was started

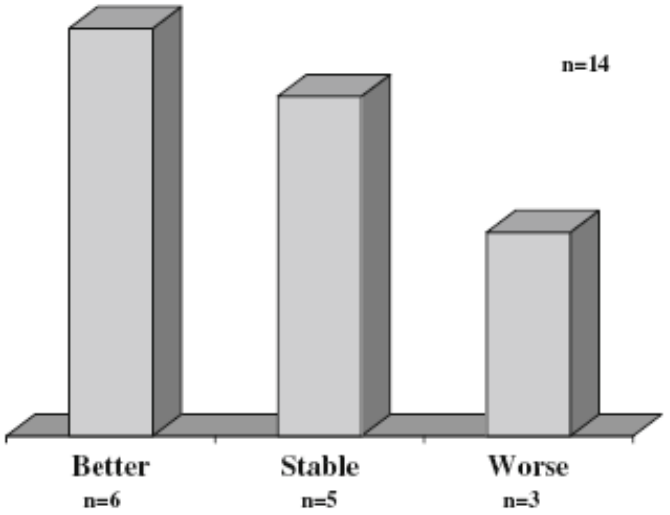


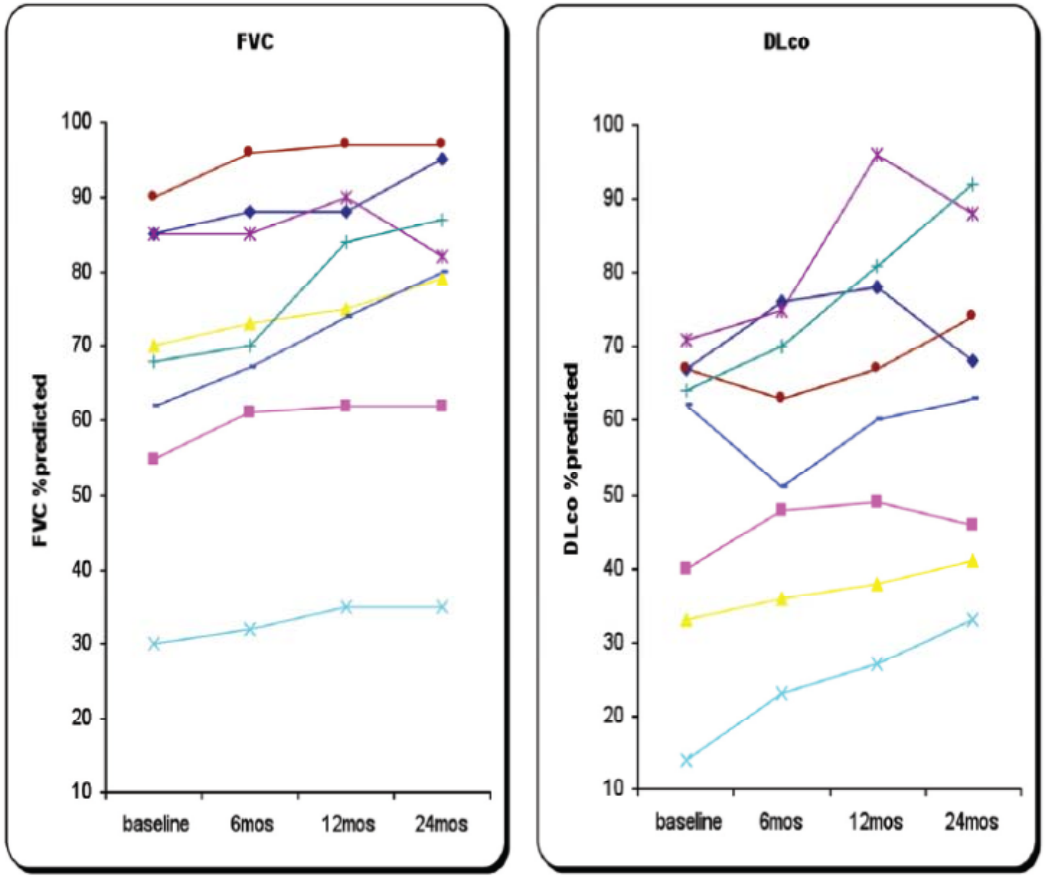
Fig. 2 Summary of the outcome of patients who had either improved, stable or worse FVC over 12 months of treatment

Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis

D. Daoussis[1], S.C. Liossis[1], A.C. Tsamandas[2], C. Kalogeropoulou[3], F. Paliogianni[4], C. Sirinian[2], G. Yiannopoulos[1], A.P. Andonopoulos[1]

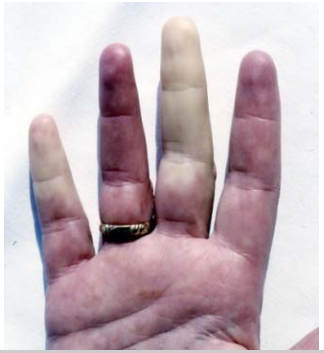
Clin Exp Rheumatol 2011.

- Estudio de extensión
- 24 meses
- 8 pacientes
- 4 ciclos de RTX
- CVF ↑ 12.79%



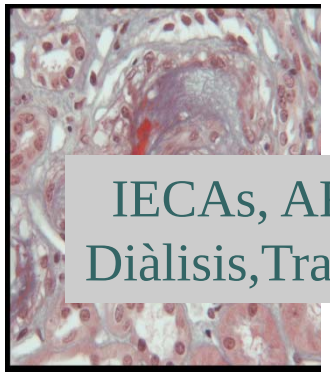
ESCLERODERMIA
Tractament

Micofenolat
Metotrexate



Antagonistes Ca
Antiagregants

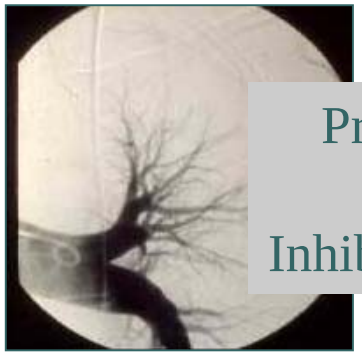
Antagonistes Ca
Antiagregants
Prostaciclina
ARE, IFDE-5



IECAs, ARA II
Diàlisis,Trasplantament

IBP
Procinètics
Antibiòtics cíclics

Micofenolat
Ciclofosfamida
Rituximab



Prostaciclina
AREs
Inhibidors FDE-5

Treatment of Systemic Lupus Erythematosus

A 2012 Update

Joan T. Merrill, M.D.

Bulletin of the NYU Hospital for Joint Diseases 2012;70(3):172-6

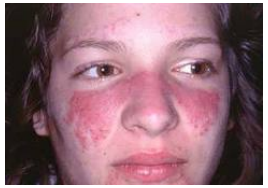


Table 1 Current Treatment Options for SLE in Clinical Practice: 2012

Treatment/Indication	Not Organ Threatening	Organ Threatening	Nephritis Induction	Nephritis Maintenance	Refractory Disease
Antimalarials	+	+	+	+	+
Steroids	+	+	+	+	+
Mycophenolate		+	+	+	+
Azathioprine		+		+	+
Methotrexate		+			+
Leflunomide		+			+
Cyclophosphamide			+		+
Cyclosporine/tacrolimus					+
Belimumab					+
Rituximab/other biologics					+
IVIG/plasma exchange					+
Stem cell transplant					+

Lupus nephritis

KDIGO Clinical Practice Guideline

for Glomerulonephritis

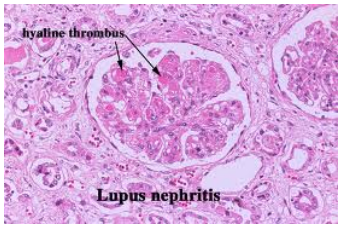
Kidney International Supplements (2012) **2,** 221–232

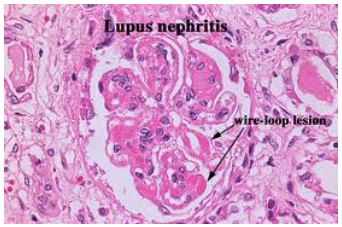
Diagnosis and treatment of lupus nephritis

Consensus document from the systemic auto-immune disease group (GEAS) of the Spanish Society of Internal Medicine (SEMI) and the Spanish Society of Nephrology (S.E.N.)

Guillermo Ruiz-Irastorza[1], Gerard Espinosa[2], Miguel A. Frutos[3], Juan Jiménez-Alonso[4], Manuel Praga[5], Lucio Pallarés[6], Francisco Rivera[7], Ángel Robles-Marhuenda[8], Alfons Segarra[9], Carlos Quereda[10]

Nefrologia 2012;32(Suppl.1):1-35





12.2: Class II LN (mesangial-proliferative LN)

12.2.1: Treat patients with class II LN and proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

12.2.2: We suggest that class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (see Chapter 5). (*2D*)

12.3: Class III LN (focal LN) and class IV LN (diffuse LN)—initial therapy

12.3.1: We recommend initial therapy with corticosteroids (*1A*), combined with either cyclophosphamide (*1B*) or MMF (*1B*).

12.3.2: We suggest that, if patients have worsening LN (rising SCr, worsening proteinuria) during the first 3 months of treatment, a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. (*2D*)

PDN 1mg/kg/dia 6-12 mesos ± polsos MTPDN

+

CF polsos mensuals 0.5-1 g/m^2 x 6 mesos (NIH regim) o
Polsos CF 500 mg/15 dies x 3 mesos (regim B) o Eurolupus regim) o
CF oral 1-1,5 mg/Kg/dia (150 mg/dia) x 2-4 mesos (regim C)

MMF(màxim 3 g/d) x 6 mesos (regim D) resposta equivalent a CF x 6 mesos
AZA no superior a MMF

Tractament de manteniment

12.4: Class III LN (focal LN) and class IV LN (diffuse LN)—maintenance therapy

12.4.1: We recommend that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with azathioprine (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose oral corticosteroids (≤10 mg/d prednisone equivalent). (*1B*)

12.4.2: We suggest that CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. (*2C*)

12.4.3: We suggest that, after complete remission is achieved, maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression. (*2D*)

12.4.4: If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. (*Not Graded*)

12.4.5: While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, we suggest that treatment be increased to the previous level of immunosuppression that controlled the LN. (*2D*)

12.5: Class V LN (membranous LN)

12.5.1: We recommend that patients with class V LN, normal kidney function, and non–nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

12.5.2: We suggest that patients with pure class V LN and persistent nephrotic proteinuria be treated with corticosteroids plus an additional immunosuppressive agent: cyclophosphamide (*2C*), or CNI (*2C*), or MMF (*2D*), or azathioprine (*2D*).

12.6: General treatment of LN

12.6.1: We suggest that all patients with LN of any class are treated with hydroxychloroquine (maximum daily dose of 6–6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. (*2C*)

12.8: Relapse of LN

12.8.1: We suggest that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (*2B*)

12.8.1.1: If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then we suggest a non–cyclophosphamide-based initial regimen be used (Regimen D, Table 28). (*2B*)

12.8.2: Consider a repeat kidney biopsy during relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty whether a rising SCr and/or worsening proteinuria represents disease activity or chronicity. (*Not Graded*)

12.11: Systemic lupus and pregnancy

12.11.1: We suggest that women be counseled to delay pregnancy until a complete remission of LN has been achieved. (*2D*)

12.11.2: We recommend that cyclophosphamide, MMF, ACE-I, and ARBs not be used during pregnancy. (*1A*)

12.11.3: We suggest that hydroxychloroquine be continued during pregnancy. (*2B*)

12.11.4: We recommend that LN patients who become pregnant while being treated with MMF be switched to azathioprine. (*1B*)

12.11.5: We recommend that, if LN patients relapse during pregnancy, they receive treatment with corticosteroids and, depending on the severity of the relapse, azathioprine. (*1B*)

12.11.6: If pregnant patients are receiving corticosteroids or azathioprine, we suggest that these drugs not be tapered during pregnancy or for at least 3 months after delivery. (*2D*)

12.11.7: We suggest administration of low-dose aspirin during pregnancy to decrease the risk of fetal loss. (*2C*)

Novel Biological Treatments for Systemic Lupus Erythematosus: Current and Future Modalities

Shira Bezalel MD, Ilan Asher MD, Daniel Elbirt MD and Zev Moshe Sthoeger MD

IMAJ • VOL 14 • AUGUST 2012

Table 1. Key biological treatments for SLE

Biological agent	Target	Current status	References
Rituximab (MabThera®)	CD20 (B cells)	Clinical trials failed, off-label usage	[2-8]
Belimumab (Benelysta®)	BLyS (B cells)	FDA-approved	[11-13]
Epratuzumab (LymphoCIDE®)	CD22 (B cells)	Clinical trial in progress	[15,16]
Tocilizumab (Actemra®)	IL-6 receptor	Clinical trial in progress	[27,28]
Anti-IFNα Sifalimumab (Rontalizumab®)	INFα	Clinical trial in progress	[30,31]
Rigerimod Lupozor® RNP-based peptide	Tolerogenic peptide	Clinical trial in the near future	[33]
hCDR1 edratide, hCDR1-based peptide	Tolerogenic peptide	Clinical trial in the near future	[35]

Síndrome de Sjögren

- Tractament simptomàtic:
  - Saliva artificial
  - Llàgrimes artificials
  - Lubricants oculars
  - Botons llagrimalls
  - Sialagogs: pilocarpina

Efficacy and Safety of an Intraoral Electrostimulation Device for Xerostomia Relief

A Multicenter, Randomized Trial

ARTHRITIS & RHEUMATISM
Vol. 63, No. 1, January 2011, pp 180–190

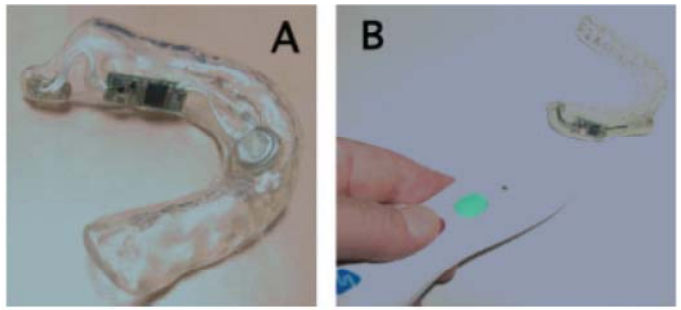
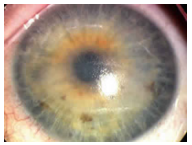


Figure 1. The intraoral electrostimulation device with the electronic circuit on the lingual side (**A**) and with the electronic circuit on the buccal side (**B**), switched on and off by the remote control.

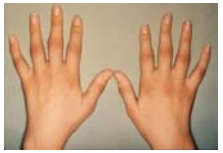
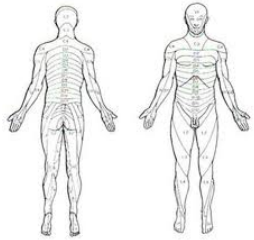
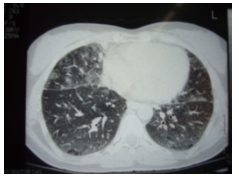
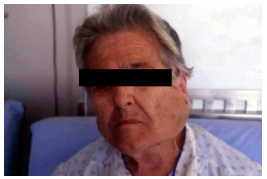
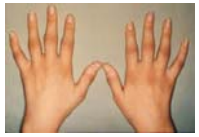
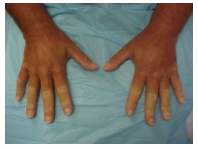
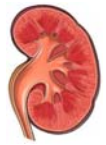





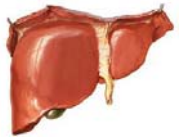
Table 2 Effect of immunomodulating or immunosuppressive medications in the treatment of sicca features in primary Sjögren's syndrome.[41,48–50]

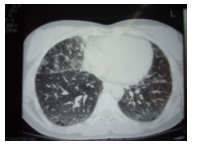
Agent	Formulation and dose	Outcome
Ciclosporin[48]	5 mg/kg body weight daily	Improvement of subjective measures of xerostomia Retardation of evolution of histopathological lesions No improvement of objective indices
	Topical drops (twice daily)	Improvement in objective and subjective indices
Methotrexate[48]	0.2 mg/kg body weight weekly	Improvement in subjective measures No improvement of objective indices
Azathriopine[48]	1 mg/kg body weight daily	No improvement detected Adverse effects
Corticosteroids[48]	Systemic Local	Limited evidence of improvement Induction of corneal lesions
Hydroxychloroquine[48,49]	200 mg daily	No improvement in sicca symptoms Inhibition of glandular cholinesterase activity receptor
D-penicillamine[48]	First 3 months 250 mg daily, next 3 months 500 mg daily	Marginal improvement in sicca symptoms
Thalidomide[48]	50–300 mg daily	Adverse effects/unsuitable
Infliximab[48]	3 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter	No detectable improvement
Etanercept[48]	25 mg subcutaneously twice a week	No detectable improvement
Interferon-α[48]	150 IU 3 times daily for 24 weeks (oromucosal route)	Improvement in oral and ocular symptoms, increase in unstimulated whole saliva flow
Nucleoside analogs[48]	Zidovudine 250 mg twice daily	Significant improvement in sicca symptoms and objective measures
Rituximab[41,50]	375 mg/m^2 weekly for 4 weeks (intravenously)	Improvement of immunohistopathological features and subjective sicca features, increase of salivary function in patients with residual salivary function; increased incidence of human antichimeric antibodies associated with serum sickness features











Manifestation	Main therapeutic modalities
Fatigue[1]	Tricyclic antidepressants (with caution), exercise, myofascial therapy
Musculoskeletal[1,27]	Nonsteroidal anti-inflammatory drugs, hydroxychloroquine, methotrexate
Raynaud's phenomenon[28,29]	Avoidance of cold and stress exposure, calcium-channel blockers
Vasculitis[24,39,40]	Prednisolone (0.5–1.0 mg/kg body weight per day) Cyclophosphamide (0.5–1 g/m^2 of body surface/month) Plasmapheresis Rituximab (375 mg/m^2 weekly, for 4 weeks)
Lymphoma[39,41–43]	Nucleoside analogs, rituximab (with standard lymphoma therapies)
Parenchymal involvement	
Kidney	
Immune-complex-mediated glomerulonephritis[32]	Prednisolone (0.5–1.0 mg/kg body weight per day) Intravenous cyclophosphamide (0.5–1.0 g/m^2 body surface per month)
Interstitial nephritis, tubular dysfunction or renal tubular acidosis[24]	Oral potassium and sodium carbonate (3–12 g per day)
Liver	
Primary biliary cirrhosis[24]	Ursodeoxycholic acid
Autoimmune hepatitis[34]	Corticosteroids, prednisolone (0.5–1.0 mg/kg body weight per day) Azathioprine (2 mg/kg body weight per day)
Lung	
Bronchial and/or bronchiolar involvement[35] (commo… indolent course)	Little effect of steroids and β-agonists
Interstiti…	
Neurologic	
Central nerv…	…e days) …month
Peripheral n…	Cyclophosphamide (0.5–1.0 g/m^2 of body surface per month) Azathioprine (2 mg/kg body weight per day) Plasmapheresis

Experience of Intravenous Immunoglobulin Therapy in Neuropathy Associated With Primary Sjögren's Syndrome: A National Multicentric Retrospective Study

STÉPHANIE RIST,[1] JÉRÉMIE SELLAM,[2] ERIC HACHULLA,[3] CHRISTELLE SORDET,[4] XAVIER PUÉCHAL,[5] PIERRE-YVES HATRON,[3] CLAUDE-LAURENT BENHAMOU,[1] JEAN SIBILIA,[4] AND XAVIER MARIETTE,[6] ON BEHALF OF THE CLUB RHUMATISMES ET INFLAMMATION

Conclusion. IVIG may be useful in the treatment of SS-associated sensorimotor neuropathies or nonataxic sensory neuropathy without any necrotizing vasculitis. The benefit of such therapy in the SS-related ataxic neuropathy seems less clear.

Arthritis Care & Research
Vol. 63, No. 9, September 2011, pp 1339–1344

Infliximab in Patients With Primary Sjögren's Syndrome

A Pilot Study

Serge D. Steinfeld,[1] Paul Demols,[1] Isabelle Salmon,[1] Robert Kiss,[2] and Thierry Appelboom[1]

ARTHRITIS & RHEUMATISM
Vol. 44, No. 10, October 2001, pp 2371–2375

Inefficacy of Infliximab in Primary Sjögren's Syndrome

Results of the Ra

ARTHRITIS & RHEUMATISM

Etanercept in the T
Sjögren's Syndrom

MICHIEL M. ZANDBELT, PETER C.M.
LEO B.A. van de PUTTE, FRANK H.J. va

Conclusions In common practice, the use of rituximab in pSS is mostly restricted to patients with systemic involvement. This prospective study shows good efficacy and tolerance of rituximab in patients with pSS and systemic involvement.

Rituximab Treatment in Patients With Primary Sjögren's Syndrome

An Open-Label Phase II Study

J. Pijpe,[1] G. W. van Imhoff,[1] F. K. L. Spijkervet,[1] J. L. N. Roodenburg,[1] G. J. Wolbink,[2] K. Mansour,[1] A. Vissink,[1] C. G. M. Kallenberg,[1] and H. Bootsma[1]

ARTHRITIS & RHEUMATISM
Vol. 52, No. 9, September 2005, pp 2740–2750

Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry

Jacques-Eric Gottenberg, Gael Cinquetti, Claire Larroche, et al.

Ann Rheum Dis 2013;**72**:1026–1031.

Novel approaches in the treatment of myositis and myopathies

Ther Adv Musculoskel Dis

(2012) 4(5) 369–377

Jemima Albayda and Lisa Christopher-Stine

Therapeutic advances in myositis

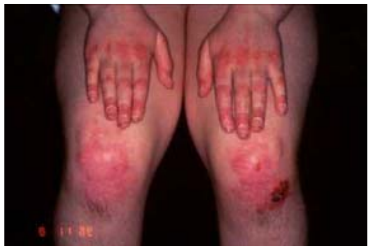
Curr Opin Rheumatol 2012, 24:635–641

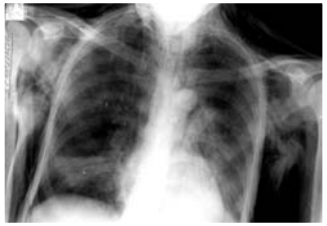
Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

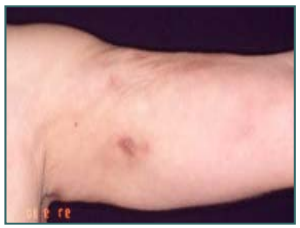
A Randomized, Placebo-Phase Trial

ODDIS ET AL

ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 314–324







KEY POINTS

- Corticosteroids and conventional immunosuppression with MTX and azathioprine is still the first-line treatment for polymyositis and dermatomyositis.
- CsA and tacrolimus is efficacious in refractory polymyositis and dermatomyositis especially in patients with ILD.
- MMF is efficacious in refractory skin disease in dermatomyositis and in ILD.
- Rituximab has shown good results in refractory polymyositis and dermatomyositis but further studies are needed to clarify its role.
- New theurapeutic agents like ACTH, etanercept, tocilizumab and some novel therapeutic agents like fingolimod or antitype 1 IFN therapy are being studied in myositis.

Intravenous immunoglobulin (IVIG) is an excellent choice in refractory or rapidly progressive, severe myositis and has demonstrated efficacy in a controlled trial in dermatomyositis [18]. Polymyositis

Curr Opin Rheumatol 2012, 24:635–641

Anti-inflammatory and immunosuppressive drugs and reproduction

Table 1

Effect of non-steroidal anti-inflammatory drugs, glucocorticosteroids a

Drug	FDA risk[a]	Transplacental passage	Human teratogenicity	Fetal/neonatal ad
Non-steroidal anti-inflammatory drugs	B/D	Yes	No	In late pregnancy arteriosus, reduct
Prednisone	B	Limited	Increase in oral clefts	Rare (cataract, ac
Dexamethasone	C	Yes	Not reported[b]	Neurodevelopme
Betamethasone	C	Yes	Not reported[b]	Neurodevelopme
Bisphosphonates	C	Not studied	Not reported	Two cases of hyp newborn infant

Details and references are given in the text. [a]The United States Food and Drug A no risk in controlled clinical studies in humans; B, human data reassuring or whe animal studies show risk or are not done; D, positive evidence of risk, benefit ma maternal use in the first trimester.

Table 2

Non-steroidal anti-inflammatory drugs, corticosteroids and bisphospho

Drug	Secretion into breast milk	Effect on nur
Non-steroidal anti-inflammatory drugs	In low concentrations	No adverse e
Prednisone	0.025% of maternal dose	No adverse e
Dexamethasone	Not studied	Not known
Betamethasone	Not studied	Not known
Bisphosphonates	Pamidronate not detected, no reports on other bisphosphonates	No adverse effect in one case [91]

Avoid

Insufficient data. Risk-benefit must be weighed before breastfeeding

Conclusion and recommendation (Tables 1 and 2)

- Non-selective and selective COX inhibitors can prevent or retard ovulation. The frequency of ovulation inhibition is unknown (evidence level IV).
- Non-selective COX inhibitors are not teratogenic and can be continued during the first and second trimester (evidence level I).
- At present there are no reliable data on selective COX-2 inhibitors; they should therefore be avoided during pregnancy (evidence level IV).
- After gestational week 20, all NSAID (except aspirin at less than 100 mg/day) can cause constriction of the ductus arteriosus and impair fetal renal function (evidence level I).
- All NSAID except LDA should be withdrawn at gestational week 32 (evidence level IV).
- There is no consensus on when to stop LDA before delivery. Some advise cessation of LDA treatment 1 week before a planned delivery with epidural anaesthesia (evidence level IV). Other experts do not stop LDA in pregnant patients with antiphospholipid syndrome, regarding the benefit of LDA as being greater than the small risk of haematoma connected with epidural anaesthesia (evidence level II).
- Breastfeeding immediately before a dose can help to minimize infant exposure to NSAID (evidence level IV).

Arthritis Research & Therapy 2006, **8**:209

Table 3

Effect of immunosuppressive, cytotoxic and biological drugs on human pregnancy and reproduction

Drug	FDA risk[a]	Transplacental passage	Human teratogenicity	Fetal/neonatal adverse effects	Long-term effects in offspring	Impairment of fertility
Chloroquine/ hydroxychloroquine	C/C	Yes	No	Not at recommended doses	No impairment of vision or hearing	Not studied
Sulphasalazine	B	Fetal like maternal serum concentration	No	Case reports of aplastic anaemia and neutropenia at >2g maternal dose	Not studied	In men: oligospermia, decreased sperm motility, abnormal forms
Leflunomide	X	No data	Data not conclusive	None published	Not studied	Not studied
Azathioprine Mercaptopurine	D[b]	Yes	No	Sporadic congenital anomalies. Transient immune alterations in newborn infants	Normal immune responses in childhood. One case report of late development of autoimmunity.	No
Methotrexate	X	Methotrexate + polyglutamates	Yes	Cytopenia	None reported	Oligospermia at high doses
Cyclophosphamide	D	Yes – animal data	Yes	Chromosomal abnormalities. Cytopenia	Anecdotal	In males and females
Cyclosporine	C	10–50% of maternal plasma concentration	No	Transient immune alterations	None reported	No
Tacrolimus	C	Yes	Not reported	Hyperkalaemia, renal impairment	Not studied	Not studied
Mycophenolate mofetil	C	Yes	3 reports of congenital abnormalities	Not reported	Not studied	Not studied
Intravenous immunoglobulin	C	Yes	No	No fetal effects reported	Not studied	Not studied
Etanercept	B	Yes	Not reported	Not reported	Not studied	Not studied
Infliximab	B	Not reported	Not reported	Not reported	Not studied	Data not conclusive

Table 4

Immunosuppressive, cytotoxic and biological drugs during lactation

Drug	Secretion into breast milk	Effect on nursing infant	Breastfeeding allowed
Chloroquine	0.55% of maternal dose [100,102]	No adverse effects	Compatible with breastfeeding
Hydroxychloroquine	0.35% of maternal dose [103,104]	No adverse effects	Compatible with breastfeeding
Sulphasalazine	Sulphasalazine and sulphapyridine secreted at 5.9% of maternal dose [120]	Well tolerated, 1 case of bloody diarrhoea [121]	Allowed in the healthy full-term infant
Leflunomide	No data published	No data published	Avoid because of theoretical risk
Azathioprine (AZA)/ 6-mercaptopurine (6-MP)	AZA and its metabolites detected in milk [135]	9 children nursed (AZA) without adverse effects, 1 child (6-MP) well	Avoid because of theoretical risk
Methotrexate	Excreted in low concentrations. Milk:plasma ratio of 0.08 [155]	Not known	Avoid because of theoretical risk
Cyclophosphamide	Secreted (amount unknown) [172]	Suppression of haematopoiesis reported in one nursing child [169]	Contraindicated during lactation
Cyclosporine	Milk:plasma concentration < 1; wide variability in drug disposition [188]	No adverse effects observed in 9 breastfed children [188]	No consensus, weigh risk/benefit
Tacrolimus	Minute amounts secreted, nursing infant exposed to 0.06% of mother's dose [197]	1 child nursed without side effects [197]	Breastfeeding probably possible
Mycophenolate mofetil	No human studies	Not known	Avoid because of theoretical risk
Intravenous immunoglobulin	No data published	Not known	Breastfeeding probably possible
Etanercept	Secreted at 0.04% of maternal dose [207]	Not known	Data inconclusive, weigh risk/benefit
Infliximab	Secreted in small amount [211]	Not known	Avoid because of theoretical risk