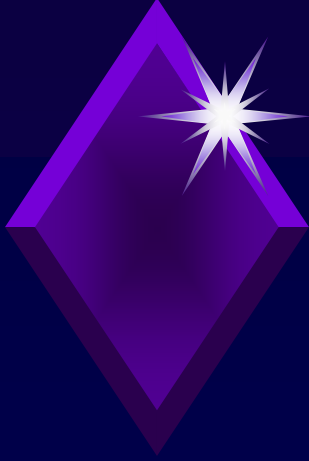


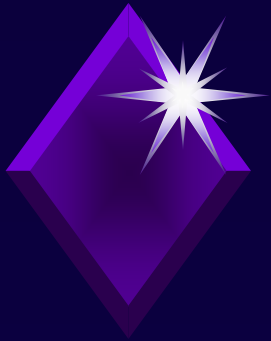
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



MCTD-Treatment

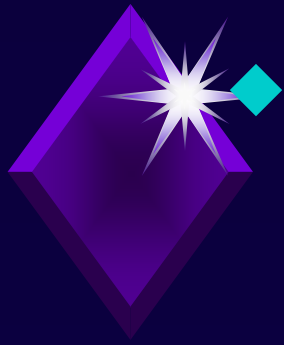
Dr Mirfeizi

Associate Professor of Rheumatology
Emam Reza Hospital, MUMS



Overview

- ◆ The initial assumption by Sharp and co-workers that MCTD was responsive to corticosteroid therapy & yielded a favorable outcome has not been well established



- ◆ No controlled clinical trials performed
- ◆ Treatment: conventional therapies in similar clinical manifestations in other rheumatic diseases such as SLE, SSc and PM.
- ◆ Therapy should be individualized for each patient



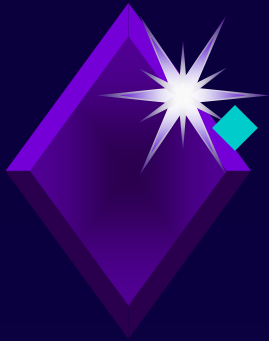
Immunosuppressive therapy & steroids remain the therapeutic mainstay for MCTD.

- ◆ Steroid-sparing treatments for MCTD, commonly used as second-line therapy, include :

Oral or intramuscular **methotrexate**,
cyclosporine, **azathioprine**,
mycophenolate mofetil.

- ◆ A retrospective study of **161** patients with MCTD showed that **58%** required aggressive immunosuppression & only **3%** achieved disease control using symptomatic therapies

Cappelli S, et al. Arthritis Rheum. 2012

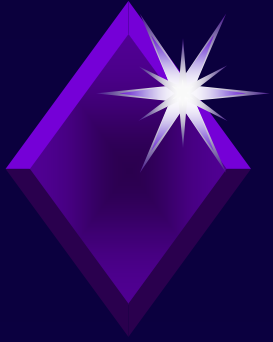


Some clinical manifestations are responsive to steroids :

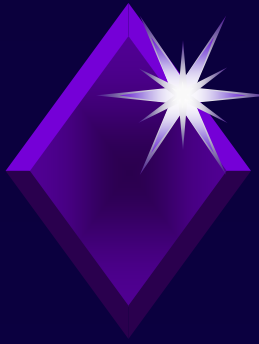
- ◆ Inflammatory Manifestations such as fever,
- ◆ Serositis
- ◆ Myositis
- ◆ Arthritis
- ◆ Skin rash

◆ Cytotoxic (immunosuppressive)treatment:

- ◆ Sclerodactyly
- ◆ Moderate oesophageal disease
- ◆ RP
- ◆ Sclerodermatous bowel disease
- ◆ Pulmonary interstitial disease



Constitutional Symptoms



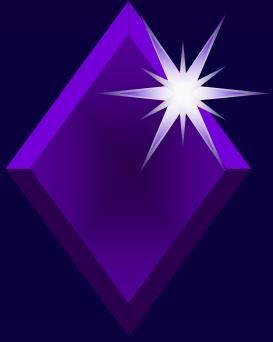
- ◆ Fever, fatigue, unspecific arthralgias or myalgias usually respond :

- ◆ NSAIDs
- ◆ Hydroxychloroquine
- ◆ low-dose of prednisone, it depends on the severity.

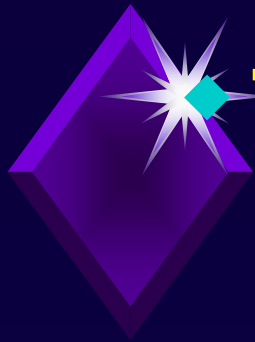
- ◆ The possibility of fibromyalgia or reactive depression should always be considered & treated optimally

- Unresponsive cases to glucocorticoids

- ◆ flares of discomfort & pain in MCTD is due to :
 - ◆ myofascial pain syndrome
 - ◆ fibromyalgia



Joint involvement

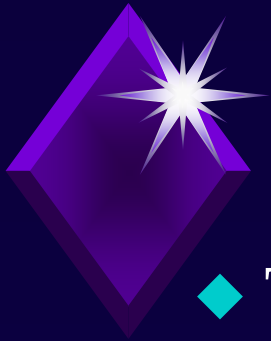


Treatment of mild joint involvement :

- ◆ NSAIDs,
- ◆ hydroxychloroquine
- ◆ oral prednisone with good response

◆ Treatment of severe joint involvement:

- ◆ Methotrexate
- ◆ If mtx is contraindicated, DMARD used in RA, such as leflunomide or azathioprine

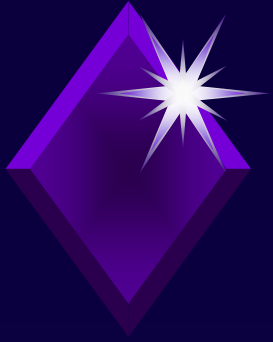


- ◆ TNF inhibitors are not recommended. if needed, patients must be followed carefully for the development of SLE-like syndrom

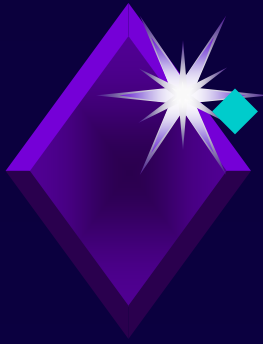
Christopher-Stine L. J Rheumatology. 2003

- ◆ The experience with its use is limited & there are case reports that anti-TNF-a was associated with development of an SLE-like syndrome

Natalia C, Rheumatology, 2016.

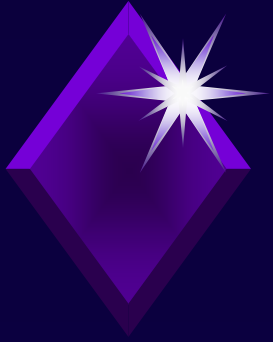


Muscle Disease

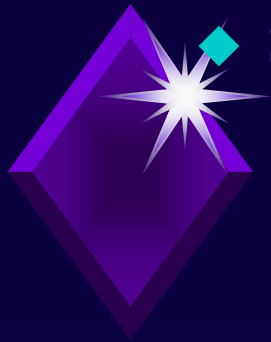


Patients with acute onset of severe myositis, accompanied by fever, respond to high doses of corticosteroids

- ◆ Myalgias in the absence of myositis:
 - ◆ NSAIDs
 - ◆ Hydroxychloroquine
 - ◆ low-dose prednisone



Skin Involvement



- ◆ SLE-like skin rash, oral ulcerations & photosensitivity :
 - topical steroids
 - prednisone
 - hydroxychloroquine

- ◆ For more severe cases
 - Immunosuppressants: (cyclophosphamide , Cyclosporine)

- ◆ For refractory symptoms: (IVIG)

- ◆ Hypocomplementemic urticarial vasculitis usually responds to hydroxychloroquine after a period of corticosteroid dependence

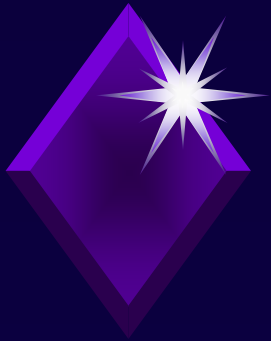
- ◆ Sclerodermatous-like skin manifestations :
 - ◆ often responsive to steroid therapy



Raynaud's phenomenon

- ◆ Calcium channel blockers
- ◆ Prostaglandin
- ◆ Phosphodiesterase 5 inhibitors
- ◆ Endothelin receptor antagonist
- ◆ Topical nitroglycerin
- ◆ In addition, it appears that subcutaneous, local doses of botulinum toxin A may be efficacious

Iorio ML, Semin ArthritisRheum 2012

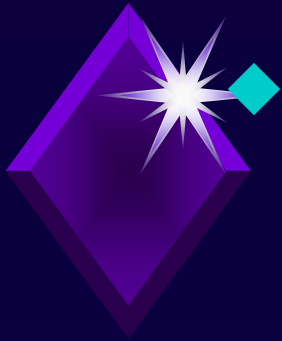


preventive measures

- ◆ Avoidance of cold temperatures
- ◆ Avoidance triggering factors
 - ◆ smoking
 - ◆ sympathomimetic agents.
 - ◆ avoid β -blockers

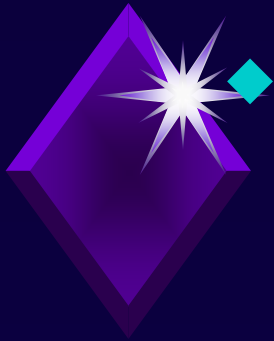
calcium channel blockers

- ◆ Nifedipine
- ◆ Amlodipine
- ◆ felodipine
- ◆ isradipine



severe ischaemic digital lesions :

- ◆ prostaglandin-analogues
 - ◆ intravenous prostaglandin: **iloprost**, has documented effects
- ◆ Anticoagulation
- ◆ Hyperbaric oxygen
- ◆ Bosentan for the prevention of new digital ulcers (Similar to SSc)

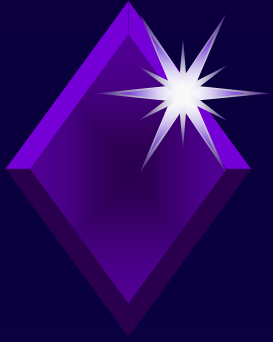


◆ Modest improvement of vascular symptoms

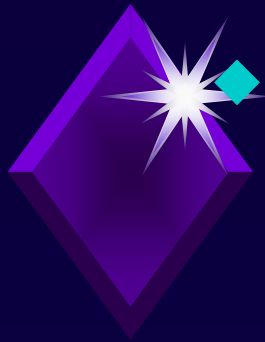
- ◆ Prazocin
- ◆ Losartan
- ◆ Pentoxifylline

◆ Successful treatment of severe refractory RP:

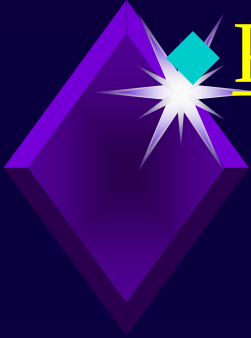
- ◆ Combination therapy i.e. Rituximab, methylprednisolone, cyclophosphamide



PH associated with MCTD

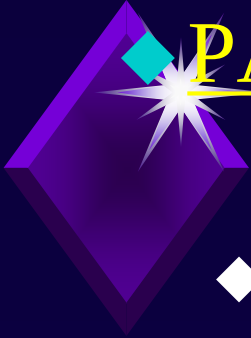


- ◆ There are no specific guidelines in the treatment of PH associated with MCTD
- ◆ The treatment options are derived from studies of:
 - ◆ PAH-specific therapies in idiopathic PAH
 - ◆ PAH associated with SSc
- ◆ Pulmonary arterial hypertension (PAH): the main cause of death among patients with MCTD
- ◆ Early diagnosis with routine echocardiography is recommended for all patients.



PAH can be more specifically treated with:

- ◆ Calcium Channel Blocker
- ◆ Endothelin receptor antagonists (bosentan, ambrisentan, or macitentan)
- ◆ Phosphodiesterase 5 inhibitors (sildenafil, tadalafil, or vardenafil)
- ◆ Prostanoids (epoprostenol, treprostinil, or inhaled iloprost, beraprost, selexipag)
- ◆ Anticoagulation



PAH can be more specifically treated with:

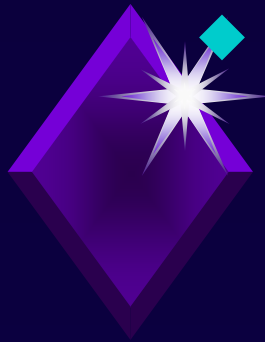
- ◆ prolonged immunosuppression (beginning with glucocorticoids & combining with cyclophosphamide or mycophenolate if necessary)

- ◆ Angiotensin converting enzyme inhibitors

- ◆ Guanylate cyclase stimulators (**Riociguat**)

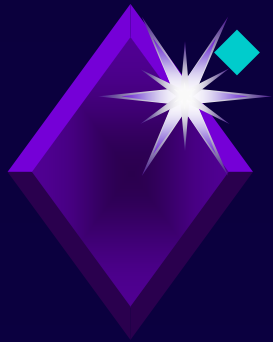
Jais X, Arthritis Rheum. 2008

- ◆ In end-stage disease, a heart-lung transplant needs to be considered .



- ◆ In treatment-resistant cases, a combination of 2 & even 3 of these treatment options can be used.
- ◆ The most preferred therapeutic option is an oral treatment with endothelin receptor antagonist in combination with phosphodiesterase5 inhibitors
- ◆ Recent reports indicate that **selexipag**, an oral, selective prostacyclin receptor, shows promise

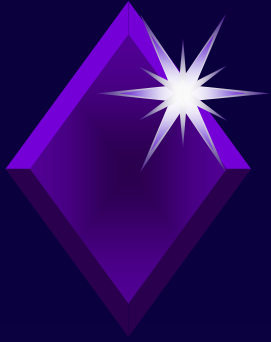
McLaughlin VV, J Am Cardiol. 2015



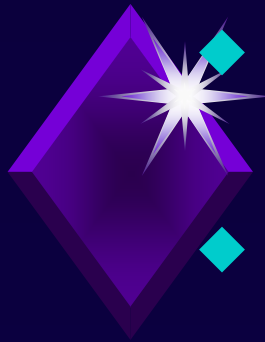
SLE- or MCTD-associated PAH, in contrast to other forms of PAH respond to immunosuppressive therapy

- ◆ In a retrospective study with 23 SLE- or MCTD-PAH patients by Jais et al :
 - ◆ All responders to IVCY were in WHO functional class III or less.
 - ◆ The cardiac index was significantly higher in responders than in nonresponders.

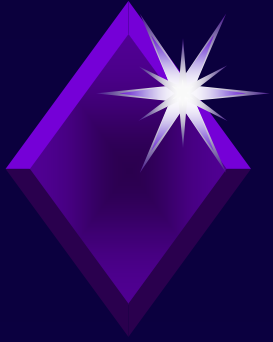
Jais X, Arthritis Rheum. 2008



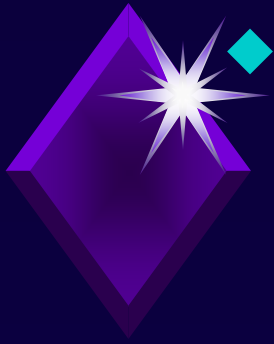
Pulmonary Manifestations



- ◆ Mild cases with pleurisy usually respond to NSAIDs
- ◆ if symptoms persist: varying doses of corticosteroids (about 20 mg/day)
- ◆ Immunosuppressive agents are rarely indicated to treat them
- ◆ Severe ILD is also treated with intravenous cyclophosphamide.
- ◆ Fibrotic lung disease is resistant to corticosteroids & immunosuppressives
- ◆ A new class of drugs, tyrosine kinase inhibitors (e.g., imatinib) may be effective in some patients



Cardiovascular disease



◆ Pericarditis

- ◆ NSAID

- ◆ short course of prednisone—about 20 mg/day:
(corticosteroids depending on the severity)

- ◆ Massive pericardial effusion with cardiac tamponade
rarely occurs & it may need surgical drainage

◆ Myocarditis (moderate to severe)

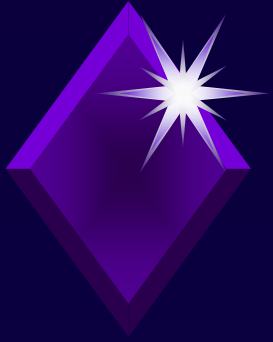
- ◆ high-dose steroid therapy

- ◆ common therapy employed to treat congestive heart failure if it is present

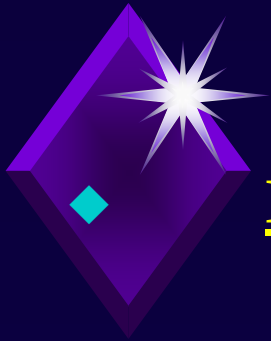
- ◆ Trial of steroids & cyclophosphamide

- ◆ Azathioprine

- ◆ IVIG



Gastrointestinal problems



Dysphagia: Mild—no treatment

◆ **Reflux**

- ◆ proton pump inhibitor. Consider Nissen fundoplication
- ◆ Severe—Calcium channel antagonist, alone or in combination with an anti-cholinergic agent
- ◆ Corticosteroid (In contrast to SSc)

◆ **Intestinal dysmotility**

- ◆ Prokinetic agents such as metoclopramide, & erythromycin.

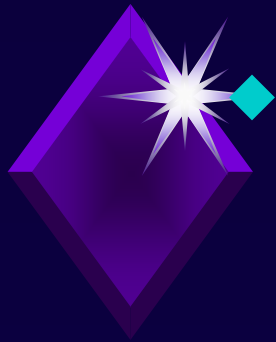


- **Small bowel bacterial overgrowth**

- ◆ tetracycline, erythromycin

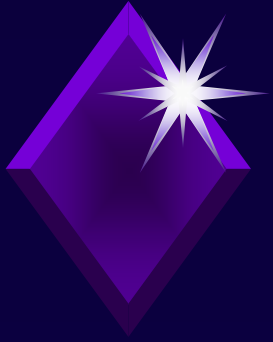
- ◆ **Heartburn/Dyspepsia**

- ◆ Raise head of bed, discontinue smoking, lose weight, and avoid caffeine. H₂ antagonists, H⁺, proton pump blockers. Metoclopramide trial. Consider H. Pylori infection in recalcitrant cases

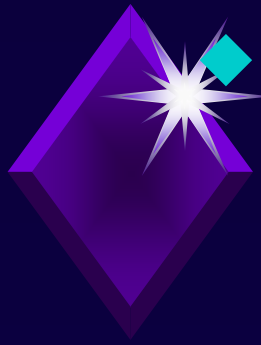


- ◆ Study of 10 patients with MCTD evaluated the effectiveness of prednisone (an average dose of 25 mg/day) in the treatment of esophageal dysmotility
- ◆ Significant improvement in lower esophageal sphincter pressure, improvement in proximal esophageal peristaltic waves.

Pope JE, Up todate. 2017

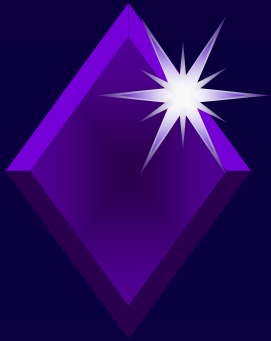


Renal impairment



Membranous Glomerulonephropathy

- Mild : no treatment required
- Progressive proteinuria: trial of ACE inhibitor; trial of low dose aspirin combined with dipyridamole.
- Severe: trial of prednisone, 15-60 mg/day plus intermittent pulse cyclophosphamide or daily chlorambucil or rituximab

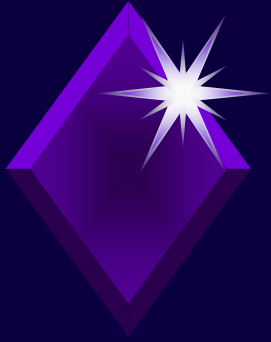


➤ Nephrotic syndrome

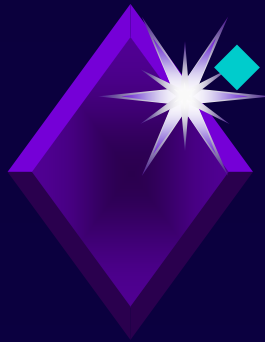
- Steroids alone seldom effective.
- Low dose aspirin combined with dipyridamole to prevent thrombotic complications.
- ACE inhibitor to reduce protein loss.
- Trial of prednisone, 15-60 mg/day plus monthly pulse cyclophosphamide or rituximab
- ◆ May require dialysis/transplantation

➤ Scleroderma-like renal crisis :

- ACE inhibitor
- Intravenous prostacyclin (Epoprostenol)
- Short-term haemodialysis if necessary, continuous peritoneal dialysis often works well if longterm renal replacement is needed



Neurological disease



◆ Major intracranial manifestations

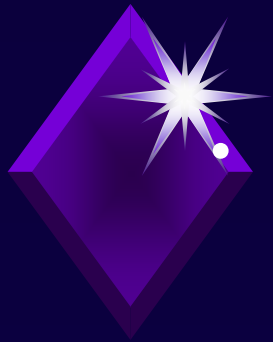
- ◆ stroke prevention
- ◆ immunosuppression
- ◆ symptomatic treatment

◆ Trigeminal neuropathy:

- ◆ No effective therapy for numbness.
- ◆ Trial of an anti-epileptic (e.g., gabapentin) or tricyclic anti-depressant (e.g., nortryptiline) for pain

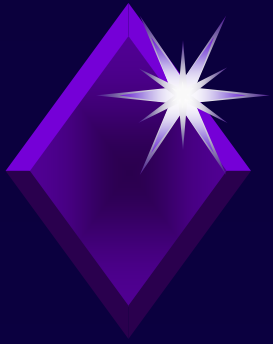
◆ Aseptic meningitis:

- ◆ Discontinue NSAIDs
- ◆ Short course of high-dose prednisone, about 60 mg/day

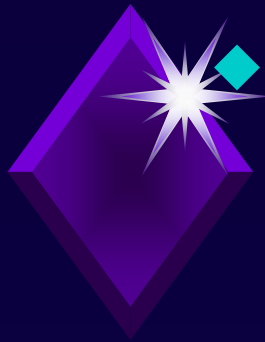


Steroids plus cyclophosphamide for serious (non-stroke) neurological complications :

- neuropsychiatric manifestations
- optic neuritis
- neuropathy
- coma
- brainstem disease or transverse myelitis



*“Biological disease-modifying
anti-rheumatic drugs”*



- ◆ A few reports of both adult and juvenile MCTD cases treated with B cell depletion therapy with **rituximab** with success,

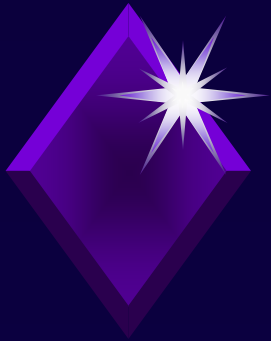
- ◆ **Rituximab mainly for ;**

- ◆ Resistant arthritis
- ◆ Myositis
- ◆ Thrombocytopenia
- ◆ Hemolytic anemia
- ◆ severe anti-synthetase syndrome

- ◆ **Tocilizumab:**

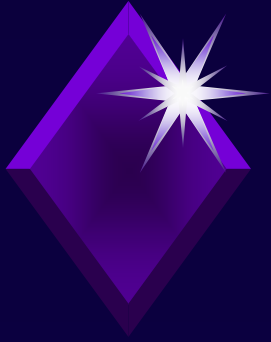
- ◆ Effective to treat joint manifestations (Juvenile MCTD)

Natalia Cabrera, Paediatric rheumatology.2016

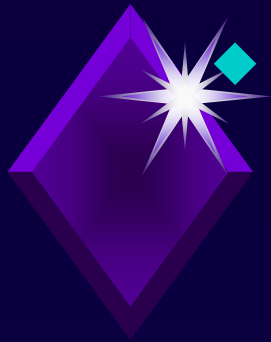


OTHER TREATMENT:

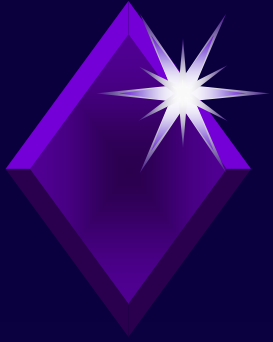
- In patients with refractory disease
 - Plasmapheresis
 - IV/IG
 - Successful autologous peripheral blood stem cell transplantation in a patient with refractory myositis



Further Outpatient Care



- ◆ Patients with stable disease & no recent changes in medications
 - ◆ every 2-4 months, undergo routine laboratory evaluation,
- ◆ Patients with active disease
 - ◆ every 3-6 weeks, depending on the severity of disease.
- ◆ screening and early detection of PAH
- ◆ PFT (spirometry with lung volumes) with DLCO
- ◆ Transthoracic echocardiogram (TTE)
- ◆ N-terminal pro-B-type natriuretic peptide (NT-Pro BNP)
- ◆ Use of 6-minute walk stress echocardiography
 - ◆ (for predicting the development of PAH)



SUMMARY AND RECOMMENDATIONS



- ◆ Patients with MCTD : variable prognosis.
- ◆ There is no consensus about the treatment of MCTD
- ◆ Some features (eg, pleurisy, aseptic meningitis) responsive to glucocorticoids, while scleroderma-like features, especially PAH, are steroid unresponsive.
- ◆ Features of fibromyalgia, a mood disorder, or deconditioning should be distinguished from manifestations of active MCTD that may require glucocorticoids.
- ◆ Risk of inducing ventricular arrhythmias, digitalis is relatively contraindicated in patients with myocarditis.
- ◆ Anti-malarials: should be used with caution in overlap patients with a fascicular or bundle branch block, because of the risk of causing a complete heart block or an idiosyncratic hepatitis
- ◆ Patients with MCTD may also evolve into a clinical picture more consistent with SLE, scleroderma, or RA

Thanks for your
attention

