IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

ROLE OF CYCLOSPORINE A (CsA) IN MANAGEMENT OF INTERSTITIAL LUNG DISEASES ASSOCIATED WITH RHEUMATOID ARTHRITIS (RA-ILD)

Bandari Vamshipriya[1]* PharmD 5th year

Dr.A. Srinivasa rao[2] M.Pharm, Ph.D, F.I.C, Principal

Dr.A.V.kishore babu[3] PharmD(PB), PhD, HOD

Bhaskar pharmacy college, yenkapally, moinabad, rangareddy.

Abstract

Background: Interstitial lung disease associated with Rheumatoid Arthritis (RA-ILD) is due to pathology and complication of disease or due to prolonged use DMARDS or conventional drugs used for management of RA.

Principle of results: Cyclosporine A is an immunosuppressive drug which inhibits the t-cell activation and decrease the ILD related reaction with high efficacy and minimal adverse effects. So cyclosporine is considered for prophylactic and therapeutic management of RA-ILD treatment.

Conclusion: cyclosporine A is effective drug for treatment of intestitinal lung disease and its complications. It is more effective with combination with methotrexate and corticosteroids than monotherapy which has been proven in various previous literatures. So the cyclosporine is choice of drug for effective treatment of intestinal lung disease associated with rheumatoid arthritis to prevent further complications like airway and pleural diseases, respiratory infections etc.

New aspects in review ;Compare to conventional drugs used in management of rheumatoid arthritis cyclosporine A is better choice for prevention of complications like ILD, other lung infections and other systemic illness. It has major role in suppression of inflammatory reaction in Interstitial lung disease associated with Rheumatoid Arthritis. Upon combination its has higher efficacy rate than monotherapy .it has better therapeutic range and low risk profile but on over usage it lead to nephrotoxicity

KEYWORDS:

"Rheumatoid arthritis" , "interstitial lung disease" , "cyclosporine A", "methotrexate", "corticosteroids", conventional DMARDS" '

Introduction:

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory illness characterized by polyarthritis of small and large joints which in the course of time may progress to disability [1, 2]. Due to its pathogenesis, this condition affects internal organs, particularly heart, lungs, kidneys, blood vessels, brain, and therefore is regarded as a systemic illness [3] .It is characterized by symmetrical erosive synovitis and progressive disability, often complicated by extra-articular manifestations. Among them, lung involvement is common, and it can include a wide spectrum of disorders, ranging from airways and pleural disease, bronchiotactasis, and nodules, to infection and drug toxicity [4, 5, 6] The cause of RA is not fully understood but it is multi factorial. It is considered as autoimmune disease. It can occurred due to environmental influence like bacteria , virus or genetic markers such as DR4 (HLA-DR4) associated with triggering the inflammatory process or TNF -ALPHA ,IL-1, IL-6 and growth factors propagate inflammatory process or inflamed synovium [7] RA is characterised by morning stiffness, malaise, anorexia, accompanied by symmetrical tender and swollen joints. Pain in joints is common and aggravated by movement.

Current rheumatoid arthritis management emphasis of the benefits of early disease modifying anti-rheumatic drugs (DMARDs). These agents are characterized by the ability to reduce or reverse the signs and symptoms, disability and improve quality. The medication like NSAIDS, corticosteroids, hydroxychloroquine is used in the management of RA. In long-term corticosteroid-treated patients, there is a tendency for severe extra pulmonary and miliary tuberculosis [8].

Interstitial lung diseases (ILDs) are a group of diseases that affects the lung parenchyma tissue causing irreversible damage through fibrosis and chronic inflammation, depriving gas exchange in affected individuals [9] ·The effects in ILDs are observed largely in the lung interstitum and differentiating them from one other is challenging as they often share comparable physiological, clinical and radiological features [10] Their known aetiology of ILDs include those that may have genetic predisposition which includes pulmonary manifestation of existent rheumatoid arthritis (RA) [11] .About 10% of the RA patients develop a clinically significant ILD that is responsible for 10–20% of mortality, with a mean survival of 5–8 years [12, 13, 14, 15,16] . The role of immunosuppressants in usual interstitial pneumonia (UIP) in RA, shows a better response in ILD patterns different to UIP has been suggested by some retrospective studies [17, 18, 19, 20]. The cyclosporine play an important role in management of intestinal lung diseases associated with rheumatoid arthritis shown in some research studies .

Actions of cyclosporine A:

CsA inhibits T cell activation by interfering with calcium-dependent signalling events involved in lymphokine Gene transcription. Once it enters a cell, CsA binds to cyclophilin and this complex competitively inhibits the enzymatic activity of calcineurin, a serine/Threonine phosphatase required for the Dephosphorylation of nuclear factor for

Activated T cells (NF-AT) and activated Protein-1 (AP-1)[21] . This blockade Prevents NF-AT and AP-1 translocation into the nucleus and results in the failure to initiate the transcription of several T-cell cytokine genes, such asIL-2 [22], IL-3, IL-4, tumour necrosis Factor-α (TNF-α), granulocyte-macrophage colony stimulating factor (GM-CSF), and interferon-γ (IFN-γ)[23,24] . The result is inhibition of T-cell activation and suppression of T-cell dependent immune responses. CsA also appears to have additional actions. More recently the role of CsA in attenuating fibrosis has been explored in animal models of IPF and they have been shown to exhibit their anti-fibrotic effect by degrading hypoxia inducible factor-1α [25]. The dual action of CsA may thus be of an advantage to achieving considerable attenuation in the overall progression of the disease.

RESULTS:

fig-1

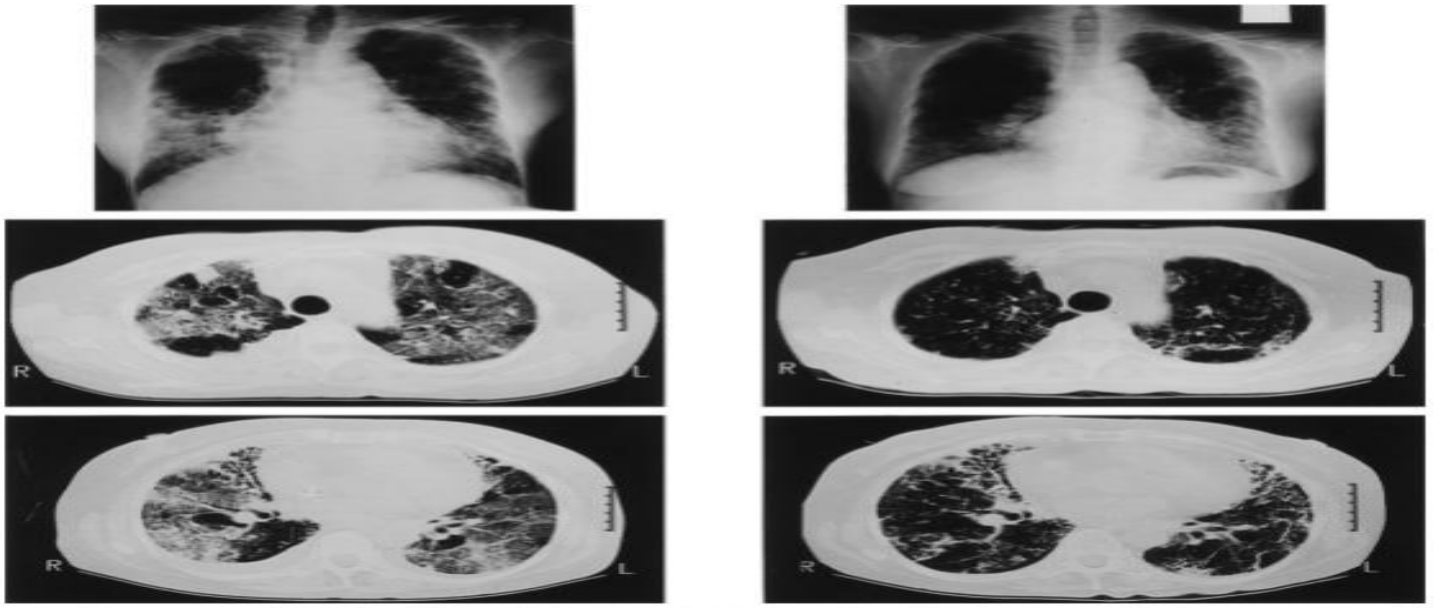

FIG. 1. Chest X-ray and CT before (left) and after (right) the initiation of combined CyA + prednisolone therapy. (Top left) Chest X-ray showing diffuse reticular infiltrates in both lung fields. (Lower two panels, left) Chest CT demonstrating bilateral patchy areas of ground-glass appearance in the outer and inner zones. Note the lack of honeycombing. (Top right) Chest X-ray showing remarkable improvement (compare with left side). (Lower two panels, right) The ground-glass appearance disappeared on chest CT 3 months after initiating the combination treatment. Note the presence of slight irregular pleural thickening but no obvious honeycombing.

Discussion:

The intestinal lung disease associated with rheumatoid arthritis is characterised by slow and insipidus in progression up to10years. This form of acute lung intestinal disease is treated early with oral corticosteroids with high doses which leading to serious adverse effects in patients. But now this now is replaced by cyclosporine which shows better therapeutic effects than steroids which was used as conventional therapy [26, 27, 28] .The study further examines the role of immunosuppressive drugs such as cyclosporine in these specific patient population. Cyclosporine (CsA) was shown to be effective in these patients illustrated clearly by the significant decrease in physiological parameters such as %FVC, %DLCO and composite physiologic index, since the years of CsA initiation with the best outcomes observed in 2 years after dosage. The affectivity was especially enhanced in these patients who were also on low doses of prednisolone (PSL), demonstrating an anti-inflammatory additive effect of these drugs shows completely differential mechanisms, can attenuate the disease progression.

The benefits of cyclosporine

CsA used for the treatment of RA in 1980, used after the observational study of a therapeutic effect in psoriatic patients. In RA patients, CsA was used as a "rescue therapy" in patients earlier who were non-responders to other common DMARDs and in monotherapy. The patients how had long-standing disease at entry with poor prognostic factors and several previous failed drugs, and CsA was administered at high doses (ranging between 5 &10mg/Kg/day) [29, 30, 31] shows good therapeutic efficacy .In patients with early RA using lower doses of CsA demonstrated good control over clinical and radiologic progression [32, 33, 34, 35 , 36] . When treating patients with cyclosporine (mean dose3 mg/Kg/day) or other common DMARDs, CsA group showed a significant delay in erosion progression, with acceptable tolerability [37] When analysis was performed on daily treatment basis shows slowing radiologic progression of joint damage with CsA and parenteral gold [38 . According to these clinical trial data, CsA monotherapy shows at least similar efficacy to the other conventional DMARDs. These findings led to the use of combination therapy in several clinical trials,with additive efficacy when cyclosporine [39] was combined with methotrexate (MTX), antimalarial agents or gold salts [40,41,42,43,44,45,46] .The efficacy of cyclosporine for the treatment of RA has been proven . Few reports suggest successful cyclosporine use in progressive ILD or acute interstitial pneumonitis in association with RA.

Spontaneous remission is extremely rare in progressive ILD associated with RA, the improvement of the lung disease was mostly considered to be the effect of cyclosporine. Cyclosporine has highly selective immunosuppressive properties. This agent appear to reduce interleukin-2 synthesis by activated T-cell and to disrupt cytokine dependent T lymphocyte-macrophage interaction, and thus prevents fibroblast mediated fibrosis that is thought to be important in the pathogenesis of ILD .It has been successfully used in patients with ILD related to inflammatory myositis [47], also when presenting as acute respiratory distress syndrome [48]. However, the use of calcineurin inhibitor is often limited by their side effects and their efficacy in RA-ILD remains undefined and needs more dedicated studies.

Conclusion

The respiratory safety of RA therapy is an important element while choosing the best treatment for patients with RA with active joint disease and coexisting ILD. Cyclosporine is very useful in treatment of ILD-RA shows good efficacy and minimal side-effects and prevents further complications of RA. Compare to monotherapy with cyclosporine to combination therapy with methotrexate and other corticosteroids have greater efficacy and low risk profile. So the cyclosporine is choice of drug for effective treatment of intestinal lung disease associated with rheumatoid arthritis to prevent further complications like airway and pleural diseases, respiratory infections etc .Compare to conventional drugs used in management of rheumatoid arthritis cyclosporine A is better choice for prevention of complications like ILD, other lung infections and other systemic illness. It has major role in suppression of inflammatory reaction in interstitial lung disease associated with Rheumatoid Arthritis. Upon combination its has higher efficacy rate than monotherapy .it has better therapeutic range and low risk profile but on over usage it lead to nephrotoxicity and other serious adverse drug events.

Annexure-1

Abbreviations

RA- rheumatoid arthritis

ILD – Interstitial lung disease

RA-ILD- Interstitial lung disease associated with Rheumatoid Arthritis

CsA- cyclosporine A

MTX- methotrexate

Mg-milligram

Kg-kilogram

Figure-1

https://www.google.com/search?rlz=1C1JJTC_enIN938IN939&q=interstitial+lung+disease+associated+with+rheumatoid+arthritis&tbm=isch&source=lnms&sa=X&ved=2ahUKEwj1lMnJqaqAAxUGGYgKHb5rDQsQ0pQJegQIDBAB&biw=1280&bih=772&dpr=1

Reference

1. Prescribing pattern in Rheumatoid Arthritis patients in a tertiarycareteaching hospitalShakti B. Dutta, Mirza A. Beg, ShaluBawa, Amanjot Kaur, Subhash Vishal http://dx.doi.org/10.18203/2319-2003.ijbep20172247
2. Chopra A, Patil J, Billampelly V, Relwani J, Tandale HS. Prevalence of Rheumatic diseases in a rural population in Western India: A WHO-ILAR COPCORD Study. J Assoc Physicians India. 2001;49:240-6
3. Wong JB, Ramey DR, Singh G. Long-term morbidity, mortality, and economics of rheumatoid arthritis. Arthritis Rheum. 2001;44:2746-9
4. Prete, M.; Racanelli, V.; Digiglio, L.; Vacca, A. Dammacco, F.; Perosa, F. Extra-articular manifestations of rheumatoid arthritis: An update Autoimmun. Rev. 2011, 11, 123–131. [CrossRef]
5. Yunt, Z.X.; Solomon, J.J. Lung Disease in Rheumatoid Arthritis. Rheum. Dis. Clin. N. Am. 2015, 41, 225–236. [CrossRef]
6. Esposito, A.J.; Chu, S.G.; Madan, R.; Doyle, T.J.; Dellaripa, P.F. Thoracic Manifestations of Rheumatoid Arthritis. Clin. Chest Med. 2019, 40, 545–560. [CrossRef] [PubMed]
7. Comprehensive pharmacy review by Leon shargel pg 1097-1098
8. Kim HA, Yoo CD, Baek HJ, Ahn C, Han JS et al (1998) Mycobacterium tuberculosis infection in a corticosteroid-treated rheumatic disease patient population Clin Exp Rheumatic 16:9-13

9. Raghu G, Brown KK. Interstitial lung disease: clinicalevaluation and keys to anaccurate diagnosis. Clin ChestMed 2004;25:409-19, v.

10. Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018;27. doi: 10.1183/16000617.0076-2018.

11. Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritisassociated interstitial lung disease: the relevanceof histopathologic and radiographic pattern. Chest 2009;136:1397-405

12. Bongartz, T.; Nannini, C.; Medina-Velasquez, Y.F.; Achenbach, S.J.; Crowson, C.S.; Ryu, J.; Vassallo, R.; Gabriel, S.E.; Matteson, E.L. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: A population-based study. Arthritis Rheum. 2010, 62, 1583–1591.[CrossRef] [PubMed]

13. O'Dwyer, D.; Armstrong, M.E.; Cooke, G.; Dodd, J.D.; Veale, D.J.; Donnelly, S.C. Rheumatoid arthritis (RA) associated interstitial lung disease (ILD). Eur. J. Intern. Med. 2013, 24, 597–603. [CrossRef]

14. Flaherty, K.R.; Travis, W.D.; Colby, T.V.; Toews, G.B.; A Kazerooni, E.; Gross, B.H.; Jain,Strawderman, R.L.; Flint, A.; Lynch, J.P.; et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. Am. J. Respir. Crit. Care Med. 2001, 164, 1722–1727. [CrossRef] [PubMed]

15. Song, J.W.; Lee, H.K.; Lee, C.K.; Chae, E.J.; Jang, S.J.; Colby, T.V.; Kim, D.S. Clinical course and outcome of rheumatoid arthritis related usual interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis. 2013, 30, 103–112. [PubMed]

16. Lee, H.K.; Kim, D.S.; Yoo, B.; Seo, J.B.; Rho, J.Y.; Colby, T.V.; Kitaichi, M. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest 2005, 127, 2019–2027. [CrossRef] [PubMed]

17. Yamano, Y.; Taniguchi, H.; Kondoh, Y.; Ando, M.; Kataoka, K.; Furukawa, T.; Johkoh, T.; Fukuoka, J.;Sakamoto, K.; Hasegawa, Y. Multidimensional Improvement in Connective Tissue

18. Disease-Associated Interstitial Lung Disease: Two Courses of Pulse Dose Methylprednisolone Followed by Low-Dose Prednisone and Tacrolimus. Respirology 2018, 23, 1041–1048. [CrossRef)

19.. Brito Y, Glassberg MK, Ascherman DPRheumatoid arthritis-associatedinterstitial lung disease: current conceptsCurrRheumatol Rep. 2017;19(12):79.

20. http://dx.doi.org/10.18203/2319-2003.ijbep20172247

21. SCHREIBER SL, CRABTREE GR: The mech-Anism of action of cyclosporin A and FK 506.Immunol Today 1992; 13: 136-42.

22. GRANELLI-PIPERNO A: In situ hybridization For interleukin 2 and interleukin 2 receptor mRNA in T cells activated in the presence or absence of cyclosporin A. J Exp Med 1988

23. SIGAL NH, DUMONT FJ: Cyclosporin A, FK 506 and rapamycin: pharmacologic probes of lymphocyte signal transduction. Ann Rev Immunol 1992; 10: 519-60.

24. HEROLD HC, LANCKI DW, MOLDWIN RL, FITCH FW: Immunosuppressive effects of cyclosporine A on cloned T cells. J Immunol1986; 136: 1315-21.

25. Yamazaki R, Kasuya Y, Fujita T, et al. Antifibrotic effects of cyclosporine A on TGF-β1-treated lung fibroblasts and lungs from bleomycin-treated mice: role ofhypoxiainducible factor-1α. FASEB 2017;31:3359-71
26. The effectiveness of immunosuppressive cyclosporin in attenuating the progression of interstitial lung diseases Mathew Suji Eapen1 ,Archana Vijay Gaikwad1 ,Isobel E. Thompson1 ,Wenying Lu1 , Stephen Myers1 ,Pawan Sharma2,3, Sukhwinder Singh Sohal1
27. https://www.google.com/search?rlz=1C1JJTC_enIN938IN939&biw=1280&bih=817&q=The+effectiveness+of+immunosuppressive+cyclosporin+in+attenuating+the+progression+of+interstitial+lung+diseases+Mathew+Suji+Eapen+,Archana+Vijay+Gaikwad+1+,Isobel+E.+Thompson+,Wenjing+Lu1+,+Stephen+Myers+,Pawan+Sharma+2.3,+Sukhwinder+Singh+Sohal&spell=1&sa=X&ved=2ahUKEwjf9rLjxaKAAxWZ8jgGHUTvDRAQBSgAegQICxAB
28. The effectiveness of immunosuppressive cyclosporin in attenuating the progression of interstitial lung diseases Mathew Suji Eapen1 ,Archana Vijay Gaikwad1 ,Isobel E. Thompson1 ,Wenying Lu1 , Stephen Myers1 ,Pawan Sharma2,3, Sukhwinder Singh Sohal1

29.. WEINBLATT ME, COBLYN JS, FRASER PA et al.: Cyclosporin A treatment of refractory
rheumatoid arthritis. Arthritis Rheum 1987; 30: 11-7.
30. MADHOK R, TORLEY HI, CAPELL HA: A study of the long-term efficacy and toxicity of
cyclosporine A in rheumatoid arthritis. J Rheumatol 1991; 18: 1485-9.
31. TUGWELL P, BOMBARDIER C, GENT M et al.:Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. Lancet 1990; 335: 1051-5.
32. AHERN MJ, BRADLEY J, HARRISON W, LAING B, HOLLINGSWORTH P, BAYLISS C:
A randomised double blind trial of cyclosporine and azathioprine in refractory rheumatoid arthritis. Aust N J Z Med 1991; 21: 844-9.
33. KRUGER K, SCATTENKIRCHNER M: Comparison of cyclosporin A and azathioprine in the treatment of rheumatoid arthritis: results of a double blind multicenter study. Clin Rheumatol 1994; 13: 248-55
34. VAN RIJTHOVEN AW, DIJKMANS BA, THE HS, et al.: Comparison of cyclosporin and D-
penicillamine for rheumatoid arthritis: a randomised, double blind, multicenter study. J Rheumatol 1991; 18: 815-20.
35. FORRE O: Radiologic evidence of disease modification in rheumatoid arthritis patients treated with cyclosporine. Results of a 48- week multicenter study comparing low-dose cyclosporine with placebo. Norwegian Arthritis Study Group. Arthritis Rheum 1994; 37: 1506-12
36. PASERO G, PRIOLO F, MARUBINI E et al.:Slow progression of joint damage in early rheumatoid arthritis treated with cyclosporin A. Arthritis Rheum 1996; 39: 1006-15.

37. ZEIDLER HK, KVIEN TK, HANNONEN P et al.: Progression of joint damage in early active severe rheumatoid arthritis during 18 months of treatment: comparison of low-dose cyclosporin and parenteral gold. Br J Rheumatol 1998; 37: 874-82.
38. KVIEN TK, ZEIDLER HK, HANNONEN P etal.: Long term efficacy and safety of cyclosporine versus parenteral gold in early rheumatoid arthritis: a three year study of radiographic progression, renal function, and arterial hypertension. Ann Rheum Dis 2002; 61:511-16.
39. DROSOS AA, VOULGARI PV, KATSARAKI A,ZIKOU AK: Influence of cyclosporin A on radiological progression in early rheumatoid arthritis patients: a 42-month prospective study. Rheumatol Int 2000; 19: 113-18.
40. BENSEN W, TUGWELL P, ROBERTS R: Combination therapy of cyclosporin with methotrexate and gold in rheumatoid arthritis (2 pilot studies). J Rheumatol 1994; 21: 2034-8
41.. SALAFFI F, CAROTTI M, CERVINI C: Combination therapy of cyclosporin A with methotrexate or hydroxychloroquine in refractory rheumatoid arthritis. Scand J Rheumatol 1996; 25: 16-23.
42. TUGWELL P, PINCUS T, YOCUM D: Combination therapy with cyclosporin and methotrexate in severe rheumatoid arthritis. N Engl J Med 1995; 333: 137-41
43.. BENDIX G, BJELLE A: Adding low-dose cyclosporin A to parenteral gold therapy in rheumatoid arthritis : a double-blind placebo-controlled study. Br J Rheumatol 1996; 35: 1142-9.
44. VAN DE BORNE BEEM, LANDEWÉ RBM, GOEI THE HS: Combination therapy in re-cent onset rheumatoid arthritis: a randomised > □: double blind trial of the addition of low dose
cyclosporin to patients with low dose chloroquine. Scand J Rheumatol 1998; 1493-8
45.. TIRRI G, LA MONTAGNA G, SALAFFICombination therapy with cyclosporin A and hydroxychloroquine in early active severe rheumatoid arthritis [Abstract 397]. Arthritis Rheum 1997; 40 (Suppl. 9): S97.
46. MARCHESONI A, BATTAFARANO N, ARRE- GHINI M, PANNI B, GALLAZZI M, TOSI Radiographic progression in early rheumatoid arthritis: a 12-month randomised controlled study comparing the combination of cyclosporine and methotrexate with methotre-
xate alone. Rheumatology 2003; 42: 1545-9
47. Sharma, N.; Putman, M.S.; Vij, R.; Strek, M.E.; Dua, A. Myositis-associated Interstitial Lung Disease: Predictors of Failure of Conventional Treatment and Response to Tacrolimus in a US Cohort. J. Rheumatol. 2017, 44, 1612–1618. [CrossRef]
48. Guglielmi, S.; Merz, T.M.; Gugger, M.; Suter, C.; Nicod, L.P. Acute respiratory distress syndrome secondary to antisynthetase syndrome is reversible with tacrolimus. Eur. Respir. J. 2008, 31, 213–217. [CrossRef] [PubMed]

.