National Jewish Health
Breathing Science is Life.

JOURNAL CLUB

Article Summary by: Liudmila Kastsianok, MD, RhMSUS and Jinny Tavee, MD

ARTICLE

Huapaya JA, Hallowell R, Silhan L, Pinal-Fernandez I, Casal-Dominguez M, Johnson C, Albayda J, Paik JJ, Lin CT, Hussien A, Mammen AL, Christopher-Stine L, Danoff SK. Long-term treatment with human immunoglobulin for antisynthetase syndrome-associated interstitial lung disease. Respir Med. 2019 Jul-Aug;154:6-11. doi: 10.1016/j.rmed.2019.05.012. Epub 2019 May 21. PMID: 31176796.

CLINICAL QUESTION

What is the rationale for IVIG use in patients with respiratory muscle failure and ILD?

SUMMARY

The antisynthetase syndrome (AS) is a disorder characterized by the presence of autoantibodies to one of the tRNA synthetases with involvement of the musculoskeletal, respiratory, and dermatologic systems, and is often accompanied by Raynaud's phenomenon, fevers, rashes, and mechanic's hands. One of the main factors that predict the overall prognosis of this condition is pulmonary involvement in the form of interstitial lung disease (ILD), which has been associated with significant morbidity and mortality.

The evidence for treatment of AS-ILD is based on case reports, case series, and retrospective studies. Expert consensus recommends the use of corticosteroids and immunosuppressive agents as the mainstay of treatment. Data to guide the selection and duration of initial steroid-sparing agents is lacking. Treatment tends to follow a non-standard approach based on the experience of each center, clinician preference, and side effect profile. If patient fails to respond to traditional therapies, the use of other salvage agents such as rituximab and human intravenous immunoglobulin (IVIG) has been described. Current evidence of IVIG use in AS-ILD is limited and mainly in the context of acute exacerbation. Some reports have described use of IVIG in early disease as a first line therapy.

IVIG has been used successfully to treat refractory polymyositis (PM) and dermatomyositis (DM).
IVIG mechanism of action includes alterations in the function of T cells, B cells, and dendritic cells, changes in inflammatory cytokine production and gene expression.

Methods:
The objective of the study was to describe clinical outcomes of AS-ILD patients receiving IVIG.
This study was a retrospective analysis of medical records of patients with AS at the Johns Hopkins myositis center and ILD clinic from March 2006 until March 2016. Patients who received IVIG to treat ILD were included in the study. ILD was described as presence of the interstitial lung infiltrates on high-resolution CT scan. Refractory ILD was defined as the decline in lung function with worsening respiratory symptoms who failed corticosteroids and two immunosuppressive agents (such as azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CYC), tacrolimus, cyclosporine A (CsA), methotrexate (MTX), and rituximab. Disease flare was defined as the decline in lung function with worsening respiratory symptoms that required hospitalization and use of high-dose steroids (intravenous methylprednisolone or oral prednisone) to control disease after ruling out other causes such as heart disease, volume overload and infections.

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The IVIG protocol consists of 400 mg/kg/day administered intravenously for 5 consecutive days per month for a period of 6 months. ILD therapy initiation, continuation, discontinuation and dose adjustment were at the discretion of expert pulmonologists.

Results: Data from 17 patients were collected and analyzed.
Patients' demographics and characteristics:

- 11 (65%) were females and 9 (53%) were African American (AA)
- 10 patients tested positive for Jo1 antibody, 3 for anti-PL-12, 3 for anti-PL-7, and 1 for anti-EJ
- 7 (41%) patients met criteria for DM, 5 (29%) for PM, 2 (12%) for DM-overlap syndrome, and 1 (6%) for ADM
- 15 (88%) patients had proximal muscle weakness and 14 (82%) had elevated creatine kinase and aldolase
- The mean age of respiratory symptoms was 49.3 years (SD 9.5)
- 9 (53%) of patients were never smokers

Median follow up was 24.6 months. 14 patients had refractory disease. 16 (94%) patients received IVIG with the primary indication being ILD. 12 patients had NSIP, 2 had UIP, and 1 OP. 12 (70%), 12 (70%) and 6 (35%) used Aza, MMF, and MTX respectively, prior to IVIG. Less than 25% used CYC, tacrolimus, rituximab prior to IVIG initiation. 3 patients also received additional immunosuppression after they had been started on IVIG. The mean percent-predicted forced vital capacity (FVC%) (p=0.048) and percent-predicted diffusing capacity of the lungs for carbon monoxide (DLCO%)(p=0.0223) increased over time. The mean prednisone dose decreased over time (P< 0.001). 7 patients achieved a >10% increase in FVC%, including 2 who used IVIG as initial treatment. Five patients showed a > 10% increase in DLCO% and TLC%. 9 (53%) of patients experienced side effects such as breast swelling, headaches, dizziness, dyspnea, nausea, chills, elevated blood pressure, confusion, malaise, urticarial, leukopenia, acute pulmonary embolism, abdominal pain.

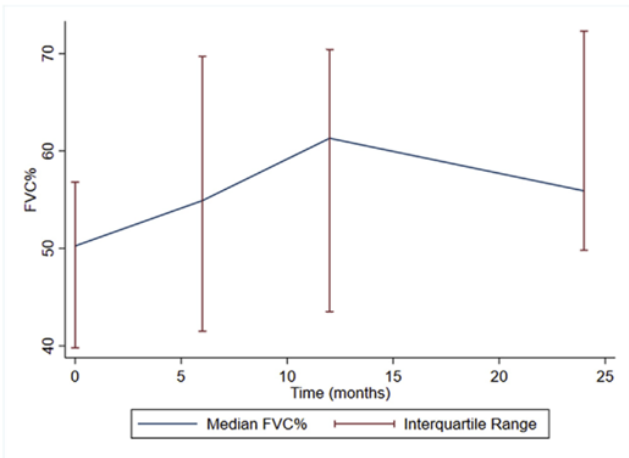

Fig. 1. Percent-predicted forced vital capacity (FVC%) in patients with AS over time.

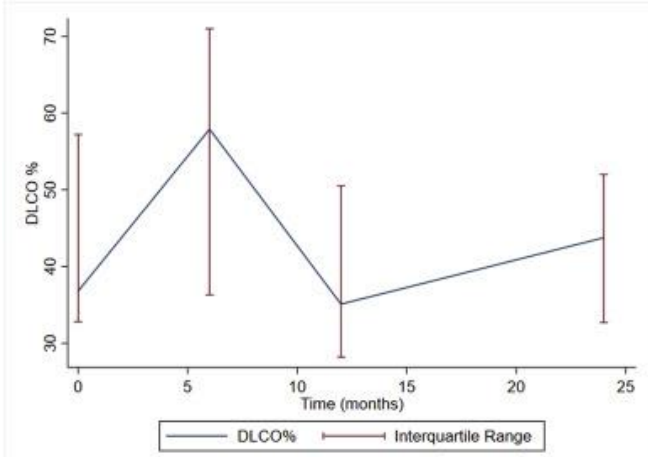

Fig. 2. Percent-predicted diffusing capacity for carbon monoxide (DLCO%) in patients with AS over time.

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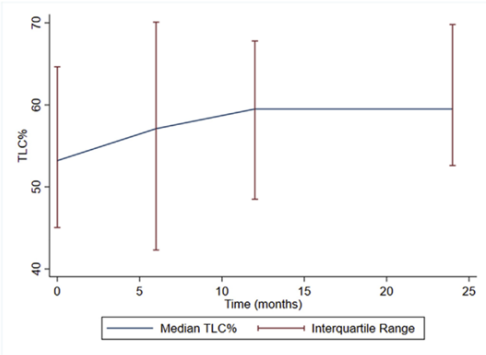

Fig. 3. Percent-predicted total lung capacity (TLC%) in patients with AS over time.

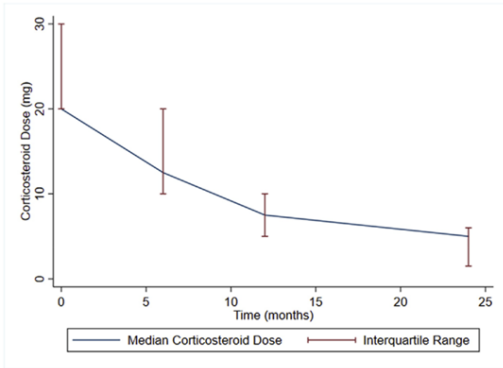

Fig. 4. Prednisone dose in patients with AS over time.

The study showed that IVIG is a potential salvage therapy in patients with active progressive AS-ILD who are not responding to the combination of steroids and first line immunosuppressant drugs. IVIG demonstrated steroid-sparing and clinical improvement in the long-term management of AS-ILD but was also associated with side effects.

GROUP OPINION

After discussion with the National Jewish Health ILD and rheumatology group in regards to IVIG use and experience in connective tissue diseases:

- The majority of providers would not use IVIG as initial therapy because high dose IVIG is limited by FDA approval guidelines and there are a limited number of studies.
- IVIG would be used as a salvage therapy usually in combination with other immunosuppressants.
- The typical case to use IVIG would be a patient with AS-ILD or PM/DM with muscle involvement, dysphagia, and profound or rapidly progressive physiologic impairment without improvement with IV glucocorticoids.
- IVIG may possibly be underused in CTD-ILD.

Overall, there are not a lot of data for clinical scenarios and circumstances when IVIG could be most helpful when patients do not have significant or resistant muscle disease or dysphagia.

The group agrees that IVIG can be used as a salvage therapy in cases where other immunosuppressants failed to control the disease, disease progressed, there were side effects to other immunosuppressants, or there is a history of severe infection.

On behalf of the National Jewish Health ILD and Rheumatology Providers: Rebecca Keith, MD, Zulma Yunt, MD, Joshua Solomon, MD, Tristan Huie, MD, Evans Fernandez, MD, Matthew Koslow, MD, Liudmila Kastsianok, MD, Mehrnaz Maleki, MD, Tho Truong, MD, and Richard Meehan, MD.

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References:

1. G.R. Connors, et al. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? Chest 138 (6) (2010) 1464–1474.
2. R.W. Hallowell, S.K. Danoff, Interstitial lung disease associated with the idiopathic inflammatory myopathies and the antisynthetase syndrome: recent advances, Curr.Opin. Rheumatol. 26 (6) (2014) 684–689.
3. T. Matsushita, et al. Clinical evaluation of anti-aminoacyl tRNA synthetase antibodies in Japanese patients with dermatomyositis, J. Rheumatol. 34 (5) (2007) 1012–1018.
4. B. Hervier, et al. Clinical manifes-tations of anti-synthetase syndrome positive for anti-alanyl-tRNA synthetase (anti-PL12) antibodies: a retrospective study of 17 cases, Rheumatology 49 (5) (2010) 972–976.
5. C.V. Oddis, Update on the pharmacological treatment of adult myositis, J. Intern. Med. 280 (1) (2016) 63–74.
6. T. Mimori, et al. Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment, Curr. Rheumatol. Rep. 14 (3) (2012) 264–274.
7. J. Morisset, et al. Management of myositis related interstitial lung disease, Chest 150 (1) (2016) 1118–1128.
8. B. Wallace, et al. Management of connective tissue diseases associated interstitial lung disease: a review of the published literature, Curr. Opin.Rheumatol. 28 (3) (2016) 236–245.
9. S.C. Mathai, et al. Management of interstitial lung disease associated with connective tissue disease, Br. Med. J. 352 (2016) h6819.
10. C. Sharp, et al. Rituximab in autoimmune connective tissue disease-associated interstitial lung disease, Rheumatology (Oxford, England) 55 (7) (2016)1318–1324.
11. Y. Allenbach, et al. Efficacy of rituximab in refractory inflammatory myopathies associated with anti-synthetase autoantibodies: an open-label, phase II trial, PLoS One 10 (11) (2015) e0133702.
12. S. Chartrand, et al. Rituximab for the treatment of connective tissue disease-associated interstitial lung disease, Sarcoidosis Vasc. Diffuse Lung Dis.: Off. J. WASOG/ World Assoc. Sarcoidosis Other Granulomatous
13. C.J. Bakewell, G. Raghu, Polymyositis associated with severe interstitial lung disease: remission after three doses of IV immunoglobulin, Chest 139 (2) (2011)441–443.
14. H. Murota, et al. Successful treatment with regimen of intravenous gamma globulin and cyclophosphamide for dermatomyositis accompanied by interstitial pneumonia, opportunistic infection and steroid psychosis, Allergol. Int.: Off. J. Jpn. Soc. Allergol. 55 (2) (2006) 199–202.
15. E. Diot, et al. , IV immunoglobulin might be considered as a first-line treatment of severe interstitial lung disease associated with polymyositis, Chest 140 (2) (2011) 562–563.
16. Y. Suzuki, et al. Intravenous immunoglobulin therapy for refractory interstitial lung disease associated with polymyositis/dermatomyositis, Lung 187 (3) (2009) 201–206.
17. M.C. Dalakas, et al. A controlled trial of high-dose intravenous immuneglobulin infusions as treatment for dermatomyositis, N. Engl. J. Med. 329 (27)(1993) 1993–2000.
18. N. Miyasaka, et al. Effects of intravenous immunoglobulin therapy in Japanese patients with polymyositis and dermatomyositis resistant to corticosteroids: a randomized double-blind placebo-controlled trial, Mod. Rheumatol./Jpn. Rheumatism.Assoc. 22 (3) (2012) 382–393.
19. E. Saito, et al. Efficacy of high-dose intravenous immunoglobulin therapy in Japanese patients with steroid-resistant polymyositis and dermatomyositis, Mod. Rheumatol./Jpn. Rheumatism Assoc. 18 (1) (2008) 34–44.
20. A. Quick, R. Tandan, Mechanisms of action of intravenous immunoglobulin in inflammatory muscle disease, Curr. Rheumatol. Rep. 13 (3) (2011) 192–198.