ramr
American Review of Respiratory Medicine
Revista Americana de Medicina Respiratoria

ORIGINAL ARTICLE

ISSN 1852-236X

Interstitial Lung Disease Associated with Idiopathic Inflammatory Myopathies. Multicenter Study Conducted in the Province of Córdoba, Argentina

Enfermedad pulmonar intersticial asociada a miopatías inflamatorias idiopáticas. Estudio multicéntrico en la provincia de Córdoba, Argentina

Nigra, Natalia Paola[1,2]; Moyano, Viviana[1,2]; Cuestas, Érica[2]; Farrell, Pamela[1]; Tissera, Yohana[3,4]; Savio, Verónica[3]; Casas, Juan Pablo[2]; Uribe Echeverría, Malisa[1]; Alba, Paula[3,5]; Meras, Nidia[3]; Babini, Alejandra[2], Arismendi Ferla, María Virginia[1]

Received: 03/13/2025
Accepted: 07/11/2025

Correspondence
Natalia Paola Nigra. E-mail: natipnigra@gmail.com

ABSTRACT

Introduction: Idiopathic inflammatory myopathies (IIMs) are a group of autoimmune diseases characterized by muscle weakness and extra-muscular manifestations. Diffuse interstitial lung disease (DILD) is a common complication of IIMs, associated with a worse prognosis and higher mortality rates. The objectives of our study were: 1- To describe the clinical, radiological, serological, respiratory functional characteristics, and treatment of patients with DILD associated with IIM. 2- To compare subgroups of IIM patients with and without DILD.

Materials and Methods: An observational, descriptive, multicenter study was conducted, including patients diagnosed with IIM (with and without associated DILD) between 2017 and 2021 from three centers in the city of Córdoba (Hospital Córdoba, Hospital Italiano, and Sanatorio Allende).

Results: The study included a total of 47 patients with IIM, with a mean age of 44.7 years; 74.5% of them were female. DILD was present in 55.3% of patients, most frequently in association with antisynthetase syndrome (46.2%). The Jo-1 antibody was the most prevalent (38.5%), and the most common CT pattern was NSIP (non-specific interstitial pneumonia) (57.79%). The mean baseline FVC (forced vital capacity) was 62.2% of predicted, the mean DLCO (diffusing capacity of the lungs for carbon monoxide) was 52.5%, and 50% of patients showed a drop in oxygen saturation during the six-minute walk test (6MWT). The most frequently used initial treatment regimen was systemic corticosteroids combined with mycophenolate (68%). In refractory cases, Rituximab was administered. When comparing subgroups, patients with DILD showed a higher prevalence of antisynthetase syndrome and respiratory symptoms, whereas those without DILD had more pronounced muscle involvement and ANA-positive antibodies.

Conclusions: In our study of patients with IIM-associated DILD, there was a predominance of middle-aged women, with an autoimmune profile of anti-Jo-1 positivity and an NSIP CT pattern. The treatments used in these patients proved to be effective and safe.

Key words: Diffuse interstitial lung disease; Idiopathic inflammatory myopathies; Antisynthetase syndrome; Jo-1 antibody

Rev Am Med Resp 2025;25:117-123. https://doi.org/10.56538/ramr.NBKX4553

[1] Pulmonology Service, Hospital Italiano de Córdoba, Córdoba, Argentina
[2] Pulmonology Service, Sanatorio Allende, Córdoba, Argentina
[3] Rheumatology Service, Hospital Italiano de Córdoba, Córdoba, Argentina.
[4] Rheumatology Service, Instituto Médico Strusberg
[5] Faculty of Medical Sciences, Universidad Nacional de Córdoba, Córdoba, Argentina

RESUMEN

Introducción: Las miopatías inflamatorias idiopáticas (MII) son un conjunto de enfermedades autoinmunes que se caracterizan por debilidad muscular y manifestaciones extra-musculares. La enfermedad pulmonar intersticial difusa (EPID) es una complicación común de las MII, asociándose a un peor pronóstico y mayor mortalidad. Los objetivos de nuestro estudio fueron 1- Describir las características clínicas, radiológicas, serológicas, funcionales respiratorias y el tratamiento de pacientes con EPID asociada a MII 2- Comparar los subgrupos de pacientes con MII con y sin EPID.

Materiales y métodos: Se realizó un estudio observacional, descriptivo y multicéntrico, incluyendo a pacientes con diagnóstico de MII (con y sin EPID asociada) dentro del periodo 2017 a 2021 de 3 centros de la ciudad de Córdoba (Hospital Córdoba, Hospital Italiano y Sanatorio Allende).

Resultados: Se incluyeron 47 pacientes con MII con una edad promedio de 44,7 años, el 74,5% de sexo femenino. El 55,3% tenía EPID, con el síndrome antisintetasa más frecuentemente (46,2 %), el anticuerpo Jo-1 el más prevalente (38,5%) y el patrón tomográfico de NINE (57,79%). La FVC media inicial fue del 62,2% del predicho, la DLCO media del 52,5% y un 50% presentó caída de la saturación de oxígeno en el test de la marcha. El esquema terapéutico inicial más utilizado fueron los corticoides sistémicos con micofenolato en el 68 % y en los casos refractarios, el Rituximab. Al comparar los subgrupos, los pacientes con EPID presentaron mayor prevalencia de síndrome antisintetasa y síntomas respiratorios, mientras que aquellos sin EPID mostraron mayor compromiso muscular y anticuerpos ANA positivos.

Conclusiones: En nuestro estudio de pacientes con EPID asociada a MII predominaron las mujeres de edad media con perfil autoinmune anti Jo-1 positivo y patrón tomográfico de NINE. Los tratamientos utilizados en estos pacientes demostraron ser efectivos y seguros.

Palabras clave: Enfermedad pulmonar intersticial difusa; Miopatías inflamatorias idiopáticas; Síndrome antisintetasa; Anticuerpo Jo-1

INTRODUCTION

Diffuse interstitial lung diseases (DILDs) are a group of heterogeneous entities with variable behavior, sharing similar clinical, functional, and radiological characteristics.[1]

On the other hand, idiopathic inflammatory myopathies (IIMs) are a group of autoimmune diseases characterized by muscle weakness and other systemic manifestations. Currently, five main types of inflammatory myopathies are recognized: dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), overlap myositis (which includes the antisynthetase syndrome), and inclusion body myositis (IBM).[2] Their diagnosis is based on clinical findings, laboratory tests (muscle enzymes and autoantibodies), electromyography, and skeletal muscle histopathology.[3-4] It is estimated that 50-60% of patients present myositis-specific autoantibodies (MSAs) that confirm the diagnosis, define phenotypes, and correlate with clinical manifestations.[5]

DILD is one of the most common complications of IIMs, and its presence is associated with a worse prognosis and higher mortality rates.

The course and severity of IIMs are highly variable, ranging from mild forms to severe, treatment-refractory cases.[6] With the exception of IBM, the cornerstone of treatment for IIMs is the administration of glucocorticoids and immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate. In cases of refractory disease, intravenous immunoglobulin, rituximab, cyclophosphamide, cyclosporine A, and tacrolimus have been used. Currently, knowledge about treatment options is limited because these drugs have not been directly compared in clinical trials.[2,7]

The objectives of our study were: a) To describe the clinical, radiological, serological, respiratory functional characteristics, and treatment of patients with DILD associated with IIM, and b) To compare subgroups of IIM patients with and without DILD.

MATERIALS AND METHODS

Patients and data collection An observational, descriptive, multicenter study was conducted involving patients from three centers in the city of Córdoba (Hospital Córdoba, Hospital Italiano, and Sanatorio Allende) who sought care between 2017 and 2021. The study included individuals over 18 years of age diagnosed with idiopathic inflammatory myopathies (with or without associated DILD). Patients with overlap syndrome involving another autoimmune disease, DILD secondary to another connective tissue disease, or interstitial pneumonia with autoimmune features (IPAF) were excluded. Patients diagnosed with inclusion body myositis (IBM) were also excluded.

Procedures: the medical records of patients with IIM were reviewed, and the following data were collected:

a) *Demographic data*: sex and age at the time of diagnosis.
b) *Type of myopathy*: polymyositis, dermatomyositis, or antisynthetase syndrome, according to the diagnostic criteria published in 2017 by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR).[8]
c) Clinical manifestations.
d) *Autoimmune serology*: patients were tested using an autoimmune panel that included ANA antibodies and a myositis panel (containing antibodies Jo-1, PM-Scl, PL-7, PL-12, Mi-2, Ku, and SRP).
For the subgroup of patients with associated DILD, the following additional data were collected:
e) Tomographic pattern: high-resolution chest CT scans were performed and evaluated by a specialist in diagnostic imaging. The tomographic patterns were classified according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines for idiopathic interstitial pneumonias as follows: usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), organizing pneumonia (OP), acute interstitial pneumonia (AIP), respiratory bronchiolitis–associated interstitial lung disease (RB-ILD), and desquamative interstitial pneumonia (DIP). Images were evaluated both at the time of diagnosis and during follow-up.[9] Disease status was categorized as stable, improved, or progressive (defined by an increase or appearance of new reticulations, ground-glass opacities, traction bronchiectasis/bronchiolectasis, honeycombing, or loss of lung volume).
f) *Pulmonary function tests (PFTs)*: spirometry, diffusing capacity for carbon monoxide (DLCO), and the six-minute walk test (6MWT) were evaluated at the time of diagnosis. Forced vital capacity (FVC) and DLCO were recorded as percentages (%) of predicted values. In the six-minute walk test, desaturation (oxygen drop) was assessed.
g *Pharmacologic treatment:* systemic glucocorticoids (GCS), methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), intravenous immunoglobulin (IVIg), rituximab (RTX), cyclophosphamide (CYC), hydroxychloroquine (HCQ), and leflunomide (LEF). Initial treatment was defined as the initial therapy administered after diagnosis and maintained for at least three months. Second-line treatment was prescribed in cases of lack of initial response.

Statistical methodology The collected data were entered into an Excel-like database, which was later used for statistical analysis. For quantitative variables, measures of central tendency and dispersion (mean and standard deviation) were calculated, while categorical variables were expressed as absolute and percentage distributions. Chi-square tests were applied to compare variables according to treatment response. A significance level of 0.05 was used in all cases. Statistical analyses were performed using InfoStat software (version 2020).

Ethical considerations Approval for this study was obtained from the Institutional Health Research Ethics Committee of Sanatorio Allende. All complementary studies performed were part of the routine follow-up for these patients. Data analysis was conducted using patients' medical records, maintaining participant confidentiality at all times.

RESULTS

General characteristics Information was collected from 47 patients with IIM, with a mean age of 44.7 years. Females represented 74.5% of the cohort. Regarding the type of myopathy, 40.4% of patients were diagnosed with dermatomyositis, 34.1% with polymyositis, and 25.5% with antisynthetase syndrome. 55.3% (26 patients) had DILD (Figure 1). The most prevalent antibodies were: ANA in 40.4%, Jo-1 in 27.7%, Ro in 6.4%, AMA in 6.4%, PL-12 in 4.3%, and Mi-2 in 4.2%. Less fre-

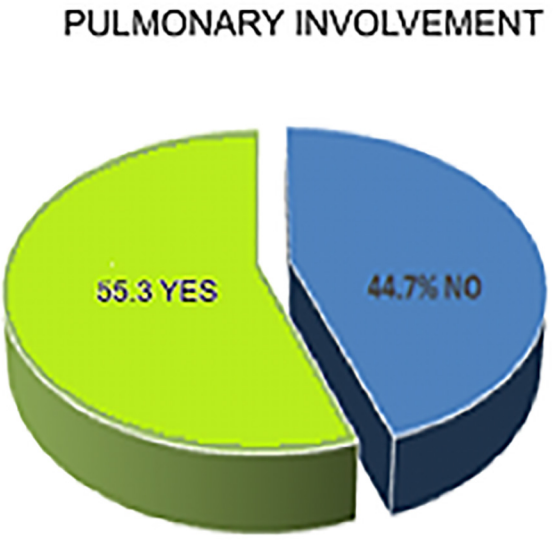

Figure 1. Distribution of the sample according to pulmonary involvement (DILD).

quent antibodies included SRP, Rib P, Pm-Scl100, and RNP, present in 2.1% of patients.

Subgroup with DILD In the group of 26 patients with DILD, the mean age was 48.3 years, and 80.8% were female. Most patients were diagnosed with antisynthetase syndrome (46.2%), followed by polymyositis (30.8%) and dermatomyositis (23.1%).

The most frequently reported symptoms were: dyspnea (84.6%), cough (50%), muscle weakness (50%), joint involvement (42.3%), symptoms meeting the SICCA (Sjögren's International Collaborative Clinical Alliance) criteria and cutaneous-mucosal involvement (42.3%). Other clinical manifestations included Raynaud's phenomenon (23.1%) and dysphagia (15.4%).

The most prevalent antibody was Jo-1, found in 38.5% of cases, followed by ANA in 26.9%. Other antibodies detected included: AMA (7.7%), Ro (7.7%), Pm-Scl100 (4%), SRP (4%), and RNP (3.8%).

The most common tomographic pattern was NSIP in 57.79%, followed by UIP in 34.61%. For the remaining 7.6%, imaging data were unavailable.

Regarding lung function, at diagnosis patients had a mean FVC of 62.2% of predicted, mean DLCO of 52.5% of predicted, and significant oxygen desaturation during the 6MWT in 50% of cases.

Pharmacologic treatment was analyzed in DILD patients who had clinical, pulmonary function, and/or imaging follow-up from the start of therapy, resulting in a total of 19 patients included in this analysis.

Initial treatment

The most commonly used initial therapeutic regimen was systemic corticosteroids (CS) combined with MMF, administered to 68% of patients. In 2 patients (10.48%), a third drug was added, MTX. Another 2 patients received CS with HCQ. Less frequent combinations included CS with AZA, and CS with MTX + RTX (5.24% in both cases).

Second-line treatment

In refractory cases (9 patients), RTX was the main therapeutic option, accounting for a total of 75%; 50% of those in monotherapy and the other 25% in combination with IVIg (Table 1). Other less common treatment combinations included CS with MMF and CS with AZA.

Changes in medication were primarily due to lack of response to treatment. No cases of drug-related toxicity were reported.

al and second-line treatments.

Mortality

Two deaths were recorded in the analyzed group. One was a patient with antisynthetase syndrome who initially received CS + AZA, but due to refractoriness, treatment was switched to IVIg + RTX + CS, without success. The other case involved a dermatomyositis patient who began treatment with CS and MMF and later escalated to RTX, also without achieving a favorable response.

Subgroup without DILD

Among the 21 patients with DILD, the mean age was 39.8 years, and 57.1% were female. The most prevalent symptom was muscle weakness (90.5%).

TABLE 1. Distribution of the sample according to initial and second-line treatments

Treatments	Therapeutic regimen	Number of patients	Percentage of patients
Initial treatment (n=19)	CS+MMF	13	68.40%
	CS+MMF+RTX	2	10.50%
	CS+HCQ	2	10.50%
	CS+MTX+RTX	1	5.30%
	CS+AZA	1	5.30%
Second-line treatment (n=8)	CS+MMF	4	44.40%
	RTX	2	22.20%
	CS+AZA	2	22.20%
	RTX+IVIg	1	11.10%

Regarding the autoimmune profile, the most frequent antibodies were: ANA (57.1%), Jo-1 (14.3%), Mi-2 (9.5%), and AMA and Ro (4.8% each).

Comparison between subgroups

Among patients with IIM-associated DILD, there was a higher prevalence of antisynthetase syndrome, respiratory symptoms, and anti-Jo-1 positivity.

Patients without DILD most commonly exhibited higher muscle involvement, dysphagia, and ANA positivity (Table 2). *Table 2. Comparison between IIM subgroups with and without DILD.*

DISCUSSION

In our study, we described the main characteristics of patients with DILD associated with IIMs.

The prevalence of DILD among IIM patients was 55.3%, which is consistent with literature findings ranging from 20% to 86%.[10,11] Similarly, we observed the expected predominance of middle-aged women affected by this condition.

Regarding clinical manifestations, it is noteworthy that muscle weakness was present in only half of patients with DILD; these findings align with other publications.[12,13]

TABLE 2. Comparison between IIM subgroups with and without pulmonary involvement

Variables	Categories	Total (n=47)	DILD		p-value
			Yes	No	
Age (years)	Age	44.7 +/- 16	48.3 +/- 13.6	39.8 +/- 17.9	0.081
Sex	Female	74.50%	80.80%	57.10%	0.27
	Male	25.50%	19.20%	33.30%	
Diagnosis	Dermatomyositis	40.40%	23.10%	61.90%	
	Polymyositis	34%	30.80%	38.10%	
	Antisynthetase syndrome	25.50%	46.20%	0%	
Clinical manifestations	Dyspnea	53.20%	84.60%	14.30%	0.0001
	Cough	34%	50%	14.30%	0.013
	Muscle weakness	68.10%	50%	90.50%	0.001
	SICCA	25.50%	34.60%	14.30%	0.096
	Cutaneous-mucosal involvement	42.60%	34.60%	52.40%	0.382
	Joint involvement	34%	42.30%	23.80%	0.153
	Raynoud	68.10%	23.10%	9.50%	0.201
	Dysphagia	25.50%	15.40%	47.60%	0.016
Lung function	FVC %	-	61.10%	-	
	DLCO%	-	52.20%	-	
	SpO_2 drop in 6MWT	-	50%	-	
Tomographic pattern	UIP	-	57.70%	-	
	NSIP	-	34.60%	-	
	No data	-	7.70%	-	
Autoimmune profile	ANA	40.40%	26.90%	57.10%	0.015
	Jo-1	27.70%	38.50%	14.30%	0.042
	AMA	6.40%	7.70%	4.80%	0.612
	Mi2	4.30%	0%	9.50%	0.026
	Pm-Scl 100	2.10%	3.80%	0%	0.336
	Ro	6.40%	7.70%	4.80%	0.612
	PL-12	4.30%	7.70%	0%	0.179
	RNP	2.10%	3.80%	0%	0.285

ANA positivity was observed in 40.4% of the total study population and in 26.9% of patients with DILD. The presence of negative ANA results in patients with antisynthetase antibodies is not uncommon, due to the cytoplasmic localization of the autoantigens. This fact, in the absence of extrapulmonary symptoms, could lead to an erroneous assumption of idiopathic DILD, potentially delaying diagnosis and timely treatment.[14,15]

The anti-Jo-1 antibody was the most frequent specific marker, while anti-Ro was the most common myositis-associated antibody identified. There is still debate regarding its correlation with the course of the disease.[16]

The most common tomographic pattern was NSIP, in line with previous publications.[16] We also observed cases of UIP, but OP –reported in the literature as the second most common pattern– was absent in our cohort.

In our study, we also analyzed the treatment received by patients with DILD associated with IIMs, and found that the most commonly used initial regimen was that of CS together with other immunosuppressants, mainly MMF; and in refractory cases, RTX was the primary treatment. Currently, there are no clinical trials comparing the efficacy of these agents; therefore, drug selection relies mainly on observational studies, expert opinion, local experience, tolerance, and availability.[17,18]

Some limitations of our study include its retrospective and multicenter design, which may have contributed to data loss. Additionally, there was heterogeneity in the autoimmune panels available across centers and over time.

CONCLUSIONS

In our multicenter study, DILD associated with IIMs predominantly affected middle-aged women with an anti-Jo-1-positive autoimmune profile, NSIP tomographic pattern, and restrictive pulmonary functional impairment. A higher prevalence of anti-Jo-1 antibodies was observed among patients with DILD, while ANA positivity and muscle symptoms were more common in those without pulmonary involvement. The treatments used in these patients proved to be effective and safe.

Conflict of interest

The authors of this work have no conflicts of interest to declare in relation to this publication.

REFERENCES

1. Margallo Iribarnegaray J, Churruca Arróspide M, Matesanz López C, Pérez Rojo R. Enfermedad pulmonar intersticial difusa [Interstitial Lung Disease]. Open Respir Arch 2023;5:100248. Spanish. https://doi.org/10.1016/j.opresp.2023.100248.
2. Selva-O'Callaghan A, Pinal-Fernandez I, Trallero-Araguás E, Milisenda JC, Grau-Junyent JM, Mammen AL. Classification and management of adult inflammatory myopathies. Lancet Neurol. 2018;17:816-28. https://doi.org/10.1016/S1474-4422(18)30254-0.
3. Carstens PO, Schmidt J. Diagnosis, pathogenesis and treatment of myositis: recent advances. Clin Exp Immunol. 2014;175:349-58. https://doi.org/10.1111/cei.12194.
4. Findlay AR, Goyal NA, Mozaffar T. An overview of polymyositis and dermatomyositis. Muscle Nerve. 2015;51:638-56. https://doi.org/10.1002/mus.24566.
5. Betteridge ZE, Gunawardena H, McHugh NJ. Novel autoantibodies and clinical phenotypes in adult and juvenile myositis. Arthritis Res Ther. 2011;13:209. https://doi.org/10.1186/ar3275.
6. Marie I, Hachulla E, Hatron PY, et al. Polymyositis and dermatomyositis: short term and longterm outcome, and predictive factors of prognosis. J Rheumatol. 2001;28:2230-7.
7. Schmidt J. Current Classification and Management of Inflammatory Myopathies. J Neuromuscul Dis. 2018;5:109-29. https://doi.org/10.3233/JND-180308
8. Lundberg IE, Tjärnlund A, Bottai M, et al; International Myositis Classification Criteria Project Consortium, the Euromyositis Register, and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (UK and Ireland). 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. Arthritis Rheumatol. 2017;69:2271-82. doi: 10.1002/art.40320. Erratum in: Arthritis Rheumatol. 2018;70:1532. https://doi.org/10.1002/art.40691.
9. Hovinga M, Sprengers R, Kauczor HU, Schaefer-Prokop C. CT Imaging of Interstitial Lung Diseases. Multidetector-Row CT of the Thorax 2016;27:105-30. https://doi.org/10.1007/978-3-319-30355-0_7
10. Vij R, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. Chest .2013143:814-24. https://doi.org/10.1378/chest.12-0741
11. Tiniakou E, Mammen AL. Idiopathic Inflammatory Myopathies and Malignancy: a Comprehensive Review. Clin Rev Allergy Immunol . 2017;52:20-33. https://doi.org/10.1007/s12016-015-8511-x
12. Rojas-Serrano J, Herrera-Bringas D, Mejía M, et al. Prognostic factors in a cohort of antisynthetase syndrome (ASS): serologic profile is associated with mortality in patients with interstitial lung disease (ILD). Clin Rheumatol. 2015;34:1563-9. https://doi.org/10.1007/s10067-015-3023-x
13. Lega JC, Fabien N, Reynaud Q, et al. The clinical phenotype associated with myositis-specific and associated autoantibodies: a meta-analysis revisiting the so-called antisynthetase syndrome. Autoimmun Rev. 2014;13:883-91. https://doi.org/10.1016/j.autrev.2014.03.004

14. Fischer A, Swigris JJ, du Bois RM, et al. Anti-synthetase syndrome in ANA and anti-Jo-1 negative patients presenting with idiopathic interstitial pneumonia. Respir Med. 2009;103:1719-24. https://doi.org/10.1016/j.rmed.2009.05.001
15. Fidler L, Doubelt I, Kandel S, et al. Screening for myositis antibodies in idiopathic interstitial lung disease. Lung. 2019;197:277-84. https://doi.org/10.1007/s00408-019-00212-9
16. Johnson C, Connors GR, Oaks J, et al. Clinical and pathologic differences in interstitial lung disease based on antisynthetase antibody type. Respir Med. 2014;108:1542-8. https://doi.org/10.1016/j.rmed.2014.09.003
17. Waseda Y, Johkoh T, Egashira R, et al. Antisynthetase syndrome: pulmonary computed tomography findings of adult patients with antibodies to aminoacyl-tRNA synthetases. Eur J Radiol. 2016;85:1421–6. https://doi.org/10.1016/j.ejrad.2016.05.012
18. Moghadam-Kia S, Aggarwal R, Oddis CV. Treatment of inflammatory myopathy: emerging therapies and therapeutic targets. Expert Rev Clin Immunol. 2015;11:1265-75. https://doi.org/10.1586/1744666X.2015.1082908.