Research & Reviews: Journal of Pharmaceutical Analysis e-ISSN: 2320-0812

Interstitial Lung Disease Associated with Systemic Sclerosis: New Molecules, New Routes of Administration

Esther F Vicente-Rabaneda[1*], Elena González-Sánchez[2], Esther San Antonio[2], Antonio Muñoz-Callejas[2], Ana Urzainqui[2*], Santos Castañeda[1,2,3]

[1]Department of Rheumatology, Hospital Universitario de La Princesa, Madrid, Spain
[2]Department of Immunology, Hospital Universitario de La Princesa, Madrid, Spain
[3]Department of Medicine, Universidad Autónoma de Madrid (UAM), Madrid, Spain

Commentary

Received: 07-Feb-2023, Manuscript No. JPA-23-88864; **Editor assigned:** 10- Feb-2023, Pre QC No. JPA-23-88864 (PQ); **Reviewed:** 24- Feb-2023, QC No. JPA- 23-88864; **Revised:** 03-Mar-2023, Manuscript No. JPA-23-88864 (R); **Published:** 10-Mar - 2023, DOI: 10.4172/2322-0066.12.1.002

***For Correspondence:**
Esther F Vicente-Rabaneda, Department of Rheumatology, Hospital Universitario de La Princesa, Madrid, Spain
E-mail: efvicenter@gmail.com
Ana Urzainqui, Department of Immunology, Hospital Universitario de La Princesa, Madrid, Spain
E-mail: urzainquimayayo@gmail.com

Citation: Vicente-Rabaneda EF, et al. Interstitial Lung Disease: Associated with Systemic Sclerosis; New

Interstitial Lung Disease (ILD) associated with SSc (SSc-ILD) is one of the most relevant manifestations of the disease, related to loss of quality of life and decreased life expectancy [1,2]. Its pathogenesis is complex and not yet fully elucidated, but microvascular damage inducing activation of endothelial cells, and the activation of B cells, T cells, and monocytes-macrophages leading to release of autoantibodies and proinflammatory cytokines are involved. As a consequence, recruitment of fibroblasts and myofibroblasts, excessive extracellular matrix deposition and development of fibrosis in early stages are increased [3,4]. Current therapeutic strategies for SSc-ILD include immunosuppressive treatments such as mycophenolate mofetil, treatments against inflammatory mechanisms including rituximab or tocilizumab, and anti- fibrotic treatments such as nintedanib or pirfenidone [5–8]. These systemic therapies are associated with adverse events, which may be enhanced whenever they are used in combination to target both inflammation and fibrosis. In this context, everolimus, an inhibitor of Mammalian Target of Rapamycin (mTOR) kinase activity, whose mechanism of action consists of forming a complex with FK Binding Protein (FKBP)-12, which binds to mTOR, blocking the PI3K/Akt/mTOR pathway appears to be an attractive alternative therapy for SSc-ILD. It has been shown *in vitro* to present immunoregulatory and anti-proliferative properties on B and T lymphocytes, and fibroblasts, respectively [9–13].

Molecules, New Routes of Administration. RRJ Pharm Anal. 2023;12:002

However, its use is limited by its toxicity, such as dyslipidemia, bone marrow toxicity or pneumonitis. Although the factors associated with everolimus-induced lung toxicity are still poorly understood, recent data suggest an association with STAT3 polymorphisms (rs4796793), the percentage of NKT cells in peripheral blood, and high doses of the drug that have been shown to up-regulate markers of epithelial to mesenchymal transition of bronchial/pulmonary cells both at gene and protein level [14–17].

In order to reduce its side effects, everolimus has been encapsulated in PEGylated liposomes decorated with high molecular weight hyaluronic acid (PEG-LipHA+Ev) to vehicle it inside the cells. *In vitro* studies on cells obtained from Broncho Alveolar Lavage (BAL) and peripheral blood of Connective Tissue Diseases (CTD) patients with ILD have shown that LipHA+EV acts specifically on cells expressing a high rate of CD44 (but not in CD44-negative cells), inhibiting cell proliferation and decreasing phosphorylation level of mTOR, with additional anti-inflammatory effect on alveolar macrophages and lymphocytes [13].

At a preclinical level, we have investigated the efficacy of Lip-HA+Ev in PSGL-1-deficient mice. PSGL-1 is an adhesion molecule expressed on all leukocyte subsets and the main ligand for P-selectin, being PSGL-1/P-selectin interaction relevant not only for acute inflammation, but also for the maintenance of immune homeostasis [18–20].

PSGL-1-deficient mice spontaneously develop a SSc-like autoimmune syndrome characterized by fibrosis, vascular damage, autoantibodies, pulmonary arterial hypertension and the spontaneous and progressive development of ILD with aging [21,22]. This animal model resembles human SSc-ILD showing an imbalance in Th1/Treg populations in the lung, with an increase in the percentage of IFN-γ producing B cells and T cells and a reduction of Treg [21].

Interestingly, intratracheal administration of LipHA+Ev directed specifically against lung cells that express CD44 in PSGL-1-deficient mice showed an anti-apoptotic and anti-inflammatory effect, with a decrease in BAL myofibroblasts and the degree of lung inflammation at histological level, as well as a decrease in the severity of peribronchial and interstitial lung fibrosis, from moderate to mild levels[23]. *In vitro* studies and preclinical evidence of nanotherapy with LipHA+Ev suggest that it is an efficient strategy to treat inflammation and pulmonary fibrosis, opening the possibility of a more specific inhaled route with fewer side effects than the systemic route, for the treatment of inflammatory and fibrosing lung diseases such as SSc-ILD.

CONFLICT OF INTERESTS

The authors have no conflicts of interests related with this manuscript.

ACKNOWLEDGEMENTS

We thank the UAM animal facility for animal breeding and care and the Cytometry Unit and Statistical and Methodological Support Unit of the Hospital de La Princesa (Madrid), for technical support.

FUNDING

Our research work targeted nanotherapy with everolimus in PSGL-1 deficient mice was supported by European Innovative Research & Technological Development (ARROW-NANO Project, EURONANOMED AC 2017/00027) and by Spanish Ministry of Health and Instituto de Salud Carlos III (ISCIII) (co-financed by European Regional Development Fund, Fondos FEDER) [grant numbers: AC17-00027, FIS-PI17-01819, and FIS-PI20-01690].

REFERENCES

1. Distler O, et al. Recent advances in the management of systemic sclerosis-associated interstitial lung disease. Curr Opin Pulm Med. 2022;28:441-447.
2. Cottin V, et al. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res. 2019;20:13.
3. Wijsenbeek M, et al. Spectrum of fibrotic lung diseases. N Engl J Med. 2020;383:958-968.
4. Spagnolo P, et al. Thoracic involvement in systemic autoimmune rheumatic diseases: pathogenesis and management. Clin Rev Allergy Immunol. 2022; 63:472-489.
5. Vicente-Rabaneda EF, et al. Efficacy and safety of biological drugs in interstitial lung disease associated with connective tissue diseases. Expert Opin Drug Saf. 2022;21:311-333.
6. Distler O, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med. 2019; 380:2518-2528.
7. Khanna D, et al. An open-label, phase ii study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the lotuss trial. J Rheumatol. 2016;43:1672-1679.
8. Rahaghi FF, et al. Expert consensus on the management of systemic sclerosis-associated interstitial lung disease. Respir Res. 2023;24:6.
9. Hausch F, et al. FKBPs and the Akt/mTOR pathway. Cell Cycle. 2013; 12:2366-2370.
10. Cova E, et al. Antibody-engineered nanoparticles selectively inhibit mesenchymal cells isolated from patients with chronic lung allograft dysfunction. Nanomedicine (Lond). 2015;10:9-23.13.208.
11. Chiesa E, et al. Hyaluronic acid-decorated chitosan nanoparticles for cd44-targeted delivery of everolimus. Int J Mol Sci. 2018;19:2310.
12. Woodcock HV, et al. The mTORC1/4E-BP1 axis represents a critical signaling node during fibrogenesis. Nat Commun. 2019;10:6.
13. Pandolfi L, et al. Liposomes loaded with everolimus and coated with hyaluronic acid: A promising approach for lung fibrosis. Int J Mol Sci. 2021;22:7743.
14. Yamamoto K, et al. STAT3 polymorphism associates with mTOR inhibitor-induced interstitial lung disease in patients with renal cell carcinoma. Oncol Res. 2022;29:11-23.
15. Willemsen AECAB, et al. Baseline effector cells predict response and NKT cells predict pulmonary toxicity in advanced breast cancer patients treated with everolimus and exemestane. Int Immunopharmacol. 2021;93: 107404.
16. Granata S, et al. *In vitro* identification of new transcriptomic and miRNomic profiles associated with pulmonary fibrosis induced by high doses everolimus: looking for new pathogenetic markers and therapeutic targets. Int J Mol Sci. 2018;19:1250.

17. Tomei P, et al. Everolimus-induced epithelial to mesenchymal transition (EMT) in bronchial/pulmonary cells: when the dosage does matter in transplantation. J Nephrol. 2016;29:881-891.
18. Urzainqui A, et al. Functional role of P-selectin glycoprotein ligand 1/P-selectin interaction in the generation of tolerogenic dendritic cells. J Immunol. 2007;179:7457-7465.
19. Nuñez-Andrade N, et al. P-selectin glycoprotein ligand-1 modulates immune inflammatory responses in the enteric lamina propria. J Pathol. 2011; 224:212-221.
20. González-Tajuelo R, et al. P-Selectin preserves immune tolerance in mice and is reduced in human cutaneous lupus, Sci Rep. 2017;7:41841.
21. Gonzalez-Tajuelo R, et al. Spontaneous pulmonary hypertension associated with systemic sclerosis in P-selectin glycoprotein ligand 1-deficient mice. Arthritis Rheumatol. 2020;72:477-487.
22. Perez-Frias A, et al. Development of an autoimmune syndrome affecting the skin and internal organs in P-selectin glycoprotein ligand 1 leukocyte receptor-deficient mice. Arthritis Rheumatol. 2014;66:3178-3189.
23. González-Sánchez E, et al. Targeted nanotherapy with everolimus reduces inflammation and fibrosis in scleroderma-related interstitial lung disease developed by PSGL-1 deficient mice. Br J Pharmacol. 2022;179:4534-4548.