Biologic Treatments in Interstitial Lung Diseases

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Interstitial lung diseases (ILD) represent a group of heterogeneous parenchymal lung disorders with complex pathophysiology, characterized by different clinical and radiological patterns, ultimately leading to pulmonary fibrosis. A considerable proportion of these disease entities present with no effective treatment, as current therapeutic regimens only slow down disease progression, thus leaving patients, at best case, with considerable functional disability. Biologic therapies have emerged and are being investigated in patients with different forms of ILD. Unfortunately, their safety profile has raised many concerns, as evidence shows that they might cause or exacerbate ILD status in a subgroup of patients. This review article aims to summarize the current state of knowledge on their role in patients with ILD and highlight future perspectives.

Keywords: interstitial lung diseases, biologic treatments, pulmonary fibrosis, treatment, safety

INTRODUCTION

Interstitial lung diseases (ILD) are a group of heterogeneous parenchymal lung disorders, characterized by different clinical and radiological patterns (1, 2). Despite an exponential increase in our knowledge and the advent of novel therapies, treatment remains ineffective for a considerable proportion of patients (3–13). Biologic treatments comprise a wide group of compounds with natural origin produced by biotechnology and other cutting-edge technologies (14); yet, this term mainly refers to the subgroup of complex molecules representing targeted therapy, such as monoclonal antibodies and receptor fusion proteins (15). The last years have seen the emergence of biologic treatments for the treatment of several immune and oncologic disorders (16–18). The most extensively used are tumor necrosis factor-α (TNF-α) inhibitors, B-cell-targeted therapies, T cell co-stimulatory molecule blockers, and immune check point inhibitors. With regards to ILDs, there is established knowledge on the use of biologic therapies in patients with connective tissue disorders (CTD-ILDs) and sarcoidosis (12, 16, 19–21). Despite old skepticism (7, 22–27), there has been recently a shift toward targeting the immune system as a therapeutic option for different forms of interstitial lung inflammation and fibrosis (9, 28–33). Unfortunately, their safety profile has raised many concerns, as evidence shows that they might exacerbate or cause de novo development of ILD in a subgroup of patients (34–36) (Table 1). This review article aims to summarize the current state of knowledge on their role in patients with ILD and highlight future perspectives.
SARCOIDOSIS (TABLE 2)

Prednisolone remains the cornerstone of sarcoidosis treatment (55). Biologic therapies currently represent a fruitful therapeutic alternative in sarcoidosis cases refractory to first line immunomodulatory agents including corticosteroids, methotrexate, azathioprine, leflunomide and mycophenolate mofetil (56). TNFα inhibitors in combination with low dose prednisolone or methotrexate have been suggested in: (i) chronic progressive pulmonary disease, (ii) debilitation by lupus pernio, (iii) persistent neurosarcoidosis, (iv) persistent cardiac sarcoidosis (55). Infliximab has shown superior response rates in pulmonary sarcoidosis compared to etanercept and adalimumab (46, 47, 50, 51, 57). In particular, a randomized controlled trial (RCT) enrolling 148 patients with chronic pulmonary sarcoidosis showed that infliximab led to a statistically significant 2.5% improvement in forced vital capacity (FVC%pred) after 24 weeks of treatment (46). Results from other non-randomized trials were rather conflicting (47, 48). Unfortunately, almost 2/3 of patients with sarcoidosis receiving infliximab demonstrated relapse following drug-cessation (49). Adalimumab has shown acceptable tolerability and efficacy profile as indicated by improvements in FVC% pred, 6 Minute-Walk-Distance (6MWD) and Borg scale over a period of 52 weeks in a small cohort of patients with refractory pulmonary sarcoidosis (50). A phase 2 trial of etanercept in patients with pulmonary sarcoidosis was prematurely terminated due to unfavorable outcomes (51). Furthermore, golimumab (TNFα inhibitor) and ustekinumab (a monoclonal antibody targeting both IL-12 and IL-23) failed to show efficacy in patients with pulmonary and/or cutaneous sarcoidosis in an RCT with 173 patients (52). Finally, rituximab had an acceptable safety profile but inconsistent efficacy in a small cohort of patients with different genetic backgrounds and refractory pulmonary sarcoidosis; thus, its use through a personalized medicine approach could be viable in the future (53).

Elevated C-reactive protein (CRP) levels and TNFα Gly308Ala polymorphisms have been found to be predictive of response to anti-TNFα therapy, while soluble IL-2 receptor serum levels ≥4,000 pg mL⁻¹ at start of therapy were predictive of relapse (49, 58). Moreover, 18F-FDG-PET showed remarkable predictive accuracy in identifying patients that responded or relapsed following infliximab treatment (48, 49).

A broad spectrum of adverse events have been associated with the use of TNF-α inhibitors including anaphylactic reactions, reactivation of latent infections, neurological (i.e., demyelinating diseases) and autoimmune disorders and maybe in some cases malignancy (55, 59, 60). The paradoxical response, denominated sarcoid-like granulomatosis, has also been reported (61).

In conclusion, current evidence based on expert opinion suggests the use of biologic treatments in severe refractory pulmonary sarcoidosis. TNFα-inhibitors are preferred for patients with persistent disease despite treatment with corticosteroids and other second-line immunomodulatory compounds, especially in cases of life-threatening disease. However, such strategies need thorough pre-treatment evaluation and multidisciplinary approaches (12).

IDIOPATHIC PULMONARY FIBROSIS (FIGURE 1, TABLE 3)

The treatment of IPF has been revolutionized by the advent of two novel compounds, pirfenidone and nintedanib (3–11). Nevertheless, both compounds only slow down disease progression; thus, at best leave patients with considerable functional disability. Therefore, the need for alternative therapeutic options remains amenable (75–78).

Biologic agents represent one such option, yet with disappointing results. The clinical trial of carlumab, a monoclonal antibody against CC-chemokine ligand 2 (CCL2), was stopped prematurely as patients in the carlumab-treatment-arm experienced greater functional decline compared to the patients in the placebo-treatment-arm (62). TNFα-blocking agents such as etanercept showed no efficacy in patients with IPF (63). Imatinib, a tyrosine kinase inhibitor with multiple biologic properties, did not affect survival or lung function of patients with IPF (64). The study of sintuzumab, a monoclonal antibody against lysyl oxidase-like 2 (LOXL2), was also a negative study (69). Most recently, two anti-IL-13 monoclonal antibodies have entered the pipeline of clinical trials for IPF. Tralokinumab had an acceptable safety and tolerability profile; yet, key efficacy endpoints were not met (70). Monotherapy with lebrikizumab, another anti-IL-13 monoclonal antibody, did not result in a benefit on lung function or mortality over 52 weeks (65). Combination of lebrikizumab and pirfenidone was well-tolerated but did not meet the primary endpoint of FVC% decline; yet, a trend toward beneficial effects on mortality and acute exacerbations was observed (66, 67). Furthermore, SAR156597, a monoclonal bispecific antibody targeting IL-4 and IL-13, failed to halt disease progression either as monotherapy or in combination with standard-of-care antibiotics (72). A Phase 2 open label trial of pamrevlumab (FG-3019), a monoclonal antibody blocking the downstream effects of connective tissue growth factor (CTGF), showed an acceptable safety and efficacy profile and thus a phase III clinical trial is currently anticipated (68, 79, 80). Safety and efficacy of VAY736, a monoclonal antibody against the cytokine...
TABLE 2 | Biologic treatments in pulmonary sarcoidosis.

| Study             | Biologic agent | Mechanism of action                        | Number of patients/Outcome                                      | References |
|-------------------|----------------|--------------------------------------------|-----------------------------------------------------------------|------------|
| Baughman et al.   | Infliximab     | Chimeric monoclonal antibody against TNF    | 148 patients Improvement of 2.5% in FVC over 24 weeks            | (46)       |
| Rossman et al.    | Infliximab     | Chimeric monoclonal antibody against TNF    | 19 patients No significant improvement over 6 and 14 weeks       | (47)       |
| Vorselaars et al. | Infliximab     | Chimeric monoclonal antibody against TNF    | 56 patients Improvement of 6.6% in FVC Uptake value on 18F-FDG-PET predictive of response | (48)       |
| Vorselaars et al. | Infliximab     | Chimeric monoclonal antibody against TNF    | 47 patients Relapse 62% Increased SUV, IL-2r predictors          | (49)       |
| Sweiss et al.     | Adalimumab     | Humanized monoclonal antibody against TNF   | 11 patients Improvement in FVC (4), stabilization in FVC (7), improvement in 6MWD (5), improvement in Borg (9) over 24/52 weeks | (50)       |
| Utz et al.        | Etanercept     | Receptor antagonist of TNF                  | 17 patients Excessive treatment failure                         | (51)       |
| Judson et al.     | Ustekinumab/    | Humanized monoclonal antibody against IL12,IL23 and against TNF, respectively | 173 patients (pulmonary or cutaneous)                           | (52)       |
|                   | golimumab      |                                             | No significant improvement over 28 weeks                        |            |
| Sweiss et al.     | Rituximab      | Humanized monoclonal antibody against CD20  | 10 patients >5% improvement in FVC (5) improvement by >30 m in 6MWD (5) over 24/52 weeks | (53)       |
| NCT02888080       | Canakinumab    | Human monoclonal antibody against IL-1b     | Change in PFTs from baseline to week 24/Recruiting              | (54)       |

CD, Cluster of Differentiation; IL, interleukin; 18F-FDG-PET, Fluorodeoxyglucose (18F) Positron Emission Tomography; FVC, Forced Vital Capacity; PFTs, Pulmonary Function Tests; SUV, Standardized Uptake Value; TNF, Tumor Necrosis Factor; 6MWD, 6 Minute Walk Distance.

FIGURE 1 | Studies investigating biologic treatments in patients with IPF.

BlyS, a B cell activating factor, is also currently being tested in a phase 2 study (71). BG00011 (STX-100), a humanized monoclonal antibody against integrin αvβ6, demonstrated an acceptable safety profile and its efficacy is currently investigated in a phase 2b study (66, 81). Finally, rituximab ± intravenous immunoglobulin showed 1-year survival benefit in a small cohort of patients with IPF undergoing acute exacerbation compared to historical controls (82). A Phase 2 trial of rituximab in IPF aiming to reduce titers of autoantibodies to HEp-2 Cells over a 9-months period of follow up, has been recently...
completed (73, 83). In addition, the results of autoantibody reduction for acute exacerbations of IPF (STRIVE-IPF) are greatly anticipated (74).

**CONNECTIVE TISSUE DISEASE-ASSOCIATED INTERSTITIAL LUNG DISEASE (CTD-ILD) RHEUMATOID ARTHRITIS**

Pulmonary complications represent an important extra-articular feature of rheumatoid arthritis and a major cause of mortality and worse quality of life (16). The decision to treat them requires a multidisciplinary approach weighting: (i) the disease severity and patients’ clinical status, (ii) the potential benefits of early therapy (i.e., treatment of inflammation before fibrosis is established) and (iii) the risk of adverse events (i.e., immunosuppression especially for patients with established fibrosis or severe bronchiectatic lesions). Given the lack of consensus over clinical trials, management is currently based on expert opinion. The recent emergence of novel anti-fibrotic compounds for the IPF/UIP-lung holds promise for the RA/UIP-lung (84–87) and the first randomized trial of antifibrotics in RA-ILD (TRAIL trial) is currently under investigation (84). To this end, biologic treatments may present with beneficial outcomes in a proportion of patients with refractory RA-ILD.

Rituximab represents the most widely used biologic treatment in patients with rapidly progressive RA-ILD who are unresponsive to first line therapeutic compounds including corticosteroids and methotrexate (88). Unfortunately, evidence is based on small observational studies and thus further data is required (89–97). A recent prospective, observational cohort study enrolling 43 patients on rituximab and 309 patients on TNF-α inhibitors, demonstrated better long-term survival in patients receiving rituximab than in those receiving TNF-α inhibitor, as event rates were 53.0 and 94.8 per 1,000 person years, respectively (98).

The use of TNF-α inhibitors yielded controversial safety and efficacy results in patients with RA-ILD. Caveats following their use in CTD-ILD parallel those previously described in sarcoidosis. Despite their effectiveness in improving clinical status and slowing down articular disease progression, lung toxicity remains a major concern (99–103). Small case series of patients with RA-ILD have shown that infliximab and etanercept could improve dyspnea and cough, as well as stabilize disease functional status (104–107). On the other hand, safety concerns have been raised for current TNF-α inhibitors infliximab (108–111), etanercept (112–116), adalimumab (117–121), golimumab (90), and certolizumab (37, 122, 123) considering reports for ILD exacerbation. Importantly, TNF-α induced ILD could be rapidly progressive and even fatal, especially in patients with preexisting ILD (34, 124–127). Nonetheless, large cohorts of patients with RA reported no association between anti-TNF agents and ILD development or progression (128, 129). Caution should be used for elderly patients, as they represent a high-risk and frail group of patients (100). Data for other agents including abatacept, tocilizumab and anakinra are still scarce. Abatacept has shown an acceptable safety and efficacy profile, as assessed by dyspnea, functional indicators and radiological extent of inflammation, in both large RCTs (130) and smaller case studies (45, 90, 102, 131, 132). The use of tocilizumab yielded conflicting results and it seems to be beneficial only in a small subgroup of patients with RA-ILD (42, 90, 102, 126, 133–137). Isolated cases of ILD-exacerbation following treatment with tocilizumab have been described (138). Finally, anakinra, an IL-1 receptor antagonist, is rarely, if ever, employed, in the treatment of patients with RA-ILD (126, 139).

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**TABLE 3 | Phase 2 clinical trials for biologic treatments in patients with IPF.**

| Biologic agent | Mechanism of action | Outcome | References |
|----------------|---------------------|---------|------------|
| Carluemab      | CCL2 inhibitor      | Negative study | NCT00786201 (63) |
| Etanercept     | Receptor antagonist of TNF | Negative study | NCT00063869 (63) |
| Imitinib       | Tyrosine kinase inhibitor | Negative study | NCT00131274 (64) |
| Lebrikizumab   | anti- IL13          | Monotherapy: Negative study | NCT01872689 (65–67) |
| Pamrevlumab (FG-3019) | Monoclonal antibody against CTGF | Positive phase 2 open label trial | NCT01262001 (68) |
| smituzumab     | Anti-LOXL2          | Negative study | NCT01769196 (69) |
| Tralokinumab   | Anti-IL13           | Negative study | NCT01629667 (70) |
| BG000111 (STX-100) | Humanized monoclonal antibody against integrin αvβ6 | Pending | NCT01371305 (66) |
| VAY736         | Monoclonal antibody against BlyS/BAFF-R | Pending | NCT03287414 (71) |
| SAR156597      | Bispecific monoclonal antibody against IL-4 and IL-13 | Negative study | NCT02921971 (72) |
| Rituximab      | anti-CD20           | Pending | NCT01969409 |
|                |                     |         | NCT03286556 (73, 74) |
SCLERODERMA

Until recently, the standard treatment for systemic sclerosis-associated ILD (SSc-ILD) was considered to be cyclophosphamide, based on the results of Scleroderma Lung Study (140). However, previously reported data from small-scale studies depicted beneficial effects of mycophenolate mofetil in SSc-ILD (141–143). The recently reported large-scale, randomized, double-blind Scleroderma Lung Study II comparing head-to-head cyclophosphamide vs. mycophenolate mofetil disclosed that mycophenolate mofetil was as effective as cyclophosphamide but with a better safety profile. Thus, mycophenolate mofetil has been established as the current standard of care for SSc-ILD (144). The statistically significant but clinically rather small benefit from the use of such treatment along with the commonly resistant nature of SSc-ILD, clearly underscores the need for novel treatments. Biologic agents, particularly rituximab, have been evaluated in small-scale studies in a minority of patients with progressive, treatment-resistant disease (145). The results of a multicenter, open label, comparative study evaluating rituximab on top of standard treatment (n = 33) vs. standard treatment alone (n = 18) showed that patients in the rituximab group had a 6% increase of FVC compared to baseline values at 2 years of treatment, a benefit that apparently was preserved later on; however, the number of patients at 7 years of treatment was too small for safe conclusions (146). Direct comparison between the rituximab group and the standard-treatment group disclosed a statistically significant benefit for the rituximab-treated patients. Other studies have reported results along the same lines (19, 20, 145, 147–149). Nevertheless, formal, multicenter, large-scale studies are clearly needed to evaluate the value of B-cell depletion treatment(s) in patients with SSc-ILD. A phase III trial evaluating the effects of the anti-IL-6 receptor monoclonal antibody tocilizumab was terminated despite relatively promising results in the earlier phase trials (150, 151) and the results from the use of belimumab, an anti-BLyS monoclonal antibody, have been evaluated only in one study with a small number of patients (n = 9) with clinically non-significant SSc-ILD (152).

MYOSITIS/ ANTISYNTHETASE SYNDROME

ILDs represent disease paradigms of unknown pathogenesis, unpredictable clinical course and relatively ineffective therapeutic approaches. Biologic therapies may offer an effective alternative in progressive and refractory cases. Early identification of these patients is of paramount importance. Unfortunately, current physiologic biomarkers neither provide mechanistic insights in disease endotypes nor they predict disease clinical course. While ILDs are associated with several underlying mechanisms, currently applied regimens target specific pathways and thus there is still an amenable need for novel compounds. The development of biologics for the treatment of fibrotic lung diseases may hold promise considering the potential for disease modulation (163).

Biologic agents have shown to have a major impact in severe refractory cases of sarcoidosis. Furthermore, canakinumab, a human monoclonal antibody against IL-1 b, has entered the pipeline of clinical trials for sarcoidosis and the results are greatly anticipated (54). Unfortunately, the majority of biologic agents in IPF have, so far, led to disappointing results mainly due to the fact that they target immune-mediated inflammation and not fibrosis. Application of oncologic and personalized medicine approaches represent crucial steps toward successful implementation of biologic agents in lung fibrosis (164). The advent and implementation of high-throughput computational tools could identify biomarkers able to distinguish patients’ endotypes and thus predict the subgroup of patients which are more likely to benefit from specific biologic interventions (165, 166). Biologic enrichment of future clinical trials and implementation of biomarkers as endpoints could have a crucial impact toward this direction. Systematic pre-treatment assessment for latent infections and immunocompromise is mandatory prior treatment initiation to avoid undesirable adverse-events. Thoughtful monitoring and multi-disciplinary care with rheumatologists and pulmonologists are strongly encouraged.

AUTHOR CONTRIBUTIONS

TK and AV wrote the manuscript. The manuscript was significantly modified by DB, S-NL, and AT. All authors offered intellectual contribution.
REFERENCES

1. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. (2013) 188:733–48. doi: 10.1164/rccm.201308-1483ST.

2. Raghu G, Rocheweg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An official ATS/ERS/IAS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. (2015) 192:e3–19. doi: 10.1164/rccm.201506-1063ST.

3. Tsouvelakis A, Karampitsakos T, Kontou M, Granitias A, MalIiou I, Anagnostopoulos T, et al. Safety and efficacy of nintedanib in idiopathic pulmonary fibrosis: a real-life observational study. Pulm Pharmacol Ther. (2018) 49:61–6. doi: 10.1016/j.pupt.2018.01.006.

4. Tsouvelakis A, Karampitsakos T, Ntoliou P, Tzilas V, Bourou E, Markozannes E, et al. Longitudinal “real-world” outcomes of pirfenidone in idiopathic pulmonary fibrosis in Greece. Front Med. (2017) 4:213. doi: 10.3389/fmed.2017.00213.

5. Tsouvelakis A, Ntoliou P, Karampitsakos T, Tzilas V, Anevilas S, Bourou E, et al. Safety and efficacy of pirfenidone in severe Idiopathic Pulmonary Fibrosis: a real-world observational study. Pulm Pharmacol Ther. (2017) 46:48–53. doi: 10.1016/j.pupt.2017.08.011.

6. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatsake D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. (2011) 377:7660–9. doi: 10.1016/S0140-6736(11)60405-4.

7. Fletcher S, Jones MG, Spinks K, Sgalla G, Marshall BG, Limbrey R, et al. The safety of new drug treatments for idiopathic pulmonary fibrosis. Expert Opin Drug Safety. (2016) 15:1483–9. doi: 10.1080/14740338.2016.1218470.

8. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. (2014) 370:2083–92. doi: 10.1056/NEJMoa1402582.

9. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. (2011) 365:1079–87. doi: 10.1056/NEJMoa1103690.

10. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. (2014) 370:2071–82. doi: 10.1056/NEJMoa1402584.

11. Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS trials. Respir Med. (2016) 113:74–9. doi: 10.1016/j.rmed.2016.02.001.

12. Spagnolo P, Rossi G, Trisellini R, Sverzatelli N, Baughman RP, Wells AU. Pulmonary sarcoidosis. Lancet Respir Med. (2018) 6:389–402. doi: 10.1016/S2213-2600(18)30064-X.

13. Wells AU, Denton CP. Interstitial lung disease in connective tissue disease–mechanisms and management. Nat Rev Rheumatol. (2014) 10:728–39. doi: 10.1038/nrrheum.2014.149.

14. https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm.

15. Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med. (2004) 356:125–33. doi: 10.1056/NEJMoa030511.

16. Bourou D, Antoniou KM, Tsouvelakis A, Siafakas NM. Interferon-gamma 1b for the treatment of idiopathic pulmonary fibrosis. Expert Opin Biol Ther. (2006) 6:1051–60. doi: 10.1517/14712598.6.10.1051.

17. Karampitsakos T, Woolard T, Bourou D, Tsouvelakis A. Toll-like receptors in the pathogenesis of pulmonary fibrosis. Eur J Pharmacol. (2017) 808:35–43. doi: 10.1016/j.ejphar.2016.06.045.

18. Wuyts WA, Agostini C, Antoniou KM, Bourou D, Chambers RC, Cottin V, et al. The pathogenesis of pulmonary fibrosis: a moving target. Eur Respir J. (2013) 41:1207–18. doi: 10.1183/09031936.0007012.

19. Karampitsakos T, Tzilas V, Tringidou R, Steiropoulos P, Aidinis V, Papiris SA, et al. Lung cancer in patients with idiopathic pulmonary fibrosis. Pulm Pharmacol Ther. (2017) 45:1–10. doi: 10.1016/j.pupt.2017.03.016.

20. Karampitsakos T, Tsouvelakis A, Chrysikos S, Bourou D, Tsangaris I, Fares WH. Pulmonary hypertension in patients with interstitial lung disease. Pulm Pharmacol Ther. (2018) 22:292–301. doi: 10.1016/j.pupt.2018.03.002.

21. Papaioannou O, Karampitsakos T, Barbayianni I, Chrysikos S, Xylourgidis N, Tzilas V, et al. Metabolic disorders in chronic lung diseases. Front Med. (2018) 5:857–68. doi: 10.3389/fmed.2017.00213.

22. Tsouvelakis A, Zacharis G, Oikonomou A, Mikroulis D, Margaritiopoulou G, Koutsopoulos A, et al. Increased incidence of autoimmune markers in patients with combined pulmonary fibrosis and emphysema. BMC Pulm Med. (2013) 13:31. doi: 10.1186/1471-2466-13-31.

23. Panopoulos ST, Sfikakis PP. Biological treatments and connective tissue disease associated interstitial lung disease. Curr Opin Pulm Med. (2011) 17:362–7. doi: 10.1097/MCP.0b013e3283483e3a.

24. Chen J, Shi S, Li F, Yang J, Cho WC, Liu X. Biologics-induced interstitial lung diseases in rheumatoid patients: facts and controversies AU - Chen, Juan. Exp Opin Biol Ther. (2017) 17:265–83. doi: 10.1080/147122598.2017.1287169.

25. Yunt ZX, Solomon JF. Lung disease in rheumatoid arthritis. Rheumat Dis Clin N Am. (2015) 41:225–36. doi: 10.1016/j.rdc.2014.12.004.

26. Glaspole IN, Hoy RF, Ryan PF. A case of cetolizumab-induced interstitial lung disease in a patient with rheumatoid arthritis. Rheumatology. (2013) 52:2302–4. doi: 10.1093/rheumatology/ket175.

27. Atzeni F, Boiard L, Salii S, Benucci M, Sarzi-Puttini P. Lung involvement and drug-induced lung disease in patients with rheumatoid arthritis. Exp Rev Clin Immunol. (2013) 9:649–57. doi: 10.1586/1744666X.2013.811173.

28. Toussirot E, Berthelot JM, Pertuiset E, Bouvard R, Gaudin P, Wendling D, et al. Pulmonary nodulosis and aseptic granulomatous lung disease occurring in patients with rheumatoid arthritis receiving tumor necrosis factor-alpha-blocking agent: a case series. J Rheumatol. (2009) 36:2421–7. doi: 10.3899/jrheum.090030.
40. Peno-Green L, Lluberas G, Kingsley T, Branley S. Lung injury linked to etanercept therapy. *Chest.* (2002) 122:1858–60. doi:10.1378/chest.122.5.1858

41. Lioe H, Lioe F, Seroussi B, Mayaud C, Cadranel J. Rituximab-induced lung disease: a systematic literature review. *Eur Respir J.* (2010) 35:681–7. doi:10.1183/09031936.00080209

42. Kawashiri SY, Kawakami A, Sakamoto N, Ishimatsu Y, Eguchi K. A fatal case of acute exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab. *Rheum Int.* (2012) 32: 4023–6. doi:10.1007/s00296-010-1525-x

43. Ikekawa K, Hanaoka M, Ushiki A, Yamamoto H, Kubo K. A case of organizing pneumonia induced by tocilizumab. *Intern Med.* (2011) 50:2191–3. doi:10.2169/internmed.50.5497

44. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T. A case of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum.* (2004) 50:1761–9. doi:10.1002/art.20303

45. Wada T, Akiyama Y, Yokota K, Sato K, Funakubo Y, Mimura T. A case of rheumatoid arthritis complicated with deteriorated interstitial pneumonia after the administration of abatacept. *Jpn J Clin Immunol.* (2012) 35:433–8.

46. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, Dubois R, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med.* (2006) 174:795–802. doi:10.1164/rccm.200603-402OC

47. Rossman MD, Newman LS, Baughman RP, Teirstein A, Weinberger SE, Miller W Jr, et al. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* (2006) 23:201–8.

48. Vorselaars AD, Vervoorde A, van Mooresl CH, Keijzers RG, Rijkers GT, Scholand MB, et al. Infliximab therapy in patients with chronic sarcoidosis. *Semin Arthr Rheumat.* (2015) 46:1740–50. doi:10.1016/S2213-2600(15)00199-X

49. Vorselaars AD, Crommelin HA, Deneer VH, Meek B, Claessen AM, Keijzers RG, et al. Association of the TNF-alpha G-308A polymorphism with other treatment approaches. *Eur Respir J.* 2019; 54:1296–307. doi:10.1164/rccm.201603-402OC

50. Utz JP, Limper AH, Kalra S, Specks U, Scott JP, Vuk-Pavlovic Z, et al. Risk factors for relapses of chronic sarcoidosis. *Am J Respir Crit Care Med.* (2002) 165:1858–60. doi:10.1164/rccm.200206-0964OC

51. Utz JP, Corte TJ, Glassberg MK, Costabel U, Lancaster LH, Kardatzke D, et al. The RIFF study (Cohort A): a phase II, randomized, double-blind, placebo-controlled trial of leflunomide as monotherapy in patients with idiopathic pulmonary fibrosis. *D12 Immunother Lung Dis.* 197: A168.

52. Raghu G, Brown KK, Costabel U, Cottin V, Wells AU, et al. CC-chemokine ligand 2 inhibition in idiopathic pulmonary fibrosis: a phase 2 trial of carlumab. *Eur Respir J.* (2015) 46:1740–50. doi:10.1183/13993003.01558-2014

53. Raghu G, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. *Am J Respir Crit Care Med.* (2008) 178:948–55. doi:10.1164/rccm.200709-1446OC

54. Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR, et al. Imitinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. *Am J Respir Crit Care Med.* (2010) 181:604–10. doi:10.1164/rccm.200906-0964OC

55. Ogura T, Scholand MB, Glaspole I, Maher TM, Kardatzke D, Kaminski J, et al. The RIFF study (Cohort B): a phase II, randomized, double-blind, placebo-controlled trial of leflunomide in combination with pirfenidone in patients with idiopathic pulmonary fibrosis. *D12 Immunother Lung Dis.* 197: A168.

56. Raghu G, Brown KK, Collard HR, Cottin V, Gibson KE, Kaner RJ, et al. Efficacy of simtuzumab versus placebo in patients with idiopathic pulmonary fibrosis: a randomised, double-blind, controlled, phase 2 trial. *Lancet Respir Med.* (2017) 5:22–32. doi:10.1016/S2213-2600(16)30421-0

57. Parker JM, Glaspole IN, Lancaster LH, Haddad TJ, Shio D, Rosseti SL, et al. A phase 2 randomized controlled study of tralokinumab in subjects with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* (2018) 197:94–103. doi:10.1164/rccm.201704-0784OC

58. ClinicalTrials.gov. STX-100 in Patients With Idiopathic Pulmonary Fibrosis (IPF). Available online at: https://clinicaltrials.gov/ct2/show/NCT01371305

59. Kundoh Y, Corte TJ, Glassberg MK, Costabel U, Lancaster LH, Kardatzke D, et al. The RIFF study (Cohort B): A phase II, randomized, double-blind, placebo-controlled trial of leflunomide in combination with pirfenidone in patients with idiopathic pulmonary fibrosis. *D12 Immunother Lung Dis.* 197: A168.

60. Raghu G, Brown KK, Collard HR, Cottin V, Gibson KE, Kaner RJ, et al. Efficacy of simtuzumab versus placebo in patients with idiopathic pulmonary fibrosis: a randomised, double-blind, controlled, phase 2 trial. *Lancet Respir Med.* (2017) 5:22–32. doi:10.1016/S2213-2600(16)30421-0

61. Raghu G, Brown KK, Collard HR, Cottin V, Gibson KE, Kaner RJ, et al. Efficacy of simtuzumab versus placebo in patients with idiopathic pulmonary fibrosis: a randomised, double-blind, controlled, phase 2 trial. *Lancet Respir Med.* (2017) 5:22–32. doi:10.1016/S2213-2600(16)30421-0

62. Raghu G, Richeldi L, Crestani B, Wang P, Bejiut R, Esperet C, Soubrâne C. Safety and efficacy of SAR156979 in idiopathic pulmonary fibrosis (IPF): a phase 2, randomized, double-blind, placebo-controlled study. *A93 ILD: Clin Trial.* 197: A2441.

63. ClinicalTrials.gov. Autoantibody Reduction Therapy in Patients With Idiopathic Pulmonary Fibrosis (ART-IPF). (2014). Available online at: https://clinicaltrials.gov/ct2/show/NCT01969409

64. ClinicalTrials.gov. Autoantibody Reduction Therapy for Acute Exacerbations of Idiopathic Pulmonary Fibrosis (STRIVE-IPF). (2018). Available online at: https://clinicaltrials.gov/ct2/show/NCT03287414

65. Yu G, Tzouvelekis A, Wang R, Herzao-Maya JD, Ibarra GH, Srivastava A, et al. Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function. *Nat Med.* (2018) 24:49–59. doi: 10.1038/nm.4447

66. Tzouvelekis A, Yu G, Lino Cardenas CL, Herzao-Maya JD, Wang R, Woolard T, et al. SH2 domain-containing phosphatase-2 is a novel antifibrotic regulator in pulmonary fibrosis. *Am J Respir Crit Care Med.* (2017) 195:500–14. doi:10.1164/rccm.201602-0329OC
Karampitsakos et al. Biologic Treatments in Interstitial Lung Diseases

77. Albert RK, Schwartz DA. Revealing the secrets of idiopathic pulmonary fibrosis. N Engl J Med. (2019) 380:94–6. doi: 10.1056/NEJMcbr1811639

78. Spagnolo P, Tsouvelakis A, Bonella F. The management of patients with idiopathic pulmonary fibrosis. Front Med. (2018) 5:148. doi: 10.3389/fmed.2018.00148

79. Raghu G, Scholand M, Andrade JDE, Lancaster L, Mageto YN, Goldlin JG, et al. Safety and efficacy of anti-CTGF monoclonal antibody FG-3019 for the treatment of idiopathic pulmonary fibrosis (IPF): results of Phase 2 clinical trial two years after initiation. Am J Resp Crit Care Med. (2014) 189:A1426.

80. ClinicalTrials.gov. Evaluate the Safety and Efficacy of FG-3019 in Patients With Idiopathic Pulmonary Fibrosis. Available online at: https://clinicaltrials.gov/ct2/show/NCT01890265

81. Mouled M, Culver DA, Hamblin MJ, Golden JA, Veeraraghavan S, Enever R, et al. Randomized, double-blind, placebo-controlled, multiple dose, dose-escalation study of BG00011 (Formerly STX-100) in patients with idiopathic pulmonary fibrosis (IPF). D14 ILD Clin Res. 197:A7785.

82. Donahoe M, Valentine VG, Chien N, Gibson KF, Raval JS, Saul M, et al. Autoantibody-targeted treatments for acute exacerbations of idiopathic pulmonary fibrosis. PAS ONE. (2015) 10: e0127771. doi: 10.1371/journal.pone.0127771

83. Redente EF, Aguilar MA, Black BP, Edelman B, Bahadur A, Humphries MJ, et al. Phase II Study of Pirfenidone in Patients With RAILD (National Lung Institute). (2017). Available online at: https://clinicaltrials.gov/ct2/show/NCT02399178

84. ClinicalTrials.gov. Evaluate the safety and efficacy of anti-CTGF monoclonal antibody FG-3019 for the treatment of idiopathic pulmonary fibrosis (IPF): results of Phase 2 clinical trial two years after initiation. Am J Resp Crit Care Med. (2014) 189:A1426.

85. ClinicalTrials.gov. Phase II Study of Pirfenidone in Patients With Idiopathic Interstitial Lung Disease. Available online at: https://clinicaltrials.gov/ct2/show/NCT01890265

86. Febriyan, Litsch, G, Bertram C, Rook GB, Aitchison D, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years’ experience at a single centre. Rheumatology. (2017) 56:1348–57. doi: 10.1093/rheumatology/kex072

87. Fernández-Díaz C, Martin-Lopez M, Carrasco-Cubero M, Reina-Sanz D, Rubio-Mu-oz P, Urruticoechea-Araña A, et al. FRI0226 Rituximab in rheumatoid arthritis with interstitial lung disease: a multicenter study. Ann Rheum Dis. (2017) 76:569–70.

88. Druce KL, Iqbal K, Watson KD, Symmons DPM, Hyrich KL, Kelly C. Mortality in patients with interstitial lung disease treated with rituximab or TNFi as a first biologic. RMD Open. (2017) 3:e000473. doi: 10.1136/rmdopen-2017-000473

89. Perez-De-Lis M, Retamozo S, Flores-Chavez A, Kostov B, Perez-Alvarez R, Brito-Zeron P, et al. Autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry). Expert Opin Drug Saf. (2017) 16:1255–71. doi: 10.1080/14740338.2017.1372421

90. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reisoga JM, Retamoza S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheumat. (2011) 41:256–64. doi: 10.1016/j.semarthrit.2010.11.002

91. Dixon WG, Hyrich KL, Watson KD, Lunt M, Symmons DP, BSRR Control Centre Consortium, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. (2010) 69:1086–91. doi: 10.1136/ard.2009.120626

92. Jani M, Hirani N, Matteson EL, Dixon WG. The safety of biologic therapies in RA-associated interstitial lung disease. Nat Rev Rheumatol. (2014) 10:284–94. doi: 10.1038/nrrheum.2013.197

93. Komiyama, T, Ishii H, Fujita N, Oka H, Iwata A, Sonoda H, et al. Adalimumab-induced interstitial pneumonia with a improvement of pre-existing rheumatoid arthritis-associated lung involvement. Int Med. (2011) 50:749–51. doi: 10.2169/internalmedicine.50.4748

94. Vasallo R, Matteson E, Thomas CF Jr. Clinical response of rheumatoid arthritis-associated pulmonary fibrosis to tumor necrosis factor-alpha inhibition. Chest. (2002) 122:1093–6. doi: 10.1378/chest.122.3.1093

95. Antoniou KM, Mamousli M, Malagari K, Kritikos HD, Bouros D, Saiasful NM, et al. Infliximab therapy in pulmonary fibrosis associated with collagen vascular disease. Clin Exp Rheumatol. (2007) 25:23–8.

96. Bagaglia E, Galeazzi M, Rottoli P. Infliximab treatment in a patient with rheumatoid arthritis and pulmonary fibrosis. Eur Respir J. (2004) 24:708. doi: 10.1183/09031936.04.000794

97. Wang Y, Xu SQ, Xu JH, Ding C. Treatment with etanercept in a patient with rheumatoid arthritis-associated interstitial lung disease. Clin Med Insights Case Reports. (2011) 4:49–52. doi: 10.4137/CMRCR.S8150

98. Mori S, Imaura F, Kiyofuji C, Sugimoto M. Development of autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry). Modern Rheumatol. (2006) 16:251–5. doi: 10.3109/10165006.004915

99. Ostör A, Chilvers ER, Somerville MF, Lim AV, Lane SE, Crisp AJ, et al. Pulmonary complications of infliximab therapy in patients with rheumatoid arthritis. J Rheumatol. (2006) 33:622–8.

100. Takeuchi T, Tatsuki Y, Nomagami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. (2008) 67:189–94. doi: 10.1136/ard.2007.072967

101. Tai K, Kagawishi Y, Shinoda K, Hounoki H, Ogawa R, Sugiyama H, et al. Interstitial pneumonitis associated with infliximab therapy without methotrexate treatment. Rheumatol Int. (2009) 30:275–76. doi: 10.1007/s00296-009-0953-6

102. Lindsay K, Melson R, Jacob BK, Mestry N. Acute progression of interstitial lung disease: a complication of etanercept particularly in the presence of rheumatoid lung and methotrexate treatment. Rheumatology. (2006) 45:1048–9. doi: 10.1093/rheumatology/kel090
131. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. *Respir. Med.* (2016) 54:376–9. doi: 10.1016/j.resmed.2016.03.001

132. Mera-Varela A, Perez-Pampin E. Abatacept therapy in rheumatoid arthritis with interstitial lung disease. *J Clin Rheumatol.* (2014) 20:445–6. doi: 10.1097/RHU.0000000000000084

133. Mohr M, Jacobi AM. Interstitial lung disease in rheumatoid arthritis: response to IL-6R blockade. *Scand J Rheumatol.* (2011) 40:400–1. doi: 10.3109/03009742.2011.589722

134. Shetty A, Hanson R, Korsten P, Shawagfeh M, Aрами S, Volkv S, et al. Tocilizumab in the treatment of rheumatoid arthritis and beyond. *Drug Des Devel Ther.* (2014) 8:349–64. doi: 10.2147/DDDT.S41437

135. Picchianti Diamanti A, Markovic M, Argento G, Giovagnoli S, Ricci A, Lagana B, et al. Therapeutic management of patients with rheumatoid arthritis and associated interstitial lung disease: case report and literature review. *Ther Adv Respir Dis.* (2017) 11:64–72. doi: 10.1177/1753456316668870

136. Wendling D, Vidon C, Godfrin-Velnet M, Rival G, Guillot X, Prati C. Exacerbation of combined pulmonary fibrosis and emphysema syndrome during tocilizumab therapy for rheumatoid arthritis. *Joint Bone Spine Revue du Rhum.* (2013) 80:670–1. doi: 10.1016/j.jbspin.2013.03.009

137. Fernández-Díaz C, Narvaez-Garcia J, Martín-López M, Rubio-Muñoz P, Castañeda-Sanz S, Vegas-Revena N, et al. THU0134 Interstitial lung disease and rheumatoid arthritis. multicenter study with tocilizumab. *Ann Rheum Dis.* (2017) 76:251–2. doi: 10.1136/annrheumdis-2017-eular.3580

138. Akiyama M, Kaneko Y, Yamaoka K, Kondo H, Takeuchi T. Association of disease activity with acute exacerbation of interstitial lung disease during tocilizumab treatment in patients with rheumatoid arthritis: a retrospective, case-control study. *Rheumatol Int.* (2016) 36:881–9. doi: 10.1007/s00296-016-3478-3

139. Cohen SB. The use of anakinra, an interleukin-1 receptor antagonist, in the treatment of rheumatoid arthritis. *Rheum Dis Clin North Am.* (2004) 30:365–80. doi: 10.1016/j.rdc.2004.01.005

140. Tashkin DP, Elashoff R, Clements P, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* (2006) 354:2655–66. doi: 10.1056/NEJMoa055120

141. Liossis SN, Bounas A, Andonopoulou AP. Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. *Rheumatology.* (2006) 45:1005–8. doi: 10.1093/rheumatology/kei211

142. Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. *J Rheumatol.* (2013) 40:640–6. doi: 10.3899/rhum.121043

143. Kowal-Bielecka O, Landewe R, Avouac J, Chwiesio S, Minati I, Czirjak L, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis.* (2009) 68:620–8. doi: 10.1136/ard.2008.096677

144. Tashkin DP, Roth MD, Clements P, Furst DE, Khanna D, Kleerup EC, et al. Long-term efficacy of B cell depletion therapy on lung and skin involvement in diffuse systemic sclerosis. *Semin Arthr Rheum.* (2015) 45:428–36. doi: 10.1016/j.semarthrit.2014.09.002

145. Jordan S, Distler JH, Maurer B, Huscher D, van Laar JM, Allanoire Y, et al. Effects and safety of rituximab in systemic sclerosis: an analysis
from the European Scleroderma Trial and Research (EUSTAR) group. Ann Rheum Dis. (2015) 74:1188–94. doi: 10.1136/annrheumdis-2013-204522

150. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet. (2016) 387:2630–40. doi: 10.1016/S0140-6736(16)00232-4

151. Khanna D, Denton CP, Lin CJF, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). Ann Rheum Dis. (2018) 77:212–20. doi: 10.1136/annrheumdis-2017-211682

152. Gordon JK, Martyanov V, Franks JM, Bernstein EJ, Szymonifka J, Magro C, et al. Belimumab for the treatment of early diffuse systemic sclerosis: results of a randomized, double-blind, placebo-controlled, pilot trial. Arthritis Rheumatol. (2018) 70:308–16. doi: 10.1002/art.40358

153. Watanabe K, Handa T, Tanizawa K, Hosono Y, Taguchi Y, Noma S, et al. Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias. Respir Med. (2011) 105:1238–47. doi: 10.1016/j.rmed.2011.03.022

154. Lambotte O, Kott R, Maigne G, Blanc FX, Goujard C, Delfraissy JF. Efficacy of rituximab in refractory polymyositis. J Rheumatol. (2005) 32:1369–70.

155. Brulhart L, Waldburger JM, Gabay C. Rituximab in the treatment of antisynthetase syndrome. Ann Rheum Dis. (2006) 65:974–5. doi: 10.1136/ard.2005.045898

156. Andersson H, Sem M, Lund MB, Aalokken TM, Gunther A, Walle-Hansen R, et al. Long-term experience with rituximab in antisynthetase syndrome-related interstitial lung disease. Rheumatology. (2015) 54:1420–8. doi: 10.1093/rheumatology/kev004

157. Zappa MC, Trequattarini T, Mattioli F, Rivitti R, VigiIarloco R, Maroccia A, et al. Rituximab treatment in a case of antisynthetase syndrome with severe interstitial lung disease and acute respiratory failure. MultidisCIP Res Med. (2011) 6:183–8. doi: 10.1186/2049-6958-6-3-183

158. Vandenbroucke E, Grutters JC, Altenburg JM, Boersma WG, ter Borg EI, van den Bosch JM. Rituximab in life-threatening antisynthetase syndrome. Rheumatol Int. (2009) 29:1499–502. doi: 10.1007/s00296-009-0859-x

159. Dosa O, Ruzieh M, Oraibi O. Successful Treatment of life-threatening interstitial lung disease secondary to antisynthetase syndrome using rituximab: a case report and review of the literature. Am J Ther. (2016) 23:e639–45. doi: 10.1097/MTJ.0000000000000245

160. Marie I, Dominique S, Janvesse A, Levesque H, Menard JF. Rituximab therapy for refractory interstitial lung disease related to antisynthetase syndrome. Respir Med. (2012) 106:581–7. doi: 10.1016/j.rmed.2012.01.001

161. Keir CJ, Maher TM, Ding D, Abdullah R, de Lauretis A, Wickremasinghe M, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respir Care. (2014) 19:353–9. doi: 10.1111/resp.12214

162. Zou J, Li T, Huang X, Chen S, Guo Q, Bao C. Basiliximab may improve the survival rate of rapidly progressive interstitial pneumonia in patients with clinically amyopathic dermatomyositis with anti-MDA5 antibody. Ann Rheum Dis. (2014) 73:1591–3. doi: 10.1136/annrheumdis-2014-205278

163. Karampitsakos T CS, Tailes V, Dimakou K, Bouros D, Tzouvelekis A. Idiopathic pulmonary fibrosis. Time to get personal. Pneumon. (2018) 31:71–80.

164. Doyle TJ, Lee JS, Dellaripa PF, Lederer IA, Matteson EL, Fischer A, et al. A roadmap to promote clinical and translational research in rheumatoid arthritis-associated interstitial lung disease. Chest. (2014) 145:454–63. doi: 10.1378/chest.13-2408

165. Spagnolo P, Tzouvelekis A, Maher TM. Personalized medicine in idiopathic pulmonary fibrosis: facts and promises. Curr Opin Pulm Med. (2015) 21:470–8. doi: 10.1097/MCP.0000000000000187

166. Tzouvelekis A, Herazo-Mayo J, Sakamoto K, Bouros D. Biomarkers in the evaluation and management of idiopathic pulmonary fibrosis. Curr Topics Med Chem. (2016) 16:1587–98. doi: 10.2174/1568026616666150930 120959

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