SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2021; 38 (1); e2021001 DOI: 10.36141/svdld.v38i1.11520

Acute exacerbations of interstitial lung disease: what is the best treatment?

Keith C. Meyer
MD, MS, Professor of Medicine, Section of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, University of Wisconsin School of Medicine and Public Health, USA

There is an increasing recognition that patients with various forms of chronic fibrosing interstitial lung diseases (CFILD) are at risk for an acute exacerbation (AE) of their disease that can rapidly lead to death (1). While acute exacerbations of Idiopathic pulmonary fibrosis (AE-IPF) appear to be more common than acute exacerbations for other forms of CFILD and a considerable number of manuscripts have been published on risk factors, pathogenesis and treatments, no randomized and adequately powered clinical trials of therapies for AE-CFILD have been published to date. But because only a relatively small number of patients at any single center develop an AE over time, such a study would be very difficult to perform. Furthermore, funding entities with adequate resources to support a large clinical trial of licensed drugs are reluctant to support an evaluation drugs that are off patent.

Treatment approaches to fibrotic lung diseases and, especially, IPF have evolved considerably over the past two decades. The first clinical practice guideline on the diagnosis and management of patients with IPF (2) suggested that cytotoxic drugs such as azathioprine or cyclophosphamide (CYC) could be useful to diminish or stop the progression of IPF. But these drugs had never been tested in randomized controlled trials that were adequately powered with robust endpoints. But over a decade later a key National Institutes of Health (NIH) sponsored study provided results that went against the assumption that the cytotoxic agent, azathioprine, was beneficial in treating patients with IPF (3). In contrast to the perception that azathioprine in combination with low-dose corticosteroids may be a useful therapy for IPF, treatment with azathioprine was shown by the PANTHER-IPF trial to actually be detrimental to a substantial number of patients and associated with a significantly increased risk of adverse events including hospitalization and death when compared to controls. Additionally, a prospective study of CYC for patients with progressive IPF did not find benefit, and drug-related adverse events occurred in two-thirds of this study cohort (4). Recently updated clinical practice guidelines on the management of patients with IPF do not support the use of cytotoxic drugs for the treatment of IPF (5).

The advent of anti-fibrotic therapy with pirfenidone or nintedanib has had a significant impact on disease progression in IPF, and new data support anti-fibrotic therapy using nintedanib for patients with CFILD (,7). Nonetheless, significant numbers of patients with IPF as well as those with CFILD other than IPF can suffer acute exacerbations of their fibrotic lung disease despite treatment with anti-fibrotic drugs. While many retrospective case series that examined different drug therapies for acute exacerbations of IPF have been published in the literature (8), no therapy other than lung transplantation has been shown to provide long-term survival in a randomized clinical trial. However, despite a lack of clinical trial evidence, current international consensus guidelines make a weak recommendation, based on very low quality evidence, that corticosteroids should be used to treat the majority of patients with

AE-IPF in addition to supportive care (9).

In this issue of the journal Innabi et al. (10) review published literature on the treatment of ILD associated with connective tissue disease (CTD) with CYC and note that significant although modest benefit has been found for patients with ILD associated with systemic sclerosis. They also examined published literature on using CYC to treat acute exacerbations of ILD (AE-ILD) and conclude that cumulative studies, which are predominantly single-center, retrospective, and inadequately powered, do not support significant benefit when using CYC to treat acute exacerbations of IPF or CTD-ILD. Additionally, they note that while consensus criteria have been established that define acute exacerbations of IPF (11), specific criteria for diagnosing acute exacerbations of other non-IPF forms of ILD have yet to be determined, and a standardized approach to treatment of AE-ILD has yet to be established.

Because toxicities associated with CYC therapy are substantial and such therapy must be carefully monitored for adverse events (12), adequately powered, randomized, controlled trials should be conducted to prove whether or not CYC or other pharmacologic therapies provide significant benefit for patients who develop an episode of AE-ILD. A number of registered trials (www.clinicaltrials.gov) are seeking a definitive answer to this question, and the Phase 3 multi-center, double-blind, randomized, placebo-controlled EXAFIP study (NCT02460588) is being conducted in France to evaluate the efficacy of methylprednisolone with or without CYC for treating AE-IPF (13). While a number of other registered Phase 2 or 3 trials are also evaluating therapies for AE-IPF, no trials have been registered for treating acute exacerbations of non-IPF ILD.

Acute exacerbations of IPF can even occur in patients with a limited extent of fibrosis and well-preserved lung function (12), and the widespread acute lung injury that characterizes AE-IPF is an important cause of accelerated disease progression and mortality. Randomized, controlled trials that evaluate novel therapies for acute exacerbations of IPF as well as non-IPF fibrosing ILDs are much needed. In this regard, a recent study by Donahoe et al. (14) that sought to reduce autoantibodies via a combination of plasma exchange, administration of rituximab, and intravenous immunoglobulin showed that some patients with AE-IPF had prolonged survival responses. A better understanding of the pathogenesis and triggers of acute exacerbations as well as optimal strategies for prevention and making an early diagnosis of AE-IPF and acute exacerbations of other forms of chronic fibrosing ILD will likely lead to improved survival for patients with these devastating forms of fibrotic ILD. Clearly, successful treatment of episodes of AE-CFILD remains elusive, and progress is likely to be slow and incremental. Treatment strategies that employ novel approaches and biologic response modifiers rather than cytotoxic drugs may prove to be of significant benefit to patients.

Table 1. Therapies for acute exacerbations of IPF

Pharmacologic	Corticosteroids (e.g. high-dose, pulsed intravenous)* Corticosteroids plus immunomodulatory/cytoxic agents** - Cyclophosphamide - Calcineurin inhibitors (Cyclosporine A, tacrolimus) Rituximab with plasma exchange** Human recombinant thrombomodulin** Antibiotics (e.g. macrolides, co-trimoxazole)** Anti-fibrotic drugs (e.g. continue if already using prior to AE)**
Non-pharmacologic	Supportive care - Supplemental oxygen - Symptom palliation (e.g. opioids for relief of dyspnea) - Assisted ventilation Hemoperfusion with polymyxin B-immobilized fibers** Lung transplantation

*Weak recommendation, very low quality evidence (Reference 9); **Unproven therapy; no guideline recommendation

References

1. Kolb M, Bondue B, Pesci A, Miyazaki Y, Song JW, Bhatt NY, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018 Dec 21;27(150):180071. doi: 10.1183/16000617.0071-2018. PMID: 30578331.
2. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000 Feb;161(2 Pt 1):646-64. doi: 10.1164/ajrccm.161.2.ats3-00. PMID: 10673212.
3. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012 May 24;366(21):1968-77. doi: 10.1056/NEJMoa1113354. Epub 2012 May 20. PMID: 22607134; PMCID: PMC3422642.
4. Zisman DA, Lynch JP 3rd, Toews GB, Kazerooni EA, Flint A, Martinez FJ. Cyclophosphamide in the treatment of idiopathic pulmonary fibrosis: a prospective study in patients who failed to respond to corticosteroids. Chest. 2000 Jun;117(6):1619-26. doi: 10.1378/chest.117.6.1619. PMID: 10858393.
5. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015 Jul 15;192(2):e3-19. doi: 10.1164/rccm.201506-1063ST. Erratum in: Am J Respir Crit Care Med. 2015 Sep 1;192(5):644. Dosage error in article text. PMID: 26177183.
6. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019 Oct 31;381(18):1718-1727. doi: 10.1056/NEJMoa1908681. Epub 2019 Sep 29. PMID: 31566307.
7. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020 May;8(5):453-460. doi: 10.1016/S2213-2600(20)30036-9. Epub 2020 Mar 5. PMID: 32145830.
8. Biondini D, Balestro E, Sverzellati N, Cocconcelli E, Bernardinello N, Ryerson CJ, et al. Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF): an overview of current and future therapeutic strategies. Expert Rev Respir Med. 2020 Apr;14(4):405-414. doi: 10.1080/17476348.2020.1724096. Epub 2020 Feb 3. PMID: 31994940.
9. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68. doi: 10.1164/rccm.201807-1255ST. PMID: 30168753.
10. Innabi A, Gomez-Manjarres D, Alzghoul B, Chizinga M, Mehrad B, Patel D. Cyclophosphamide for the treatment of Acute Exacerbation of Interstitial Lung Disease: A Review of the Literature.
11. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 2016 Aug 1;194(3):265-75. doi: 10.1164/rccm.201604-0801CI. PMID: 27299520.
12. Baughman RP, Meyer KC, Nathanson I, Angel L, Bhorade SM, Chan KM, et al. Monitoring of nonsteroidal immunosuppressive drugs in patients with lung disease and lung transplant recipients: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Nov;142(5):e1S-e111S. doi: 10.1378/chest.12-1044. PMID: 23131960; PMCID: PMC3610695.
13. Naccache JM, Montil M, Cadranel J, Cachanado M, Cottin V, Crestani B, et al. Study protocol: exploring the efficacy of cyclophosphamide added to corticosteroids for treating acute exacerbation of idiopathic pulmonary fibrosis; a randomized double-blind, placebo-controlled, multi-center phase III trial (EXAFIP). BMC Pulm Med. 2019 Apr 11;19(1):75. doi: 10.1186/s12890-019-0830-x. PMID: 30971235; PMCID: PMC6458697.
14. Donahoe M, Valentine VG, Chien N, Gibson KF, Raval JS, Saul M, et al. Autoantibody-Targeted Treatments for Acute Exacerbations of Idiopathic Pulmonary Fibrosis. PLoS One. 2015 Jun 17;10(6):e0127771. doi: 10.1371/journal.pone.0127771. Erratum in: PLoS One. 2015;10(7):e0133684. PMID: 26083430; PMCID: PMC4470587.