Editorial

Can Large Simple Trials Help Us Understand When and How to Use Generic Drugs for Uncommon Diseases?

Treatment of interstitial lung disease associated with connective tissue disease (CTD-ILD) is an area of high unmet medical need. A 1-year cyclophosphamide (CYC) treatment regimen improved scleroderma (SSc)-associated ILD (SSc-ILD) in a randomized placebo-controlled trial[1], but failed to sustain improvement after 2 years[2]. A second multicenter trial of 6 months of CYC for SSc-ILD did not demonstrate efficacy[3]. Even given a possible modest benefit, CYC is undesirable for chronic or repetitive use due to its toxicity, making the ascertainment of other treatments for CTD-ILD a high priority.

In this issue of *The Journal*, Fischer, *et al*[4] report apparent broad utility of mycophenolate mofetil (MMF) in the treatment of CTD-ILD. MMF has been gaining acceptance for treatment of CTD-ILD based on earlier small studies, including those of the authors[5] and others[6,7,8,9,10,11] and a recent metaanalysis[12]. This body of work suggests that MMF can confer stability or modest improvement in pulmonary function tests (PFT). The Scleroderma Lung Study-II (SLS-II) [a US National Institutes of Health (NIH)-sponsored randomized, blinded comparison of 2-year treatment with MMF versus 1-year treatment with CYC, plus 1-year followup for SSc-ILD] completed enrollment of about 140 subjects (http://clinicaltrials.gov/show/ NCT00883129). It will be 2 more years, however, before analysis of SLS-II is completed.

The Fischer, *et al* study, although neither randomized nor blinded, has several important strengths. First, it comprises the largest published groups of MMF-treated patients with SSc-ILD as well as other CTD-ILD. Second, there appears to be broad benefit of MMF, irrespective of the specific CTD diagnosis, or of ILD histologic subtype. The study benefits from relatively uniform dosing of MMF at 2 grams per day or greater throughout virtually the entire cohort, low rates of patient withdrawal from the treatment, and long followup, with pulmonary function testing performed in a reproducible manner at uniform intervals.

Although the current study provides strong evidence of its utility, there remain significant unknowns in how to optimally use MMF in CTD-ILD. Although both SLS-II and the current retrospective study of Fischer, *et al* have used doses of 2 to 3 grams per day, the best dose for CTD-ILD has not been rigorously studied. Although the toxicity of MMF appears tolerable, the longterm toxicity of MMF in this setting remains unknown. Whether MMF has additional disease-modifying benefits such as in improving the cutaneous involvement of SSc remains unclear[13,14,15,16]. Finally, as the authors note, it is unclear how long patients should be treated with MMF to avoid progression of lung fibrosis.

The use of MMF in CTD-ILD is actually better studied compared to other drugs used in uncommon conditions such as CTD. In part, therapeutic knowledge is lacking because the pharmaceutical industry has had little interest in pursuing uncommon secondary indications for patented drugs that have a lucrative primary market. Once patent life has expired, there is virtually no financial incentive for pursuing studies to examine possible efficacy of an approved generic drug for uncommon indications.

Although the NIH sponsor studies such as SLS-II, the NIH budget does not permit the conduct of numerous trials of approved drugs for uncommon secondary indications, even when a good rationale exists to do so, due to high costs associated with double-blind randomized trials. Some of the biggest costs in such trials are incurred in the process of blinded treatment assignment, through the production of placebos or comparator, controlling study drug and comparator through investigational pharmacies, and the requirement for attribution of adverse events. Additional costs arise from slow enrollment in trials due to patient reluctance to enroll in blinded protocols. As a consequence of these costs and disincentives, many potentially useful agents remain inadequately tested for secondary indications.

See MMF and CTD-associated ILD, *page 640*

The concept of the large simple trial (LST) is not new[17], and has long ago been successfully implemented in evaluating therapies for common diseases[18,19,20]. However, the use of LST in uncommon conditions such as CTD has yet to be widely adopted. The European Scleroderma Observational Study (ESOS; http://www.ssc-esos.net/home.asp) is a large observational study comparing the primary outcome of the modified Rodnan skin score, as well as secondary outcomes including PFT in SSc patients receiving: (1) methotrexate, (2) MMF, (3) CYC, or (4) no immunosuppression. This trial will provide data directly comparing these treatments in a "real-life" setting, but treatment allocation is not randomized, so the effects of selection bias will render the results subject to interpretation.

The Institute of Medicine recently conducted a 2 day workshop on the use of LST in the electronic health record (EHR) era, which one of us (DLD) co-chaired. Several conclusions arose: First, many trials collect more data than is necessary to answer the primary outcome measure and necessary safety assessments. This excess data collection leads to increased cost with little to no scientific benefit. With simplified data collection, trials can be much larger or longer for the same or lower cost. Second, for randomized trials that need extremely large sample size, or for trials for rare diseases, baseline and limited followup data may be electronically collected from the EHR with addition of a treatment assignment or randomization variable. Currently, data for patients in trials are printed out from the EHR and entered manually into a computerized trial data management system. It is now becoming possible to electronically download trial data directly from an EHR, avoiding data entry errors and costs. Coupling the LST and EHR will allow rigorous evaluation of new interventions for patients with a low event rate (large sample size) or for patients with uncommon diseases where patient recruitment is a challenge.

We believe that randomization of treatment assignment in LST will enable clinical investigators to make valid, if not ironclad, conclusions about how to use available drugs for secondary indications, to a degree that multiple small nonrandomized studies do not. For some studies and indications, blinding of treatment assignment, while desirable, may not be as necessary, especially if the outcome ascertainment is a practice standard and is done routinely by those not directly involved in the trial, thus minimizing bias. Allowing the randomization process and larger comparison groups to filter the inherent noise in human studies minimizes the need to control such noise through difficult-to-meet inclusion/exclusion criteria which can delay trial completion for months or years. Large randomized protocols could be valuable in better understanding optimal dose, potential toxicity of drug, and best duration of therapy by enrolling real-world patients. Even comparator studies between different agents could conceivably be performed in a cost-effective and expedient yet conclusive manner using such designs.

As an example, we propose a large simple multicenter trial of MMF in CTD-ILD, to answer a straightforward question raised by Fischer, *et al*: How long does a patient with CTD-ILD need to receive MMF? Patients agreeing to participate would be randomized to withdrawal after 3 consecutive stable pulmonary function tests over 12–18 months, versus continuation of MMF for an additional several years after such stability. The ascertainment of reasons for withdrawal of drug or dosing changes could be facilitated by the participation of pharmacy benefit plans in data collection; most other data could be captured through the EHR.

A critical issue for any study is funding. Elimination of the costs of blinding and excessive data collection makes LST cheaper. The use of accepted standard of care measurements minimally susceptible to subjective bias for the monitoring of disease, such as PFT performed at regular intervals, allows reasonable data comparison between study arms. Given reduced costs, the NIH could fund more studies by paying only for protocol development, minimal data collection, and data analysis. Patient advocacy groups could contribute to the development of such trials and their enrollment. Payors have incentive to optimize the costs of treatment, and could participate in the funding of trials and in data acquisition through their large databases, in order to better understand optimal drug regimens. Payors including Medicare might contribute to the process by recommending specific LST for funding, to clarify best practice in areas with high cost, but significant unmet medical need.

Analysis of shared pathophysiologic pathways between diseases for which drugs have received FDA-approved indications and diseases of high unmet medical need should be routinely performed. LST based on those analyses and several subsequent encouraging small pilot studies have the potential to markedly improve the effective utilization of existing drugs for secondary indications. Randomized LST demonstrating benefit of generic drugs with established safety records for secondary indications ought to prompt consideration for a provisional approval process by the FDA and other regulatory authorities for such indications.

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REFERENCES

1. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst

DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655-66.
2. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007;176:1026-34.
3. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006;54:3962-70.
4. Fischer A, Brown K, 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.
5. Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, et al. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest 2006;130:30-6.
6. Liossis SN, Bounas A, Andonopoulos AP. Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. Rheumatology 2006;45:1005-8.
7. Zamora AC, Wolters PJ, Collard HR, Connolly MK, Elicker BM, Webb WR, et al. Use of mycophenolate mofetil to treat scleroderma-associated interstitial lung disease. Respir Med 2008;102:150-5.
8. Gerbino AJ, Goss CH, Molitor JA. Effect of mycophenolate mofetil on pulmonary function in scleroderma-associated interstitial lung disease. Chest 2008;133:455-60.
9. Saketkoo LA, Espinoza LR. Rheumatoid arthritis interstitial lung disease: Mycophenolate mofetil as an antifibrotic and disease-modifying antirheumatic drug. Arch Intern Med 2008;168:1718-9.
10. Simeon-Aznar CP, Fonollosa-Pla V, Tolosa-Vilella C, Selva-O'Callaghan A, Solans-Laque R, Vilardell-Tarres M. Effect of mycophenolate sodium in scleroderma-related interstitial lung disease. Clin Rheumatol 2011;30:1393-8.
11. Koutroumpas A, Ziogas A, Alexiou I, Barouta G, Sakkas LI. Mycophenolate mofetil in systemic sclerosis-associated interstitial lung disease. Clin Rheumatol 2010;29:1167-8.
12. Tzouvelekis A, Galanopoulos N, Bouros E, Kolios G, Zacharis G, Ntolios P, et al. Effect and safety of mycophenolate mofetil or sodium in systemic sclerosis-associated interstitial lung disease: A meta-analysis. Pulm Med. 2012;2012:143637.
13. Derk CT, Grace E, Shenin M, Naik M, Schulz S, Xiong W. A prospective open-label study of mycophenolate mofetil for the treatment of diffuse systemic sclerosis. Rheumatology 2009;48:1595-9.
14. Herrick AL, Lunt M, Whidby N, Ennis H, Silman A, McHugh N, et al. Observational study of treatment outcome in early diffuse cutaneous systemic sclerosis. J Rheumatol 2010;37:116-24.
15. Le EN, Wigley FM, Shah AA, Boin F, Hummers LK. Long-term experience of mycophenolate mofetil for treatment of diffuse cutaneous systemic sclerosis. Ann Rheum Dis 2011;70:1104-7.
16. Mendoza FA, Nagle SJ, Lee JB, Jimenez SA. A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. J Rheumatol 2012;39:1241-7.
17. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med 1984;3:409-22.
18. Rovelli F, De Vita C, Feruglio GA, Lotto A, Selvini A, Tognoni G. GISSI trial: Early results and late follow-up. Gruppo Italiano per la sperimentazione della streptochinasi nell'infarto miocardico. J Am Coll Cardiol 1987;10 Suppl B:33B-39B.
19. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) collaborative group. Lancet 1988;2:349-60.
20. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989;321:129-35.

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