Immunosuppression for interstitial lung disease in systemic sclerosis – novel insights and opportunities for translational research

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Systemic sclerosis (SSc) is a chronic inflammatory disorder characterized by a disturbance in fibroblast function culminating in the telltale skin thickening and fibrosis of visceral organs. Interstitial lung disease (ILD) is common (Steele et al. 2011) and is the leading cause of death in this disease (Steen and Medsger 2007). The immunohistopathogenesis of SSc-ILD is characterized by immune dysfunction and inflammation. Thus, immunosuppression has been hypothesized as a useful treatment for SSc-ILD. However, randomized clinical

trials (RCTs) have thus far only revealed a modest effect of immunosuppression (Hoyles et al. 2006; Tashkin et al. 2006). We believe that these small observed effects are due, at least in part, to the actual design of the RCTs, in particular subject selection, which did not properly identify patients likely to respond to treatment.

SSc is an uncommon disease, with an estimated prevalence ranging from 7–489/million and incidence from 0.6–122/million/year (Chiffot et al. 2008). This rarity has undoubtedly contributed to the paucity of RCTs examining the benefit of immunosuppression in this disease. To date, only cyclophosphamide and azathioprine have been evaluated in RCTs of subjects with SSc-ILD. In the Scleroderma Lung Study ($N=158$) (Tashkin et al. 2006), SSc-ILD subjects with less than 7 years of disease duration who had not previously received cyclophosphamide were randomized to oral cyclophosphamide or placebo for 1 year. Those treated with cyclophosphamide had a smaller decline than those on placebo in forced vital capacity (FVC) (adjusted difference of 2.5 % [95 % CI 0.3, 4.8 %, $p=0.03$] favouring cyclophosphamide). In the Fibrosing Alveolitis in Scleroderma Trial (FAST; $N=45$) (Hoyles et al. 2006), SSc-ILD subjects with an average of 5 years of disease who had not been previously treated were randomized to receive 6 monthly infusions of cyclophosphamide followed by 6 months of oral daily azathioprine, or placebo. Although not statistically significant, the adjusted between-group difference in FVC of 4.2 % showed a strong trend in favour of the treated group (95 % CI -0.57 , 8.95 , $p=0.08$). Mycophenolate mofetil (MMF) is a third immunosuppressant that is currently being tested in an ongoing RCT in subjects with SSc-ILD (Scleroderma Lung Study II [**Investigators of the Canadian Scleroderma Research Group:** M. Baron, Montreal, Quebec; J. Pope, London, Ontario; J. Markland, Saskatoon, Saskatchewan; D. Robinson, Winnipeg, Manitoba; N. Jones, Edmonton, Alberta; N. Khalidi, Hamilton, Ontario; P. Docherty, Moncton, New Brunswick; E. Kaminska, Hamilton, Ontario; A. Masetto, Sherbrooke, Quebec; E. Sutton, Halifax, Nova Scotia; J-P. Mathieu, Montreal, Quebec; M. Hudson, Montreal, Quebec; S. Ligier, Montreal, Quebec; T. Grodzicky, Montreal, Quebec; Carter Thorne, Newmarket, Ontario; S. LeClercq, Calgary, Alberta; M. Fritzler, Mitogen Advanced Diagnostics Laboratory, Calgary, Alberta.](http://</p></div><div data-bbox=)

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www.sclerodermalungstudy.org/). The two completed trials have been interpreted as supporting a “modest” benefit of immunosuppression in SSc-ILD.

The spectrum of SSc-ILD is broad. Some patients have mild, stable abnormalities, others slowly progressive disease and others, yet, rapidly progressive disease (White 2003). There are still few known predictors of progression. Demographic variables, in particular male sex and black race (Barnett 1978; Steen et al. 1985; Greidinger et al. 1998), and seropositivity for anti-topoisomerase I antibodies have been consistently found to predict progression of SSc-ILD (Greidinger et al. 1998; Assassi et al. 2010). Early disease and low baseline FVC have also been identified by some, but not all (Assassi et al. 2010), as predictors of progressive SSc-ILD (Steen et al. 1994; Plastiras et al. 2006; Goh et al. 2008). This explains why trials in SSc-ILD have targeted patients with early disease and why mean baseline FVC in the Scleroderma Lung Study was 68 % predicted and in the FAST trial 80 % predicted.

Nevertheless, variables that predict progression may be different from those that predict treatment response in SSc-ILD (Roth et al. 2011). Indeed, a low FVC reflects disease damage rather than disease activity (Clements 1995). Thus, it is perhaps not surprising that studies that included subjects with at least moderate lung damage at baseline may have failed to show marked treatment effect. Rather than the treatment, it is possible that inappropriate subject selection was responsible for the modest results obtained in the two trials. Very little is known about predictors of treatment response in SSc-ILD (Roth et al. 2011).

We hypothesized that, given the poor results of the trials to date, SSc-ILD patients with better baseline FVC could have better treatment response than those with poorer baseline FVC. However, testing such a hypothesis is challenging. On the one hand, RCTs on drug effectiveness may be under-powered to estimate differential treatment effects in subject subgroups. Indeed, assuming that only one-fifth of subjects progress by a FVC of 12 %, a drug that prevents all progression will appear to have an *average* FVC effect of only 2.5 % and may be mistakenly viewed as having only a trivial effect. On the other hand, data collected in observational settings is often flawed by confounding by indication. Those with worse lung function are more likely to be treated and to do worse than those with better lung function who are not treated. Thus, inevitably, treatment is associated with worse outcomes. Large datasets and robust statistical methodology are needed to overcome some of the difficulties of studying the effect of baseline FVC on treatment response in SSc-ILD.

The Canadian Scleroderma Research Group (CSRG) is a well-established, pan-Canadian, multi-center group of clinicians and basic science researchers funded by CIHR, patient organizations and industry. It follows a cohort of over 1300

SSc subjects at 12 sites. All subjects in the registry are treated by their local physician and their clinical data is systematically collected yearly using a standardized data collection protocol. Serum is also collected yearly and stored in a central biobank.

In addition, novel statistical techniques have been developed to address issues of non-randomization and confounding that have traditionally undermined the results from observational studies. In particular, an approach that yields estimates consistent with *the causal effects* of treatment is the class of inverse-probability weighted (also called inverse-propensity weighted) marginal structural models (Hernán et al. 2001; Choi et al. 2002; Hernan et al. 2002). Simply put, this type of analysis attempts to balance potential confounders amongst treated and untreated subjects by re-weighting observations according to the inverse of the probability of receiving their observed exposure. The approach is similar to analysis via propensity matching estimators (Rubin 1997). However, by weighting, rather than matching subjects, one is able to make use of all of the subject level data available for the analysis. Another advantage of weighting is that fewer assumptions need to be made about the underlying probability models (Hernán et al. 2001). Finally, missing data due to subject dropout can be accounted for in a straightforward manner by incorporating the estimated probability of study completion in the weight for each subject (Hernan et al. 2002). To summarize, within the context of the marginal structural model, we attempt to correct for bias due to confounding (both due to the observational nature of the data and the time-varying confounding) and bias due to subject dropout, and to estimate the causal effect of treatment.

To date, the large CSRG dataset and the statistical tools described have allowed us to overcome issues related to the rarity of SSc, to leverage the variability that is inherent in clinical practice and to produce robust, high-impact data on a variety of SSc-related subjects (Hudson et al. 2011). Hence, we believe that our dataset has the potential to identify subsets of SSc-ILD patients who may be more likely to benefit from immunosuppression. There is strong precedent for the use of this type of study design coupled with sophisticated statistical analysis that addresses issues of confounding to determine the effectiveness of medical interventions in situations where RCTs are not always feasible or available (Choi et al. 2002; Sterne et al. 2005; MacKenzie et al. 2006; Cotter et al. 2008; Palella et al. 2009). It is highly relevant to note that influential groups, including the National Institute for Clinical Excellence, the United Kingdom’s drug approval body committed to basing drug approvals on the highest standards of evidence, have recently advocated in favour of well-designed and carefully analyzed and interpreted observational studies as appropriate substitutes for RCTs, in particular in rare diseases for which there is a

serious lack of data and for which it may not be feasible to undertake RCTs (Rawlins 2008).

Thus, in order to test our hypothesis, we undertook a retrospective cohort study using data from the CSRG registry to determine whether baseline FVC was associated with treatment response in SSc-ILD. As of July 2012, there were 1326 subjects with complete drug data in the CSRG registry. Of these, 87 (6.6 %) were currently taking cyclophosphamide, MMF or azathioprine at the time of their baseline visit. Subjects currently exposed to immunosuppressants were younger, less likely to be women, and had shorter disease duration (Table 1). They were more likely to have diffuse SSc, ILD and more severe disease.

To determine the effect of immunosuppression on lung function, we analyzed subjects who had complete data for their baseline and two-year follow-up visit ($N=471$). We classified subjects as exposed if they were reported to be “currently taking” cyclophosphamide, MMF, or azathioprine at the baseline visit. The outcome of interest was

FVC at 2 years. In a naïve cross-sectional analysis with no weighting, FVC at 2 years was not different in the exposed compared to the unexposed subjects (difference in FVC 1.9 %, 95 % CI −1.0, 4.8, adjusted for differences in baseline FVC, corticosteroid use, modified Rodnan skin score, patient-reported shortness of breath, presence of ILD and disease duration), demonstrating the potential effect of confounding by indication and lack of randomization between the two groups. However, after introducing inverse probability-of-treatment weights, we estimated a statistically significant difference in FVC of 3.9 % (95 % CI 1.5, 6.4) in favour of the exposed compared to unexposed subjects.

More interestingly, in subset analyses, subjects with FVC > 100 % at baseline (ie. normal lung function) exposed to immunosuppressants had a 5.2 % (95 % CI 3.0, 7.4) better lung function than those who were unexposed. In subjects with an FVC of 80 % (somewhat diminished), the difference in lung function was only 2.4 % (95 % CI −0.9, 5.7). Finally, in those with an FVC of 60 %, there was no difference in FVC

Table 1 Baseline characteristics of CSRG subjects, according to immunosuppressant status

	Subjects currently taking immunosuppressants	Subjects not currently taking immunosuppressants
N	87	1326
Age	51.7±12.2	55.9±12.2
Women, %	78.2	87.0
Disease duration, years	6.2±6.0	11.1±9.6
Disease subset		
Limited, %	42.5	65.5
Diffuse, %	57.5	34.5
Modified Rodnan skin score (range 0–51)	12.4±10.8	9.6±9.3
Subjects with interstitial lung disease, %	58.1	28.4
Patient-reported shortness of breath (range 0–10)	3.8±3.1	1.9±2.5
Pulmonary function tests at baseline		
FVC, % predicted	79.8±21.6	93.0±18.7
N (%) with FVC > 100 %	14 (21.2 %)	370 (37.9 %)
N (%) with FVC 80–100 %	14 (21.2 %)	374 (38.3 %)
N (%) with FVC 60–80 %	26 (39.4 %)	190 (19.5 %)
N (%) with FVC < 60 %	12 (18.0 %)	42 (4.3 %)
DLCO, % predicted	57.5±21.4	70.5±20.4
Physician global assessments (range 0–10)		
Disease activity	4.1±2.5	2.7±2.2
Disease severity	3.8±2.5	2.3±2.1
Disease damage	5.2±2.2	3.1±2.2
Proportion with SSc-related autoantibodies		
Topoisomerase, %	32.4	14.8
Centromere, %	5.6	36.1
RNA polymerase III, %	16.4	18.4
Pm/Scl, %	20.4	13.8
Proportion on corticosteroids, %	47.1	11.5

FVC Forced vital capacity,
DLCO Diffusing capacity of the
lung for carbon monoxide

in patients exposed to immunosuppression compared to the unexposed (−0.4 %, 95 % CI −5.5, 4.7).

It is interesting to note that our estimates using the inverse probability-of-treatment weights were in close agreement with the results of previous trials. In the Scleroderma Lung Study, the subjects at baseline had a mean FVC of 68 % and the estimated difference at 1 year was 2.6 % in favour of the treated group. In the FAST trial, subjects at baseline had a mean FVC of 80 % and the estimated difference at 1 year was 4.2 %. Our data is consistent with these findings and suggests that baseline FVC may be a predictor of response to immunosuppressants in SSc-ILD.

We can conclude three important things from this relatively basic analysis. First, despite the fact that these are observational data, one can, with the correct analysis, obtain reliable estimates of the effect of exposure on treatment outcome. Second, longitudinal registries have the advantage of large sample sizes and marked heterogeneity in subjects and exposures. Analysis of these datasets, especially in the setting of a standardized, prospective, data collection protocol that generates detailed clinical phenotypic data, offers a useful alternative to trials that are difficult and costly to conduct, especially in a rare, slowly evolving disease such as SSc. Finally, this type of study design and data analysis creates novel opportunities to pursue translational research. There is a well-defined need to identify and effectively treat SSc-ILD, and in particular to correctly identify patients that are likely to respond to such therapies. However, markers of treatment response remain elusive. Since all CSRG subjects have yearly stored sera, the results from this analysis can be used to facilitate the search for biomarkers of treatment response. It creates novel opportunities for clinical researchers and basic scientists to pursue the study of SSc-ILD in a rational and productive manner.

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