Immunosuppression does not prevent severe gastrointestinal tract involvement in systemic sclerosis

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ABSTRACT

Objective. *We aimed to test the hypothesis that exposure to immunosuppression in early systemic sclerosis (SSc) could modify the risk of developing new onset severe gastrointestinal (GIT) involvement.*

Methods. *A total of 762 subjects with <3 years of disease duration and without severe GIT disease at baseline study visit were identified from combined longitudinal cohort data from the Canadian Scleroderma Research Group (CSRG) and Australian Scleroderma Interest Group (ASIG). The primary exposure was ever use of methotrexate, cyclophosphamide, mycophenolate mofetil and/or azathioprine during the study period. Severe GIT disease was defined as: 1-malabsorption, 2-hyperalimentation, 3-pseudo-obstruction, and/or 4-≥10% weight loss in association with the use of antibiotics for bacterial overgrowth or oesophageal stricture. The change in the hazard of severe GIT disease due to exposure was estimated using a marginal structural Cox proportional hazards model fit by inverse probability of treatment weights (IPTW) to address potential confounding.*

Results. *Study subjects were 81.5% female, had a mean age of 53.7±13.0 years and mean disease duration at baseline of 1.4±0.8 years. During a mean follow-up of 4.0±2.6 years, severe GIT involvement developed in 11.6% of the 319 subjects exposed to immunosuppression and in 6.8% of the 443 unexposed subjects. In an IPTW-adjusted analysis, exposure to immunosuppression was not associated with severe GIT disease (weighted hazard ratio 0.91, 95% confidence interval 0.52–1.58).*

Conclusion. *In this large inception SSc cohort, the risk of severe GIT involvement was not modified by exposure to immunosuppression.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disorder characterised by vasculopathy, immunologic abnormalities and fibrosis affecting both skin and visceral organs (1, 2). Although there is no cure, accumulating evidence shows that immunosuppression may be effective in stabilising and perhaps improving manifestations of SSc, including skin thickening and interstitial lung involvement (ILD) (3-7). Current recommendations support the use of immunosuppressive drugs for treatment of these manifestations of SSc (8, 9).

The gastrointestinal tract (GIT) is the most commonly involved internal organ in SSc, with disease affecting up to 90% of patients (10-12). Recent analyses of an international SSc inception cohort revealed that severe GIT involvement was seen in more than 15% of subjects by the fourth year of the disease (13). Severe GIT disease in SSc has been associated with markers of inflammation (13, 14), suggesting a possible role for immunosuppression. However, current treatments for GIT involvement in SSc are directed at alleviating symptoms and the role of immunosuppressive drugs is largely unknown especially prior to onset of severe GIT involvement (11, 15, 16). Without a clear comprehension of the relative benefits, clinicians are understandably reluctant to initiate preventative treatment given the known toxicity of these drugs.

The objective of this study was therefore to determine if in the early phase of SSc, exposure to immunosuppressive drugs was associated with the prevention of new onset severe GIT involvement. We hypothesised that in subjects without severe GIT disease at baseline, exposure to methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF) and/or cyclo-

phosphamide (CYC) (usually given for skin, lung, joint or muscle involvement) would be associated with a lower risk of developing severe GIT disease during follow up.

Patients and methods

Patient source

Subjects were SSc patients enrolled in either the Canadian Scleroderma Research Group (CSRG) registry or the Australian Scleroderma Cohort Study (ASCS). Briefly, to be included in the CSRG, subjects must fulfil a diagnosis of SSc verified by an experienced rheumatologist, be ≥18 years of age and be fluent in English or French. Over 98% of the subjects in this cohort meet the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc (17). Patients in the ASCS are recruited by Australian Scleroderma Interest Group (ASIG) investigators from 12 Australian centres specialising in the care of patients with SSc, according to similar inclusion criteria. All patients fulfilled either the 1980 ACR (18) or LeRoy and Medsger criteria for SSc (19). Nine subjects from the ASCS database did not meet the 2013 ACR/EULAR classification criteria (20).

The inception cohort was defined as the subset of subjects with disease duration <3 years since the onset of the first non-Raynaud's symptom attributable to SSc at the time of their baseline study visit. We included all SSc subjects who met these criteria and had at least one follow-up visit in the CSRG cohort between January 2005 and July 2017 or in the ASCS between January 2007 and June 2017. Subjects with severe GIT involvement (defined below) at their baseline study visit were excluded.

Ethics committee approval for this study was obtained at McGill University (Montreal, Quebec, Canada) and at all participating CSRG and ASCS study sites. All subjects provided informed written consent to participate in the registries.

Definition of exposure

Medication history was recorded by study physicians at each study visit as past, current or never. Immunosuppression was defined as exposure to MTX, AZA, MMF and/or CYC. There were no subjects exposed to rituximab or tocilizumab during the study period, and treatment with intravenous immunoglobulins (IVIg) was not systematically recorded. Exposure was defined using a time-dependent variable: at each visit, patients were categorised as being exposed (ever exposed) or unexposed (never exposed) to immunosuppression.

Definition of outcome

Severe GIT disease was defined using a previously published definition (21). According to this definition, severe GIT disease was considered present if a physician reported 1) the presence of malabsorption, 2) the need for hyperalimentation, 3) one or more episodes of pseudo-obstruction, and/or 4) a ≥10% weight loss in association with the use of antibiotics for small intestinal bacterial overgrowth (SIBO) within the last year or oesophageal stricture. Malabsorption was defined in the CSRG registry by physician reports that the patient answered yes to, "Do you pass stools that are difficult to flush, particularly foul smelling or associated with a ring of grease in the toilet bowl," and/or low ferritin with no blood loss, elevated INR, low vitamin B12 (in the absence of pernicious anaemia), low carotene, or low magnesium or calcium otherwise unexplained. Malabsorption was defined in the ASCS registry as presence of chronic diarrhoea within the last year and being actively treated with cyclic antibiotics. Hyperalimentation was defined as nutritional supplementation either through a regular feeding tube (nasogastric or percutaneous endoscopic gastrostomy) or intravenous total parenteral nutrition (TPN). Episodes of pseudo-obstruction were identified by physician reports. Oesophageal strictures in the CSRG were identified by physician reports of subjects requiring oesophageal dilatation, whereas the ASCS defined oesophageal stricture as those having definite evidence on either endoscopy or barium swallow.

Covariates

Demographic and lifestyle characteristics (age, sex, ethnicity, education and smoking status) were collected through patient self-report at the baseline registry visit. Disease duration was recorded by study physicians at that time.

At baseline and annual visits, study physicians performed standardised histories and physical examinations and recorded the presence and/or history of digital ulcers, telangiectasias, inflammatory myositis and inflammatory arthritis. C-reactive protein (CRP) levels were measured by local laboratories. Skin involvement was assessed using the modified Rodnan skin score (mRss), a validated measure of skin thickening in SSc (22). This score ranges from 0 (no involvement) to 3 (severe thickening) in 17 areas (total score range 0–51) (23). Subjects were classified into limited (lcSSc; skin involvement distal to the elbows and knees with or without facial involvement) and diffuse cutaneous subsets (dcSSc; skin involvement proximal to the elbows and knees, with or without truncal involvement). Those with a clinical diagnosis of SSc, but no skin involvement were included with the lcSSc subset (24). The presence of ILD was determined using a published clinical decision tool (25). According to this algorithm, ILD was considered present if a high-resolution computed tomography (HRCT) scan of the lung was interpreted by an experienced radiologist as showing ILD or, in the case where no HRCT was available, if either a chest x-ray was reported as showing either increased interstitial markings (not thought to be due to congestive heart failure) or fibrosis, and/or if a study physician reported the presence of typical "velcro-like crackles" on physical examination. Pulmonary function tests were performed in local laboratories working in accordance with American Thoracic Society standards. The percent predicted value for forced vital capacity (FVC) was extracted from laboratory reports. Pulmonary hypertension was defined as an estimated systolic pulmonary artery pressure (sPAP) ≥45 mmHg measured using the Doppler flow measurement of the tricuspid regurgitant jet on echocardiography (an estimate that correlates strongly with the values reported in right-sided heart catheter studies) (26).

Table I. Baseline characteristics of study subjects as a whole and stratified according to exposure to immunosuppression at baseline or during follow-up (n=762).

	All cohort (n=762) n (%) or mean (S.D.)	Missing	Exposed (n=319) n (%) or mean (SD)	Unexposed (n=443) n (%) or mean (SD)	*p*-values
Age, years	53.7 (13.0)	3	51.1 (12.2)	55.6 (13.3)	<0.001
Female, %	620 (81.5)	1	248 (77.7)	372 (84.2)	0.025
Caucasian, %	624 (87.8)	51	266 (85.8)	358 (89.3)	0.161
Indigenous, %	13 (1.8)	51	3 (1.0)	10 (2.5)	0.132
Education (>high school), %	269 (40.5)	97	137 (46.3)	132 (35.8)	0.006
Current smoker, %	94 (13.0)	37	38 (12.1)	56 (13.7)	0.526
Disease duration, years	1.4 (0.8)	1	1.4 (0.7)	1.6 (0.8)	0.031
Diffuse disease, %	326 (42.8)	1	204 (63.9)	122 (27.6)	<0.001
mRss (0-51)	12.1 (11.1)	5	16.8 (11.2)	8.6 (9.7)	<0.001
Interstitial lung disease, %	231 (31.2)	21	123 (38.9)	108 (25.4)	<0.001
FVC, % predicted	92.8 (20.1)	93	90.3 (19.3)	94.6 (20.6)	<0.001
Pulmonary hypertension, %	64 (10.8)	172	15 (5.9)	49 (14.5)	0.010
Digital ulcers, %	313 (41.4)	6	137 (42.9)	176 (40.3)	0.461
Telangiectasias, %	411 (55.2)	18	162 (50.9)	249 (58.5)	0.042
Inflammatory myositis, %	37 (5.3)	70	28 (9.4)	9 (2.3)	<0.001
Inflammatory arthritis, %	179 (27.0)	99	96 (34.3)	83 (21.7)	<0.001
SF-36 PCS, mean (S.D.)	38.2 (11.8)	214	36.1 (11.6)	39.9 (11.6)	<0.001
SF-36 MCS, mean (S.D.)	46.4 (12.5)	214	45.8 (12.7)	46.9 (12.3)	0.304
Autoantibodies					
Anti-centromere, %	222 (33.3)	94	37 (13.5)	185 (47.1)	<0.001
Anti-topoisomerase, %	141 (21.3)	99	88 (32.5)	53 (13.6)	<0.001
Anti-RNA polymerase III, %	123 (21.5)	190	70 (28.0)	53 (16.5)	<0.001
C-reactive protein, mg/L	9.2 (22.7)	129	9.6 (23.2)	8.9 (22.2)	0.001
Prior immunosuppressants*, %	62 (8.1)	1	37 (11.6)	25 (5.7)	0.003

SD: standard deviation; mRs: modified Rodnan skin score; FVC: forced vital capacity; SF-36: Short Form 36; MCS: mental component summary; PCS: physical component summary.
*Methotrexate, azathioprine, cyclophosphamide and/or mycophenolate mofetil.

At baseline and annual visits, subjects completed version 2 of the Medical Outcomes Study Short Form-36 (SF-36)(27). The SF-36 covers 8 domains that can be summarised into a Physical Component Summary (PCS) score and a Mental Component Summary (MCS) score(28). Scores in each domain range from 0 to 100 with greater scores reflecting better health status. The summary scores are normalised, with a mean of 50 (SD ± 10). The SF-36 has been previously validated in rheumatic diseases including SSc (29-31).

Serology

Autoantibody analysis of the CSRG cohort was performed at baseline in a central laboratory, Mitogen Advanced Diagnostics Laboratory at University of Calgary (Calgary, Alberta, Canada). Anti-centromere (CENP-A and CENP-B; ACA), anti-topoisomerase I (ATA) and anti-RNA polymerase III (RP11 and RP155; ARNAP) antibodies were detected by Euroline systemic sclerosis profile line immunoassay (LIA) (Euroimmun, Lübeck, Germany) according to manufacturer's instructions. The analyses of the ASCS cohort were performed at local laboratories according to local assay and protocol. With the intent of optimising specificity, antibodies were reported as absent (negative, equivocal and low titres) and present (moderate and high titres).

Statistical analysis

Descriptive statistics were used to summarise baseline demographic and clinical characteristics. Continuous variables were presented with mean ± standard deviation (SD) and categorical variables were presented with counts and percentages.

In order to account for imbalance in measured confounders between exposed and unexposed groups, inverse probability of treatment weighting (IPTW) was used to fit a marginal structural Cox proportional hazards model (32, 33). Each person-visit was treated as an observation. Propensity scores representing the probability of being exposed at a given visit were calculated using a pooled logistic regression adjusting for baseline covariates (sex, age, disease duration, disease subtype, exposure to immunosuppression prior to baseline visit) and time-varying covariates (mRss, ILD, myositis and arthritis). For the 'ever/never' exposure definition, the probability of ever being exposed was always set to 1 after the initial exposure. The above exposure model along with a second exposure model unadjusted for the time-dependent covariates were used to compute the stabilised weights for each person-visit. These weights were then used in a weighted multivariable Cox proportional hazards model to estimate the parameters of the marginal structural model. This model was conditional on ever/never exposure to immunosuppressive drugs at the given visit, and adjusted for sex, age, disease duration, disease subset and exposure to immunosuppression prior to baseline visit. Hazard ratios and 95% confidence intervals were generated.

Multivariate imputation by chained equations (MICE) was performed to account for missing time-fixed and time-varying covariates. Imputation based on exposure to immunosuppressive drug, presence of severe GIT dis-

Table II. Balance diagnostics before and after weighting in a single imputed dataset*.

	# of observations (# of exposed subjects)	Covariates	Standardised mean difference** Before weighting	After weighting
Baseline visit	762 (215)	Disease duration	-0.13	-0.01
		Age	-0.34	-0.08
		Diffuse subset	0.77	0.07
		Female	-0.10	0.02
		Immunosuppression prior to baseline	0.20	-0.02
		Arthritis	0.36	0.03
		ILD	0.14	-0.10
		Myositis	0.12	-0.08
		mRss	0.71	0.01
v1	381 (63)	Disease duration	-0.37	-0.29
		Age	-0.12	0.20
		Diffuse subset	0.82	0.10
		Female	-0.38	-0.14
		Immunosuppression prior to baseline	0.37	0.04
		Arthritis	0.37	-0.14
		ILD	0.26	-0.01
		Myositis	0.61	0.12
		mRss	0.90	0.07
v2	249 (15)	Disease duration	0.26	0.31
		Age	-0.33	-0.08
		Diffuse subset	0.56	-0.02
		Female	0.23	0.33
		Immunosuppression prior to baseline	0.46	-0.05
		Arthritis	0.14	0.09
		ILD	0.56	0.08
		Myositis	0.21	-0.07
		mRss	0.57	0.16

mRSS: modified Rodnan skin score; ILD: interstitial lung disease.
*Balance diagnostics for v3, v4, v5, v6 and v7 were not possible because of small numbers of exposed patients: number of subjects for v3 was n=169 (10 exposed), v4 n=123 (5 exposed), v5 n=78 (2 exposed), v6 n=51 (1 exposed) and v7 n=31(2 exposed).
**In the event that there was no variation in covariates in either exposed or unexposed groups, the group with variation was used to set the standard deviation.

Table III. Marginal structural Cox model using inverse probability of treatment weights to assess the association between exposure to immunosuppression and risk of new onset severe GIT disease, adjusted for potential confounders.

	Hazard ratio	95% CIs
Exposure to immunosuppressive drugs (time-varying ever *vs*. never exposure)	0.91	(0.52, 1.58)
Female	1.02	(0.54, 1.92)
Age	0.98	(0.96, 1.00)
Disease duration	1.06	(0.77, 1.46)
Diffuse subset	1.88	(1.08, 3.29)
Immunosuppressive drugs prior to baseline	1.33	(0.62, 2.87)

CI: confidence interval.

ease, all covariates already included in the regression model and other relevant baseline variables (smoking status, FVC % predicted, pulmonary hypertension, digital ulcers, telangiectasias, SF-36 PCS, C-reactive protein and cohort (*i.e*. Canadian or Australian)) was performed using the *mice* package in R (34). Missing values of binary variables were predicted by logistic regression, whereas continuous variables were predicted by predictive mean matching. Fifty imputed datasets were used to estimate the regression coefficients and variances. Inverse probability weights and treatment effects were estimated within each imputed dataset. All 50 estimates of treatment effects were combined into an overall estimate using Rubin's rules (35).

Balance of baseline and time-varying covariates before and after weighting was assessed in a single imputed dataset (randomly chosen from the 50) according to exposure history using the *confoundr* package in R(36). Standardised mean differences (SMD) were calculated at every visit using the mean difference divided by the weighted average of the SD of currently ever-exposed *versus* currently unexposed subjects (37, 38).

All statistical analyses were performed with R 3.5.1 (http://r-project.org).

Results

The CSRG and ASCS collected data on 806 subjects with <3 years of disease duration. Forty-four subjects were excluded because they had severe GIT involvement at baseline visit. Thus, 762 subjects without severe GIT disease at baseline (418 Canadian and 344 Australian subjects) were included in this study. Among these 762 subjects, 319 subjects were exposed to immunosuppressive drugs at baseline or during a mean follow-up period of 4.0±2.6 years, and 443 were not exposed (Table I). Exposed subjects (*i.e*., those who were exposed at some point at or after baseline) were younger and more likely to be male and have diffuse skin involvement compared to those unexposed over follow-up. They also had shorter disease duration, more extensive skin involvement, lower SF-36 PCS, higher education level, lower FVC and higher CRP. Exposed subjects were also more likely to have ILD, myositis and arthritis, less likely to have pulmonary hypertension and more likely to have been exposed to immunosuppression prior to study baseline. Exposed subjects were more frequently positive for ATA or ARNAP, and less frequently positive for ACA. Of the exposed subjects, 169, 33, 58, and 112 were exposed to MTX, AZA, MMF and CYC, respectively. Severe GIT disease developed in 37 (11.6%) of the exposed and in 30 (6.8%) of the unexposed subjects during follow-up.

Balance diagnostics before and after weighting are presented in Table II. Baseline covariates were very well balanced after weighting. Balance in time-dependent covariates was also achieved

up to the third visit, but the small number of newly-exposed subjects thereafter precluded further comparisons.

In the marginal structural Cox proportional hazards model incorporating IPTW, subjects exposed to immunosuppression had a similar risk of developing severe GIT disease compared to unexposed subjects: weighted hazard ratio (HR) 0.91 [95% confidence interval (CI) 0.52-1.58] (Table III). In this model, diffuse skin involvement was an independent predictor of severe GIT disease, while there was a trend towards age being inversely related to the risk of severe GIT disease.

Discussion

In this large SSc cohort of patients with early disease (mean 1.4 years), with a large proportion of subjects with dcSSc (43%) and established damage (ILD 30% and digital ulcers 40%), we aimed to determine if treatment with immunosuppressive drugs was associated with a decreased risk of developing severe GIT disease. Contrary to our hypothesis, we found no evidence in this inception cohort of more than 700 subjects that exposure to immunosuppression modified risk of severe GIT involvement. To our knowledge, this is the first study to assess the role of immunosuppression for primary prevention of severe GIT disease in SSc.

The pathogenesis of GIT involvement in SSc is thought to involve neuropathy, myopathy, fibrosis, and possibly autoantibodies (39-44). The role for inflammation remains largely unknown but our earlier results suggested that inflammatory manifestations of SSc were associated with severe GIT involvement in the early course of the disease (13). Nevertheless, this study does not support immunosuppression to prevent severe GIT disease. Whether early sub-clinical disease prior to clinical onset of SSc involves an inflammatory phase responsive to immunosuppression remains unknown. Future studies focussed on pre-clinical SSc may help elucidate this question.

This study is not without limitations. First, non-severe GIT involvement (GIT involvement not meeting our definition of severe GIT disease) may have been present in a fair proportion of subjects. A recent study showed that >70% of SSc subjects had *any* symptomatic GIT involvement within the first year of their disease (45). However, the risk of progression to severe GIT disease was not reported in that study. There is an urgent need to study mild to moderate GIT disease and to identify preventative measures before it progresses to severe disease. Second, the presence of severe GIT disease was not objectively verified and relied largely on physician reports. However, the fact that all study physicians were rheumatologists with experience in the care of patients with SSc provides support for the validity of these diagnoses. Third, the medication data collected in this study was only nominal (*i.e.* "current" or "past" exposure) and there was no detail in regard to treatment duration, start/stop dates or dosage. Such misclassification may have biased the results towards the null. Fourth, the potential difference between different types of immunosuppressive drugs could not be assessed given that the sample size between subgroups was too small to apply the IPTW technique. Lastly, our study did not assess the effect of biologic medications (such as rituximab and tocilizumab) or IVIg and further studies will be required to assess if medications other than those that we studied can impact the development of severe GIT involvement in SSc.

Our use of marginal structural modelling incorporating IPTW and multiple imputation is a major strength in this study, allowing us to address issues of non-randomisation, confounding bias and missing data, thus yielding estimates that are more consistent with the causal effects of treatment, especially in the context of time-varying exposures and confounders (46, 47). Although there is always potential for residual bias from unmeasured confounding, our cohort encompassed different types of common SSc manifestation including the most common indications for immunosuppressive drugs. In addition, although balance in covariates was only estimated for the first three visits, it was acceptable after weighting.

Conclusion

In this large inception SSc cohort study using robust computational methods, we found no evidence that immunosuppressive drugs prevent the onset of severe GIT disease. Future research will be needed to identify ways to prevent and treat severe GIT involvement in SSc.

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Competing interests

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