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Polypharmacy, drug-drug interactions, and adverse drug reactions among systemic sclerosis patients: a cross-sectional risk factor study.

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INTRODUCTION

- Systemic sclerosis (SSc) can affect all organs and treatment is based on the symptomatic management of organ damages and, in some severe cases, on immunosuppressive therapies. These medications are not without side effects and can contribute to polypharmacy.
- Polypharmacy, drug-drug interactions (DDI) and related adverse drug reaction (ADR) are understudied in systemic sclerosis.
- The aim of this work was to determine the prevalence and determinants of DDI and ADR in a real-life cohort of SSc patients.

METHODS

- We performed an analysis of the drug prescriptions of the first hundred consecutive SSc patients admitted to the daily scleroderma clinic of Cochin Internal Medicine University Hospital between January 2020 and April 2023.
- Inclusion criteria: patients with SSc according to the ACR/EULAR 2013 criteria, informatics-based drug prescription, and a one-year follow-up.
- DDI were identified using 2 prescription analysis applications (VIDAL and POSOS) and classified into 4 types (contraindicated, not recommended, precaution for use, and warning).
- To assess ADR, all adverse events (AE) occurring during follow-up were evaluated by two medical experts experienced in SSc and AE were graded according to the Common Terminology Criteria for AE based on their severity. Any AE considered was adjudicated by a pharmacovigilance expert committee using the World Health Organization – Uppsala Monitoring Centre.
- Risk factors for DDI and ADR were then identified using multivariate analysis.

RESULTS

Polypharmacy

One hundred and eight SSc patients were included. The median number of medications per patient was 6 [4-9]. One hundred and one (93.5%) patients had at least 2 medications on their prescriptions. Seventy-one (65.7%) patients had 5 or more medications, and 23 (21.3%) had 10 or more. The most prescribed medications were calcium channel blockers (81.5%), proton-pump inhibitors (PPI) (74.1%) and cholecalciferol (53.7%).

Drug-drug interactions

Seventy-two (66.7%) patients had DDIs on their prescriptions at inclusion.The median number of DDI per patient was 3 [1-8], with a total number of 421 DDIs in the study (117 (28%) warning, 268 (64%) precautions for use, 31 (7%) recommended, and 5 (1%) contraindicated). Patients with DDIs had more medications than patients without DDIs (7 [5-10] versus 3 [2-5], $p < 0.0001$). Patients with DDI received significantly more PPI ($p < 0.0001$), prednisone ($p < 0.0001$), mycophenolate mofetil (MMF) ($p < 0.001$), sodium alginate (SA) ($p < 0.001$), lipid-lowering drugs ($p < 0.05$), and domperidone ($p < 0.01$) than patients without.The main DDI involved domperidone-prednisone, esomeprazole-SA, esomeprazole-MMF, and lansoprazole-MMF.

Adverse drug reactions

Six (8.3%) patients experienced ADRs during the one-year follow-up. One ADR (1.4% of SSc patients with DDI) was classified as grade IV according to CTCAE (cardiac arrest due to ventricular tachycardia), 4 (5.6%) were grade III (falls, orthostatic hypotension, and tendon rupture), and 1 (1.4%) was grade II (Bowen's disease). Patients with ADRs had more medications (14 [10-18] versus 7 [5-10]: $p < 0.001$) and more DDIs (12 [7-32] versus 3 [1-6]; $p < 0.001$) than patients without ADRs. Multivariate analysis confirmed that the number of prescribed medications was independently positively associated with DDIs (OR: 2.25 [1.52-3.32], $p < 0.0001$) as well as with ADRs (OR: 1.68 [1.17 - 2.40], $p < 0.01$).

RESULTS

Clinical characteristics

Male sexe, diffuse SSc, elevated modified Rodnan skin score and interstitial lung disease were risk factors for DDI.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Male	9.21 (1.29 - 398.55)	0.012	7.79 (0.59 - 102.99)	0.12
Diffuse cutaneous SSc	4.69 (1.54 - 17.00)	0.002	3.22 (0.34 - 30.29)	0.31
Anti-topoisomerase antibodies	1.72 (0.69 - 4.47)	0.21		
Anti-centromere antibodies	0.43 (0.17 - 1.08)	0.04	1.48 (0.23-9.69)	0.68
Anti-RNA polymerase III antibodies	4.38 (0.54 - 199.55)	0.14		
Raynaud's phenomenon	0.47 (0.46 - 2.56)	0.34		
Calcinosis cutis	0.93 (0.30 - 3.06)	0.88		
Digital ulcers	1.39 (0.55 - 3.66)	0.45		
modified Rodnan skin score	2.30 (0.83 - 6.28)	0.07	0.90 (0.77 - 1.05)	0.18
Pulmonary arterial hypertension	2.47 (0.47 - 24.58)	0.25		
Interstitial lung disease	2.71 (1.09 - 6.75)	0.02	1.00 (0.17 - 5.96)	0.99
Forced vital capacity	0.97 (0.96 - 0.99)	0.007	0.98 (0.95 - 1.01)	0.25
Gastroesophageal reflux	2.5 (0.88 - 7.01)	0.05	1.03 (0.22 - 4.60)	0.97
Lower GI involvement	1.38 (0.30 - 8.55)	0.65		
Number of prescribed medications	1.99 (1.51 - 2.62)	< 0.0001	2.25 (1.52 - 3.32)	< 0.0001

95% CI: 95% confidence interval; GI: gastro-intestinal; OR: odds ratio; RNA: ribonucleic acid; SSc: systemic sclerosis

***Table 1**. Factors associated with DDI in SSc.*

Characteristics, n (%) or median [IQR]	SSc patients with drug interactions (n=72)	SSc patients with adverse events (n=6)	SSc patients without adverse events (n=66)	p
Number of prescribed medications per patient	7 [5-10]	14 [10-18]	7 [5-10]	< 0.001
Number of drug interaction per patient	3 [1-7.5]	12 [7-32]	3 [1-6]	< 0.001
Total number of drug interactions	421	104	317	-
Type of interaction:				
warning	117 (28)	14 (13)	103 (32)	< 0.001
precaution for use	268 (64)	77 (74)	191 (60)	< 0.05
not recommended	31 (7)	11 (11)	20 (6)	0.19
contraindicated	5 (1)	2 (2)	3 (1)	0.60
Most frequent drug interactions:				
domperidone / prednisone	9 (13)	2 (33)	7 (11)	0.16
esomeprazole / SA	9 (13)	(0)	9 (14)	> 0.99
esomeprazole / MMF	9 (13)	(0)	9 (14)	> 0.99
lansoprazole / MMF	9 (13)	(0)	9 (14)	> 0.99
cholecalciferol /SA	8 (11)	1 (17)	7 (11)	0.52
domperidone / SA	8 (11)	1 (17)	7 (11)	0.52
SA / prednisone	7 (10)	2 (33)	5 (8)	0.07
diltiazem / domperidone	6 (9)	1 (17)	5 (8)	0.42

%: percentage; IQR: interquartile range; MMF: mycophenolate mofetil; n: number; SA: sodium alginate; SSc: systemic sclerosis.

***Table 2**. DDI in SSc. patients with or without AE.*

DISCUSSION

- After one year of follow-up, we found a prevalence of 8.3% of DDI-related ADR in SSc patients. Some AE had significant consequences for the prognosis of patients.
- Demographic factors (notably older age) were not associated with the occurrence of DDI or ADR. It could be due to the fact that SSc patients are early-on polymedicated at a young age.
- In univariate analysis, the occurrence of DDI was related to severe illness. It could be explained by the therapeutic classes most often prescribed in these patients which are more frequently associated with DDI.

CONCLUSION

- **SSc patients are significantly exposed to** :

polypharmacy

DDIs

related ADRs

- **especially in cases of** :

severe illness

5 or more medications are prescribed

- **Patients with SSc should be routinely screened for polypharmacy, DDI and ADR.**

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