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# THE RESULTS OF A THREE YEAR ANALYSIS ON SARCOIDOSIS PATIENTS REGISTERED IN THE REGIS ELECTRONIC REGISTRY

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***Abstract***

***Introduction.*** *Registries are necessary particularly for rare diseases. The REGIS registry was developed to improve scientific research in the field of interstitial lung diseases (ILDs).*

***Material and Method.*** *We analysed 144 patients with interstitial lung diseases enrolled during a three year period, selected the sarcoidosis cases and analysed the data with Excel 2007 Software.*

***Results.*** *A number of 26 sarcoidosis patients were included (18.06% out of the total), of which 46.15% were female, with an average age of 41.34±9.84 years; 23.08% were smokers. 88.46% pf patients had mediastinum pulmonary involvement: stage II in 17 patients, stage III in 5 patients and stage IV in one patient; only 3 patients had extra thoracic involvement. The medical investigations performed were: chest X-ray (96.15%), thoracic HRCT (96.15%) that identified hilar adenopathy (96%), nodules (68%), with peribronchovascular localization (44%); spirometry (96.15%) that revealed an average CV of 94.99±23.07% out of the predicted value, DLCO 78.41±19.39% out of the predicted value; bronchoalveolar lavage (38.46%); serum angiotensin-converting enzyme (73.08%) and pulmonary or lymph node biopsy (80.77%). The patients that needed treatment (46.15%) were administered oral corticosteroids (10 patients), acetylcysteine (1 patient) and pirfenidone (1 patient).*

***Conclusions.*** *The number of patients enrolled is low as a result of the voluntary reporting, especially in severe cases and with access to all investigations needed for diagnosing.*

***Keywords:*** *REGIS registry, sarcoidosis, registry, rare diseases, interstitial lung diseases.*

# Internal Medicine

## Original papers

***Rezumat***

***Introducere****. Registrele sunt necesare mai ales pentru bolile rare. Registrul REGIS a fost dezvoltat pentru a îmbunătăți cercetarea științifică în domeniul pneumopatiilor interstițiale difuze.*

***Material și metodă.*** *S-au analizat 144 de pacienți cu pneumopatie interstițială difuză înregistrați pe o perioadă de trei ani, dintre care s-au selectat cazurile de sarcoidoză și au fost analizate cu Software-ul Excel 2007.*

***Rezultate.*** *Au fost incluși un număr de 26 de pacienți cu sarcoidoză (18.06% din total), dintre care 46.15% erau de sex feminin, cu o vârstă medie de 41.34±9.84 ani, 23.08% erau fumători. 88.46% dintre pacienți aveau afectare mediastino-pulmonară: stadiul II la 17 pacienți, stadiul III la 5 pacienți și stadiul IV la 1 pacient; doar 3 pacienți aveau afectare extra-toracică. Investigațiile realizate au fost: radiografie toracică (96.15%), HRCT toracic (96.15%) care a identificat adenopatii hilare (96%), noduli (68%), cu localizare peribonho-vasculară (44%); spirometrie (96.15%) care a arătat CV medie de 94.99± 23.07% din valoarea prezisă, DLCO 78.41± 19.39% din valoarea prezisă; lavaj bronho-alveolar (38.46%); angiotensin convertaza serică (73.08%) și biopsie pulmonară sau ganglionară (80.77%). Pacienților care au necesitat tratament (46.15%) li s-au administrat corticosteroizi oral (10 pacienți), acetilcisteină (1 pacient) și pirfenidonă (1 pacient).*

***Concluzii.*** *Numărul de pacienți înregistrați este scăzut ca urmare a raportării voluntare, cu raportarea mai ales a cazurilor severe și cu acces la toate investigațiile necesare diagnosticului.*

***Cuvinte cheie:*** *Registrul REGIS, sarcoidoză, registru, boli rare, pneumopatii interstițiale difuze.*

## Introduction

Low-prevalence diseases can pose multiple difficulties in terms of diagnosis, management and advance in the understanding of the pathogenic mechanisms and clinical phenotypes, because of the limited experience of clinicians who rarely encounter such cases. Long term registries that have a prospective design can overcome these difficulties, as a better understanding of the manifestations of the heterogeneous group of rare diseases can be practical for the creation of a database useful in epidemiology research, and also for a better therapy for the patients that suffer from such diseases[1].

The role of registries is to try and define future standards of care, and also to try and find the best therapeutic and monitoring methods for these patients. These desiderata are based on the current lack of specific treatment agents and easily accessible biomarkers for monitoring diseases, and so rare diseases registries represent the main point of scientific research in the field of rare diseases[1].

Diffuse interstitial lung diseases are considered low prevalence diseases, with estimated incidence and prevalence that vary depending on the region on the globe and the methods used. An increase in epidemiological data is estimated in time, on the one hand due to the improvement of study methods and on the other hand due to the increasing level of interest in these diseases in the medical world and the improvement of the diagnostic process[2]. What makes the estimation process problematic is the difficulty of diagnosing diseases because of their low prevalence and confusing them with other more prevalent diseases, but also because of the unevenness of the terminology - arguments that support the necessity of developing a rare disease registry.

The efforts in developing diffuse interstitial lung disease registries faced a shortcoming in the inclusion process, namely the fact that, in many cases, not all cases from the geographic regions they were conceived for could be entered. For example, the registry in the Bernaillo region in Mexico, in 1988, reported a 81/100000 male prevalence, respectively 67/100000 female prevalence[3]. Another shortcoming is the ICD coding of diffuse interstitial lung diseases, where a limited number of codes (J84 group) covers in a non-discriminatory manner a large number of different diseases (considered to be over 200).

We can notice a significative variability between registries, especially when referring to the geographic regions they serve. A good example is represented by the Japanese registry in Hokkaido, that estimates a 4.1/100000 prevalence[4], compared to the Czech registry that estimates a 7-12/100000 prevalence[5] and, furthermore, the Finnish registry estimates a prevalence of 16-18/100000[6].

Another argument that outlines the geographic variability of diffuse interstitial lung disease prevalence is represented by the retrospective studies, that estimate a 7.6/100000 prevalence for Spain[7] and for Greece a prevalence of 17.3/100000[8].

Sarcoidosis is a systemic disease of unknown cause that frequently affects the lungs and thoracic lymph nodes and is characterised by non-caseous granulomas and lymphocytic infiltrates[9]. It is a rare disease, with a high incidence and prevalence variability, for example a Korean study shows an incidence of 1.3 - 3.4 per 100000 inhabitants and a prevalence of 3.4 per 100000 inhabitants[10],



compared with the populations of northern European countries, where the annual incidence is estimated at 5 - 40 cases per 100000 inhabitants[11].

In Romania it is difficult to quantify the prevalence of sarcoidosis, because of the difficulty in diagnosing it, the lack of clinical suspicion and the heterogeneity of extrapulmonary localisation[9].

**Material and Method**

The REGIS registry is an online registry dedicated to diffuse interstitial lung diseases and sarcoidosis, created by the Romanian Pneumology Society's Working Group on ILD and sarcoidosis. It is available at www.regis.ro and it contains the registry per se - in which authorised specialists from the entire country can register their patients' data, with personalised access using their username and password, an educational platform and a patient dedicated page.

We have collected patient information (demographic data, medical history, clinical and lab work results, recommended treatment and the monitoring results), which we used to create an Excel 2007 database. Thus, out of the total number 144 patients with diffuse interstitial lung disease and sarcoidosis enrolled over a three year period, we selected the sarcoidosis cases for further analysis.

**Results**

The sarcoidosis patient group consists of 26 cases (18.06% of all patients with ILDs). 96.15% of patients presented pulmonary involvement - 8% type I, 68% type II, 20% type III and 4% type IV, respectively three patients presented extra thoracic impairment (2 cases of lymph node involvement and 1 case of hepatic and splenic involvement).

46.15% of patients were female with an average age of 41.34±9.84 years, 80.77% from an urban environment. Six patients (23.08% of the total number) were smokers (50% active smokers and 50% past smokers). The 23.08% of patients that were exposed, in 50% of cases were exposed to respiratory allergens.

The symptoms reported by patients had a median duration from onset of 13.4 months (between 0.5 and 180) and consisted of coughing in 57.69% of cases, joint pain in 38.46% of cases, dyspnoea in 34.61% of cases, fever in 23.07% on cases, skin lesions in 15.38% of cases and chest pain in 15.38% of cases. Clinical examination revealed 4 cases of erythema nodosum, 2 cases of peripheral adenopathy, one case of crackles and one of joint deformities.

Further investigations consisted of chest X-ray in 96.15% of cases, thoracic HRCT in 96.15% of cases, spirometry in 96.15% of cases, bronchoalveolar lavage in 38.46% of

cases; serum angiotensin converting enzyme in 73.08% of cases and lung or mediastinal biopsies in 80.77% of cases.

Chest X-ray revealed mediastinal or hilar adenopathy in 76.92% of patients, reticular opacities or bilateral infiltrates in 26.92% of patients, condensation processes in 19.23% of cases and miliary in 11.53% of patients.

Thoracic HRCT revealed hilar adenopathy in 96% of patients, nodules in 68% on patients, ground glass opacities in 36% of patients, fibrous strands in 12% of patients and one case of each of the following lesions - miliary lesions, honeycomb lesions, emphysema and bronchiectasis. The localisation of the lesions was peribronchovascular in 44% of cases, basal in 20%, subpleural in 12% of cases and inside the superior lobes in 8% of cases.

Functional respiratory tests showed normal spirometry in 68% of cases, a restrictive pattern in 20% of cases, an obstructive pattern in 8% of cases and a mixed pattern in 4% of cases. Respiratory volume levels: a vital capacity of 94.99± 23.07% out of the predicted value, a maximum expiratory volume per second of 91.52± 23.59% out of the predicted value, DLCO of 78.41± 19.39% out of the predicted value.

Bronchoalveolar lavage was performed in 38.46% of cases and was conclusive in 90% of them - 77.78% of cases with lymphocytic alveolitis and 22.12% with a mixed pattern.

Serum angiotensin converting enzyme was measured in 73.08% of patients, 78.94% of the values being higher or equal 50. Other assessed parameters were haemoglobin (in 73.08% of cases) with a mean value of 14.09±1.02 g/dL, white blood cell count (in 71.53% of cases) with a 6952.62±220.32/dL mean value, erythrocyte sedimentation rate (in 65.38% of cases) with a mean value of 24.76 mm/1 hour (5,60) and creatinine (in 57.69% of cases) with a mean value of 0.958±0.13 mg/dL.

Pulmonary or lymph node biopsy was performed in 80.76% of cases, with 8 pulmonary biopsies and 8 mediastinoscopies.

46.15% of patients required treatment and received oral corticosteroids (10 patients), acetylcysteine (1 patient) and pirfenidone (1 patient). None of the patients were submitted for a lung transplant. Also, in 23.07% of cases, follow-up visits were recorded.

**Discussions**

REGIS is a pioneering initiative that aims to gather information in the diffuse interstitial lung diseases and sarcoidosis field in Romania, by setting up a registry meant to collect in one place information about patients with these diseases from various centres throughout the country. The data collected through this registry can constitute a milestone for further clinical and epidemiological research in our country.

Even if this registry is a novelty, it is limited by the small number of registered cases, which can be attributed to the exclusive voluntary reporting by specialists and to the low rate of diagnosed cases in our country.

Other problems are the fact that patients go to third party care centres, where, even if they benefit from the full investigation and treatment panel, they are in an advanced stage of the disease, in which the lung function is decreased. In addition, excepting experienced treatment centres, this category of patients is incorrectly diagnosed.

The batch of registered sarcoidosis cases is small, probably representing only a small part of the sarcoidosis patients regularly diagnosed in Romania. From this point of view, the obtained data cannot be used for



epidemiological evaluations. The small number of registered cases is the consequence of the exclusive voluntary reporting by the attending physicians, with limited availability for other activities except their current ones.

Also, a predominance of severe cases or cases that required complex diagnostic tests (lung or mediastinal biopsy in 80% of cases) can be seen, which can also be explained by a selection of such cases for registration, other simpler cases (for example, typical cases, that do not pose diagnostic issues or that do not need treatment) being overlooked and unrecorded.

The data obtained show a predominance of non-smokers, a slight male preponderance and the young age of patients. It can also be observed that complex imaging scans were performed almost always on the examined lot. The ventilatory function was preserved, with a median vital capacity and a maximum expiratory volume per second within normal range and a slight decrease of the alveolar-capillary diffusion, consistent with literature data.

A large number of patients (over 80%) underwent surgical biopsy, obtained through mediastinoscopy or thoracotomy. Even though bronchoalveolar lavage is considered one of the most useful investigations for diagnosing sarcoidosis, both for demonstrating lymphocytic alveolitis and for the differential diagnosis of other diseases, in this study lot it was used in less than 40% of patients.

This can be attributed to the limited practice of bronchoalveolar lavage in Romania, where it is only routinely performed in Bucharest, while in other treatment centres, because of the lack of a dedicated lavage lab, is probably easier to perform to surgical biopsies. In most patients serum angiotensin converting enzyme was determined, a biomarker that can be useful for diagnosing and monitoring sarcoidosis. Currently, this is the only marker that is widely available in Romania, other serum markers (for example, IL2 soluble receptor) are costly and are not covered by the insurance system, so they have limited use.

Less than half of patients received treatment, suggesting that the others have limited impairment or have the potential for spontaneous resolution of the disease. It is noteworthy that none of the patients presented sarcoidosis related cardiac involvement, which is a particularity in our country.

This can be attributed to the under diagnosing of cardiac involvement in sarcoidosis, either by referring to cardiology units only patients with cardiac symptoms, or by failing to systematically look for cardiac involvement in patients diagnosed with any type of sarcoidosis by the pneumology units

## Conclusions

The analysis of the registered sarcoidosis cases in the REGIS registry for diffuse interstitial lung diseases and sarcoidosis reveals a predominance in males, non-smokers and young patients. For establishing a diagnosis complex tests were performed: CT, complex functional tests, such as determining a serum marker - serum angiotensin converting enzyme in a large proportion of patients. We can notice a large number of patients that have had a surgical biopsy technique (over 80%) and only a small number that has had bronchoalveolar lavage (less than 40%), probably because of the limited availability of this procedure in the country.

The small number of cases and the predominance of complex cases suggest a preselection process performed by the physicians that entered the data in the registry. The small number of cases is attributed to the exclusive voluntary reporting by physicians involved in the project, with limited time availability. Another probability is the selection of cases in which the diagnosis was based on a full set of tests, those with incomplete investigations remaining unreported. The small number of cases makes the obtained data not relevant from an epidemiological point of view.

Registering the sarcoidosis cases (and other diffuse interstitial lung diseases) in REGIS fulfils the objective of unifying the terminology used to describe these cases and of accumulating a coherent data base to study the particularities of these diseases in our country. To fulfil the epidemiological desideratum, coherent complementary activities are necessary which involve dedicated personnel in the collection of clinical data in a geographic region and their systematic entering into the registry, which can be the focus for future operational projects.

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