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ORIGINAL RESEARCH ARTICLE

Drug-Gene Risk Stratification in Patients with Suspected Drug-Induced Interstitial Lung Disease

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Abstract

Background Pulmonary toxicity has been associated with drug use. This is often not recognized in clinical practice, and underestimated.

Objective We aimed to establish whether polymorphisms in certain genes corresponding with a metabolic pathway of drug(s) used are associated with pulmonary toxicity in patients with suspected drug-induced interstitial lung disease (DI-ILD).

Methods This retrospective observational study explored genetic variations in three clinically relevant cytochrome P450 (CYP) iso-enzymes (i.e., CYP2D6, CYP2C9, and CYP2C19) in a group of patients with a fibroticinterstitial lung disease, either non-specific interstitial pneumonia ($n = 211$) or idiopathic pulmonary fibrosis ($n = 256$), with a suspected drug-induced origin.

Results Of the 467 patients, 79.0% showed one or more polymorphisms in the tested genes accompanied by the use of drug(s) metabolized by a corresponding affected metabolic pathway (60.0% poor metabolizers and/or using two or more drugs [likely DI-ILD], 37.5% using three or more [highly likely DI-ILD]). Most commonly used drugs were statins (63.1%) with a predominance among men (69.4 vs 47.1%, $p < 0.0001$). Nitrofurantoin, not metabolized by the tested pathways, was prescribed more frequently among women (51.9 vs 4.5%, $p < 0.00001$).

Conclusions In our cohort with suspected DI-ILD, 79% carried one or more genetic variants accompanied by the use of drugs metabolized by a corresponding affected pathway. In 60%, the diagnosis of DI-ILD was likely, whereas in 37.5%, it was highly likely, based on CYP analyses. This study underlines the importance of considering both drug use and genetic make-up as a possible cause, or at least a contributing factor, in the development and/or progression of fibrotic lung diseases.

Clinical Trial Registration ClinicalTrials.gov identifier NCT00267800, registered in 2005.

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Key Points

In this study of patients with suspected drug-induced interstitial lung diseases, 60% had potential risk factors for developing drug-induced interstitial lung diseases.

Our results indicate that the occurrence of drug-induced pulmonary toxicity is at least partly linked to inter-patient variation in genes and drug use.

The results highlight the importance of considering both drug use and genetic make-up as possible causes, or at least contributing factors, in the development and/or progression of fibrotic lung diseases.

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1 Introduction

Interstitial lung diseases (ILDs) are characterized by inflammation and/or fibrosis within the interstitial space. The causes of fibrotic ILD vary from identifiable causes, including autoimmune or exposure-related causes, to those classified as idiopathic, i.e., idiopathic interstitial pneumonias [1]. The pathological pattern, usual interstitial pneumonia or idiopathic pulmonary fibrosis (IPF), can also be seen in individuals with fibrotic hypersensitivity pneumonitis or fibrotic drug-induced pneumonitis, as well as fibrotic non-specific interstitial pneumonia (NSIP) [1–3]. In turn, morphological patterns in drug-induced ILD (DI-ILD) are diverse, and outcomes correspondingly vary considerably [4, 5].

An increasing number of therapeutic agents have been associated with drug-induced lung injuries [6–10]. A high index of suspicion and a systematic approach are necessary to properly identify the culprit drug and secure the diagnosis of DI-ILD [5, 6]. Early intervention by timely withdrawal of the inciting agent plays a key role in minimizing and potentially reversing the adverse drug reactions (ADRs) and avoiding long-term sequelae [5]. So far, however, drugs are often not recognized, and hence underestimated, as serious causative triggers of ILD [5, 8, 11–13]. Various individual factors influence the metabolism and elimination of drugs, including extrinsic factors such as comedications, including illicit drugs, and intrinsic factors that affect the disposition, including genes, gender, and age [14, 15]. An individual's pharmacogenetic profile may impact on how they respond to various drugs, as the vast majority of individuals carry at least one pharmacogenetic variant [16]. The increasing role of pharmacogenetics (PGx) is vital in improving modern medical and prescribing practices [14, 17].

Cytochrome P450 (CYP) iso-enzymes, responsible for a significant part of drug metabolism, have been detected in many human tissues, including lung tissue [18]. Genetic variations in drug-metabolizing enzymes may boost the drivers and/or causation of DI-ILD by inducing the formation of reactive oxygen species or other reactive metabolites (phase I) or by reducing the scavenging of these reactive oxygen species or reactive metabolites (phase II) [12, 19, 20]. Previous studies acknowledged that both clinical and genetic risk stratification (PGx) allow an efficient analysis of risk factors and have the potential to optimize drug therapy and more accurate prevention of DI-ILD in the future and that pre-emptive drug-gene testing may reduce the incidence of ADRs [17, 19–25].

2 Aim

The aim of this retrospective study was to assess whether the drug use of patients with suspected DI-ILD is associated with carrying polymorphisms in the tested *CYP* genes (i.e., *CYP2D6*, *CYP2C9*, and *CYP2C19)* affecting the corresponding metabolic pathways.

3 Materials and Methods

3.1 Study Design and Ethical Statement

Patients who were referred to the ILD Center of Excellence at St. Antonius Hospital, Nieuwegein, the Netherlands (a tertiary referral center) between 2010 and 2019 with a fibrotic idiopathic interstitial pneumonia, i.e., either NSIP ($n = 211$) or IPF ($n = 256$), with a suspicion of DI-ILD, were considered for this retrospective observational study. In this sample of patients with unexplained ILD and a history of drug use, genotyping of certain specified genes was included in the diagnostic work-up. A multidisciplinary team used the following diagnostic criteria: a history of drug exposure, clinical presentation (including dyspnea and hypoxia), pulmonary function impairment, exercise intolerance, high-resolution computed tomography scan abnormalities (including multifocal areas of ground-glass opacity with intralobular interstitial thickening), if available, bronchoalveolar lavage fluid analysis results and/or histopathology consistently matching earlier reports in the literature, exclusion of other causes of ILD, and finally improvement or stabilization after drug cessation [3, 8].

The study was conducted according to the principles of the Declaration of Helsinki (version 5, 2004) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The protocol was approved by the Medical Research Ethics Committees United of St. Antonius Hospital (approval R05-08A). All adult participants provided written informed consent to participate in this study.

3.2 Data Collection

Demographic information of the included patients, i.e., gender, age at diagnosis, and drug use at diagnosis, were collected. Data on drug use were recorded and retrospectively supplemented with pharmacy data recorded in the hospital's electronic health records. The drugs used were classified according to their metabolic pathways as inhibitors and/or substrates for the enzymes studied. All patients were treated within standard dosages as used in clinical practice. No patient was treated with an unusually high dosage of any of the drugs used.

3.3 Genotyping

In all subjects, genomic DNA was isolated from venous EDTA-anticoagulated blood. In this study, genotyping was carried out for the most clinically relevant variants of

CYP genes (*CYP2D6*, *CYP2C9*, and *CYP2C19*). *CYP2C9* (*CYP2C9*2* [C430T], *CYP2C9*3* [A1075C]), *CYP2C19* (*CYP2C19*2* [G681A], *CYP2C19*3* [G636A], and *CYP2C19*17* [C806T]), *CYP2D6* (*CYP2D6*3* [A2549del], *CYP2D6*4* [G1846A], *CYP2D6*6* [T1707del], *CYP2D6*5* [del], and *CYP2D6* copy number variation) alleles were identified by real-time polymerase chain reaction using the StepOnePlus™ Real-Time PCR System and TaqMan GTXpress Master/Drug Metabolizing Genotyping Assay mixes (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's instructions.

In accordance with conventional classification systems, individuals were classified as poor metabolizers if they carried two non-functional alleles; as intermediate metabolizers (IMs) if they carried one non-functional allele; as normal metabolizers if they carried one allele associated with reduced or increased activity and one functional allele or two functional alleles, and as ultra-rapid metabolizers if they carried at least two copies of a functional allele plus a reduced activity allele, two copies of an increased function allele (*CYP2C19*17*), or three or more copies of a functional allele. The laboratory that performed the tests is ISO certified (ISO 15189:2012).

3.4 Risk Stratification and Statistics

Each patient with so far unexplained ILD was assessed for the risk of having developed an actual severe DI-ILD after starting a particular drug. Accordingly, their past and present drug use was recorded. The assessment of the risk of developing DI-ILD started by addressing the diagnostic criteria. All metabolic pathways of the drugs used were assessed for the CYP enzyme(s) we tested. Additionally, we assessed whether patients carrying genetic variants used at least one drug metabolized by the corresponding affected metabolic pathways. Those using one drug metabolized by an affected pathway were considered as having possible DI-ILD, those using at least two drugs metabolized by a corresponding affected metabolic pathway (IMs), or were poor metabolizers, were considered as likely to have developed DI-ILD, and those using three or more drugs were considered as highly likely to have DI-ILD.

All patients were 'risk assessed' only once, so for example, having a poor metabolizer and/or IM or even three IMs in combination with drug use in all pathways only counted once. Furthermore, this group of patients was included in the study population because of their diagnosis (DI-ILD), and we retrospectively gathered and combined their genotypes and drug use to confirm and find possible causes and/or commonalities. Drugs metabolized by other pathways also associated with ILD (i.e., nitrofurantoin, sulfasalazine, or bleomycin) represented another metabolizing risk factor, which was, however, beyond the scope of this study.

To compare the distribution of polymorphisms between the patients studied (all Caucasian) and a general Caucasian population, controls were collected from the literature [26–28]. Statistical analyses were performed with SPSS version 28.0 software for Windows (SPSS Inc., Chicago, IL, USA). A Chi-square statistical analysis was used to compare the categorical distributions of *CYP* polymorphisms. Actual allele distributions were compared with the expected frequencies calculated using the Hardy–Weinberg equilibrium. A p value < 0.05 was considered statistically significant. Where necessary, a Bonferroni correction was applied ($p < 0.02$).

4 Results

In the cohort studied ($n = 467$; 69.0% male), all with a DI-ILD, either NSIP or IPF, 386 (82.7%) patients demonstrated at least one polymorphism in the tested *CYP* genes (*CYP2D6*, *CYP2C9*, and *CYP2C19*). Of these 386 cases, 369 (79.0%) used at least one drug metabolized by an affected metabolic pathway (Fig. 1).

Demographics and phenotypes regarding CYP2D6, CYP2C9, and CYP2C19 are presented in Table 1, as well as genotype frequency data from controls derived from the literature. These results indicate a statistically significantly higher percentage of poor metabolizers in *CYP2D6* ($p =$

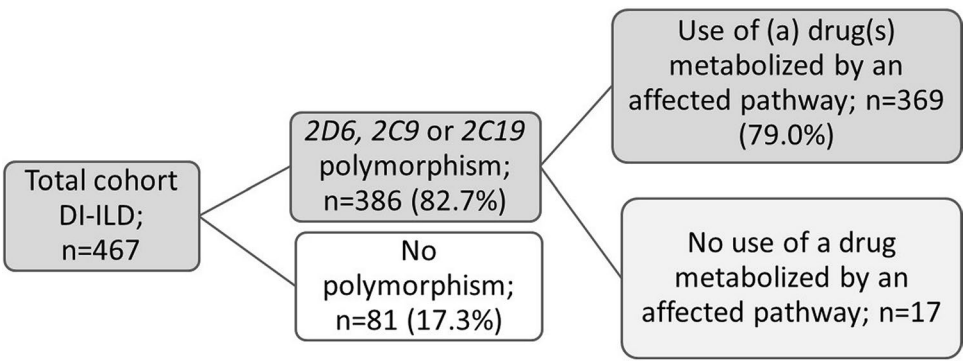

Fig. 1 Flow chart presenting the results of genotyping. *DI-ILD* drug-induced interstitial lung disease

0.01) in our DI-ILD cohort, compared with the controls [26–28].

The genotype distributions for our cohort were consistent with the Hardy–Weinberg equilibrium. According to the Hardy–Weinberg principle, the gene frequencies in the study cohort were not significantly different from those in a general healthy population. The major reason why they developed an ILD therefore strongly indicates (multiple) drug use of our study cohort, in combination with the presence of one or more polymorphism(s).

Table 2 summarizes the number of drugs used in our cohort, subdivided into patients with and without polymorphisms in one or more of the tested *CYP* genes. Sixty percent (280/467) of the patients used at least two drugs metabolized by a corresponding affected metabolic pathway (IMs), or were poor metabolizers, who were considered to be likely DI-ILD cases. Three or more drugs were used by 37.5% of the patients studied, classifying them as highly likely DI-ILD cases. In terms of overall gender, more men were affected (IPF: 83.6% male patients vs 16.4% female patients [$p = 0.008$], NSIP: 56.8% male patients vs 43.2% female patients [$p = 0.005$]).

Drug use in these 369 patients differed between men and women (Table 3). The most frequently used drugs metabolized by CYP enzymes were statins, used by 63.1% of patients (69.4% male versus 47.1% female [$p < 0.0001$]; Table 3).

As expected, the most frequently prescribed drug metabolized by other pathways, nitrofurantoin, was predominantly used by women (4.5% men vs 51.9% women [$p < 0.00001$]; Table 3).

Furthermore, only two patients used other drugs known for their pulmonary toxicity, one using bleomycin and one using sulfasalazine. Neither of these is metabolized by the CYP enzymes investigated.

The Summary of Product Characteristics list as well as Pneumotox® were used to assess whether pulmonary ADRs have been reported for the most commonly used drugs (Table 3) [29, 30]. Please also see the Appendix in the Electronic Supplementary Material for a summary of the characteristics and metabolic pathways of drugs used concomitantly in our study cohort.

5 Discussion

In this retrospective study in a cohort of patients with two fibrotic ILDs (NSIP or IPF), 79.0% had one or more gene variants predicted to be functionally deleterious, in the three *CYP* genes we tested, accompanied by the use of drugs metabolized by an corresponding affected metabolic pathway. Of these 369 patients, 280 (60%) used two or more drugs, and were considered to possess potential risk factors explaining the development of DI-ILD. Overall, statins

Table 1 Summary of demographic data and phenotypes regarding CYP isoenzymes CYP2D6, CYP2C9, and CYP2C19 of 467 Caucasian patients with suspected drug-induced interstitial lung diseases and controls [26–28]

Characteristics	NSIP	IPF	*p* value	Total	Controls [26–28]	*p* value
n (%)	211 (45.2)	256 (54.8)	**0.003**	467 (100)	NA	NA
Gender, male, *n* (%)	122 (57.8)	200 (78.1)	**< 0.0001**	322 (69.0)	NA	NA
Age, years, mean (range)	68 (29–90)	70 (38–89)	NA	69 (29–90)	NA	NA
CYP2D6, *n* (%)						
NM	96 (46.5)	130 (50.8)	0.26	226 (48.4)	(53.6)	0.02
IM	95 (45.0)	97 (37.9)	0.12	192 (41.1)	(38.9)	0.32
PM	18 (8.5)	24 (9.4)	0.75	42 (9.0)	(6.0)	**0.01**
UM	2 (1.0)	5 (1.9)	0.37	7 (1.5)	(1.5)	1.0
CYP2C9, *n* (%)						
NM	135 (64.0)	157 (61.3)	0.56	292 (62.5)	(58.7)	0.08
IM	69 (32.7)	89 (34.8)	0.64	158 (33.8)	(35.9)	0.32
PM	7 (3.3)	10 (3.9)	0.74	17 (3.7)	(5.4)	0.07
CYPC19, *n* (%)						
NM	132 (62.5)	172 (67.2)	0.30	304 (65.1)	(66.0)	0.67
IM	62 (29.4)	62 (24.2)	0.21	124 (26.6)	(26.5)	0.96
PM	5 (2.4)	14 (5.5)	0.09	19 (4.1)	(2.5)	0.04
UM	12 (5.7)	8 (3.1)	0.17	20 (4.3)	(5.0)	0.46

Data are expressed as absolute numbers, with percentages or rangein parentheses

CYP cytochrome P450, *IM* intermediate metabolizer, *IPF* idiopathic pulmonary fibrosis, *NA* not available/applicable, *NM* normal metabolizer, *NSIP* non-specific interstitial pneumonia, *PM* poor metabolizer, *UM* ultra-rapid metabolizer

Bold values indicate statistical significance

Table 2 Numbers of drugs used by patients with suspected DI-ILD subdivided into those possessing a *CYP2D6*, *CYPC9*, and/or *CYP2C19* polymorphism, with or without a drug metabolized by an affected metabolic pathway, and those without any of the tested polymorphisms

	Cohort of cases with suspected drug-induced interstitial lung diseases, $n = 467$		
	CYP2D6/2C9/2C19 polymorphism; use of drug(s) by an affected metabolic pathway, $n = 369$ (79.0)	*CYP2D6/2C9/2C19* polymorphism; no use of a drug by an affected metabolic pathway, $n = 17$ (3.6)	No polymorphism; use of drug(s) by a tested not-affected metabolic pathway, $n = 81$ (17.4)
≥ 3 drugs/PM	175 (37.5)	1 (0.2)	40 (8.6)
≥ 2 drugs/PM	280 (60.0)	5 (1.1)	67 (14.3)
1 drug	89 (19.1)	10 (2.1)	14 (3.0)
0 drugs	0	2 (0.4)	0
Nitrofurantoin	66 (14.1)	8 (1.7)	21 (4.5)
CYP2D6 polymorphism	230 (62.3)	11 (64.7)	0
≥ 3 drugs	89 (24.1)	0	26 (32.1)
≥ 2 drugs	152 (41.2)	0	27 (33.3)
1 drug	65 (17.6)	0	21 (25.9)
0 drugs	13 (3.5)	11 (64.7)	7 (8.6)
CYP2C9 polymorphism	169 (45.8)	6 (35.3)	0
≥ 3 drugs	62 (16.8)	0	21 (25.9)
≥ 2 drugs	115 (31.2)	0	34 (42.0)
1 drug	49 (13.3)	0	21 (25.9)
0 drugs	5 (1.4)	6 (35.3)	5 (6.2)
CYP2C19 polymorphism	158 (42.8)	5 (29.4)	0
≥ 3 drugs	63 (17.0)	0	23 (28.4)
≥ 2 drugs	100 (27.1)	0	23 (28.4)
1 drug	52 (14.1)	0	27 (33.3)
0 drugs	6 (1.6)	5 (29.4)	7 (8.7)

Data are expressed as absolute numbers, with percentage in parentheses

CYP cytochrome P450, *PM* poor metabolizer

were the most frequently prescribed drugs, which were used more often by men than women (69.4 vs 47.1%). The most frequently used drug not metabolized by any of the tested pathways, nitrofurantoin, was used more often by women. These findings indicate that the occurrence of drug-induced pulmonary toxicity is, at least partly, associated with variations in genes as well as drug use. Hence, PGx-informed personalized drug treatment may contribute to reducing the risk and/or progression of drug toxicity including pulmonary toxicity.

The cause of the variability in drug reactions is multifactorial. Among other factors, multidrug use is more common among older people, and consequently, drug–drug interactions are an increasing clinical problem, especially when drugs have common metabolic pathways [14]. A particular drug may itself cause toxicity, or inhibit a metabolic pathway and thus—in the case of multidrug use—cause toxicity indirectly. The website Pneumotox® provides helpful information about drugs reported to cause pulmonary toxicity [10, 29]. The ability to identify individuals who are susceptible to developing ADRs by providing information about genetic variants that may warrant changes in medication management has the potential to reduce personal drug-related morbidity [16, 17, 31]. The high rate of reduced metabolic capacity of CYP enzymes in the cohort of the present study is in line with an earlier study by Wijnen et al. [13]. It seems that genetic variations in metabolizing enzymes are able to boost the drivers of DI-ILD [12]. This suggests a potential value of personalized medicine by genotyping, aiming to improve efficacy, tolerability, and drug safety. Thus, knowledge of PGx may ultimately serve as a helpful tool in explaining toxicity and clinical response. To this end, phenotypic manifestations, therapeutic outcomes, or ADRs should be considered in relation to a patient's underlying genetic background [32]. Both genotyping and phenotyping have the potential to contribute to patient safety.

An increasing number of pharmacogenetic studies have indicated that genetic testing prior to treatment may be useful either for setting the individual dose or for making the decision to use a particular drug [17, 32, 33] as well as for reducing clinically relevant ARDs by pre-emptive pharmacogenetic testing [34, 35]. The era of very successful

Table 3 Most frequently used drugs associated with pulmonary toxicity in the group using drugs metabolized by an affected CYP iso-enzyme with at least one polymorphism in *CYP2D6*, *CYP2C9*, and/or *CYP2C19* ($n = 369$), stratified by gender [29, 30]

Drug	Total, $n = 369$	Male, $n = 265$ (71.8)	Female, $n = 104$ (28.2)	p value	CYP 2D6/2C9/2C19 SUB and/or INH	Pneumotox[a] [29]	SmPC[b] [30] +/−
Statins	233 (63.1)	184 (69.4)	49 (47.1)	< **0.0001**	2D6/2C9/2C19	5	+
Simvastatin	143 (38.8)	113 (42.6)	30 (28.8)	**0.014**	2D6/2C9/2C19	2	+
Atorvastatin	54 (14.6)	42 (15.8)	12 (11.5)	0.29	2D6/2C9/2C19	1	+
Rosuvastatin	36 (9.8)	29 (10.9)	7 (6.7)	0.22	2C9	1	+
Metoprolol	109 (29.5)	84 (31.7)	25 (24.0)	0.15	2D6	1	−
Carbasalate calcium	95 (25.7)	75 (28.3)	20 (19.2)	0.07	2C9	5	−
Acenocoumarol	80 (21.7)	62 (23.4)	18 (17.3)	0.20	2C9/2C19	5	−
Omeprazole	62 (16.8)	40 (15.1)	22 (21.2)	0.16	2D6/2C9/2C19	1	−
Amlodopine	49 (13.3)	35 (13.2)	14 (13.5)	0.95	2D6/2C9/2C19	2	−
Tamsulosin[c]	43 (11.7)	43 (16.2)	0	NA	2D6	1	−
Nitrofurantoin	66 (17.9)	12 (4.5)	54 (51.9)	< **0.00001**	NA	5	+

Data are expressed as absolute numbers, with percentage in parentheses

CYP cytochrome P450, *INH* inhibitor, *NA* not applicable, *Pneumotox.com* (Drug-Induced Respiratory Disease Website) [29], *SmPC* Summary of Product Characteristics, *SUB* substrate

Bold values indicate statistical significance

[a]Number indicates the frequency of drug-induced pulmonary toxicity, from: 1 rare (< 10 cases); 2 (10–50 cases); to 5 very common (> 200 cases)

[b]Drug-induced interstitial lung disease is mentioned in the SmPC

[c]Tamsulosin is not prescribed to women

blockbuster drugs, the profitable 'one-size-fits-all drugs', is clearly declining [31, 36]. Mounting evidence suggests PGx can improve the safety and/or efficacy of several commonly prescribed medications. The drugs with a high proportion of actionability (i.e., concerning patients carrying a genetic variant requiring a change of treatment) investigated by Swen et al. were also widely used in our study, specifically simvastatin, metoprolol, amitriptyline, atorvastatin, and anticoagulants [17].

In line with the medications identified in our study, a study by Peterson et al. among patients at a cardiovascular intensive care unit found that those with actionable results included warfarin, metoprolol, proton pump inhibitors, analgesics, and statins [37]. Previously, we observed that around 25% of patients with a cardiovascular event developed pulmonary fibrosis after starting anticoagulant therapy [38]. We found that a diffuse alveolar hemorrhage can be worsened as a complication of oral anticoagulant therapy [38]. The latter study included many patients with an unstable international normalized ratio and a higher frequency of polymorphisms, supporting the hypothesis that a diffuse alveolar hemorrhage may trigger pulmonary fibrosis [38]. Moreover, unfavorable effects of oral anticoagulants on the survival of patients with IPF have been demonstrated [39, 40]. Cheng et al. found ferroptosis is a newly discovered type of regulated cell death, characterized by the iron-dependent accumulation of lipid peroxides, which has been implicated in numerous human diseases, including pulmonary fibrosis [41].

Fibrotic pulmonary diseases, especially IPF, are characterized by a male predominance [1, 2]. This has been explained by a less frequent history of smoking or occupational exposures among women. However, the role of drug exposure has so far been studied less extensively. Like others, Jessurun et al. demonstrated that simvastatin use is associated with pulmonary toxicity [23]. Nevertheless, simvastatin-associated pulmonary toxicity is still under-recognized in clinical practice. In our cohort, drug use differed between men and women. Statins, which are associated with pulmonary toxicity, appeared to be the most frequently used drugs in the patients we studied, with a predominance among male patients, and the same applies to the beta blocker metoprolol [29]. Withdrawal of simvastatin without switching to another statin led to an improvement in almost all NSIP cases. This not only points to a potential relationship, but also shows the best clinical strategy. Switching to a hydrophilic statin yielded better outcomes than switching to another lipophilic statin (i.e., atorvastatin), which concerns not only myotoxicities, but also pulmonary toxicities [23]. It is tempting to speculate that the more frequent statin and metoprolol use in men, in addition to occupational exposures, is not only associated with the development and progression of DI-ILD, but also partly explains the well-known gender difference in the prevalence of fibrotic lung diseases.

The possibility that the incidence and/or progression of fibrotic ILD could be related to drug toxicity is still underestimated and often unrecognized. Identifying patients at

risk starts with the suspicion of drug-induced toxicity, recognition, and awareness. Systematic history taking, including occupational exposure and drug intake, is necessary in each assessment of pulmonary fibrosis, mainly because the etiology changes from 'idiopathic' to drug-induced toxicity [23]. In addition, appropriate pre-emptive pharmacogenetic screening is recommended, to improve efficacy, tolerability, and drug safety. Assessment of the allele and genotype frequencies in our cohort appeared to be useful for a better understanding of the interpersonal differences in drug and metabolite exposure, for example, the outcomes of pharmacotherapy and pulmonary toxicity. Timely withdrawal of a drug assumed to be associated with pulmonary toxicity might prevent pulmonary damage and/or progression of existing fibrotic lesions [43]. The more we know about a patient's genes and context, the better we can make disease management decisions [44]. Furthermore, exploring exposure throughout life for potential triggers, including polypharmacy in unexplained/idiopathic cases, is warranted to avoid lung damage or to reduce disease progression in the future.

5.1 Limitations

The retrospective design of our study may have resulted in incomplete data and data collection bias. Hence, we cannot determine the value of pre-emptive PGx testing, nor the reduction in pulmonary drug toxicity risk. Furthermore, we only tested a limited number of metabolic enzymes. Over-the-counter drugs such as paracetamol (acetaminophen) are often under-reported. Moreover, testing more enzymes would potentially yield more drugs used metabolized by an affected metabolizing pathway and subsequently increase the number of highly suspected drug-induced cases, which means that our results represent the lower limit of what happens in clinical practice. Additionally, no measurements for phenotyping were undertaken and so the phenotypes are inferred to be directly corresponding to the measured genotypes. However, the inclusion of drugs impacting the metabolic activity of the enzymes we tested in the risk stratifications partly compensates for this omission.

6 Conclusions

In this study, 60% of patients with suspected DI-ILD carried potential risk factors for developing DI-ILD, i.e., interpatient variation in genes and drug use. Overall, our findings show a promising role for PGx, with almost 80% of our subjects carrying at least one of the tested gene variants (*CYP2D6*, *CYP2C9*, and *CYP2C19*) predicted to be functionally deleterious and altering drug metabolization. These results underline the importance of considering drug use and genetic make-up as possible causes, or at least contributing factors, in the development and/or progression of fibrotic lung diseases. It remains to be investigated whether applying a standardized, validated, and harmonized pre-emptive pharmacogenetic test system, supporting genetically guided decision making in clinical practice, will optimize personalized pharmacotherapy and prevent the occurrence of substantial pulmonary toxicity.

Declarations

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Conflict of interest Marjolein Drent, Petal A. Wijnen, Naomi T. Jessurun, Ankie M. Harmsze, Otto Bekers, and Aalt Bast have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study was conducted according to the principles of the Declaration of Helsinki (version 5, 2004) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The protocol was approved by the Medical Research Ethics Committees United of St. Antonius Hospital (approval R05-08A).

Consent to participate All participants provided written informed consent.

Consent for publication Not applicable.

Availability of data and material Anonymized data can be made available to investigators upon request to the corresponding author.

Code availability Not applicable.

Author contributions All authors read and approved the final version. Conceptualization: MD and PAW had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: MD, NTJ, PAW. Acquisition, analysis, or interpretation of data: MD, PAW, NTJ, AB. Drafting of the manuscript: MD, NTJ, PAW, AB. Critical revision of the manuscript for important intellectual content: AB, AH, OB. Statistical analysis: PAW, MD. Administrative, technical, or material support: MD, PAW. Supervision: MD.

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