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Risk and Association of Specific HLA Alleles With Nintedanib-Induced Gastrointestinal Adverse Reactions: A Discovery Study in an Italian Population

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ABSTRACT

Idiopathic Pulmonary Fibrosis (IPF) is a progressive and fatal lung disease with limited treatment options. *Nintedanib* and *pirfenidone* are the only antifibrotic drugs approved by both the USA and European medicinal agencies, but their efficacy and tolerability remain concerns. This exploratory study investigates the association between genetic variation in the Major Histocompatibility Complex (MHC) region and adverse effects (AEs) of these therapies. HLA genotyping has been previously performed in a discovery cohort of 124 IPF Italian patients, with recorded drug-related AEs. Logistic regression analysis using an additive model identified *HLA-C*06:02* as a significant risk factor, increasing the likelihood of AEs sixfold in *nintedanib*-treated patients ($p = 0.0043$, OR = 6.54, 95% C.I. 1.80–23.75). Notably, gastrointestinal toxicity—the most common AE—was strongly associated with this allele ($p = 0.0005$, OR = 11.85, 95% C.I. 2.94–47.71). These findings suggest a potential immune-mediated mechanism involving IL-23-driven inflammation and underscore the importance of pharmacogenetic tools in tailoring anti-fibrotic therapy. Implementing genetic screening could help minimize AEs and improve patient outcomes. Larger studies are warranted to validate these associations and guide personalized treatment strategies.

1 | Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and life-threatening interstitial lung disease characterized by irreversible scarring of the lung tissue, leading to a progressive decline in respiratory function. Given its poor prognosis and limited treatment options, investigating the efficacy and tolerability of available therapies is essential for optimizing patient outcomes [1].

At present, there is no definitive cure for IPF, and only a few therapeutic interventions are available to alleviate symptoms and mitigate disease progression. Currently, two antifibrotic drugs are approved by both FDA and EMA: *nintedanib* and

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Study Highlights

- What is the current knowledge on the topic?
  - The current knowledge regarding pharmacogenetic factors influencing the toxicity and efficacy of antifibrotic drugs *nintedanib* and *pirfenidone* remains limited, with few associations reported in the literature in genes *DSP*, *CYP1A2*, and *TOLLIP*.
- What question did this study address?
  - Is it possible to predict the risk of toxicity and efficacy of antifibrotic drugs *nintedanib* and *pirfenidone* through pharmacogenetic analysis?
- What does this study add to our knowledge?
  - This study presents novel findings regarding the association between HLA alleles and drug-related AEs in a cohort of Italian Idiopathic Pulmonary Fibrosis (IPF) patients: specifically, *HLA-C*06:02* is associated with a 11-fold increased risk of gastrointestinal toxicity in *nintedanib*-treated patients.
- How might this change clinical pharmacology or translational science?
  - This exploratory study suggests a precise target for further studies aimed at discovering genetic factors involved in the response and toxicity of antifibrotic drugs.

pirfenidone. *Nintedanib* is a tyrosine kinase inhibitor that targets multiple growth factor receptors, including *fibroblast growth factor receptor* (FGFR), *vascular endothelial growth factor receptor* (VEGFR), *platelet-derived growth factor receptor* (PDGFR), *colony-stimulating factor-1 receptor* (CSF1R), and *Fms-like tyrosine kinase-3* (FLT3). By competitively binding the ATP-binding site of these receptors, *nintedanib* prevents autophosphorylation and downstream signaling, thereby reducing fibroblast proliferation and angiogenesis [2].

On the other hand, *pirfenidone* modulates fibrogenic growth factors, attenuating fibroblast proliferation, myofibroblast differentiation, and extracellular matrix deposition by suppressing *transforming growth factor beta 1* (TGF-β1) and other cytokines [3].

Although both drugs individually caused adverse effects, their effectiveness showed minimal differences [4]. However, treatment was often discontinued due to adverse events (AEs). Patients taking *pirfenidone* commonly experienced fatigue, lethargy, and skin-related issues, while those on *nintedanib* primarily reported gastrointestinal symptoms, such as diarrhea [5].

For both drugs, a personalized therapeutic approach is essential, emphasizing the importance of pharmacogenetic tools to assist clinicians in stratifying patients based on their risk of toxic effects.

Despite this need, current pharmacogenetic knowledge regarding the toxicity and efficacy of these drugs remains quite limited. A study involving 210 IPF patients investigated the association between common profibrotic polymorphisms in *mucin 5B* (MUC5B) and *desmoplakin* (DSP) and antifibrotic treatment outcomes in IPF [6]. The findings highlighted the potential role of the DSP gene variant *rs2076295* in response to *nintedanib*. Specifically, the TT genotype has been associated ($p = 0.004$) with decreased overall survival in individuals with pulmonary fibrosis treated with *nintedanib* compared to the GG + GT genotypes.

In the case of *pirfenidone*, two studies have identified a nominally significant association between a variant in the CYP1A2 gene and drug toxicity (*rs762551*, $p = 0.02$, study size = 44). This association suggests a reduced incidence of adverse drug reactions in individuals homozygous for the A allele compared to heterozygotes or those homozygous for the C allele [4]. Additionally, an association has been reported between a variant in the TOLLIP gene (*rs5743890*, $p = 0.0457$, study size = 56) and the drug's efficacy [5].

The human leukocyte antigen (HLA) complex, a group of genes located on chromosome 6, encodes cell surface proteins that are crucial for immune system function. These proteins are expressed in almost all cells and play a fundamental role in presenting peptides to immune cells. *HLA* genes are highly polymorphic, allowing them to bind a wide variety of peptides derived from both self and foreign antigens. In some cases, drugs can induce immune-mediated responses through interactions with major histocompatibility complex (MHC) molecules, leading to adverse drug reactions (ADRs) [6].

Although the role of MHC genes in drug-induced toxicity has been established for some medications, their potential involvement in *nintedanib*- and *pirfenidone*-related adverse effects has not yet been investigated. In this exploratory study, we expanded our knowledge of the pharmacogenetics of these two drugs by investigating the potential role of different alleles in the HLA region in modulating drug toxicity in a discovery cohort of Italian patients with IPF.

2 | Methods

2.1 | Cohort Description

We evaluated a cohort of 149 unrelated patients with IPF. To minimize bias in assessing drug efficacy, we excluded 27 patients receiving immunosuppressive therapy (corticosteroids or azathioprine) or those with pulmonary comorbidities (lung cancer or chronic obstructive pulmonary disease). Among the remaining 122 patients, 78 (63.93%) were treated with *nintedanib*, 30 (24.59%) with *pirfenidone*, and 14 (11.48%) did not receive antifibrotic therapy due to personal refusal or advanced age.

The toxicity of antifibrotic drugs *nintedanib* and *pirfenidone* was assessed using a combined clinical and biochemical approach. The endpoints were defined based on the severity of adverse events (AEs) and their clinical relevance. They were classified according to the Common Terminology Criteria for Adverse Events (CTCAE).

At the time of diagnosis, the two treatment groups had no significant differences in baseline characteristics. The age at diagnosis was 69.4 ± 8.1 years for the *nintedanib* group, and 69.0 ± 7.0 years for the *pirfenidone* group (Student's *t*-test, $p > 0.05$). Similarly, the

male-to-female ratio was comparable between the two groups (13% vs. 10%).

Tolerability rates did not differ significantly between the two drugs (Fisher's exact test, two-tailed, $p > 0.05$); however, better compliance was observed with *nintedanib* (79.5% [62/78]) compared to *pirfenidone* (60% [18/30]).

Nine patients experienced adverse events related to pirfenidone, most commonly presenting with erythema (7/9), followed in some cases by photosensitivity (2/9) and headache (1/9). In contrast, among the 16 patients with adverse effects caused by *nintedanib*, 12 (81% [12/16]) experienced diarrhea, while the remaining 4 reported other nongastrointestinal side effects.

Although no significant differences in drug tolerability were observed, we explored whether individual genetic factors might influence the risk of AEs. To investigate this, we analyzed existing high-resolution *HLA* genotyping data (*unpublished results*) obtained using Next-Generation Sequencing (NGS) across 17 loci (*HLA-A, -B, -C, -F, -G, -H, -E, DRB1/3/4/5, -DQA1, -DQB1, -DPA1, -DPB1, MICA*, and *MICB*) to assess potential associations with treatment-related toxicity.

2.2 | Statistical Analysis

The association between *HLA* alleles and the AEs was investigated using a standard logistic regression model implemented in the PyHLA software package [7]. The presence or absence of an AE was set as the dependent variable (outcome), with separate analyses conducted for (i) any AE, (ii) *nintedanib*-specific AEs, and (iii) *nintedanib*-induced gastrointestinal AEs. Each *HLA* allele was treated as a primary independent variable under an additive model. While both age at diagnosis and sex were considered as potential covariates, only sex was retained in the final model to control for potential confounding, despite its nonsignificant association with the outcome (Fisher's exact test, $p = 0.112$). To account for multiple comparisons arising from the testing of 17 *HLA* loci, a stringent significance threshold was applied to control the family-wise error rate. Accordingly, the statistical significance threshold was adjusted to $p < 0.003$ (calculated as 0.05 divided by 17). The robustness of the most significant finding, specifically the association for *HLA-C*06:02*, was further validated using a nonparametric permutation test. In this procedure, phenotype labels (AE presence/absence) were randomly shuffled among subjects for 10,000 iterations to generate an empirical null distribution of odds ratios (ORs). The empirical p value was then calculated as the proportion of permutations yielding an OR equal to or greater than the one observed in the original data.

3 | Results

Our findings revealed five alleles (*HLA-G*01:06, –A*01:01, C*06:02, G*01:01, A*11:01*) showing significant nominal associations with adverse drug effects when comparing patients who experienced any adverse reaction ($N = 28$) to those who did not ($N = 80$), regardless of the antifibrotic drug administered (*nintedanib* or *pirfenidone*) (Table S1).

In particular, the *HLA-G*01:06, -A*01:01, C*06:02, and A*11:01* are nominally associated with an increased risk of adverse reactions, ranging from approximately 3 times to nearly 5 times higher [OR: 5.17, 4.07, 3.71, and 2.87, respectively]. The *HLA-G*01:01* allele, on the other hand, is more prevalent in patients without adverse reactions, suggesting a potential protective effect [OR = 0.49]. We further investigated whether a specific antifibrotic drug drove the association. No significant associations were found in the *pirfenidone* group ($N = 30$) when stratifying patients by treatment, likely due to the limited sample size for this drug.

In contrast, when considering the 78 patients treated with *nintedanib*, the most notable finding was that 7 out of 16 patients who experienced adverse events were carriers of the *HLA-C*06:02* allele (43.75% of patients; allele frequency 21.88%), all of whom were heterozygous, compared to 7 carriers out of 62 patients who did not report adverse reactions (11.29% of patients; allele frequency 5.65%). This corresponds to a sixfold increased risk of toxicity for carriers of the allele (OR = 6.54, 95% CI: 1.80–23.75, $p = 0.0043$) (Table 1). Notably, all patients who experienced adverse effects were unable to tolerate either the 150 mg or the 100 mg dose of *nintedanib*, regardless of the presence of the HLA-C*06:02 allele.

In addition, the *HLA-G*01:06* allele also showed a nominal association with adverse events in *nintedanib*-treated patients. Such an allele was present in 4 out of 16 (25%) individuals with adverse reactions, including three heterozygotes and one homozygote, corresponding to an allele frequency of 15.62% ($2N = 5/32$). In comparison, the allele was found in four heterozygous individuals among the 62 patients without adverse events (3.23%; $2N = 4/124$). This results in an odds ratio of 4.47 (95% CI: 1.13–17.70, $p = 0.0328$) (Table 1).

The most common adverse effect of *nintedanib* was gastrointestinal issues, particularly diarrhea, occurring in 12 out of 16 patients (75%). Among these 12 patients, 7 (58.33%) were carriers of the *HLA-C*06:02* allele, corresponding to an allele frequency of 29.17% ($2N = 7/24$). In contrast, among the 66 patients treated with *nintedanib* but without gastrointestinal symptoms, the allele was detected in 7 individuals, with a frequency of 5.3% ($2N = 7/132$). This difference corresponds to a markedly increased risk of gastrointestinal toxicity in allele carriers (OR = 11.86, 95% CI: 2.95–47.71, $p = 0.0005$) (Table 2).

Additionally, the *HLA-G*01:06* allele showed a nominal association with gastrointestinal adverse effects. It was detected in 3 out of 12 patients affected (25%), including 1 homozygote and 2 heterozygotes, corresponding to an allele frequency of 16.67% ($2N = 4/24$). In contrast, among 66 patients without gastrointestinal symptoms, the allele was found in 5 heterozygous individuals (7.56%; $2N = 5/132$; 3.79% allele frequency). This resulted in an odds ratio of 4.14 (95% CI: 1.04–16.56, $p = 0.0445$). Cumulatively, the presence of at least one of these two risk alleles—*HLA-C*06:02 or HLA-G*01:06*—explains approximately two-thirds (66%) of the gastrointestinal toxicity cases observed in this patient cohort.

Conversely, the *HLA-G*01:01* was observed in 10 out of 12 patients with gastrointestinal adverse events (83.3%), including 1 homozygote and 9 heterozygotes, corresponding to an allele

TABLE 1 | Association between *HLA* alleles and *Nintendanib* adverse reactions. The table reports the result of a logistic regression with an additive model performed with PyHLA. The outcome is the presence of overall adverse effects to therapy with *nintedanib*.

Nintendanib								
	AE ($N=16$)		No AE ($N=62$)					
***HLA* Allele**	**$2N=32$**	**%**	**$2N=124$**	**%**	**p[a]**	**OR**	**95% CI**	
*C*06:02*	7	21.88	7	5.65	**0.0043**[b]	6.54	1.80	23.75
*G*01:06*	5	15.62	4	3.23	**0.0328**[b]	4.47	1.13	17.70
*G*01:01*	16	50	86	69.35	0.0592	0.46	0.20	1.03
*A*01:01*	5	15.62	6	4.92	0.0681	3.20	0.92	11.13
*A*11:01*	5	15.62	8	6.56	0.115	2.86	0.77	10.57

Note: $2N$ = total number of alleles (two per individual).
Abbreviations: AE, patients with adverse effects; No AE, patients without adverse effects.
[a]p value calculated using the Monte Carlo permutation method with the Python package PyHLA [8].
[b]Bold values indicate nominal associations with $p < 0.05$.

TABLE 2 | Association between HLA alleles and *Nintendanib* gastrointestinal adverse reactions. The table reports the result of a logistic regression with additive model performed with PyHLA. The outcome is the presence of gastrointestinal adverse effects to therapy with *nintedanib*. After applying Bonferroni correction for multiple testing, only the first association remained statistically significant, while all others lost significance.

Nintendanib								
	Adverse reaction (*E*) $N=12$		No reaction (*F*) $N=66$		*E* vs. *F*			
***HLA* Allele**	**$2N=24$**	**%**	**$2N=132$**	**%**	**p[a]**	**OR**	**95% CI**	
*C*06:02*	7	29.17	7	5.3	**0.0005**[b]	11.86	2.95	47.71
*G*01:06*	4	16.67	5	3.79	**0.0445**[b]	4.14	1.04	16.56
*G*01:01*	11	45.83	91	68.94	**0.0382**[b]	0.38	0.15	0.95
*A*01:01*	4	16.67	7	5.38	0.0853	3.11	0.85	11.31
*A*11:01*	3	12.5	10	7.69	0.4237	1.83	0.42	8.01

Note: $2N$ = total number of alleles (two per individual).
[a]p value calculated using the Monte Carlo permutation method with the Python package PyHLA [8].
[b]Bold values indicate nominal associations with $p < 0.05$.

frequency of 45.83% ($2N=11/24$). Among patients without gastrointestinal toxicity, the allele was present in 59 out of 66 individuals (89.39%), including 32 homozygotes and 27 heterozygotes, with an allele frequency of 68.94% ($2N=91/132$). This association corresponded to an OR of 0.38 (95% CI: 0.15–0.95, $p=0.0382$) (Table 2).

4 | Discussion

We identified five HLA alleles associated with adverse effects of antifibrotic drugs. *HLA-G*01:06, -A*01:01, -C*06:02*, and *-A*11:01* were linked to an increased risk of adverse reactions (OR up to 5.17), while *HLA-G*01:01* appeared protective (OR = 0.49). Stratified analysis found no significant associations in the *pirfenidone* group, likely due to limited sample size. However, *HLA-C*06:02* was present in 22% of *nintedanib*-treated patients, who had a sixfold higher risk of adverse events (OR = 6.54, $p=0.0043$). Notably, 30% of patients with *nintedanib*-induced diarrhea *carried HLA-C*06:02*, compared to only 5% of those without ($p=0.0005$, OR = 11.85).

The exact mechanism of *nintedanib*-induced diarrhea remains unknown, but two primary hypotheses have been proposed [9]. The first involves receptor inhibition, where VEGFR inhibition could lead to intestinal ischemia, a mechanism previously reported with other VEGFR inhibitors such as ramucirumab. Additionally, FGFR inhibition may disrupt epithelial homeostasis, leading to diarrhea through mechanisms similar to those seen with EGFR inhibition [9]. The second hypothesis suggests that direct mucosal damage by *nintedanib* or its decomposition products may cause intestinal inflammation similar to inflammatory bowel disease (IBD) [9]. If this inflammatory response is HLA-mediated, it could explain the increased susceptibility in patients carrying *HLA-C*06:02*.

This allele has already been correlated to drug toxicity and efficacy in other pharmacogenetic studies across multiple populations [10]. Patients carrying this allele are at higher risk of severe cutaneous adverse reactions (SCARs) to *sulfamethoxazole/trimethoprim*, potentially due to altered drug metabolism and immune interactions. The underlying mechanisms proposed include hapten/prohapten activation, pharmacological interaction

with immune receptors, and modification of MHC-presented peptide repertoires [11].

Moreover, another inflammatory condition, psoriatic arthritis (PsA), highlights the importance of this allele [12]. In fact, the *HLA-C*06:02* allele is strongly associated with PsA: it accounts for over 6% of the variance in disease risk, and each allele copy increases the risk of psoriasis fivefold [8]. This allele has been linked to enhanced CD8+ T-cell responses, regulation of natural killer (NK) cells, and altered antigen presentation, leading to increased cytokine production (e.g., TNF-α, IL-12, and IL-23), which contributes to chronic inflammation and tissue damage [8, 12].

Additionally, *HLA-C*06:02*-positive patients have demonstrated a better response to *Ustekinumab* [13], an IL-12/23 inhibitor, further reinforcing the connection between this allele and IL-23-driven immune responses. Notably, IL-23 also plays a dominant pathogenic role in Crohn's disease-associated ileitis, suggesting its involvement in gastrointestinal immune dysregulation [10].

Based on this, if *nintedanib* or its metabolites induce intestinal inflammation in an *HLA-C*06:02*-dependent manner, it is plausible that the mechanism involves excessive IL-23-driven immune activation, similar to the inflammatory pathways observed in PsA and IBD.

This mechanism suggests a hypothesis that could explain the increased susceptibility of *HLA-C*06:02* carriers to *nintedanib-driven* adverse effects.

Although the sample size is small (but in any case, twice as large as other studies [6, 7, 9] that have investigated genetic factors associated with the efficacy and toxicity of these drugs), this study is the first to suggest a crucial role of *HLA-C*06:02* in *nintedanib* toxicity. Given the growing use of antifibrotic therapy in IPF, further validation in larger cohorts is necessary. Understanding the role of *HLA* in drug-induced toxicity could lead to personalized antifibrotic therapy, minimizing adverse effects and enhancing patient outcomes.

Our findings underscore the need for rigorous dose-finding studies that incorporate pharmacogenetic data, even in the context of dose-sparing approaches that have been recently proposed. The idea of dose-sparing combination therapy—for example, halving the standard doses of nintedanib and pirfenidone and administering them together—is indeed an attractive hypothesis. Given the distinct yet partially complementary mechanisms of action and nonoverlapping toxicity profiles of the two drugs, such an approach could, in theory, preserve efficacy while mitigating individual drug-related adverse events. However, current data on combination therapy raise some concerns. Notably, the incidence of certain adverse events, particularly diarrhea, appears to be higher when the two drugs are used together, even at adjusted doses [14, 15]. These findings suggest that toxicities may not be fully additive or dose-proportional and could even be potentiated in some patients. This underscores the need for rigorous dose-finding studies that incorporate pharmacogenetic data to better predict which patients might benefit from such combination regimens without increased risk.

With regard to the other findings, although only marginally significant, the *HLA-G* locus may also influence patient susceptibility to antifibrotic drug toxicity. Specifically, the G**01:06* allele was associated with a higher risk of adverse events (OR = 4.47), while *G*01:01* (OR = 0.46) showed a potential protective effect.

HLA-G, through its tolerogenic properties, exerts potent immunomodulatory and anti-inflammatory effects. Its expression is tightly regulated by genetic polymorphisms in coding, 3′ untranslated regions (UTRs) and modulated by cytokine signaling, particularly IL-10 and IFN-γ, in response to inflammation or infection [16].

At the protein level, the main difference between HLA-G**01:06* and *HLA-G*01:01* lies in a C>T substitution at codon 258, resulting in a nonconservative amino acid change from threonine to methionine within the α3 domain of the HLA-G protein [17–19]. This domain contains the binding site for inhibitory receptors LILRB1 and LILRB2. Therefore, *HLA-G*01:06* may affect the molecule's binding affinity for these receptors, potentially impairing its tolerogenic capacity, as previously observed in transplantation settings [19].

Furthermore, *HLA-G* alleles are often in linkage disequilibrium with specific haplotypes in the 5′ and 3′ UTRs of the gene, which regulate transcription, mRNA stability, splicing, and ultimately soluble HLA-G production [20]. Notably, *HLA-G*01:06* is almost invariably associated with the UTR-2 haplotype, whereas *HLA-G*01:01* shows more variable associations [21].

These UTR haplotypes differ at several functional regulatory sites, including the *14-bp insertion/deletion* polymorphism, and the *+3142C>G* and +3187A>G single nucleotide polymorphisms. The UTR-2 haplotype, characterized by the *14-bp insertion, +3142G, and* +3187A variants, has been associated with lower HLA-G expression at both membrane-bound and soluble levels [21–24]. Reduced levels of soluble HLA-G may compromise immune regulation during pharmacological stress, thereby promoting inflammation and increasing susceptibility to adverse drug reactions.

This study is the first to propose a key role of *HLA-C*06:02* in *nintedanib* toxicity as well as a possible contribution of *HLA-G* alleles, particularly G**01:06* and *G*01:01*, in modulating susceptibility to adverse reactions through their impact on immune regulation. Given the increasing use of antifibrotic therapy in IPF, further validation in larger cohorts is warranted. Understanding the role of *HLA* in drug-induced toxicity could pave the way for personalized antifibrotic therapy, minimizing adverse effects and improving patient outcomes.

Author Contributions

S.M., R.L. and M.F. wrote the manuscript; S.D., A.P. and S.G. designed the research, S.M., R.L. and M.F. performed the research S.M. and M.F. analyzed the data.

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Ethics Statement

Patients were recruited and enrolled in the study protocol at the Department of Biomedical Sciences and Public Health of the University of Cagliari, the Department of Pneumology of Binaghi Hospital of the Sardinian Regional Company for the Protection of Health (ASL Cagliari). Written informed consent was obtained from all patients and controls in accordance with the ethical standards (institutional and national) of the local human research committee. The study protocol, including informed consent procedures, conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the responsible ethics committee (Ethics Committee of the Cagliari University Hospital; date of approval: May 27, 2020; protocol number GT/2020/10894). Records of written informed consent are kept on file and are included in the clinical record of each patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** cts70371-sup-0001-TableS1.docx.