4-29-2024

Rising cases of drug-induced pulmonary fibrosis: Analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) database, 2000–2022

Kenneth L. McCall
Binghamton University–SUNY, kmccall@binghamton.edu

Kelsey R. Hennig

Zachary T. Abe
Binghamton University–SUNY

Danielle N. Dattler
Binghamton University–SUNY

Karyssa L. Hurd
Binghamton University--SUNY

See next page for additional authors

Received: 14 October 2023 | Revised: 26 March 2024 | Accepted: 3 April 2024

DOI: 10.1002/pds.5797

BRIEF REPORT

WILEY

Rising cases of drug-induced pulmonary fibrosis: Analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) database, 2000–2022

Kenneth L. McCall[1] | Kelsey R. Hennig[2] | Zachary T. Abe[3] | Danielle N. Dattler[3] | Karyssa L. Hurd[3] | Sophie L. Portnoy[3] | Zoey J. Zagoria[3]

[1]Department of Pharmacy Practice, Binghamton University School of Pharmacy & Pharmaceutical Sciences, Johnson City, New York, USA

[2]Specialty Pharmacy, Shields Health Solutions, Stoughton, Massachusetts, USA

[3]School of Pharmacy & Pharmaceutical Sciences, Binghamton University, Johnson City, New York, USA

Correspondence
Kenneth L. McCall, Department of Pharmacy Practice, Binghamton University School of Pharmacy & Pharmaceutical Sciences, 96 Corliss Avenue, Johnson City, NY 13790, USA.
Email: kmccall@binghamton.edu

Abstract

Purpose: Pulmonary fibrosis (PF) is a severe, progressive disease, which may be caused by exposure to certain medications.

Methods: We queried the U.S. FDA Adverse Event Reporting System (FAERS) from 2000 to 2022, using the search terms "pulmonary fibrosis" and "idiopathic pulmonary fibrosis" and excluded reports with patients under the age of 18 years, and patients with unknown sex or age. Reports were sorted by generic drug names, counted, and plotted over time using a best-fit trendline based on an exponential function.

Results: From 2000 to 2022, there were 24 095 935 adverse drug events reported in FAERS, of which 17 520 (0.07%) were reported as PF. After excluding reports containing patients with unknown age (5255, 30%), sex (122, 0.7%), and age below 18 years old (155, 0.9%), our study included 11 988 reports. The mean age of the study sample was 66.5 ± 13.1 years, and 6248 patients (52.1%) were male. Plotting the 11 988 reports by year revealed an exponential best fit line ($R^2 = 0.88$) with a positive slope over time. The top five drug classes associated with PF were disease modifying antirheumatic drugs (DMARDs, 39.4%), antineoplastic agents (26.4%), cardiovascular agents (12.6%), corticosteroids (4.6%), and immunosuppressive agents (4.0%).

Conclusion: A 23-year analysis of the FAERS database revealed exponentially increasing adverse event reports of PF. Significant annual increases in reporting of PF suspected with DMARDs and antineoplastic agents were identified. Our study highlights important trends, which should be used to guide PF research related to drugs of potential importance.

The study was approved by the Binghamton University Institutional Review Board. IRB ID# STUDY00004072 February 3, 2023.

KEYWORDS
antineoplastic drug, antirheumatic drug, idiopathic pulmonary fibrosis, interstitial lung disease, pharmacovigilance, pulmonary fibrosis

Key Points

- Pulmonary fibrosis (PF) is a severe, progressive disease, which has been associated with exposure to certain medications.
- While pneumotoxic drugs such as amiodarone are well documented to be associated with PF, an increasing number of therapeutic agents are associated with drug-induced lung injuries.
- Reports of drug-induced pulmonary fibrosis are exponentially increasing.
- Disease-modifying antirheumatic drugs are the most common drugs implicated in reports of pulmonary fibrosis.
- Antineoplastics are the second most reported drug class involving pulmonary fibrosis.

1 | INTRODUCTION

Pulmonary fibrosis (PF) is a relentlessly progressive lung disease with a median survival of 3 to 4 years.[1] PF accounts for up to half of all cases of interstitial lung disease and represents the most severe type of interstitial pneumonias.[1] There are five main categories of PF that have identifiable causes: drug-induced, radiation-induced, environmental, autoimmune, and occupational.[1] From 2001 to 2011, the prevalence of PF increased from 202.2 cases per 100 000 to 494.5 cases per 100 000 among US Medicare beneficiaries.[2] The age-adjusted mortality from PF in men and women was 72.4 deaths/1000000 and 40.1 deaths/1000000, respectively, in 2017.[3]

The pathophysiology of PF has many proposed contributors.[1] The irreversible damage to lung tissue and dysfunctional repair mechanisms result in decreased oxygenation and ultimately death.[1] Though the pathophysiology of PF is not entirely understood, resident macrophage polarization, interleukin-6 (IL-6), and p53 protein may play a role in the progression of pulmonary fibrosis.[4]

While pneumotoxic drugs such as bleomycin and amiodarone are well documented to be associated with PF, an increasing number of therapeutic agents are associated with drug-induced lung injuries.[1] The aim of this research was to investigate the leading drugs reported in association with PF through an analysis of the US FAERS database. In doing so, we hoped to elucidate the evolving landscape of drug-induced PF by identifying trends over time.

2 | METHODS

2.1 | Procedures

The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database is a post-marketing safety surveillance program, which contains adverse event and medication error reports voluntarily submitted to the FDA by healthcare professionals and consumers. Adverse events are coded in the informatic structure of the FAERS database using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.[5] MedDRA terminology is an international set of terms structured into system/organ classes and subdivided into 80 262 lowest level terms used to standardize the information in datasets. All reports are de-identified and available via a public dashboard.[6] The study was granted exempt approval by the Binghamton University Institutional Review Board.

We queried over 24 million adverse event reports in the FAERS database between 2000 and 2022 using MedDRA search terms "pulmonary fibrosis" and "idiopathic pulmonary fibrosis". Reports of idiopathic pulmonary fibrosis were included, as drug-induced interstitial lung disease is primarily a diagnosis of exclusion.[7] Reports were extracted from the FAERS database into a Microsoft Excel file and cases were sorted by generic drug names from the National Drug Code Directory and sorted by drug class using the primary or secondary category in the AHFS pharmacologic and therapeutic classification system.[8,9] Therapeutic drug classification, however, does not necessarily reflect the intended use. Each adverse event report in the database codes a drug as either "suspect" or "concomitant". A drug was considered associated with PF for the purpose of this study when the drug was coded as "suspect" for the adverse event in the report. We collected the following characteristics for each drug-related PF report: patient age, patient sex, reporter type, date of event, and adverse event outcomes (died, life threatening, hospitalized, disabled, and/or other). The data reported by the FAERS database is limited in terms of death causality, as individual reports do not firmly establish PF as the cause for the reported outcome, only that it preceded the outcome. Incomplete reports with missing patient age or sex were removed. Cases with missing age or age less than 18 years were removed as PF is a rare condition in children and none of the clinical or radiologic findings used for the diagnosis of PF in adults apply to children.[10]

2.2 | Statistics

A list of the top 50 drugs associated with PF was created using total counts of adverse event reports with generic drugs. Year over year trends in the most common drugs, as well as relevant drug classes,

were evaluated as the number of reports of PF reported to the FDA over time. A best-fit trendline based on an exponential function was used to model the relationship between number of reports per year and time. Using time series plots, emerging reports of drug-induced PF were identified and changes over the 23-year period were assessed using GraphPad Prism version 9.3.0 for Windows.[11]

3 | RESULTS

We queried 24 095 935 reports in the FAERS database from 2000 to 2022 and identified reports involving PF. Preliminary aggregates for PF reports totaled 17 520 reports. After removing incomplete reports and reports involving persons less than 18 years of age, the study included 11 988 reports of which 6248 (52.1%) were male. The mean age of the study sample was 67.8 (SD 12.2) and 65.1 (SD 13.7) years for men and women, respectively. Many adverse event reports (33.2%) listed more than one suspected drug with a mean (SD) of 2.1 (3.3) drugs per report. Most adverse event reports were submitted by a healthcare professional (7994, 66.7%). Death and hospitalization were reported as outcomes in 3896 (32.5%) and 6293 (52.5%) of reports, respectively.

The lowest and highest number of reports per year were 252 reports in 2001 and 1049 reports in 2020, which reflected an increase of 316%. Plotting the 11 988 PF reports by year demonstrated an increasing slope over time with approximately 35 additional reports per year (estimate = 35.1, 95% CI = 27.3–42.8, $R^2 = 0.81$, P-value <0.0001) using linear regression. Plotting an exponential regression line to the number of reports per year revealed a doubling time of 9.4 years (95% CI = 7.9–11.5 years, $R^2 = 0.88$, P-value <0.0001). The number of reports per year was relatively stable from 2000 to 2009 and subsequently increased in 10 out of 13 years from 2010 to 2022.

The top 50 drugs associated with a report of PF submitted to the FDA from 2000 to 2022 are shown in Table 1 (more than one suspected drug could be listed in each report). The main drug classes reported to the FDA in association with PF in descending order were disease-modifying antirheumatic drugs (DMARDs, 39.4%), antineoplastics (26.4%), cardiovascular agents (12.6%), corticosteroids (4.6%), immunosuppressive agents (4.0%), HMG-CoA reductase inhibitors (4.0%), "other" (3.7%), analgesics (3.2%), and bone resorption inhibitors (2.2%). DMARDs and antineoplastics accounted for 11 and 13 of the top 50 drugs, respectively.

As shown in Figure 1, the number of reports per year for 9 of the top 10 drugs increased over the timeframe of the study. Year over year reporting for pulmonary fibrosis generally increased throughout the study timeframe except for 2021. In the pre-COVID timeframe from 2000 to 2019, seven of the top 10 drugs (methotrexate, etanercept, adalimumab, rituximab, hydroxychloroquine, tocilizumab, and abatacept) demonstrated an increasing slope over time. The three drugs with the steepest slopes of increasing reports over time from 2019 to 2022 were leflunomide, tocilizumab, and infliximab (Figure 1). Reports involving amiodarone did not increase over the timeframe of the study.

TABLE 1 The top 50 drugs suspected of pulmonary fibrosis by count in descending order: FAERS database 2000 to 2022.[a]

Drug (Rank 1–10)	Cases (#)	Drug (Rank 11–20)	Cases (#)	Drug (Rank 21–30)	Cases (#)	Drug (Rank 31–40)	Cases (#)	Drug (Rank 41–50)	Cases (#)
Methotrexate	1350	Prednisone	367	Azathioprine	171	Celecoxib	130	Fluticasone\Salmeterol	103
Etanercept	1032	Tofacitinib	293	Golimumab	165	Mycophenolate	130	Amlodipine	99
Adalimumab	819	Simvastatin	270	Bleomycin	158	Docetaxel	120	Tacrolimus	95
Amiodarone	792	Atorvastatin	244	Doxorubicin	152	Cyclosporine	119	Clopidogrel	94
Infliximab	565	Cyclophosphamide	244	Macitentan	149	Carboplatin	118	Etoposide	92
Rituximab	561	Sulfasalazine	222	Alendronate	147	Prednisolone	115	Gemcitabine	90
Hydroxychloroquine	515	Certolizumab	209	Nitrofurantoin	141	Paclitaxel	108	Acetaminophen	87
Abatacept	430	Ambrisentan	193	Zoledronic Acid	140	Ribavirin	108	Cisplatin	86
Leflunomide	406	Bosentan	179	Metformin	133	Aspirin	108	Gold	86
Tocilizumab	389	Oxaliplatin	175	Fluorouracil	131	Furosemide	105	Rofecoxib	84
TOTAL	6859		2396		1487		1161		916

[a]More than one suspected drug could be listed in each report.

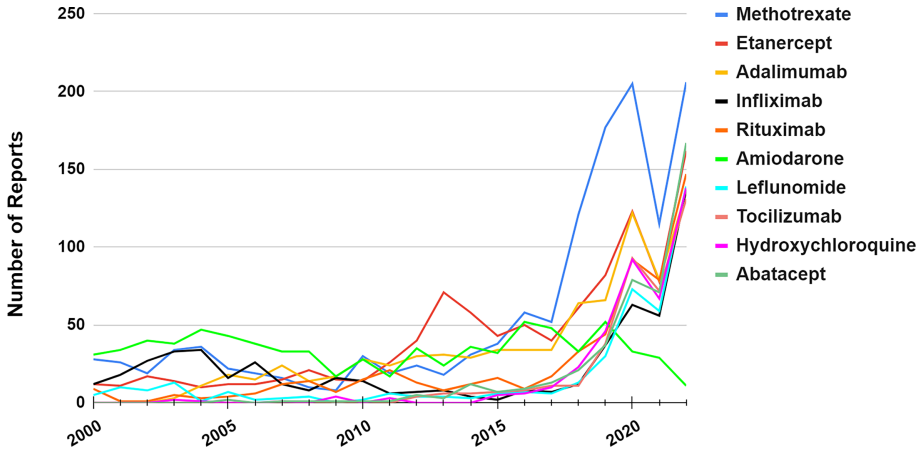

FIGURE 1 Reports of pulmonary fibrosis submitted to FAERS for the 10 most common drugs by year from 2000 to 2022.

4 | DISCUSSION

A 23-year analysis of a national database revealed significant increases and dynamic changes in adverse event reports involving PF from 2000 to 2022. This upward trend in reporting began prior to COVID-19 and appeared to accelerate during the pandemic as reflected by an exponential regression line. Significant annual increases in the reporting of PF suspected with methotrexate, etanercept, adalimumab, infliximab, rituximab, hydroxychloroquine, abatacept, leflunomide, and tocilizumab were identified. DMARDs and antineoplastics accounted for almost two-thirds of the suspected drugs in these adverse event reports.

The increases in adverse event reports involving PF reflect a vital need for further research on the causes and potential treatment. We suspect that the increased volatility in reporting in recent years may be due in part to pandemic-related effects as well as increased awareness of prescribers of the potential for pulmonary toxicity from these drugs. The decrease in overall reporting of pulmonary fibrosis in 2021 may be due to a decrease in access to routine care during the pandemic leading to a delay in diagnosis. A potential explanation for the increase in reports associated with hydroxychloroquine and tocilizumab is the expanded use of these agents during the pandemic.[12] There is also a significant possibility that post COVID-19 patients may be more likely to develop PF.[13]

DMARDs are the most common medication class implicated with adverse event reports of PF in our study. DMARDs work via various mechanisms, typically through interfering with the inflammatory cascade. Through these complex pathways, DMARDs can contribute to lung toxicity, in addition to providing immunosuppression and further risk of infection.[4] Araujo and colleagues examined reports in the FAERS database from 2003 to 2016 and identified a reporting signal involving pulmonary fibrosis with infliximab, etanercept, adalimumab, certolizumab pegol, rituximab, abatacept, and tocilizumab.[14] Perez-Alvarez et al. analyzed 122 cases of PF with the use of etanercept, and it was determined that 97% of patients on biologics were diagnosed with lung damage.[15] Regarding methotrexate, there are numerous previous studies implicating the rare adverse effect of PF.[1] Further complicating the relationship between DMARDs and PF is that chronic inflammatory diseases such as rheumatoid arthritis affect many organs and may present with pulmonary manifestations such as interstitial lung disease.[16]

Antineoplastics were the second most common medication class associated with drug-induced PF. Antineoplastics, such as bleomycin, disrupt cell replication and/or damage DNA.[4] It is theorized that PF may occur due to deposition of collagen in the lungs after cellular damage and from direct injury to the lung tissue leading to increased elastin production.[17] The lungs are inherently the most likely organs to be affected by antineoplastic agents, which may be due to the mechanisms listed above, or alternatively may be related to immunosuppressive infections.[17]

Of the top 10 most reported drugs, only amiodarone was not associated with an increase in reports over time. This finding may be due in part to longstanding vigilance on the part of prescribers regarding potential pulmonary toxicity secondary to amiodarone based on guidelines for regularly screening patients for pulmonary toxicity.[18] This would have implications for clinical practice as increased awareness and screenings may have the potential to reduced incidence of pulmonary toxicity secondary to drugs.

To our knowledge, this is the first analysis of the FAERS database focused on adverse event reports associated with PF. The results of our study are supported using a national database, allowing access to a diverse patient population, as well as over a two decade-long timeframe for reports. Limitations of the FAERS database include that it is populated with adverse event reports from healthcare professionals as well as non-healthcare professionals. There is also a risk of misclassification bias in the analysis of FAERS data as medications often prescribed to treat inflammatory or interstitial lung diseases may be included in reports, which may result in the potential for reverse causation. Another potential limitation is that FAERS is a voluntary reporting system and MedWatch reports of adverse drug events are often underreported.[19] As with most observations made from surveillance databases, the results should not be viewed in isolation and need to be put in context with other evidence. Determining causality is not within the scope of this study.[20] Future research directions could include a disproportionality analysis of PF reports, an analysis of PF reports in the World Health Organization VigiAccess database, and a subsequent analysis of reports in the post-pandemic timeframe.

5 | CONCLUSIONS

This analysis of a national database recognizes an exponential increase in the number of drug-induced PF reports from 2000 to 2022. This increase is widespread among the top 50 drugs, most notably DMARDs and antineoplastic agents. While our pharmacovigilance study has limitations, it highlights important trends, which should be used to guide research related to potential drug-induced causes of PF.

AUTHOR CONTRIBUTIONS

All authors were involved in the study conceptualization, development of methodology and analysis, writing, reviewing, and editing the manuscript. All authors have read and agreed to the published version of the manuscript.

FUNDING INFORMATION

This research did not receive any funding from agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was approved by the Binghamton University Institutional Review Board. IRB ID# STUDY00004072 February 3, 2023. All data records used in this study were obtained from a publically available database using de-identified records which are fully compliant with United States patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

ORCID

Kenneth L. McCall https://orcid.org/0000-0003-2061-108X

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How to cite this article: McCall KL, Hennig KR, Abe ZT, et al. Rising cases of drug-induced pulmonary fibrosis: Analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) database, 2000–2022. *Pharmacoepidemiol Drug Saf*. 2024;33(5):e5797. doi:10.1002/pds.5797