A drug repurposing study based on clinical big data

for the treatment of interstitial lung disease

（間質性肺疾患の治療のための

臨床ビッグデータに基づくドラッグリパーパシング研究）

(Summary)

2020

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Chapter 1. Data mining approach for an effective treatment of drug-induced ILD

The term "interstitial lung disease" or "diffuse parenchymal lung disease" is a heterogeneous group of respiratory disorders characterized by inflammation and/or fibrosis in the pulmonary alveoli as well as in the pulmonary interstitial tissues. Anti-inflammatory and anti-fibrotic agents are used for the treatment of ILD, however, only two drugs, nintedanib (tyrosine kinase inhibitor with multiple target) and pirfenidone, are approved at present for the treatment of idiopathic pulmonary fibrosis, IPF. A number of drugs have been clinically tried to treat fibrotic ILD. Yet, all trials failed to provide therapeutic benefit in the treatment of fibrotic ILD.

In this research, two clinical data were mined and analyzed in order to find drug that can suppress ILD. The databases are the Food and Drug Administration (FDA) adverse event reporting system database (FAERS) and Japan Medical Data Center insurance claims database (JMDC). These databases provide valuable resources, since the data represent real world medication usage. The objective of this chapter is to scientifically discover drug-induced ILD and to discover concomitant drug that suppress the drug-induced ILD.

Unduplicated reports from the first quarter of 2004 throughout the fourth quarter of 2019 of the FAERS were used. Drug names were mapped into unified generic names via text mining. The adverse event term used in this research was standardized MedDRA queries (SMQ) code 20000042 (interstitial lung disease) from MedDRA ver.23.0. Adverse event risk was evaluated by calculating the reporting ORs and Z-score. Incidence rate of ILD in FAERS database was also calculated.

The total number of patients in JMDC from January 2005 to August 2019 is 7,438,470 patients. A total of 17 International Classification of Disease (ICD)-10 terms related to ILD were used in this research. Amiodarone hydrochloride and dabigatran etexilate methanesulfonate were picked as drug of interest. Cases were extracted from JMDC and

analyzed for event sequence symmetry analysis. Cumulative incidence and number of ILD risk were visualized through Kaplan-Meier graph. Hazard ratio and log-rank test were calculated using R with "survival" package.

After deduplication, a total of 11,430,831 reports in FAERS database remained as unique reports. The highest association of drug and ILD was observed in amiodarone. Within amiodarone user reports, a thrombin inhibitor, dabigatran, showed the highest significance with lowest occurrence of amiodarone-associated with ILD. Based on the FAERS database analysis, amiodarone was found to elevate ILD incidence rate. Co-occurrence of dabigatran with amiodarone showed lower ILD incidence rate.

The number of predefined ILD patients were 22,855, and around 80% of them were diagnosed with interstitial lung disease. There month run-in (washout) period was used in this research. In the SSA of patients with ILD and patients receiving amiodarone, the number of patients with amiodarone then ILD sequence was observed higher than the number of patients with ILD then amiodarone sequence. Cumulative ILD incidence of amiodarone without dabigatran was observed higher than cumulative ILD incidence of amiodarone with dabigatran in 36 month observation period. The hazard ratio of amiodarone with dabigatran was significantly lower.

The clinical database used in this research provides large data to be analyzed. In the FAERS database analysis, amiodarone, was highly associated with ILD. JMDC analysis result reconfirms finding on FAERS analysis and clinical association of amiodarone with ILD. Dabigatran, a direct thrombin inhibitor was observed to have the highest association with suppression of amiodarone-associated ILD. JMDC analysis result also re-confirms analysis on FAERS database, where dabigatran co-occurrence reduces cumulative incidence of ILD.

As a conclusion, the current data mining on clinical database analysis provides finding that dabigatran can suppress amiodarone-induced ILD.

Chapter 2. Experimental validation for the effect of dabigatran on amiodarone-induced ILD

Amiodarone, an iodinated benzofuran drug was originally developed more than 5 decades ago. Key characteristics of amiodarone-induced ILD are increasing alveolar macrophages and varying degree of fibrosis. Objective of this chapter is to establish amiodarone-induced ILD in mice and evaluate the effect of dabigatran co-treatment with amiodarone.

In order to evaluate amiodarone-induced lung disease, mice were treated with amiodarone 300 mg/kg/day, 5 times a week. While, in order to evaluate dabigatran effect on amiodarone-induced ILD, co-treatment of dabigatran with dose 60 mg/kg/day, 5 times a week were used. Hematoxylin-eosin (HE) and Sirius Red staining were used for evaluation of alveolitis and fibrosis under a microscope. Gene expressions were evaluated using qRTPCR.

Amiodarone (300 mg/kg p.o., 5 days a week for 4 weeks) treatment was found to induce mice body weight decline. Increasing alveolar macrophages were observed but collagen was not increased in lungs of mice treated with amiodarone. *Pdgfra* and *Pdgfc* were upregulated by amiodarone treatment. Dabigatran (60 mg/kg p.o., 5 days a week for 4 weeks) co-treatment with amiodarone reduced amiodarone-induced body weight declining. Dabigatran co-treatment reduced intra alveolar macrophage and interstitial thickening in lung of mice treated with amiodarone. Dabigatran co-treatment with amiodarone reduced amiodarone-induced *Pdgfra* but not *Pdgfc* upregulation.

In this mouse model, alveolitis was observed in mice lungs after amiodarone treatment for 4 weeks. In lung histology, increased intra-alveolar macrophage and interstitial thickening were also observed but there was no increase in collagen deposition in lung mice. In this research, dabigatran co-treatment attenuated amiodarone-induced weight loss. Furthermore, dabigatran co-treatment has been found to improve outcome in histological

findings in amiodarone-induced ILD. These results suggest that dabigatran co-treatment has beneficial effect in amiodarone-induced ILD. From the gene expression examinations, it was revealed that the effect of dabigatran co-treatment in amiodarone-induced ILD was associated with attenuation of *Pdgfra* upregulation.

Conclusion

This study demonstrated systematical analysis on clinical databases and suggested dabigatran as a new candidate drug to suppress amiodarone-induced ILD. Although the mechanisms or the exact target is still unclear, this study suggested that dabigatran has beneficial effect in mouse model of amiodarone-induced ILD. For further study it is essential to investigate the exact target or mechanism of dabigatran in amiodarone-induced ILD and to investigate its target in correlation with fibrotic ILD.