Drugs without benefits? Confronting the challenges of drug induced interstitial lung disease

Dr Emma K Denneny (MRCP)[1,2] and Professor Joanna C Porter (PhD, FRCP)[1,2]

1. Centre for Inflammation and Tissue Repair, UCL Respiratory, University College London, London, UK.
2. Interstitial Lung Disease Service, University College London Hospitals NHS Foundation Trust, London, UK.

Corresponding author: Professor Joanna Porter, Centre for Inflammation and Tissue Repair, UCL Respiratory, University College London, London, UK; Joanna.porter@ucl.ac.uk.

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Drug induced interstitial lung disease (DILD) with an estimated incidence of approximately 4.1-12.4 cases/million/year, is implicated in ~5% of ILD cases [1]. Data varies by country, with DILD more commonly diagnosed in Japan, perhaps due to higher reporting [2]. Databases such as Pneumotox [3] collate evidence from the literature, often case reports or small series but with no large-scale assessment. At least 350 drugs have been implicated in causing lung toxicity, or pneumonitis, across a spectrum from mild radiological infiltrates to life-threatening respiratory failure [4]. This heterogeneity of presentation and lack of diagnostic standards makes DILD difficult to identify, even at individual patient level, with re-challenge to confirm toxicity rarely justified [4]. The Common Terminology Criteria for Adverse Events (CTCAE) scale [5] (Table 1) helps quantify severity and treatment includes cessation of the drug and, in more severe cases, corticosteroid use.

In this issue of Thorax, Jo *et al.* [6] report a nested case-control study using a large, nationally representative dataset of hospitalised patients in Japan to retrospectively identify patients that had developed DILD, severe enough to warrant corticosteroid therapy, after receiving a 'risk drug' from one of 42 categories associated with lung toxicity.

We applaud the methodology used in this study which identified 2342 cases of DILD out of ~42 million/hospital admissions (0.0056%). For each case the authors selected four controls matched for known DILD risk factors (primary diagnosis, gender, age± 10yr), length of stay and hospital. They were able to match 1541 (66%) cases with 5667 controls (1:4) to allow a multivariate conditional logistic regression analysis to

identify risk associated with drug categories and other factors. Of the 1541 DILD cases, 56% had been prescribed at least one risk drug during admission. Significant associations (p<0.05) were found between six categories and acute DILD: EGFR inhibitors (OR 16.84), class III anti-arrhythmics (OR 7.01), quinolones (OR 3.1), sulfamethoxazole/trimethoprim (OR 2.54), NSAIDS (OR 1.9) and beta-lactams (OR 1.54). Interestingly, statins (OR 0.53) appeared protective. The majority of DILD cases were older (88% ≥60 years) and male (70%). Other factors that increased risk were a higher Brinkmann index; underweight (BMI<18.5); Charlson Comorbidity Index ≥6; lung cancer (OR 2.38); or other cancer (OR 1.77).

This is a bold attempt to understand the impact of DILD across a much greater population than has previously been tackled, resulting in the largest series in the literature of patients with acute in-hospital DILD. The incidence was put at ~143 per 100,000 persons years (20-fold higher than a similar US study of 8,000 ICU patients [7]) with a mortality of 34.7%).

As expected with this type of study, the strengths are also limitations. Without a diagnostic gold standard Jo *et al.* applied stringent inclusion criteria to confidently identify genuine cases of DILD, an approach made possible by the sheer size of their database. They included only those patients that developed rapid onset acute pneumonitis after admission (median of 8 days) thereby missing those cases of insidious onset. Such subacute ILD may make up the majority of DILD cases as highlighted in a study using this same Japanese database, linked to community data, to identify 428 (1.65%) cases of DILD, from 25,924 patients prescribed gemcitabine,

with median onset of 65 days [8]. Jo *et al.* further sacrificed sensitivity for specificity by only including DILD cases that required corticosteroid treatment, of which 81% received high doses, implying moderate to severe disease (CTCAE grade 3-5). Patients with known ILD were excluded, further underestimating the real incidence of DILD for which pre-existing ILD is an independent risk factor, perhaps by priming the lungs prior to a 'second hit'. Additionally, only drugs prescribed in hospital and previously identified in the literature were considered to pose risk. As a result, it remains unclear how representative this highly select population is of the whole DILD spectrum (Figure 2).

Alarmingly a number of widely used drugs (antibiotics and NSAIDs) appear implicated (odds ratio's 3.1 or less). However, there is potential for reverse causation here where use of antibiotics represents treatment of existing ILD and not new disease, hence the high number. The data used for this study is entirely dependent on a national database with its own intrinsic bias, and local prescribing may explain why certain risk drugs are not identified in this study. Nitrofurantoin is a well-recognised cause of DILD (affecting 1 in 5000) with onset at 3-8 days for acute and 1-72 months for subacute ILD. However, nitrofurantoin, widely used elsewhere in the world, is not available in Japan where quinolones are used instead. Likewise, methotrexate, a folic acid antagonist, has been (almost certainly incorrectly) implicated in subacute DILD for many decades, perhaps because it is used to treat rheumatoid arthritis (RA), a disease with a high incidence (~20%) of associated RA-ILD, so distinguishing drug from disease in ILD causality has been difficult. However, acute lung toxicity due to methotrexate is recognised, albeit infrequently, and it is not clear how it has avoided detection here.

One possibility is the lower starting doses of methotrexate in Japan and the use of concomitant steroids, both of which may reduce the risk of pneumonitis.

In summary this is a well-executed study comprising the largest cohort on record of acute in-hospital DILD, albeit retrospective. It is a completely different approach to the Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card Scheme, which collects and monitors information on safety concerns involving medicines and medical devices, and so the incidence here is much higher, but this is exactly what is needed to better understand the scale of DILD. There are few surprises in the findings which support pre-existing literature and offer reassurance in the ability of a robust and specific methodology applied to a large database to identify diseases of *very* rare occurrence that lack gold-standard diagnostic criteria. The use of a nested case-control approach in such a rigorously identified subset of patients with DILD opens up the exciting possibility of identifying novel biomarkers and risk factors, genetic or other, that would be impossible, due to expense and logistics, to identify in the population as a whole. The hope is that such findings would be broadly applicable across all DILDs, not just in the very acute and severe cases considered here. The ultimate goal is to develop tools to identify DILD cases, at-risk patients and risk drugs earlier and with confidence, to better guide individual patient management and inform wider drug development and regulation.

Table 1. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0[3]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis[1]	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL[2]	Severe symptoms; limiting self-care ADL[2]; oxygen indicated	Life-threatening respiratory compromise: urgent intervention indicated (e.g., tracheostomy or intubation)	Death

[1] Pneumonitis: A disorder characterised by inflammation focally or diffusely affecting the lung parenchyma.

[2] Instrumental ADLs include preparing meals, shopping, using the telephone, managing money. Self-care ADLs include bathing, dressing, using the toilet, taking medications.

[3]Adapted from Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National Cancer Institute[5]

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