Radiological patterns of drug induced interstitial lung disease (DILD) in early phase oncology clinical trials

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Abstract (249 words)

Purpose: Drug induced interstitial lung disease (DILD) is a rare, but potentially fatal toxicity. Clinical and radiological features of DILD in the early experimental setting are poorly described.

Experimental design: 2499 consecutive advanced cancer patients on phase I clinical trials were included. DILD was identified by a dedicated radiologist and investigators, categorized per internationally recognized radiological patterns and graded per CTCAE and the Royal Marsden Hospital DILD score. Clinical and radiological features of DILD were analysed.

Results: 60 patients overall (2.4%) developed DILD. Median time to onset of DILD was 63 days (range 14-336 days). 45% of patients who developed DILD were clinically asymptomatic. Incidence was highest in patients receiving drug conjugates (7.4%), followed by inhibitors of the PI3K/AKT/mTOR pathway (3.9%). Commonest pattern seen was hypersensitivity pneumonitis (33.3%), followed by non-specific interstitial pneumonia (30%) and cryptogenic organising pneumonia (26.7%). A higher DILD score (OR 1.47, 95% CI: 1.19-1.81, p <0.001) and the pattern of DILD (OR 5.83 for acute interstitial pneumonia, 95% CI: 0.38-90.26, p=0.002) were significantly associated with a higher CTCAE grading. The only predictive factor for an improvement in DILD was an interruption of treatment (OR 0.05, 95% CI: 0.01-0.35, p=0.01).

Conclusion: DILD in early phase clinical trials is a toxicity of variable onset, with diverse clinical and radiological findings. Radiological findings precede clinical symptoms. The extent of the affected lung parenchyma, scored by the RMH DILD score, correlates with clinical presentation. Most events are low grade, and improve with treatment interruption which should be considered early.

Translational Relevance (135 words)

Multiple novel agents are currently evaluated in early phase clinical trials with little information about the risks of drug induced interstitial lung disease (DILD) and how best to safely manage this clinically. This study in a dedicated early phase trials unit details the radiological patterns of DILD seen across a broad range of novel targeted therapies over a 10year period, and correlates them with clinical outcomes. The RMH DILD score provides a means to objectively assess extent of affected lung parenchyma, which can be used to guide clinical decision making. Early treatment interruption improves outcomes and should be proactively considered. With the increasing number of complex combinations of novel agents being tested, this study provides a benchmark for the development of a well-defined algorithm for the management of DILD in the early phase clinical setting.

Introduction

Drug induced interstitial lung disease (DILD), also known as pneumonitis, is a potentially life-threatening complication of anti-cancer treatment (1-4). The risk of DILD most often only becomes apparent after marketing authorisation of new treatments and varies from up to 3% for tyrosine kinase inhibitors used in lung cancer, approximately 10% for bleomycin and up to 30% for the mammalian target of rapamycin (mTOR) inhibitors (4-7). Given the range of novel agents in early phase clinical testing, where little information about potential toxicities is available, awareness and early recognition of DILD is essential to protect patients from serious harm. The exact pathogenesis of DILD is still unknown; possible mechanisms include direct damage to the alveolar structures caused by the anti-cancer drug or immunologic responses to treatment. The latter is supported when lymphocytosis is present in bronchoalveolar lavage fluid (3,5).

DILD can present with different radiological patterns which can be categorized according to the American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonias and related disorders (8). The commonly noted radiological patterns for drug related pneumonitis include non-specific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), hypersensitivity pneumonitis (HP) and unclassifiable interstitial pneumonias (8-10). These radiological patterns correlate with typical histopathologic features. NSIP, characterised by lower lobe ground-glass opacities and marked traction bronchiectasis on computed tomography (CT) scan, shows alveolar thickening with preserved alveolar architecture on histology. Peripheral band-like consolidations and air bronchograms are CT features of COP with a histological picture of organising pneumonia. AIP is typified by bilateral patchy ground-glass opacities on CT and shows diffuse alveolar damage on histopathology, which resembles the histologic pattern found in adult respiratory distress syndrome (ARDS). CT

findings of HP include centrilobular nodules, mosaic air trapping and upper lobe distribution with poorly formed granulomas on histology (8,11).

At present, DILD is graded by the Common Terminology Criteria for Adverse Events (CTCAE) by clinical symptoms into five categories, ranging from being asymptomatic with solely radiological changes to acute respiratory impairment and death (12). The goal of this study was to correlate clinical and CT parameters of DILD in patients participating on early phase trials in a dedicated experimental trials unit.

Patients and methods

Patients

All consecutive stage IV cancer patients enrolled on phase I experimental clinical trials from 2007 to 2017 at the Drug Development Unit of the Royal Marsden Hospital (RMH) were identified and reviewed retrospectively. All trials were conducted in accordance with Good Clinical Practice guidelines and the ethical principles outlined in the Declaration of Helsinki. All patients provided informed written consent to each specific trial. Approval for this retrospective study was obtained from the Institutional Clinical Research Committee.

Eligible patients received at least one cycle of the investigational medicinal product (IMP). No patients had active pre-existing ILD at time of enrolment onto trial. Patients were excluded if longitudinal chest radiological imaging subsequent to first abnormal imaging revealed unequivocal progressive disease rather than DILD (eg lymphangitis) or alternative definitive pulmonary pathology (eg pulmonary embolism, pulmonary effusions, infection) (Figure 1A).

Methods

For all patients, demographic data and investigational treatment were recorded. In patients with DILD, the following detailed data were collected: demographics, clinical features of DILD, investigations undertaken, action taken with study medication and treatment of DILD. Clinical symptoms were attributed to DILD by treating investigators as documented in the patients' electronic health records. Clinical symptoms were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 retrospectively, as pneumonitis was not an original adverse event term before May 2009 (CTCAE version 4.0) but did not differ in grading since then (12).

Longitudinal analyses of all imaging of the patients where DILD was the predominant diagnosis was undertaken by an experienced radiologist (NT, 11 years clinical trials

experience) with classification of the CT patterns of interstitial lung disease according to the ATS/ERS criteria as previously published by Nishino et al. (8,13,14). The CT grading of DILD was undertaken by the radiologist who scored each lobe with zero, one or two points depending on whether there was no abnormality, less or more than 50% of the lobe was affected. This was termed the RMH DILD score (Figure 1B). With a possible maximum of five affected lung lobes plus lingula, the highest possible RMH DILD score consisted of 12 points (Figure 1B). If a lobe could not be assessed due to cancer involvement, this lobe was not counted and the score was calculated as a percentage of 12 points (eg in a patient with a collapsed lobe the highest possible score would be ten. In case of 5 points for pneumonitis this would be 50% of assessable lung and therefore the RMH DILD score was 6).

All patients who developed DILD had at least one follow-up CT within four weeks. All patients who were retreated with IMP underwent a second scan within four weeks after re-initiation of IMP. Radiological outcomes were classified as completely resolved, improved, stable or worsened based on the follow-up RMH DILD score. DILD was classified as unchanged if both scans showed the same score. DILD was considered to have improved if the follow-up score was lower than the initial score and to have resolved in case of a score of zero.

Figure 1

Statistical analysis

The primary endpoint was change in the radiological RMH DILD scores. The RMH DILD score and CTCAE grading were analysed using the Jonckheere-Terpstra test.

Associations between baseline characteristics and continuous variables were analysed using the Chi square test and Wilcoxon rank sum test. Ordered logistic regression analyses were used to examine the association between therapy given, action taken with respect to IMP and outcome. Data were analysed using Stata, V15.0.

Results

Incidence of pneumonitis

From January 2007 until December 2017, 2499 patients were enrolled onto experimental Phase I clinical trials in the Drug Development Unit at the Royal Marsden NHS Hospital and are included in this retrospective analysis. Baseline characteristics are displayed in Table 1. Median time of follow-up was 449 days with a wide range (range: 44 – 2293 days).

Of these, 97 patients with evolving abnormal lung imaging were analysed in more detail. Thirty-seven of these patients had a clear alternative competing cause for the CT findings and were excluded from the final analyses (CONSORT diagram, Figure 1A). 60 patients had imaging findings suggesting predominant DILD and are included in this report (Figure 1A).

The overall incidence of DILD was 2.4% (60 out of 2499; 95%CI: 0.018 – 0.031). There was no significant difference in the incidence of DILD between male and female patients (Incidence Rate Ratio (IRR)=0.82; 95% CI: 0.46-1.42; p=0.23). With respect to tumour type, the highest frequency of DILD was seen among patients with breast cancers (5.7%) followed by lung cancer (3.8%) and patients with gynaecological tumours (3.6%) (Supplementary Table 1). DILD occurred irrespective of the presence or absence of lung metastases (IRR=0.92; 95%CI 0.53-1.59; p=0.37), pre-existing respiratory conditions (IRR= 0.62; 95%CI: 0.32–1.32; p=0.08) or performance status (IRR=1.01; 95% CI: 0.56-1.76; p=0.49). Smoking history was not well documented across the whole cohort, but was identified for all

the patients who developed DILD. Fifty percent in this cohort were never-smokers (Supplementary Table 1). We identified 15 patients from the pneumonitis cohort who had prior chest irradiation, but there was no correlation between the sites of prior irradiation and location of DILD radiological changes in any of these patients.

Table 1

Clinical features

The median time to DILD was 63 days with a wide range (range from 14 to 336 days) in the overall cohort. Four cases occurred more than 6 months after the start of IMP. DILD is currently graded by CTCAE according to severity of clinical symptoms (Supplementary Table 2). In our study, importantly 27 patients (45%) were clinically *asymptomatic* at time of initial radiological abnormality (CTCAE Grade 1) (Supplementary Table 2); 19 patients (31.7%) experienced Grade 2 symptoms, 12 patients (20%) experienced Grade 3 symptoms and 2 patients (3.3%) had Grade 4 symptoms at time of initial radiological abnormality. The most frequent presenting symptoms of DILD were dyspnoea (45%), dry cough (23%) and fever (12%). Productive cough (3%) and chest pain (0%) were less common (Figure 1A).

Critically, 60% of those who were initially asymptomatic but continued dosing with IMP went on to develop symptoms.

Computed Tomography (CT) characteristics of DILD

CT patterns of DILD were classified as per the ATS/ERS classification. Hypersensitivity pneumonitis (HP) was most common (33.3%) followed by non-specific interstitial pneumonia

(NSIP, 30%) and cryptogenic organising pneumonia (COP, 26.7%) (Supplementary Table 2). CT patterns were consistent throughout the patient's clinical course in all cases. The different CT patterns of DILD showed significant associations with the severity of clinical symptoms as per CTCAE grading. Patients who developed radiological signs of AIP were significantly more symptomatic (higher CTCAE grade) than patients who presented with HP or COP ($p=0.002$, Table 2, Supplementary Figure 1A).

Importantly, a higher RMH DILD score predicted a higher CTCAE grade of DILD symptoms ($p<0.001$) (Supplementary Figure 1B, Table 2) and was statistically significant for the HP and COP subgroups ($p=0.033$ and $p=0.016$ respectively; Table 2) with a trend towards a worse clinical presentation with a higher RMH DILD score for the NSIP radiological pattern ($p=0.065$).

Pulmonary function tests (PFTs) were only undertaken in a minority of our patients (n=12), not enough for statistical analysis, but they showed a reduction up to 20% of diffusing capacity in asymptomatic patients with DILD.

Table 2

Diagnostic Conundrum of DILD

DILD is diagnosed on the basis of clinical, physiological and radiological CT findings consistent with pneumonitis; a temporal relationship between drug exposure and the onset of symptoms; and the exclusion of other contributing causes.

Microbiological testing was undertaken in all of our patients, most commonly in the form of sputum cultures, and blood or urine samples for PCR. These tests were negative in the

majority of patients. Superimposed infection was seen in 3 patients where radiological imaging clearly showed evolution of changes with infective changes developing subsequent to the initial DILD – one patient with Haemophilus influenza pneumonia, one patient with pneumococcal pneumonia, and one with metapneumovirus and Morganella infection.

Diagnostic bronchoscopy was also undertaken in eleven patients (18.3%). These were performed in either patients with severe symptoms (CTCAE Grade 3 or worse) and in patients with dramatic radiological findings and a high RMH DILD score. The main finding from bronchoalveolar lavages was lymphocytosis (n=8) with occasional pseudogranulomatous cellular aggregates. Two additional patients also had samples weakly positive results for pneumocystis jirovecii with unclear clinical significance – though both were treated with cotrimoxazole.

Patterns of DILD across different novel drug classes

DILD was seen across all novel drug classes investigated. The highest frequency of DILD was seen among patients receiving drug conjugates (7.4%) (Figure 2A). In patients who received small molecule targeted agents, DILD occurred with a frequency of 2.3% overall; most commonly in patients treated with novel agents targeting the PI3K/AKT/mTOR pathway (3.9%), followed by epigenetic agents (3.5%) and DNA repair defect inhibitors (1.3%) (Figure 2A).

The main DILD pattern induced by drug conjugates was COP (91.7%) and this occurred with a later onset (median time to onset 74 days) compared to other drug classes (Figure 2A and 2B). Drugs that inhibited the PI3K/AKT/mTOR pathways caused mainly DILD with a hypersensitivity and non-specific interstitial pneumonitis pattern (45.8% and 41.7%) but notably also caused two cases of AIP. No specific pattern of DILD was seen in patients

treated with DDR agents with one case each of HP, AIP, unclassifiable DILD and two cases of NSIP identified (Figure 2A). Over this time period, we did not see any cases of DILD in patients receiving checkpoint inhibitors but it must be noted that the overall number of patients receiving immunotherapy on early phase trials over this time period was very small.

Figure 2

Management of DILD

Out of the 60 cases with a radiological diagnosis of DILD, 7 patients (11.7%) continued on trial, 14 (23.3%) had a break from treatment and 25 participants (41.7%) permanently discontinued treatment due to symptoms of DILD. Fourteen patients had both radiological signs of DILD and disease progression and discontinued treatment. DILD was treated with steroids in 29 cases (48.3%) and antibiotics were given to 28 participants (46.7%). Neither treatment with steroids nor use of antibiotics had a significant influence on DILD outcome (p=0.23; p=0.99; Table 3). As concomitant use of steroids was often prohibited on early phase trials, only one patient received steroids while continuing with IMP treatment. All other patients only commenced steroids after interruption of IMP. Critically, continuation of treatment with IMP resulted in worsening of clinical symptoms in 42.9% of cases and worsening of DILD on imaging in 57.1% (Supplementary Figure 2). The only predictive factor for an improvement of DILD was an interruption of treatment (p=0.01) and in the majority of patients this occurred fairly rapidly over 7-10 days.

DILD improved or resolved in 63% of cases (38/60) as early as the first follow up scan (average time to follow-up scan 24 days). Fourteen participants who showed clinical and radiological improvement of DILD were retreated with IMP (temporarily discontinued) with

no recurrence of symptoms or radiological changes in 11 of these 14 patients (78.5%). Radiologically, no specific pattern of DILD was more likely or less likely to predict an improvement on the follow-up scan (p=0.27, Table 3). Similarly, the RMH DILD score on the initial scan did not predict a resolution or improvement of DILD on the follow-up scan (p=0.65).

Four patients worsened during treatment of DILD. All four had imaging with RMH DILD scores ≥6 indicating at least half of their lung volumes were affected. DILD was confirmed to be the cause of death in one patient who had an initial RMH DILD score of 5 on a routine progress scan, and was asymptomatic with an excellent partial response to therapy and so was continued on therapy. This patient then developed symptomatic DILD two weeks later with a worsening RMH DILD score of 8, deteriorated and died (Supplementary Figure 2). Three other patients with radiological DILD (all had RMH DILD scores >9) deteriorated clinically with superimposed secondary bronchial infection (two patients) and aspiration pneumonia (1 patient) which was ultimately fatal.

Table 3

Discussion

We describe the first large series of drug induced lung disease (DILD) in patients treated on early phase clinical trials of novel agents in a single centre dedicated drug development unit and comprehensively characterize the clinical, radiological findings and management of this toxicity. Any grade DILD developed in 2.4% of patients, and grade 3 or higher DILD developed in 0.6%. This is higher than the rates described in an earlier smaller study by Yonemori (7) and likely reflective of not only the breath and types of drugs tested in our unit,

but our more thorough inclusion of radiological asymptomatic DILD as well as clinical pneumonitis.

In our cohort, 55% of patients with DILD were symptomatic at presentation, but importantly 45% of cases were identified incidentally by imaging in asymptomatic patients. The median time to onset of DILD across all patients in our study was 1.5-2.5 months, but there also were patients who developed DILD much later in their treatment journey. While we cannot completely exclude the contribution of any concomitant medication, this was very carefully excluded by the treating investigator and the specialist respiratory consult; and also in the majority of cases improved with dechallenge – strongly suggesting that this was IMP-induced. The phenomenon of late onset DILD may be due to a cumulative effect of the novel agent (15,16), and the early identification of these subtle safety signals in the early phase setting would allow institution of rigorous risk mitigation in subsequent phases of clinical testing. There was no correlation between sites of prior irradiation and location of DILD. However, due to the retrospective design of this study, only an abbreviated medical history was collected from the patients who did not experience DILD and as such the data is not available for the whole cohort.

Several scoring systems exist for grading interstitial lung disease in systemic sclerosis patients that are able to predict PFT abnormalities, and therefore symptoms (17-19). Most of these scores evaluate the extent of abnormal lung changes on higher resolution computed tomography (HRCT) (19,20). In our retrospective analysis, we calculated a composite RMH DILD score by estimating the affected volume of lung in each lobe and show that the radiological pattern of DILD as defined by the ATS/ERS classification correlates with severity of DILD as has been shown before (11). Importantly, we also show that this score correlates with the clinical toxicity grades assessed by CTCAE and may have utility as a guide for clinical decision making. In patients with a high RMH DILD score (≥6), only one

patient was continued on IMP treatment – and this patient went on to develop symptoms and eventually discontinued IMP. Patients who had treatment interruption improved clinically in the most part, with the exception of the two patients who developed superimposed infection, possibly due to prolonged immunosuppression and the third patient who aspirated. Conversely, in our patients with a low RMH DILD score (<6), clinicians elected to continue IMP dosing in six patients (22.2%). Three of these patients (50%) had subsequent clinical deterioration including the patient described above with the Grade 5 DILD (Supplementary Figure 2). In patients with a low RMH DILD score (<6), in whom the causative agent was temporarily stopped (n=8) until the score improved, 75% of these (6/8 patients) were able to continue therapy without re-occurrence of DILD.

Given steroids were prohibited on the majority of our early phase trial protocols, these were only started very judiciously after the interruption of IMP. It may therefore be the scenario that patients with more severe DILD were more likely to have been empirically treated with steroids in addition of IMP discontinuation. As such we do not intend to make any conclusions regarding use of corticosteroids but highlight again the notable fact that nearly all cases of DILD improved with *interruption of drug therapy* and so clinicians should consider both of these actions in parallel.

We therefore propose a guideline for the vigilant monitoring and management of DILD due to novel therapeutic agents using the algorithm in Figure 3. Asymptomatic patients with a low RMH DILD score could be reasonably monitored with early clinical and CT thorax follow-up (10-14 days) for resolution/improvement. If symptoms arise or worsening radiological findings, then drug interruption should be considered together with steroids as clinically indicated (21). Asymptomatic patients with a high RMH DILD score or symptomatic patients should have drug interruption in addition to corticosteroids and managed together with a specialist respiratory team with continued close clinical and radiological follow-up. Patients

whose symptoms evolve despite drug holding and immunosuppression may be at high risk of super-imposed infection and will benefit from pro-active multi-disciplinary team management with consideration towards early bronchoscopy, to exclude infection, where appropriate (Figure 3).

Due to the rather small number of patients treated with immunotherapy over the duration of our study (n=57), we did not see any immune-mediated pneumonitis, and readers are referred to other reports of immune-mediated pneumonitis (22-29) for a detailed analyses of the diagnostic and therapeutic challenges of this specific immune-adverse event. The highest incidence of DILD in our cohort was seen among patients treated with drug conjugates and specifically for this drug class, the DILD pattern was predominantly COP (92%) with a delayed median onset of DILD, suggesting that some of the toxicity may be cumulative, and as such warrants closer monitoring with continuation of therapy. For agents modulating the PI3K/AKT/mTOR pathways, we found a much more varied CT pattern of DILD contrary to previously reported in the literature (6,13,14,30-33), and a variability in timing of onset with one patient only developing radiological changes after 27 months of treatment. We also show a low incidence of DILD with targeted inhibitors of DNA repair pathways, consistent with historical data with DNA damaging chemotherapy (34,35) and PARP inhibitors though with variable patterns seen (36). Both these scenarios highlight the heterogeneity of clinical presentation and timing of onset requiring constant vigilance and proactive management. DILD remains a diagnosis of exclusion and requires iterative consideration of competing diagnoses, including infection and malignant lung infiltration. (37,38).

Figure 3

Conclusion

In summary, DILD is an uncommon but potential serious toxicity which may develop at any time over the course of a patients' treatment with many of patients (45% in our series) being asymptomatic at the time of first radiological manifestation. The RMH DILD score may have utility in prognostication of asymptomatic radiological changes and guiding treatment decisions. Further research is warranted to develop better understanding of the pathogenesis of DILD and identify better prognostic markers that can drive clinical decision making.

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Table 1. Baseline characteristics

	No DILD (*N*=2.439)		**DILD (*N*=60)**		***P*-value[1]**	**Total (*N*=2.499)**	
	N	**%**	***N***	**%**		***N***	**%**
Drug Class							
Molecular targeted agents	2025	83.0	47	78.3	<0.001	2072	83.0
- PI3K/AKT/mTOR	- 591	- 24.2	- 24	- 40.0		- 615	- 24.6
- DDR	- 374	- 15.3	- 5	- 8.3		- 379	- 15.2
- Epigenetic	- 110	- 4.5	- 4	- 6.7		- 114	- 4.6
- Others	- 950	- 39.0	- 14	- 23.3		- 964	- 38.6
Drug conjugates	151	6.2	12	20.0		163	6.5
Immunotherapy	113	4.7	0	0.0		113	4.6
Hormonal therapy	74	3.0	0	0.0		74	2.9
Cytotoxic agents	27	1.1	0	0.0		27	1.0
Other	49	2.0	1	1.7		50	2.0
Gender							
Male	1134	46.5	21	35.0	0.08	1155	46.2
Female	1305	53.5	39	65.0		1344	53.8
Primary Tumour Site							
Breast	214	8.8	13	21.7	0.002	227	9.0
Lung	200	8.2	8	13.3		208	8.3
GI	709	29.1	10	16.7		719	28.8
GU	294	12.1	4	6.7		298	11.9
Gynae	449	18.4	17	28.3		466	18.6
Skin	100	4.1	0	0.0		100	4.0
Other	473	19.4	8	13.3		481	19.2
Lung Mets							
No	1226	50.3	34	56.7	0.33	1260	50.5
Yes	1210	49.7	26	43.3		1236	49.5
Smoking							
Never	835	34.2	30	50.0	<0.001	865	34.6
Former	528	21.6	18	30.0		546	21.8
Current	153	6.3	4	6.7		157	6.3
Unknown	923	37.8	8	13.3		931	37.2
Respiratory Condition							
No	2115	87.0	49	81.7	0.22	2164	86.9
Yes	315	13.0	11	18.3		326	13.1
Performance Status							
0	619	27.5	20	33.3	0.67	639	27.6
1	1612	71.5	40	66.7		1652	71.4
≥2	23	1.0	0	0.0		20	1.0
	Median	**IQR**	**Median**	**IQR**	***P*-value[2]**	**Median**	**IQR**
Age (years)	59.6	49.4-66.6	59.0	49.9-68.3	0.65	59.6	49.5-66.6

[1] Chi[2] test
[2] Rank-sum test
DILD, drug-induced interstitial lung disease; GI, gastrointestinal; GU, genitourinary.

Table 2. Logistic regression model for the association of DILD pattern, RMH DILD score and severity of DILD as per CTCAE grading

Characteristics	**Univariable OR**	**95% CI**	***P*-value**	**Multivariable OR**	**95% CI**	***P*-value**
DILD pattern						
Non-specific interstitial pneumonia (NSIP)	1.00 (ref.)	-	0.02	1.00	-	0.002
Cryptogenic organizing pneumonia (COP)	0.57	0.16-2.07		0.56	0.15-2.17	
Acute interstitial pneumonia (AIP)	24.71	1.89-324.46		5.83	0.38-90.26	
Hypersensitivity pneumonitis (HP)	0.21	0.06-0.78		0.04	0.01-0.22	
Unclassifiable	NA	NA	NA	NA	NA	NA
RMH DILD score	1.22	1.06-1.41	0.005	1.47	1.19-1.81	<0.001

DILD, drug-induced interstitial lung disease; OR, odds ratio; NA, not applicable; RMH, Royal Marsden Hospital; CTCAE, Common Terminology Criteria for Adverse Events; OR>1 indicates worse adverse event.

Table 3. Logistic regression model for the association of DILD pattern, RMH DILD score, intervention and DILD outcome (change of DILD on follow-up scan)

Characteristics	**Univariable OR**	**95% CI**	***P*-value**
Pneumonitis Type			
Non-specific interstitial pneumonia (NSIP)	1.00 (ref.)	-	0. 27
Cryptogenic organizing pneumonia (COP)	3.86	1.14-13.05	
Acute interstitial pneumonia (AIP)	3.49	0.38-32.25	
Hypersensitivity pneumonitis (HP)	1.16	0.33-4.06	
Unclassifiable	6.09	0.30-125.64	
RMH DILD score at onset of DILD	0.97	0.85-1.11	0.65
Steroid Use	0.55	0.21-1.44	0.23
Antibiotic Use	1.00	0.39-2.54	0.99
Oxygen treatment	0.73	0.23-2.30	0.59
IMP Action Taken			
Continued in trial	1.00	-	0.01
Temporarily discontinued	0.05	0.01-0.35	
Permanently discontinued	0.21	0.04-1.20	
Progressed (discontinued)	0.10	0.01-0.63	

DILD, drug-induced interstitial lung disease; OR, odds ratio; RMH, Royal Marsden Hospital; IMP, investigational medicinal product; OR>1 indicates worse outcome.

Figure 1A

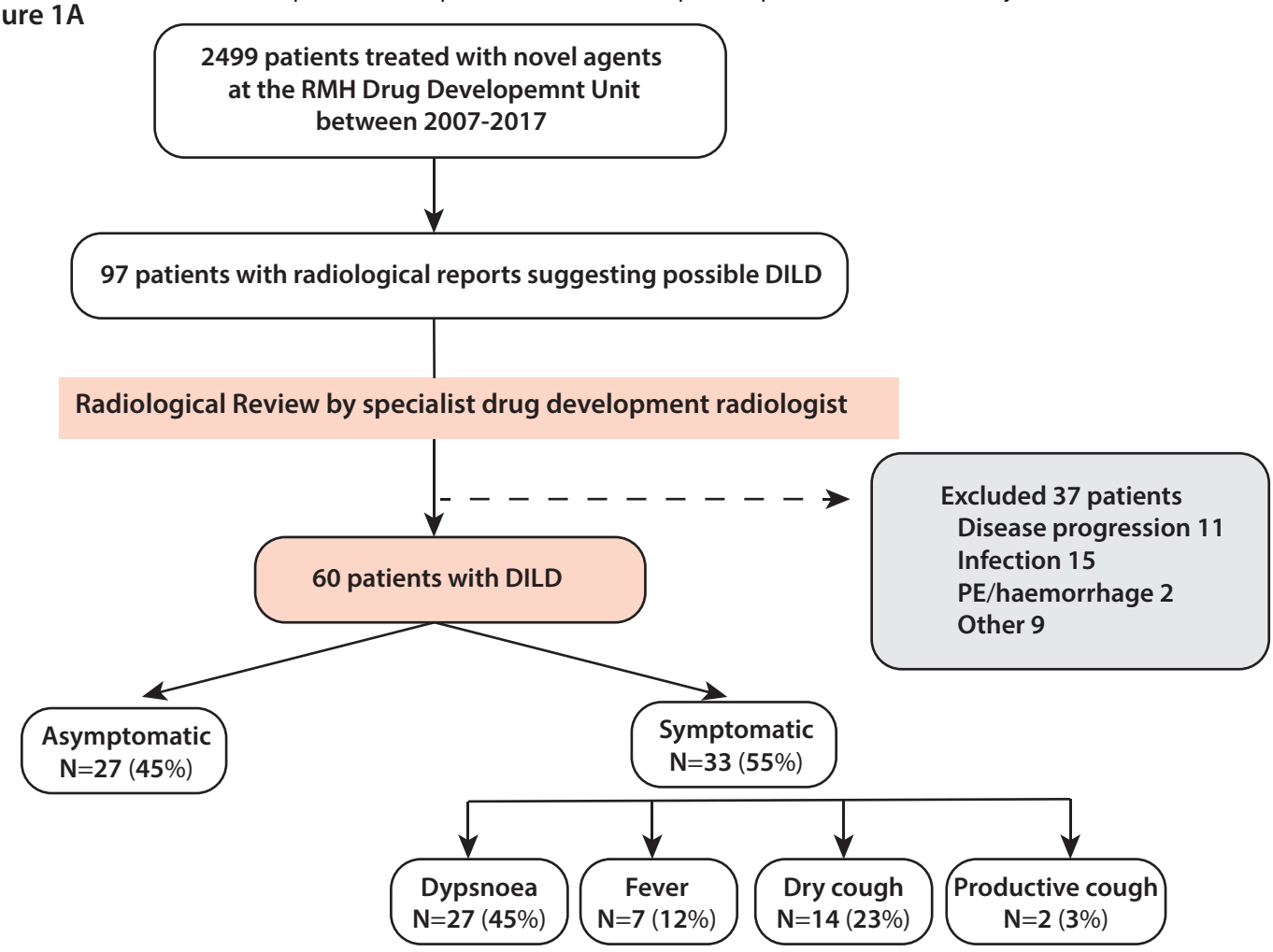


Figure 1B

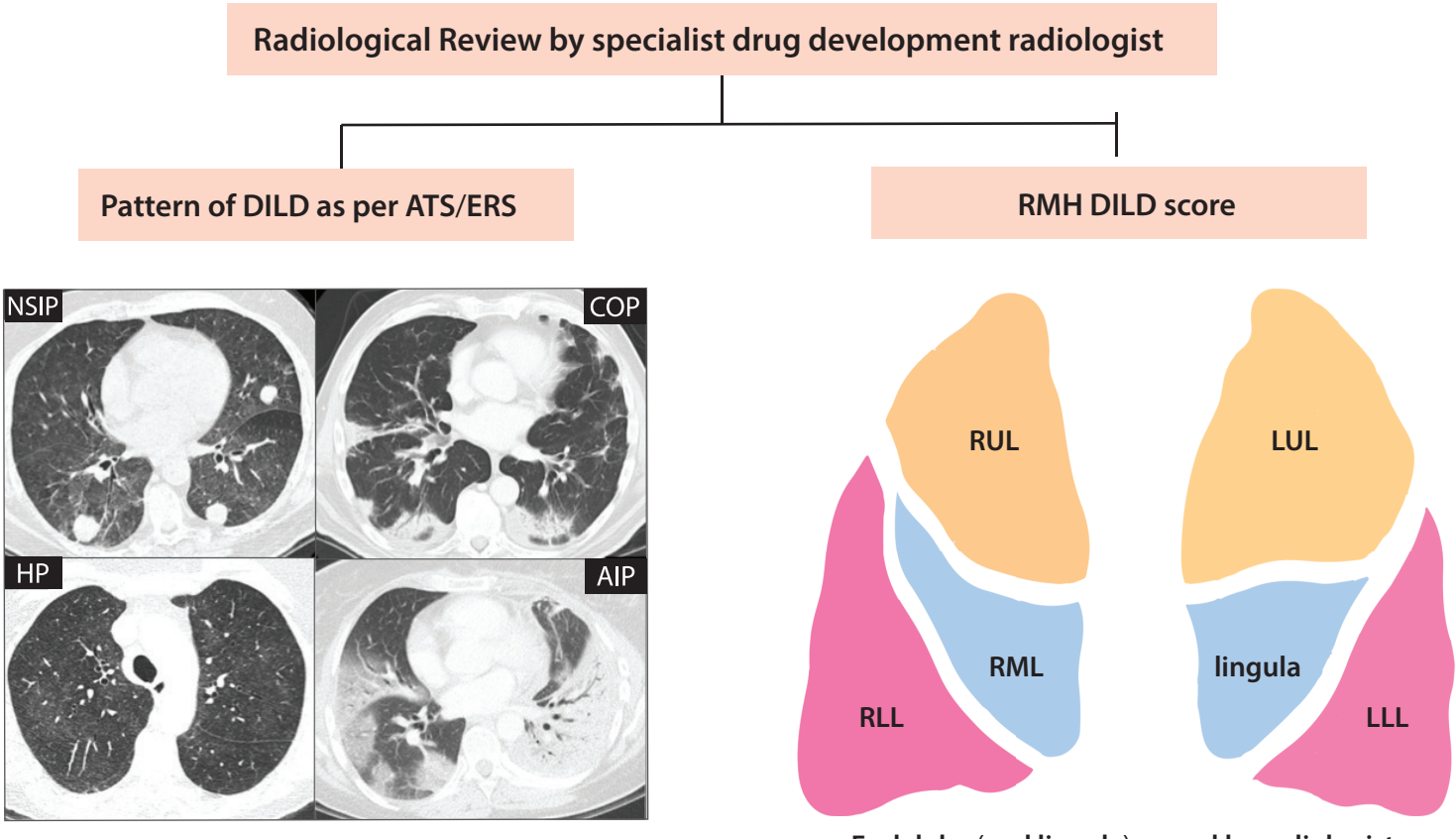


Figure 2a

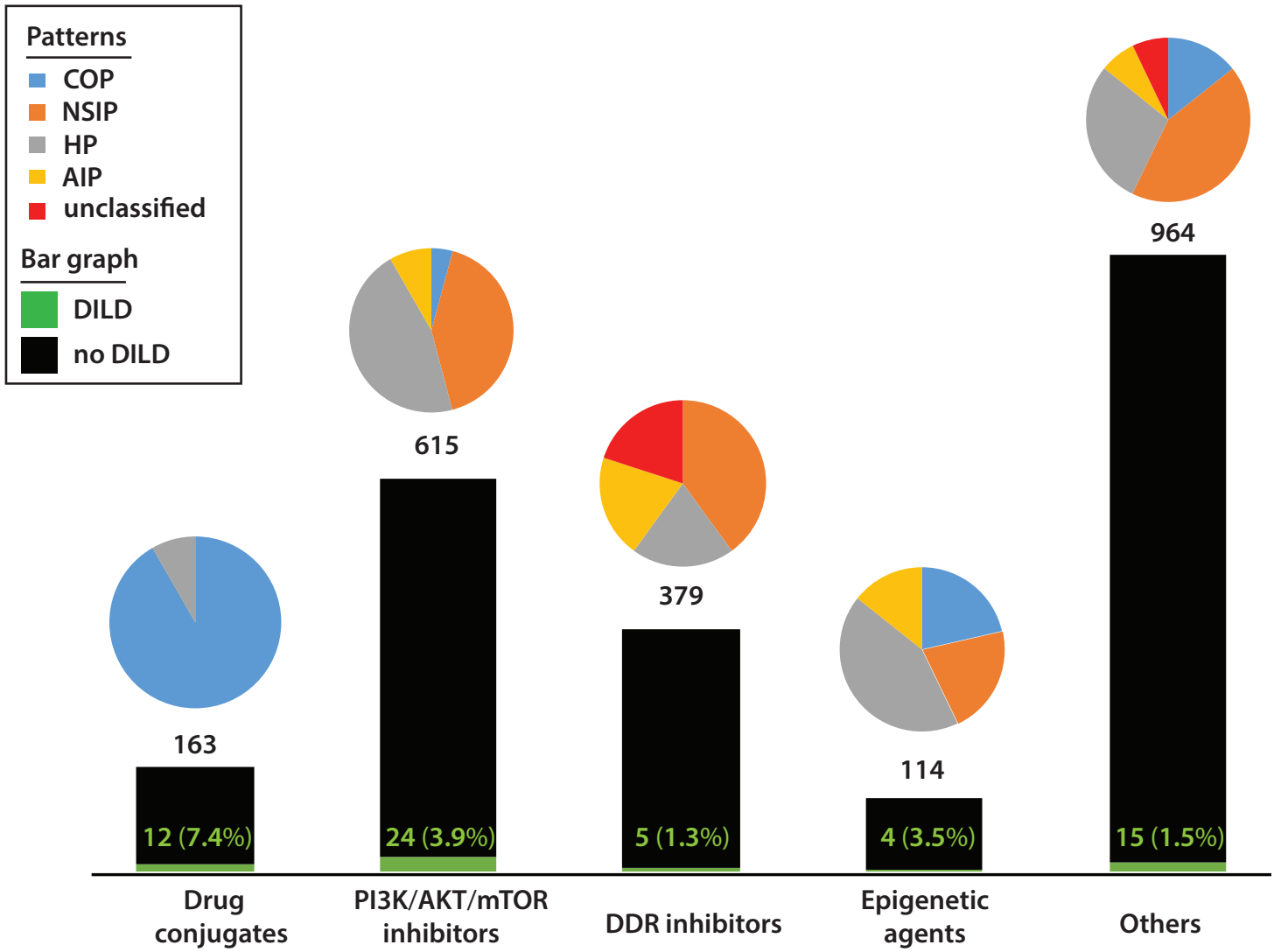


Figure 2b

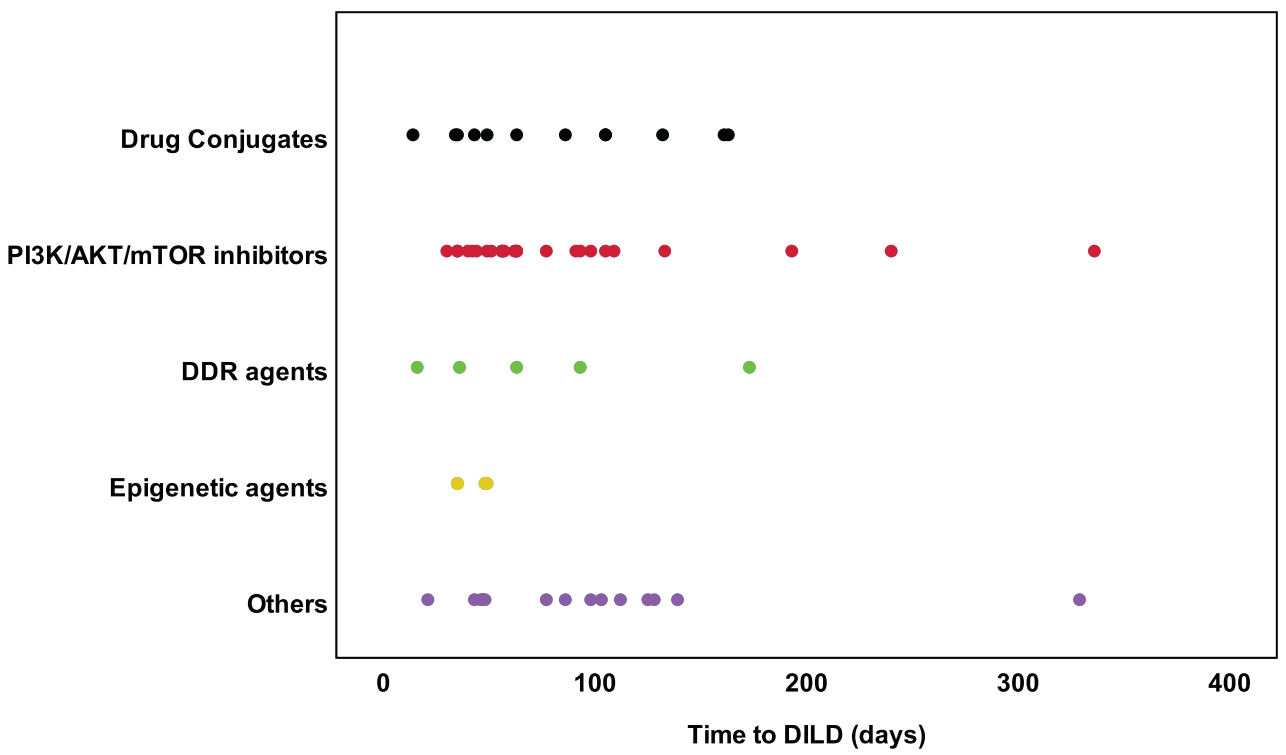
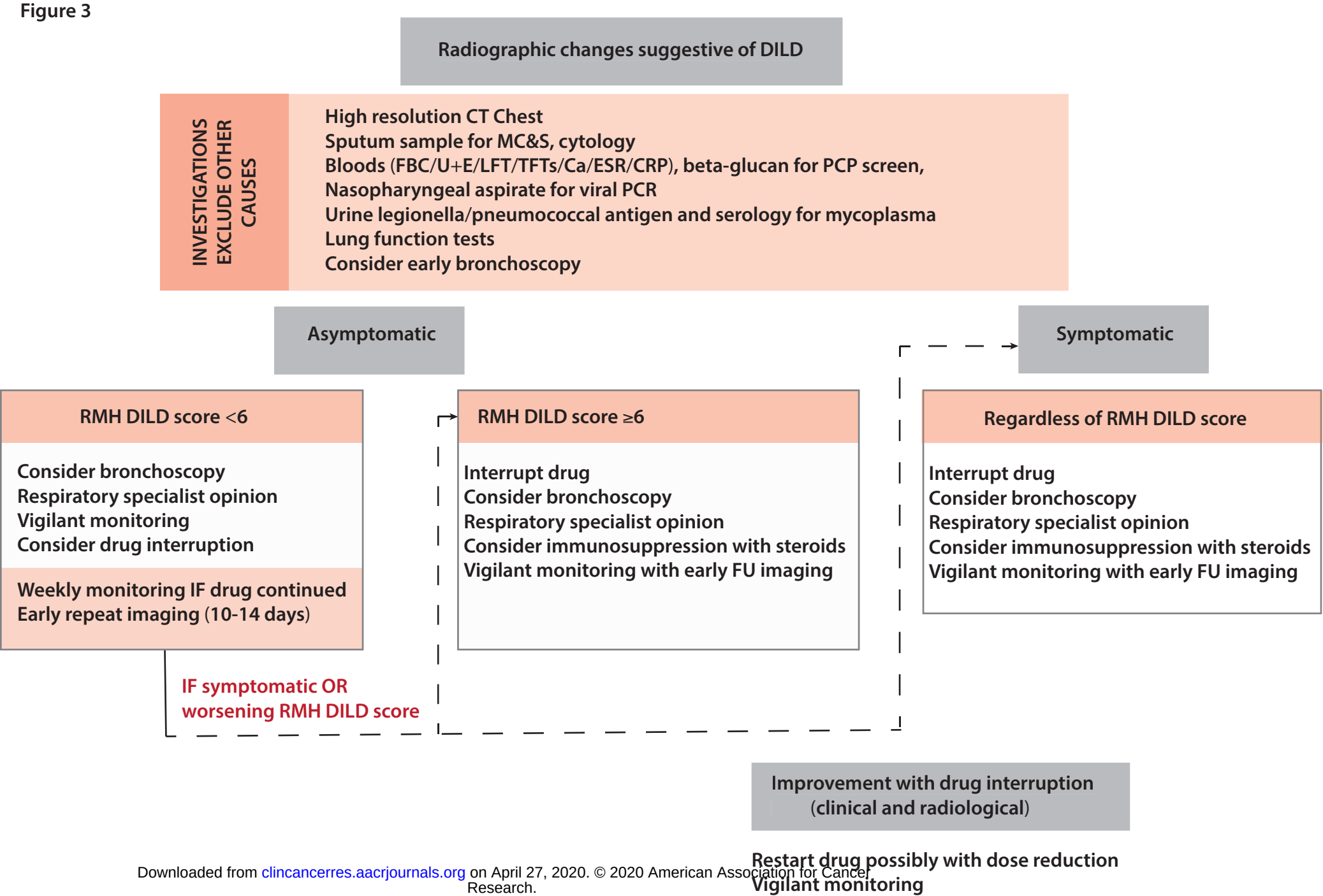


Figure 3



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