TOO ULTRA-RARE FOR CARE?

ORPHAN DRUG AVAILABILITY FOR RESPIRATORY DISEASES: A SYSTEMATIC REVIEW

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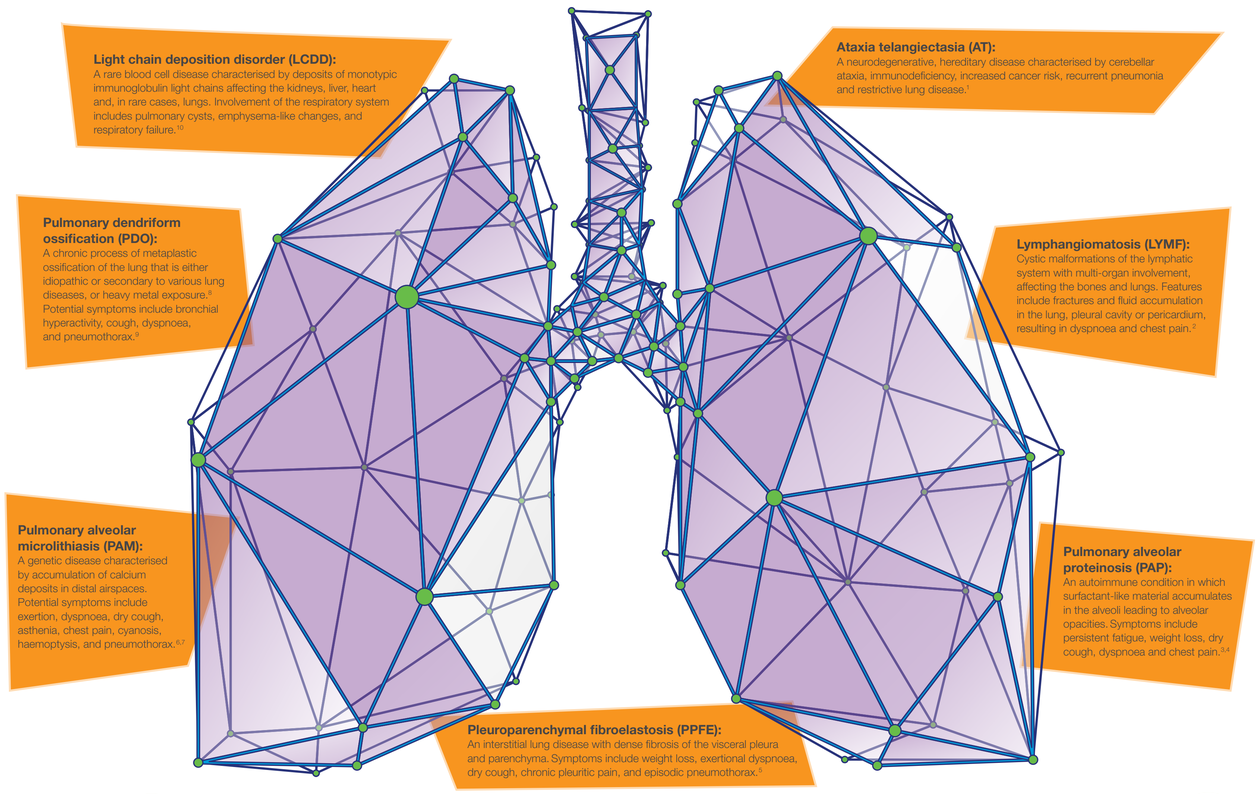


Objective

- To explore current and potential availability of evidence-supported treatments for index ultra-rare respiratory diseases.

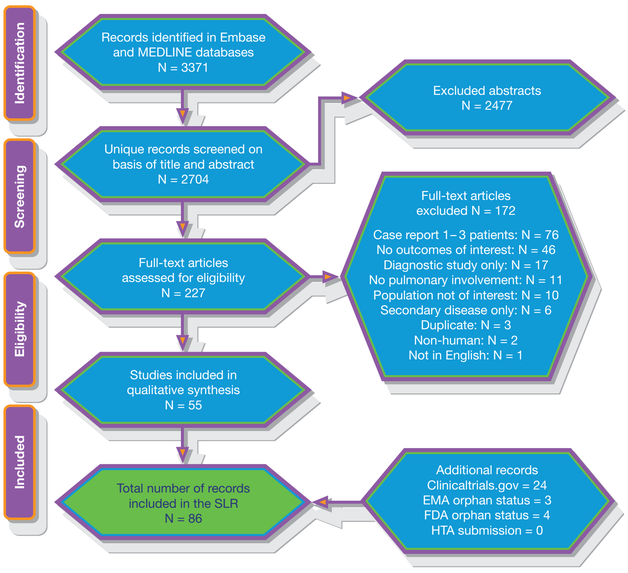
Background

- By definition, rare diseases are very uncommon; they affect, for example, <1 in 2,000 patients in the European Union (EU).[11] However, collectively these conditions represent a major burden to society as well as the individuals concerned; estimates suggest that up to 30 to 40 million patients in the EU have them. In one to two million cases, this is a respiratory disease.[12]
- Much less visible are those with an ultra-rare disease, that is, one generally considered in the EU to affect fewer than 1 in 50,000 people.[13]
- Patients with rare diseases face immense difficulties in accessing treatment.[4,14,15] These problems are greatly magnified for those with ultra-rare diseases, not least because, traditionally, the very small patient populations have made rigorous clinical trials of new therapies unfeasible or financially unviable.[16]
- However, increasingly, incentives have been established for manufacturers to develop drugs for rare and ultra-rare diseases, including the granting of orphan status[4,12,17] to medicines intended for the treatment of rare conditions.[11,18]
- We aimed to map whether, or to what extent, such initiatives were affecting the potential treatment landscape for patients with seven index ultra-rare respiratory disorders (described in figure above) that expert opinion has previously highlighted as involving particularly severe unmet needs for patients.[12]

Methods

- A multi-component systematic literature review (SLR) was undertaken (with searches in September 2019) to seek the following evidence of potential developments in the treatment landscape for each of the index diseases:
  - Details about the orphan-drug and regulatory approval status of any available treatments and about any currently experimental interventions on orpha.net, and the websites of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).
  - Reimbursement decisions of five health technology assessments (HTA) bodies (National Institute for Health and Care Excellence [NICE]; Scottish Medicines Consortium [SMC], Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG], Canadian Agency for Drugs and Technologies in Health [CADTH] and Pharmaceutical Benefits Advisory Committee [PBAC]).
  - Full-text studies or conference abstracts published since 2014 in English that are indexed in Embase and MEDLINE (via Ovid SP) reporting on children and adults receiving treatments for the underlying cause and/or clinical manifestations of disease.
  - Information on clinicaltrials.gov about studies investigating experimental/potential future treatments for the conditions.
- The findings were synthesised qualitatively and assessed for any trends in the current or potential availability of evidence-supported treatments for the conditions of interest.

Figure 1. SLR PRISMA flow chart



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Results

The landscape of evidence-supported treatments

- The database searches yielded 2704 unique records, of which 227 (10%) were reviewed at the full-text level. Ultimately, **55 studies** had assessed treatments for the conditions of interest and were included in the SLR (See Figure 1).

Table 1. The number of studies retrieved from the Embase and MEDLINE review

	AT	LCDD	LYMF	PAM	PAP	PDO	PPFE
SLR/MA	0	0	0	1	4	0	0
Open-label RCT	0	0	0	0	2	0	0
Other interventional	4	0	0	0	2	0	0
Prospective observational	0	0	0	0	2	0	0
Retrospective observational	0	1	1	2	33	0	3

Abbreviations: AT = Ataxia telangiectasia; LCDD = Light chain deposition disease; LYMF = Lymphangiomatosis; MA = Meta-analysis; PAM = Pulmonary alveolar microlithiasis; PAP = Pulmonary alveolar proteinosis; PDO = Pulmonary dendriform ossification; PPFE = Pleuroparenchymal fibroelastosis; RCT = Randomised controlled trial; SLR = Systematic literature review

- **76** of the 227 full texts were case reports involving only one to three patients, a design that did not allow definitive conclusions about the availability and use of treatment for patients with the diseases of interest. Therefore, these studies were not further considered in the review.
- Forty-three of the included studies were on PAP, four on AT, three on PPFE, three on PAM, one on LCDD and one on LYMF. No relevant studies were identified for PDO.
- The search of clinicaltrials.gov identified 24 studies (at various stages; see Table 2), 11 of which were in patients with PAP, six in AT, five in LCDD, one in LYMF, and one in PPFE. No studies were identified for PAM or PDO.

Table 2. Development, approval, and reimbursement of treatments

	AT	LCDD	LYMF	PAM	PAP	PDO	PPFE
Clinicaltrials.gov *[The number of studies retrieved from clinicaltrials.gov]*							
Completed	3	2	0	0	3	0	1
Active, not recruiting	0	2	1	0	3	0	0
Not yet recruiting	1	0	0	0	1	0	0
Recruiting	2	0	0	0	2	0	0
Enrolling by invitation	0	0	0	0	1	0	0
Terminated	0	1	0	0	1	0	0
Regulatory approval *[The number of treatments with regulatory approval for each disease]*							
EMA	2	0	0	0	1	0	0
FDA	2	0	0	0	2	0	0
Reimbursement decisions *[The number of reimbursement submissions for each disease]*							
NICE	0	0	0	0	0	0	0
SMC	0	0	0	0	0	0	0
CADTH	0	0	0	0	0	0	0
IQWiG	0	0	0	0	0	0	0
PBAC	0	0	0	0	0	0	0

Abbreviations: AT = Ataxia telangiectasia; CADTH = Canadian Agency for Drugs and Technologies in Health; EMA = European Medicines Agency; FDA = US Food and Drug Administration; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; LYMF = Lymphangiomatosis; NICE = National Institute for Health and Care Excellence; PAM = Pulmonary alveolar microlithiasis; PAP = Pulmonary alveolar proteinosis; PBAC = Pharmaceutical Benefits Advisory Committee; PDO = Pulmonary dendriform ossification; PPFE = Pleuroparenchymal fibroelastosis; SMC = Scottish Medicines Consortium

- Treatments for two of the seven ultra-rare diseases with respiratory manifestations (AT and PAP) had been awarded orphan status by the EMA and the FDA.
- Despite the number of completed or ongoing studies on and EMA/FDA approval of orphan drugs across the seven ultra-rare respiratory diseases, no reimbursement submissions are available.

PAP – the Odd Disease Out?

- Most of the identified evidence related to PAP assessed whole lung lavage (WLL) for the condition.
- The reason for the greater availability of evidence for PAP compared to the other six ultra-rare conditions are probably twofold:
  - WLL, which is currently considered the gold-standard treatment for PAP, involves the mechanical removal of surfactant material from the alveoli and may improve key respiratory clinical outcomes. Therefore, it is not surprising that a relatively large number of studies would be published on this treatment since its development.
  - The occurrence of autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF) – normally a key component in the surfactant-removal process – offers a targeted, immune-modulating treatment strategy[19-23] in PAP, with inhaled GM-CSF demonstrating some promising results.

Conclusions

- There is an obvious lack of proven and available treatments for ultra-rare respiratory diseases, and little evidence that the situation will improve substantially in coming years for the affected patients, despite incentives to research and commercialise interventions for these indications.
- For five of the conditions reviewed, there are no treatment options with designated orphan status. For the other two, designated orphan drugs and associated research reflect efforts to provide effective treatment options but have yet to result in therapies that are licensed or approved by HTA bodies.
- The needs of patients with ultra-rare respiratory diseases continue to be inadequately addressed by researchers, clinicians, manufacturers, and policymakers.