Granulomatous–lymphocytic interstitial lung disease: an international research prioritisation

To the Editor:

Granulomatous–lymphocytic interstitial lung disease (GLILD) has been defined as “a distinct clinico-radio-pathological ILD [interstitial lung disease] occurring in patients with CVID [common variable immunodeficiency disorders], associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded… usually seen in the context of multisystem granulomatous/inflammatory involvement” [1]. The immune and inflammatory complications of CVID such as GLILD are important and associated with reduced survival [2]. However, as a rare manifestation of a rare disease, the scientific understanding and evidence basis to inform effective diagnosis and management of GLILD [3] are limited. There are challenges with the definition of GLILD presented above and the terminology more widely of ILD in people with CVID, which requires further consensus. In this manuscript, we use the term GLILD to describe the heterogeneous ILD seen as part of multisystem immune dysregulation in a substantial minority of people with CVID. A recent international survey of clinicians found little uniformity in diagnostic and therapeutic interventions, identifying an urgent need for new evidence to support consensus guidance [4]. In 2019, the European Respiratory Society (ERS) established a Clinical Research Collaboration to address GLILD (eGLILDnet) [5]. eGLILDnet aims to promote the exchange of research ideas among clinicians and scientists in order to plan, conduct, evaluate and publish clinical and translational studies. Better evidence to diagnose and manage GLILD requires new multicentre research and to this end, we have conducted and here report the results of an international research prioritisation exercise in GLILD. This was a partnership between multiprofessional clinicians and people living with GLILD.

This research prioritisation exercise was based on methodology developed by the James Lind Alliance (JLA) but was not an official JLA process and did not include the final workshop stage (the final ranking was based on voting as described further below). We created an online survey using SurveyMonkey in nine European languages, open between 12 August and 14 September 2020. Dissemination of the survey was assisted by the ERS, the International Patient Organisation for Primary Immunodeficiencies (IPOPI) and the European Society for Immunodeficiencies (ESID). Clinicians were invited to provide the link to patients. The survey asked participants what questions they had about the diagnosis, treatment, follow-up and scientific understanding of GLILD. All responses were translated into English for processing.

Each individual response was separated (participants were allowed to submit more than one response in each category), given a unique number and grouped into six broad categories: diagnosis, treatment, follow-up, scientific understanding of GLILD, other aspects on GLILD and responses that were out of scope.

Next, within each category, questions and statements were grouped into themes, and a short summary was developed. The narrative summary was used to develop specific overarching questions and recommendations for development of consensus resources. Members of the eGLILDnet Steering Committee reviewed the responses and confirmed that all the original comments had been captured.

This process generated a list of seven suggestions for resource development and 27 research questions. From our knowledge of the literature, including a recent systematic review [3], none of the 27 questions had already been adequately addressed and, therefore, all 27 questions went forward to the final prioritisation.

Shareable abstract (@ERSpublications)
The first ever research prioritisation exercise in GLILD: this survey identified areas of interest in the diagnosis, treatment and management of GLILD, which can be used as a roadmap for future research [3nVuzti]


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In this final stage, respondents could vote for ≤10 of the 27 questions they most preferred to see answered. The questions were provided in both lay and technical language, again using SurveyMonkey. The survey was available in Dutch, English, German, Italian and Spanish (the surveys from the first round that generated the most frequent responses). Dissemination of the final survey was facilitated by ERS, ESID and IPOPI, together with a direct e-mail to respondents who had left contact details in the initial survey. The survey was open between 1 December 2020 and 20 January 2020. At closure, each question was ranked separately by the number of votes it received from 1) patients and carers, and 2) clinicians. A final joint list, with equal weight given to clinician and patients responses, was created by taking the average of the two ranks and ordering these.

In total, 252 people from 48 countries registered on the survey. 135 people from 33 countries left one or more questions or statements (the other 117 just left contact details). Of those leaving responses, 77 (57%) were female, 55 (41%) were male and the remainder did not respond or preferred not to say. 89 (66%) were aged 30–49 years and 39 (29%) were 50–69 years old, with fewer younger, older or preferring not to say. 23 (17%) were people affected by GLILD or carers, 41 (30%) were immunology physicians, 51 (38%) were respiratory physicians and four (3%) were allied health professionals. The five commonest countries were the UK (n=24), Spain (n=19), Germany (n=12), the Netherlands (n=12) and Italy (n=11), together accounting for 58% of respondents. There were 699 individual responses made, originally submitted in the Diagnosis (n=169), Treatment (n=187), Management (n=144), Science (n=128) and Other categories (n=70).

The 699 responses could be summarised as seven areas for resource development and 27 research questions that went forward to voting. The areas for resource development included suggestions to develop consensus diagnostic criteria for GLILD; consensus protocols for adults and children with GLILD that cover screening, diagnosis, treatment and follow-up; and to develop educational resources for patients and multiprofessional clinicians to help raise awareness of GLILD. There was also the suggestion to review the terminology of GLILD and ILD occurring in CVID.

Of the 269 people voting in the research prioritisation stage, 114 (42%) were female, 154 (57%) were male and the remaining participant left the question blank. 145 (54%) were aged 30–49 years and 101 (37%) were 50–69 years old, with fewer younger, older or preferring not to say. 47 (17%) were people affected by GLILD or carers, and 222 (83%) were clinicians: 53 (24% of clinicians) primarily worked in immunology whilst 169 (76% of clinicians) primarily worked in respiratory or internal medicine specialties. The five commonest countries were Italy (n=34), the UK (n=28), Spain (n=23), the Netherlands (n=12) and Switzerland (n=11), together accounting for 39% of respondents.

The results of the research prioritisation are reported in table 1, ordered by overall rank but also indicating rank by patients and clinicians separately. The number of votes cast for questions varied between 36 and 177. Because of the relative preponderance of respiratory clinicians over immunologists, we also analysed the data by first giving equal weight to respiratory and immunology preferences in the clinician group, then combining this with the patient rank. This analysis did not affect the top eight ranks (data not shown).

We have conducted and report the first ever research prioritisation exercise in GLILD. Importantly, our results give equal weight to the voice of clinicians and those affected by GLILD.

The three top ranked questions, addressing the role of corticosteroids and alternative regimens as first-line treatment in GLILD, would best be answered by a randomised trial of watchful waiting versus intervention in newly diagnosed patients with GLILD, with intervention randomised to corticosteroids or an alternative regime, and with weaning according to a pre-defined protocol. The eGLILDnet consortium will now work towards designing and conducting such a study. It is notable that questions directly affecting treatment decisions were prioritised over diagnostic and basic research. However, since all our questions received votes, all of these areas may still be considered relevant for further research.

In addition to prioritising research questions, the process generated seven areas for resource development. These included the need to revisit the definition and diagnostic criteria for ILD in CVID in general (and GLILD in particular), and tools to support research (such as standardised radiology reporting and a database), clinical practice (including diagnostic criteria and protocols for both adults and children), and educational resources for patients and clinicians. The eGLILDnet collaboration will work with partners to address these.

The strengths of our approach were the wide international engagement, and a prioritisation process giving equal weight in the final prioritisation list to patients and clinicians.
Develop a health-status questionnaire to assess burden in GLILD.

What is the outcome of lung transplantation for GLILD?

What is the value of thoracic MRI in the work-up of a patient with suspected GLILD?

Which epigenetic modifiers contribute to the manifestation of GLILD?

What is the value of blood or other biomarkers in assessing disease activity?

Which type of lung biopsy has the most favourable risk-benefit?

Do higher or lower dose corticosteroids have the best risk-benefit to induce remission in adults with GLILD?

Do corticosteroids or an alternative agent have the best risk-benefit to maintain remission in GLILD?

Is GLILD a pathogen-driven local manifestation of a systemic immune dysregulation?

What is the value of CT-PET in the work-up of a patient with suspected GLILD?

What is the value of BAL in the work-up of a patient with suspected GLILD?

Is immunosuppression for GLILD associated with increased risk of infection?

Are there specific risk factors in CVID for developing GLILD?

Are there specific pathological endotypes of GLILD with different natural history and treatment response?

What is the outcome of lung transplantation for GLILD?

Develop a discovery biomarker programme on blood and BAL to assist diagnosis and management of GLILD.

What is the benefit of a higher trough immunoglobulin replacement target in GLILD?

What is the value of a lung biopsy in the work-up of a patient with suspected GLILD?

What is the value of antibiotics such as piperacillin and tazobactam in treating GLILD?

What is the value of antifibrotic drugs such as pirfenidone and nintedanib in treating GLILD?

What is the optimal screening approach to detect incident cases of GLILD in people with CVID?

Are there specific genetic endotypes of GLILD with different natural history and treatment response?

Are there specific genetic endotypes of GLILD with different natural history and treatment response?

Do corticosteroids or an alternative agent have the best risk-benefit to maintain remission in GLILD?

What is the role of B-cells in the pathogenesis of GLILD?

Do corticosteroids or an alternative agent have the best risk-benefit to induce remission in adults with GLILD?

In newly diagnosed GLILD, is first-line treatment superior to watchful waiting?

Are there specific risk factors in CVID for developing GLILD?

What is the optimal screening approach to detect incident cases of GLILD in people with CVID?

Are there specific pathological endotypes of GLILD with different natural history and treatment responses?

What is the value of CT-PET in the work-up of a patient with suspected GLILD?

What is the value of blood or other biomarkers in the work-up of a patient with suspected GLILD?
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References


