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Early View

Research letter

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Granulomatous-Lymphocytic Interstitial Lung Disease: an international research prioritisation

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Introduction

Granulomatous-Lymphocytic Interstitial Lung Disease (GLILD) has been defined as '*a distinct clinico-radio-pathological interstitial lung disease occurring in patients with common variable immunodeficiency disorders (CVID), 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] is 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 multi-professional clinicians and people living with GLILD.

Method

This research prioritisation exercise was based on methodology developed by the James Lind Alliance 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 on SurveyMonkey^{TM} in nine European languages, open between 12th August and 14th 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 over-arching 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.

In this final stage, respondents could vote for up to ten 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 1st December 2020 and 20th January 2020. At closure, each question was ranked separately by the number of votes it received from (i) patients and carers and (ii) 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.

Results

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 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 4(3%) were Allied Health Professionals. The five commonest countries were UK (n=24), Spain (n=19), Germany (n=12), 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 which 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 multi-professional 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 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), United Kingdom (n=28), Spain (n=23), 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).

TABLE 1: '*Top Ten' Research Priorities with equal weight given to patient and clinician preferences, and separately for patients and clinicians.*

OVERALL RANK	PATIENT RANK	CLINICIAN RANK	**QUESTION**
1	1	1	Do corticosteroids or an alternative agent have the best risk-benefit to induce remission in adults with GLILD?
2	2	4	Do corticosteroids or an alternative agent have the best risk-benefit to maintain remission in GLILD?
3	6	2	In newly diagnosed GLILD, is first-line treatment superior to watchful waiting?
4	4	5	Are there specific risk factors in CVID for developing GLILD?
5	3	8	What is the optimal screening approach to detect incident cases of GLILD in people with CVID?
6	9	6	Are there specific pathological endotypes of GLILD with different natural history and treatment responses?
7	13	3	What is the value of a lung biopsy in the work-up of a patient with suspected GLILD?
8	7	11	What is the value of anti-fibrotic drugs such as pirfenidone and nintedanib in treating GLILD?
=9	9	14	Are there specific genetic endotypes of GLILD with different natural history and treatment response?
=9	11	12	Develop a discovery biomarker programme on blood and BAL to assist diagnosis and management of GLILD.
11	4	20	What is the benefit of a higher vs. lower trough immunoglobulin replacement target in GLILD?
12	11	15	What is the value of CT PET in the work-up of a patient with suspected GLILD?
13	8	19	Is GLILD a pathogen driven local manifestation of a systemic immune dysregulation?
=14	15	18	Is immunosuppression for GLILD associated with increased risk of infection?
=14	26	7	What is the value of broncho-alveolar lavage in the work-up of a patient with suspected GLILD?
16	18	16	What is the value of blood or other biomarkers in the work-up of a patient with suspected GLILD?
17	25	10	Do higher or lower dose corticosteroids have the best risk-benefit to induce remission in GLILD?
=18	13	23	What is the role of B cells in the pathogenesis of GLILD?
=18	15	21	Is GLILD an intrinsic dysregulation of the adaptive immune system?
=18	20	16	What is the optimal first line treatment of GLILD in children?
=18	23	13	Which type of lung biopsy has the most favourable risk-benefit?
=18	27	9	What is the value of blood or other biomarkers in assessing disease activity?
23	15	24	What is the value of bone-marrow transplantation in the treatment of GLILD?

=24	18	27	Which epigenetic modifiers contribute to the manifestation of GLILD?
=24	20	25	What is the value of thoracic MRI in the work-up of a patient with suspected GLILD?
=24	23	22	What is the outcome of lung transplantation for GLILD?
27	20	26	Develop a health-status questionnaire to assess burden in GLILD

Discussion

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 of 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 and/or consensus 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.

Limitations include the potential loss of nuance when summarising the original 699 statements, although the process was overseen by the eGLILDnet Steering Committee. To prevent loss of detailed remarks, the anonymized responses to all questions are available for interested researchers on request to the steering committee. It is notable that for some questions there was significant disparity between patient and clinician preferences (with clinicians ranking questions around diagnostic investigations higher). We used a modified version of the James Lind Alliance methodology, without the final workshop, and other methods of research prioritisation are available [6].

It is now up to the clinical and research community, working with patients, funders and the pharmaceutical industry, to develop studies to address these questions and improve the care and lives of those living with GLILD.

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