The top 10 research priorities for the treatment of bullous pemphigoid, mucous membrane pemphigoid and pemphigus vulgaris in the UK: results of a James Lind Alliance Priority Setting Partnership

Karen E. Harman,[1,2] Jag Barha,[3] Jo R. Chalmers,[1] John K.G. Dart,[4,5] Isobel Davies,[3] Patricia Ellis,[6] Douglas Grindlay,[1] Philip J. Hampton,[7] Sharleen Hill,[8] Sharon Hockey,[3] Antonia Lloyd-Lavery,[9] Maggie McPhee,[1] Ruth Murphy,[10] Saaeha Rauz,[11,12] Jane F. Setterfield,[13,14] Ingrid Thompson,[3] Melanie Westmoreland[9] and Christina Waistell[2]

1 Centre of Evidence Based Dermatology, School of Medicine, University of Nottingham, Nottingham, UK
2 University Hospitals Leicester NHS Trust, Leicester, UK
3 Patient research partner, PEM Friends patient support group, UK
4 Moorfields Eye Hospital NHS Foundation Trust, London, UK.
5 National Institute of Health Research (NIHR) Moorfields Biomedical Research Centre, London, UK
6 James Lind Alliance, University of Southampton, UK
7 Royal Victoria Infirmary, Newcastle upon Tyne, UK
8 Chelsea and Westminster Hospital NHS Foundation Trust, UK
9 Department of Dermatology, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
10 Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
11 Institute of Inflammation and Ageing, University of Birmingham, UK
12 Birmingham and Midland Eye Centre, Sandwell and West Birmingham Hospitals NHS Trust, UK
13 Host Microbiome Interaction (CHMI), Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, UK
14 St John's Institute of Dermatology & Dept Oral Medicine, Guy's and St Thomas's NHS Foundation Trust, London, UK

Correspondence: Karen E. Harman
Email: karenharman@doctors.org.uk

ORCID: JKGD - 0000-0003-4090-6950
DG - 0000-0002-0992-7182
PJH - 0000-0001-6797-2697
AL-L - 0000-0002-2339-0596
RM - 0000-0003-2159-5958
SR - 0000-0003-4627-3496
JFS - 0000-0002-6056-3273
MW - 0000-0001-8461-0807

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Dear Editor, Bullous pemphigoid (BP), mucous membrane pemphigoid (MMP) and pemphigus vulgaris (PV) are auto-immune blistering diseases that present with mucocutaneous blistering and erosions. Although distinct diseases, they share clinical and immunological features, and many treatments are common to all three. In recent years, the body of high quality evidence to support treatment recommendation has expanded but there are still many unanswered questions [1-4]. To identify priorities for future research into treatment, we conducted a *Priority Setting Partnership* (PSP) using *James Lind Alliance* (JLA) methodology[5]. JLA PSPs bring patients, their carers and clinicians together to identify and prioritise questions for research to answer, in specific conditions or areas of healthcare using consistent and transparent methodology. The aim is to inform researchers and research funders about priorities so that they can make their research as meaningful as possible to the people who need it. Given the similarities between these diseases, all three were included within this PSP.

A steering group chaired by a JLA independent advisor was composed of six patients and carers representing all three diseases, 11 healthcare professionals (six dermatologists, two with a special interest in oral medicine, two ophthalmologists, two dermatology nurses), a non-clinical researcher, an information specialist, and a project coordinator. The protocol was made publicly available (https://www.jla.nihr.ac.uk/priority-setting-partnerships/treatment-of-Pemphigus-and-Pemphigoid/). The first of two surveys was conducted between November 2019 and April 2020. Respondents were asked to submit up to five questions for research to answer about the treatment of BP, MMP and/or PV. For each question, the respondent was asked to indicate which disease(s) it related to. The survey was available online using SurveyMonkey™ and promoted to stakeholder patients, carers and healthcare professionals within the UK by partner professional organisations (see acknowledgements), the patient support group PEM Friends (https://www.pemfriendsuk.co.uk/), professional and social networks, social media, and by posters in clinical areas. Paper copies were available in clinical areas.

There were two hundred and fifty-eight respondents, including 166 patients/carers (15% BP, 44% MMP, 29% PV, 12% other/unsure), 92 healthcare professionals (60% dermatologists,

14% ophthalmologists, 11% nurses, 10% general practitioners, 3% oral medicine physicians, 2% other). Eighty-six % of respondents were from England, 5% Scotland, 3% Wales, 2% Northern Ireland, and 4% other). There were 974 questions submitted, with 325 removed as being out-of-scope, too vague or unclear. The remainder were grouped and refined to produce indicative questions, reflecting the theme of the submitted questions, expressed clearly in an understandable way. If all elements of an indicative question were already answered by research, defined as a systematic review, or randomised controlled trial, it was removed. This resulted in 46 indicative questions that were circulated online using SurveyMonkey™ in a second survey June-August 2022. Two hundred and twenty-four respondents (124 patients/carers [28% BP, 36% MMP, 29% PV, 7% other/unsure], 100 healthcare professionals [45% dermatologists, 14% oral medicine physicians, 25% ophthalmologists, 2% general practitioner, 9% nurse, 5% other) were asked to select up to 10 questions regarding the treatment of BP/MMP/PV which they thought were most important for future research to answer.

A shortlist of 17 questions was selected by the Steering Group following survey two and included the top 10 questions/uncertainties rated by patients/carers and the top 10 rated by healthcare professionals.

These 17 questions were discussed in an online workshop (September 2022) involving nine patients and carers, eight healthcare professionals and facilitated by three independent JLA advisors. Consensus was reached on the top 10 research priorities (Table 1) after three rounds of small group discussion using nominal group technique.

The strength of this project is the collaborative nature of the PSP process involving relevant stakeholders at every stage and following robust methodology.

The main challenges included getting representation from all three patient groups, overcoming potential barriers to participation from elderly patients posed by the use of an electronic survey (initially also available as paper survey) and overcoming any reticence in formulating research questions. That these were a problem is reflected by the finding that bullous pemphigoid is late onset and, despite being the commonest of these diseases in the UK, was under-represented in our PSP. We were also concerned that a PSP covering three different diseases might pose a challenge but, when the submissions were analysed, there were many uncertainties common to all three diseases. This PSP was also limited to the UK so may lack external validity.

The top 10 priorities identified in this PSP represent the key questions that patients, carers and healthcare professionals have about the treatment of BP, MMP and PV. It is hoped that researchers and funders will aim to answer these questions and uncertainties with future research for the benefit of patients.

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Table 1: Top 10 priorities for research in the treatment of bullous pemphigoid (BP), mucous membrane pemphigoid (MMP) and pemphigus vulgaris (PV) identified by a James Lind Alliance Priority Setting Partnership. Abbreviations: bullous pemphigoid (BP), mucous membrane pemphigoid (MMP), pemphigus vulgaris (PV).

1	How effective, safe and cost-efficient is rituximab (or similar biologics) in BP/PV/MMP compared to standard steroid/immunosuppressant use, when should it be started and should it be a 1st line treatment?
2	Are outcomes for patients with BP/MMP/PV better if treatment is started earlier and with 'stronger' treatments, such as an immunosuppressant or biologic, rather than escalating from 'milder' treatments if they do not work?
3	How should persistent mouth lesions be best treated in pemphigus and pemphigoid?
4	What is the best treatment for preventing and repairing scarring in MMP (medical and surgical)?
5	Is it possible to identify drugs that block the specific immune pathways for BP/MMP/PV rather than treat them with broad immunosuppressive drugs?
6	What are the risks and benefits of the different tablet and injection treatments used to treat BP/MMP/PV? (such as azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, chlorambucil, nicotinamide, dapsone, intravenous immunoglobulin, plasmapheresis)
7	What factors predict relapses in BP/MMP/PV, how can the risk of relapse be reduced and how are relapses best treated?
8	What is the best/most effective dose to prescribe for steroid tablets in BP/MMP/PV including the starting dose, when and how quickly to reduce the dose, and when to stop?
9	Can we predict the response to treatment in BP/MMP/PV and what factors affect this?
10	What is the best way to treat skin wounds in BP/MMP/PV including how should blisters/ erosions be best washed and managed and does treatment vary according to body site?

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