Is it time to give up on "self-management" of COPD exacerbations?

To the Editor:

We read with interest the report of the results of the COPE-III trial by Lenferink *et al.* [1]. This large randomised trial continues on from the authors' earlier COPE-II study [2], with personalised exacerbation action plans based on associated comorbidities. The action plans were detailed, and designed to determine symptom changes and the signs of an ensuing exacerbation. The study was negative for its primary endpoint (COPD exacerbation days) and no improvement in quality of life was found using the self-management intervention. The authors show no difference in the number of oral prednisolone courses in both arms, although per exacerbation event, it is clear that self-management dictates a significant increase of prednisolone prescription per event (95% (208/216) *versus* 71% (163/230)) and thus would have also been the initial treatment for heart failure, anxiety, depression and ischaemic heart disease events. Interestingly, the authors found that patients that benefited in the self-management arm were those that had one or more COPD exacerbations in the 12-month study period. We now know that eosinophilic inflammation is associated with increased risk of exacerbations [3] and that patients that have the best response to systemic corticosteroids have eosinophilic exacerbations [4]. We ask with interest if the authors phenotyped inflammation of the COPD patients prior to randomisation?

Undoubtedly pharmacotherapy should reflect the underlying cause, and although the authors move towards achieving this, it is difficult to be confident that self-management during symptom deterioration of COPD leads to accurate treatment to match the underlying cause. This might explain these and other findings of increased harm in interventions associated with self-management [5, 6]. Although Lenferink *et al.* [1] make a significant step in trying to manage comorbidities in their programme, systemic corticosteroids are the predominant treatment in the self-management intervention: a highly toxic and potentially ineffective intervention [7]. In parallel to personalising treatment towards comorbidities, we believe that we should also be aiming at getting the right and best treatment to the patient first. Achieving this and improving outcomes in COPD is unlikely to occur, however, with current strategies directed towards self-management, where we have an unknown explanation for symptom worsening and toxic treatment.

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COPD exacerbation self-management does not reduce COPD exacerbation days or hospitalisation, rather to more oral corticosteroid use and is rarely effective as it is not targeted http://bit.ly/33D89jF

Cite this article as: Ramakrishnan S, Bafadhel M. Is it time to give up on "self-management" of COPD exacerbations? *Eur Respir J* 2020; 55: 1902102 [https://doi.org/10.1183/13993003.02102-2019].

Sanjay Ramakrishnan and Mona Bafadhel
Nuffield Dept of Medicine – Experimental Medicine, University of Oxford, Oxford, UK.

Correspondence: Sanjay Ramakrishnan, NDM – Experimental Medicine, University of Oxford, John Radcliffe Hospital, (Room 5800, Level 5), Oxford, OX3 9DU, UK. E-mail: sanjay.ramakrishnan@ndm.ox.ac.uk

Received: 28 Oct 2019 | Accepted: 31 Oct 2019

Conflict of interest: S. Ramakrishnan reports non-financial (travel) support from AstraZeneca, outside the submitted work. M. Bafadhel reports grants from AZ, personal fees for consulting and advisory boards, and support for travel to conferences from AZ, Chiesi and GSK, outside the submitted work.

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It is time to further expand research in tailoring self-management of COPD exacerbations!

From the authors:

We are grateful to the editors of the *European Respiratory Journal* for the opportunity to respond to the letter to the editor by S. Ramakrishnan and M. Bafadhel, whom we thank for their thoughtful remarks about our COPE-III self-management trial [1]. Whereas our study did not show a significant difference in the number of COPD exacerbation days per year, the results showed that exacerbation action plans for COPD patients with comorbidities, embedded in a patient-tailored self-management intervention, reduced the duration of COPD exacerbations and the risk of respiratory-related hospitalisation, without increasing all-cause mortality [1]. In our study, we did not phenotype COPD exacerbations by airway eosinophilic inflammation prior to randomisation.

Whereas we agree that further tailoring of self-treatment interventions by adding exacerbation phenotyping could be explored in future studies, more robust studies on the effects of phenotyping, an accurate and user-friendly tool to identify eosinophilic exacerbations, and a validated cut-off point are needed before eosinophils can be used in practice to reduce systemic (either oral or intravenous) corticosteroid use, and their potential side-effects during acute COPD exacerbations [2]. In 2012, at the start of our study, treatment of acute exacerbations with a course of systemic corticosteroids for 7 days was common practice and recommended in guidelines [3], and they still are recommended. Moreover, corticosteroids have been shown to reduce the rates of treatment failure and relapse, and to improve lung function and breathlessness [4].

First, there are indications suggesting that systemic corticosteroids may be less efficacious in treating acute COPD exacerbations in patients with lower blood eosinophil levels. A study by Sivapalan *et al.* [5] in hospitalised COPD patients showed that eosinophil-guided therapy was non-inferior to systemic corticosteroid treatment for the number of days alive and out of hospital and reduced the duration of systemic corticosteroid use. The authors could not, however, entirely exclude a detrimental effect on readmissions with acute COPD exacerbations or death within the first month in the eosinophil-guided

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Tailoring self-treatment by adding exacerbation phenotyping could be explored. Evidence on phenotyping effects, an accurate tool to identify eosinophilic exacerbations, and a validated cut-off point are needed before eosinophils can be used in practice. http://bit.ly/2L4b6SR

Cite this article as: Lenferink A, van der Palen J, van der Valk PDLPM, *et al.* It is time to further expand research in tailoring self-management of COPD exacerbations! *Eur Respir J* 2020; 55: 1902225 [https://doi.org/10.1183/13993003.02225-2019].

group, and therefore recommended larger studies to determine the full safety profile of this strategy, and its role in COPD exacerbation management [5]. Furthermore, patients in both treatment groups received an 80 mg initial dose of prednisolone [5], which could have affected both the eosinophil count and outcome.

Secondly, we are in need of an accurate and easy to use tool to identify eosinophilic exacerbations with a validated cut-off point before integrating it into exacerbation action plans. Peripheral blood eosinophil counts are used as a surrogate biomarker of eosinophilic airway inflammation, but there is significant intra-subject variability in the peripheral blood eosinophil count, and several factors contribute to within-subject variability of blood eosinophil measurements [6]. Furthermore, it was found that blood eosinophils showed a significant but weak association with sputum eosinophil counts [7].

Thirdly, multiple eosinophil cut-off points in blood have been suggested [8]. While Bafadhel *et al.* [9] used the absolute blood eosinophil count cut-off of ⩾2%, Sivapalan *et al.* [5] administered systemic corticosteroids when the blood eosinophil count was at least 0.3×10^9 cells per L. Another issue that needs to be considered is the impact of this approach on non-hospitalised patients (*i.e.* in the outpatient and home setting, including patients who self-manage their exacerbations), for whom a blood sample requirement could potentially delay treatment.

S. Ramakrishnan and M. Bafadhel are correct to note that, in our study, the number of oral prednisolone courses per exacerbation was higher among the self-management group (208 courses, 216 exacerbations) compared to usual care (163 courses, 230 exacerbations) [1]. This was expected as the self-management intervention aimed to improve self-regulation skills as well as targeted uptake and optimal use of appropriate self-management behaviours by early self-recognition and self-treatment of exacerbations. More patients in the self-management group initiated oral prednisolone within 2 days of the onset of a COPD exacerbation, suggesting that patients learned to identify an exacerbation, treat it promptly, and thus reduce its duration [1]. Moreover, there was no over-treatment observed and patients were only directed to activate their action plans (*i.e.* self-initiating a course of prednisolone) after the onset of a COPD exacerbation or comorbid exacerbation. Hence, patients that could benefit from the self-management intervention were those with at least one exacerbation during the 12-month study period.

In conclusion, our study supports integrating self-management of COPD exacerbations into overall COPD management. COPD self-management interventions reduce COPD exacerbation duration and hospitalisations, and improve quality of life [1, 10]. Acute exacerbations are a major prognostic factor with detrimental effects on symptom severity, hospitalisations and mortality [4], and exacerbation action plans can help patients initiate appropriate treatment promptly and reduce the severity (and impact) of COPD exacerbations. When an accurate, affordable, and user-friendly tool to identify eosinophilic exacerbations becomes available for use at home, this might be an additional tool to further personalise self-treatment of exacerbations. Hence, rather than give up on self-management, as proposed by S. Ramakrishnan and M. Bafadhel, it is time to further expand research in tailoring self-management of COPD exacerbations!

Anke Lenferink[1,2], Job van der Palen[1,3], Paul D.L.P.M. van der Valk[1], Morton G. Burt[4,5], Peter A. Frith[4], Marjolein G.J. Brusse-Keizer[6] and Tanja W. Effing[4]

[1]Dept of Pulmonary Medicine, Medisch Spectrum Twente, Enschede, The Netherlands. [2]Dept of Health Technology and Services Research, Faculty of Behavioural, Management and Social sciences, Technical Medical Centre, University of Twente, Enschede, The Netherlands. [3]Dept of Research Methodology, Measurement, and Data-Analysis, Faculty of Behavioural, Management and Social sciences, University of Twente, Enschede, The Netherlands. [4]College of Medicine and Public Health, Flinders University, Adelaide, Australia. [5]Southern Adelaide Diabetes and Endocrine Services, Flinders Medical Centre, Adelaide, Australia. [6]Medical School Twente, Medisch Spectrum Twente, Enschede, The Netherlands.

Correspondence: Anke Lenferink, Dept of Pulmonary Medicine, Medisch Spectrum Twente, P.O. Box 50 000, 7500 KA Enschede, The Netherlands. E-mail: a.lenferink@mst.nl

Received: 20 Nov 2019 | Accepted: 24 Nov 2019

Conflict of interest: None declared.

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