Reviewer's report

Title: PDE4-targeted treatments for autoimmune diseases

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Reviewer: Clive Page

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This manuscript is an interesting and timely review evaluating the potential use of PDE4 inhibitors in the treatment of a variety of auto-immune diseases. However, the current manuscript could be improved as it is quite superficial in places:

i) It is a little surprising that the authors do not really discuss roflumilast, which is the only PDE4 inhibitor currently approved for clinical use, and in particular what has been gained from the experience of using this drug with respect to the safety of this class of drugs when administered orally to patients albeit with a different type of inflammatory disease. The problem of weight loss with roflumilast needs to be discussed as this may also be a problem for other orally active PDE4 inhibitors.

ii) The authors do not discuss the work showing that newer orally active pharmacophores that are PDE4 inhibitors do not always exhibit “classical” PDE4 like side effects.

iii) The authors have called the article “PDE4 – targeted....”, yet the way much of the article is written reads as a review of Apremilist. However, under the “Adverse effects” section, there is no mention of the side effects produced by apremilist from the clinical studies to date. If the authors stick to the current layout, these data should be included here, rather than later in the article. However, the headings used by the authors seem somewhat arbitrary as they are currently arranged e.g. why have sections on rolipram and flavonoids, but not on roflumilast or any other of the many other PDE4 inhibitors that have been evaluated?

iv) On P6 under the heading “Rolipram”, the authors suggest that the high frequency of nausea and vomiting with rolipram may be due to it also being a PDE3 inhibitor. I am not aware that other selective PDE3 inhibitors have nausea and vomiting as side effects as they tend to be cardiovascular in nature, and of course PDE3 inhibitors are used in the treatment of cardiovascular diseases. This needs to be discussed. One adverse effect that has been observed with both PDE3 and PDE4 inhibitors is mesenteric vasculitis - it is therefore perhaps surprising that this problem which has occupied a lot of toxicology time over the last decade or so is also not discussed anywhere (e.g. see FDA website for discussions covering cilomilast).

Declaration of competing interests:
I have no competing interests in relation to the manuscript.