Letters to the Editors

Letter: oral low-dose methotrexate for collagenous colitis – authors' reply

F. Fernández-Bañares*,† & J. P. Gisbert†,‡

*Department of Gastroenterology, Hospital Universitari Mutua Terrassa, Barcelona, Spain.
†Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain.
‡Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain.
E-mail: ffbanares@mutuaterrassa.es

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Sirs, We read with interest the commentary offered by Kia *et al.* concerning our recently published article on evidence-based recommendations for the management of microscopic colitis.[1] Kia *et al.* report the outcome of a series of 10 patients diagnosed with collagenous colitis and treated with oral methotrexate (10 mg/week), all of them achieving clinical remission after a period of time of 2–12 weeks.[2]

This interesting but small series yields anecdotal information regarding the present conflicting data on the usefulness of methotrexate in microscopic colitis. At present, this drug is not a first-line option in the treatment of microscopic colitis, and thus it is unclear why Kia *et al.* used it as the first-line treatment in three patients, or even as a second-line therapy in seven patients who had received as first-line drugs with unproven efficacy. Nowadays, the first-line treatment in collagenous colitis is budesonide. Methotrexate should be reserved for patients with budesonide refractory or budesonide-dependent disease.

It is also important to remember that there is a spontaneous clinical remission rate of around 20% in collagenous colitis, and that in a recent trial the placebo response rate was as high as 40%. Thus, it is difficult to make conclusions about drug efficacy in collagenous colitis without appropriate controls.

Finally, Münch *et al.* used a dose of 15 mg/week during 6 weeks which was ineffective, and then it was increased to 25 mg/week for a further 6 weeks, without response. Adverse events which prevented patients completing the study were observed in the first period of treatment, while patients were receiving 15 mg/week for at least 3 weeks of treatment. At withdrawal, none of them had clinically improved. Moreover, in the study by Münch *et al.* patients were budesonide refractory or intolerant. It could be argued that methotrexate could be useful in naïve collagenous colitis patients, but in this situation budesonide efficacy is very high, with no relevant adverse events, and useful as maintenance therapy.

In summary, we think that despite their interest, the data of Kia *et al.*[2] do not change the present recommendations for the treatment of microscopic colitis.

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Letter: avoiding misconceptions about elimination diet for eosinophilic oesophagitis

J. Molina-Infante* & A. J. Lucendo†

*Department of Gastroenterology, Hospital San Pedro de Alcantara, Caceres, Spain.
†Department of Gastroenterology, Hospital General de Tomelloso, Ciudad Real, Spain.
E-mail: xavi_molina@hotmail.com

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Sirs, Philpott *et al.* report an interesting prospective study evaluating a stepwise clinical algorithm for adult patients with eosinophilic oesophagitis (EoE): proton pump inhibitor (PPI) therapy followed by either topical steroids or elimination diet in patients unresponsive to PPIs.[1] Some noteworthy findings are reported, such as reinforcing the idea of interchangeability of therapeutic assets[2, 3] (patients initially responsive to topical steroids may also respond to PPI) and evaluating the long-term

efficacy of diet therapy. Response to PPI therapy (23%) is much lower than that reported in a recent meta-analysis (50%).[4] This is possibly related to the fact that patients were not naïve for treatment, but were included after discontinuation of previous treatment with PPI and/or topical corticosteroids. Similarly, response to a six-food elimination diet was lower (52%) than that reported in a meta-analysis with homogenous remission rate of 72% in children and adults.[5] We have several concerns regarding the methodology and interpretation of results for elimination diet:

- The elimination diet was combined with PPI therapy, whereas PPI therapy and budesonide were each given as monotherapy. This discrepancy may lead to unreplicable results. One can speculate why PPIs were not added to topical budesonide therapy in a similar way it was done with diet. The authors nicely address this controversial issue along the discussion.
- In responders to a six-food elimination diet, inflammation relapse was evaluated after 2 weeks of individual food challenge. Partial responders (not defined) had a repeat endoscopy after a further 2 weeks (data not shown). This scheme is likely based on the first study on a six-food elimination diet for adult EoE patients, in which questionably food groups were reintroduced every 2 weeks, with repeat endoscopy after the reintroduction of two food groups.[6] Apart from wheat and cow′s milk, a minor role for egg (5%) and not for legumes as food triggers was identified.[6] A 2-week challenge maybe too short for confirming a relapse of a predominantly IgG4-mediated disease,[7] strongly contrasting with the 6–12-week period that the authors waited to confirm EoE remission with PPI, steroids or diet. This is likely the reason why there was less dense eosinophilia during the individual food challenge in the study by Philppot *et al.*[1] In the remaining studies evaluating empiric six- or four-food elimination diet so far,[8–10] a minimum of 6 weeks was established after individual food challenge. Food triggers identified in these studies were extremely homogeneous (by order of frequency, by far cow′s milk, followed by wheat and eggs and then legumes/soy[8–10]). However, gastronomy differences among distinct geographical areas, like Spain, USA and Australia, may account for different food triggers of EoE. Interestingly, the authors observed patients with no food triggers identified after the whole reintroduction process. We have also observed this phenomenon[8, 9] and we can speculate that it might be associated with low intermittent intake of the culprit food, the need for challenges even longer than 6 weeks to document disease relapse in some patients, or even with the involvement of a seasonal airborne trigger.
- The authors literally state ‘At 9 months, only 10/18 (55%) of patients who responded to the elimination diet with PPI remained compliant and sustained remission’. This ‘intention-to-treat’ analysis may be somewhat tricky. The real fact is that among patients responsive to diet, 100% who were re-evaluated while compliant with avoidance of culprit foods remained on remission at 9 months.

Having stated these clarifications, we are extremely excited to see that new research groups out of Spain and the USA join the endeavour for improving patient care and outcomes in EoE with empiric elimination diets.

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Letter: avoiding misconceptions about elimination diet for eosinophilic oesophagitis – authors' reply

H. Philpott* & P. R. Gibson†

*Department of Gastroenterology, Eastern Health Clinical School, Melbourne, Vic., Australia.
†Gastroenterology, The Alfred Hospital, Melbourne, Vic., Australia.
E-mail: lachlanphilpott2003@yahoo.com.au

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Sirs, We thank Molina-Infante *et al.* for their interest and comments[1] illustrating controversies regarding treatment allocation and histological sampling of adult patients with eosinophilic oesophagitis (EoE), and our alternative emphasis on real world clinically acceptable investigation, treatment and outcome measures.

First, regarding combined use of diet with proton pump inhibitor (PPI), we agree that this methodology may not be employed by future researchers, but equally attest that previous work was marred by a lack of consistency with regard to pre-diet PPI trial and/or the use of pH studies.[2] The initial published study in this field arguably arose prior to the current understanding of PPI-responsive oesophageal eosinophilia (REE), and many patients may have been re-categorised had a PPI trial occurred prior to dietary therapy.[2] Continuing PPI therapy during the dietary therapy in our study, not only saved precious time (that would have been required for wash-out) but also the need for a repeat gastroscopy prior to commencing dietary therapy.

A second and related issue is that we did not compare diet and PPI with budesonide and PPI, but rather used budesonide monotherapy. Budesonide with PPI in our view would be foolish, given the already significant risk of oropharyngeal candidiasis with monotherapy, and because budesonide has demonstrable efficacy as a sole agent.[3]

Molina-Infante *et al.* suggest longer periods of food challenge may be required to determine individual culprit foods (e.g. 6 weeks compared to the 2-week period in our study).[4,5] This may be so, although Pedersen *et al.* demonstrated recurrent eosinophilia within 3–7 days in patients controlled on elemental diet and PPI. The notion that EoE is an IgG mediated disease, and thus of delayed onset, is controversial.[6]

In terms of 4-food or 6-food elimination diets, only two groups apart from ourselves have published data, namely that of Molina-Infante *et al.* themselves, and a North American group.[7] The only way to answer this question would be to do repeated gastroscopies at set time intervals following the introduction of each food, e.g. at 3 days, 2 weeks and 6 weeks. In reality, the need to deliver acceptable and safe treatment regimens dictated our study algorithm. That is, we deemed an extremely restrictive diet that should be used for the minimum possible period of time.

Finally, our observation that only 55% of patients remained compliant with their diet at 9 months, the rest relapsing with eosinophilia is, we believe, a fair assessment.[8] Figure 2 clearly demonstrates that 7/18 patients representing for gastroscopy had ceased treatment and relapsed, one patient dropped out and 10/18 (all compliant patients) sustained remission. The question 'can dietary therapy cause remission of EoE' has already been comprehensively answered. Our contribution is, that outside of expert centres, the response to dietary therapy and the long-term compliance, and thus success, is modest.

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