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Commentary

Lactoferrin: milking ulcers?

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The use of bovine lactoferrin (BL) was recently described by Di Mario et al. [1] as an 'add-on' component to the 7-day proton pump inhibitor (PPI), claithromycin, tinidazole-based triple therapy for *Helicobacter pylori* infection. In this preliminary report 74 patients infected with *H. pylori* with or without an active ulcer were randomly assigned to one of three groups: A, patients on rabeprazole (R), clarithromycin (C) and tinidazole (T), plus BL; B, RCT for 7 days; and C, RCT for 10 days. The eradication rates were: A, 100% (24/24); B, 76.9% (20/26); and C, 70.8% (17/24). A significant difference was found between groups A and B ($p=0.023$) and between groups A and C ($p=0.022$). Results of the complete trial, now in 150 patients, have become available and are reported in this issue of the journal [2]. On an 'intention to treat' basis, the results continue to show that BL significantly improves eradication efficacy of PPI triple therapy. Group A achieved 92% (47/51) eradication efficacy while groups B and C reached only 71% (37/52) and 70% (33/47) eradication rates, respectively. Eradication was significantly higher in group A compared with the other groups ($p=0.01$). Adverse events were similar among all three groups suggesting that BL at a dose of 200 mg bid is relatively safe and free of side-effects.

These are interesting early results which will need to be reproduced in other populations with differing *H. pylori* anti-microbial sensitivity profiles. In this Italian population, primary clarithromycin resistance is in the order of 2% compared with 10% in the USA [3] and over 15% in parts of Australia [4]. Eradication may be dependent upon primary anti-microbial resistance and results from one population group may not apply to another. Conversely, in countries with high or rising clarithromycin resistance, studying the effect of BL on eradication rates is particularly important because coupling BL with standard PPI triple therapy may help offset the progressively sagging eradication rates. Of even greater interest may be a clinical study to determine whether simultaneous use of BL with the PPI triple therapy could significantly inhibit the development of clarithromycin resistance during treatment. Such a trial would necessitate the determination of de-novo and post treatment *H. pylori* anti-microbial sensitivities; the lack of such a determination is a major limitation of the current study.

What mechanisms might be influencing the improved efficacy of triple therapy when combined with BL? There are abundant animal studies and a growing number of human studies suggesting that lactoferrin possesses multiple functions (Table 1). Lactoferrin is a siderophilin, comprising a single polypeptide chain folded into two lobes with a molecular weight of 90,000 Da [5]. The structure contains two fucose residues and several *N*-acetyl-D-glucosamine residues. It is an iron-binding glycoprotein found in human and bovine milk and in other external secretions such as tears [6]. It makes up ~0.5–1% or less of whey protein derived from cows milk, whereas human milk may contain up to 15% [5,6]. Its in vitro anti-microbial activity, iron binding related antibiotic activity, immuno-modulatory actions, and antioxidant effects appear to be but a few of the many characteristics attributed to BL which could be responsible for its synergistic effect with PPI triple therapy [1,2,5,6]. Hence, BL appears ideally suited as an adjuvant therapy on

Table 1
Summary of potential anti-*H. pylori* effects of BL

Effect	Reference
Anti microbial against *H. pylori*	[13]
Antimicrobial effect via sequestering iron from *H. pylori*	[14–16]
Immuno-modulatory activity	[14,15,17,18]
Antioxidant effects	[19,20]
Anti-adhesin activity	[21]
Mediates membrane damage and other cell wall effects	[22–26]
Macrophage lymphocytes protectant	[5]

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account of its many actions which may contribute to *H. pylori* eradication when combined with antibiotics, and because it is more likely to gain widespread acceptability due to its natural origins from milk.

At a time when metronidazole resistance is high, clarithromycin resistance is rising in many parts of the world, and *H. pylori* eradication failure is an increasing clinical problem [4,7–9], we need to focus on adjuvant therapies that can improve eradication rates. Among other adjuvants that may be of use are pronase [10] and gum mastic [11]. Pronase is a protease capable of causing extensive degradation of mucins, reducing mucus viscosity, and depleting gastric mucus. In a single study, pronase has been shown to improve the eradication rate of PPI triple therapy significantly from 76.5 to 94% ($p=0.004$) [10]. Its mechanism of action differs from that of BL in that it does not act directly against *H. pylori* but rather appears to facilitate a more effective delivery of antibiotic agents by acting on the gastric mucus layer. Gum mastic is a natural resin derived from the *Pistacia lentiscus* tree and is used as a food additive in Mediterranean countries. It has been shown to have antibacterial properties against *H. pylori* capable of killing or at least inhibiting bacterial growth [11]. Apart from identifying such novel adjuvants for *H. pylori* eradication, we also need to find clever ways of combining them in the best possible manner for use with antibiotic protocols to enhance efficacy, as it appears that we are frequently treating *Helicobacter* infection with varying sensitivities within the same gastric mucosa [12].

In summary, 'milking ulcers' may not be such a far-fetched idea. After all, lactoferrin is of bovine origin and appears to be a valuable additive to PPI triple therapy to reduce eradication failure. Results of further studies are awaited, not just with BL, but also with pronase, gum mastic, and other adjuvants. In such trials where possible, anti-microbial resistance will need to be determined prior to treatment in all patients, especially in those who have experienced eradication failure, to determine which add-on therapies might inhibit the development of antibiotic resistance. Furthermore, such adjuvant therapies should find their way into rescue or salvage protocols for patients with repeated eradication failure [9].

Conflict of interest statement

None declared.

List of abbreviations

BL, bovine lactoferrin; C, clarithromycin; PPI, proton pump inhibitor; R, rabeprazole; T, tinidazole.

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