

## Patient Information Leaflet: Anti-MAP antibiotic therapy for the treatment of Crohn's Disease

Anti-MAP antibiotic therapy is one option for the treatment of Crohn's Disease, which has been used by some specialists since the 1990's. The rationale for this treatment is based on growing evidence to support the hypothesis that Crohn's Disease is caused by the bacterium *Mycobacterium avium* subspecies *paratuberculosis* (MAP). The protocol for this combination therapy includes Rifabutin, Clarithromycin and often a 3rd agent, Clofazimine. These are DIFFERENT antibiotics to those such as ciprofloxacin or metronidazole which mainly kill the overgrowth of other gut bacteria rather than having significant action against MAP itself. Side effects of anti-MAP antibiotics can limit their use in some people. But in those who can take them, the majority will benefit from treatment and profound remissions can occur, even in those with severe disease. In some cases, major surgery has been avoided.

### What is the success rate of anti-MAP triple therapy?

In ordinary terms, of 5 people who can take it, 2 will get a complete remission, 2 will get a partial remission and one will not respond, probably because the MAP in that person is already resistant.

A review of the published scientific literature reveals 7 clinical trials which have investigated the effects of anti-MAP therapy in Crohn's Disease, with clinical remission rates ranging from 44-89%<sup>(1)</sup>. Of these, the 'landmark study' is considered to be that conducted by Selby *et al.*<sup>(2)</sup> in Australia in 2007 –it is the only large randomized controlled trial and hence the most well-known. The failure of this study to show a long-term benefit of anti-MAP therapy in Crohn's disease is regarded by many as the 'final nail in the coffin' for the MAP/Crohn's hypothesis and is a major reason for the reluctance of some Gastroenterologists to recommend this treatment to their patients. However, the trial has since been widely criticized, both in terms of the protocol used and the subsequent analysis<sup>(1,3,4)</sup>, such that it cannot be relied upon as having any clinical significance. Major flaws include the following:

- (1) Patients were not tested for MAP before entry into the trial
- (2) Sub-therapeutic doses of all 3 antibiotics were used
- (3) The clofazimine capsules used failed to dissolve, thereby not releasing the active ingredient within
- (4) The analysis of the data was flawed; the results were not based on an intention-to-treat analysis and thus underestimated the beneficial effect of treatment<sup>(4)</sup>.

Despite these flaws, the trial still demonstrated a remission rate of 66% (of 102 patients with Crohn's Disease) at 16 weeks ( $p < 0.02$ ).

A fresh start has been badly needed for a long time -but there is new hope on the horizon that the true potential of this treatment may finally be revealed. In the USA, a large multi-centered randomized-controlled trial is currently underway entitled 'Efficacy and Safety of Anti-MAP Therapy in Adult Crohn's Disease (MAPUS)'. The anti-MAP therapy being used in this trial is a fixed-dose combination of Rifabutin, Clarithromycin and Clofazimine combined into a new 3-in-1 pill called RHB-104:

<http://clinicaltrials.gov/ct2/show/NCT01951326?term=crohn%27s+disease+redhill&rank=1>

### Are there any side effects?

Overall, anti-MAP therapy is well tolerated by the majority of patients, but as with most medicines, there are potential side effects which may be experienced by some people. Common side effects include a 'tanned' appearance and aching joints. More rarely, patients may experience fevers, a rash or the more serious, but reversible, condition 'uveitis' (inflammation of a part of the eyes) which

would require treatment to be stopped. Very occasionally treatment may exacerbate disorders such as depression. Treatment should only be undertaken with close medical supervision.

#### Why do some people with Crohn's not improve with anti-MAP therapy?

- (1) A small proportion of people won't be able to tolerate treatment.
- (2) Mycobacterial resistance to antibiotics is well-described in the literature and becoming more common... so if you had a resistant strain of MAP already then the antibiotics would not work. It is not possible to do sensitivity studies prior to starting therapy because of the difficulty in culturing MAP.
- (3) Prescribing problems: The preferred regime is triple therapy with Rifabutin, Clarithromycin and Clofazimine although in some people Rifabutin and Clarithromycin alone work well. Antibiotic monotherapy is well-known to lead to resistance. Correct dosing is important as opposed to that used in the trial by Selby *et al.*
- (4) Inadequate duration of treatment: As with other mycobacterial infections, treatment needs to be continued for a long time (24-36 months) to ensure as far as possible that latent organisms are eliminated as well. In some people, particularly those who have not had longstanding Crohn's disease, improvement can appear within 4-6 weeks. In others with longstanding Crohn's disease, it can take 6 to 12 months before a real improvement occurs. In these people there is a lot of damage to the gut wall, the immune system and the delicate gut nervous system which has to be repaired.

Whilst antibiotic treatments can be a real help, they are not always a long-term solution, due to the ever-present threat of developing resistance and the ability of MAP (like other similar bacteria) to go into 'latency' (hibernation) in which state they are very difficult to kill with drugs. The prospect of a therapeutic anti-MAP Vaccine, which would avoid all these problems, is therefore a very exciting one.

- (1) Chamberlin W, Borody TJ, Campbell J. Primary Treatment of Crohn's Disease: Combined antibiotics taking centre stage. *Expert Rev Clin Immunol* 2011; 7(6): 751-760
- (2) Selby W, Pavli P, Crotty B *et al.* Two-year combination antibiotic therapy with clarithromycin, rifabutin and clofazimine for Crohn's disease. *Gastroenterology* 2007; 132(7): 2313-2319
- (3) Lipton JE, Barash DP. Flawed Australian DC trial does not end MAP controversy. *Gastroenterology* 2007; 133:1742
- (4) Feller M, Huwiler K, Schoepfer A *et al.* Long-term antibiotic treatment for Crohn's disease: systematic review and meta-analysis of placebo-controlled trials. *Clin. Infect Dis.* 2010; 50(4): 473-480