

## Treatment with drugs active against *Mycobacterium avium* subspecies *paratuberculosis* can heal Crohn's disease: more evidence for a neglected Public Health tragedy

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Contemporary research using appropriate laboratory culture and polymerase chain reaction (PCR) and other procedures is confirming unequivocally that the chronic enteric pathogen *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is present in the chronically inflamed intestinal tissues of the overwhelming majority of people suffering from Crohn's disease (CD), and that MAP is rarely found in people with normal uninfamed intestine<sup>1-3</sup>. The publication on pages 22-8 and 29-39 of the present issue of the Digest Liver Dis of two carefully researched open clinical studies of anti-MAP treatment in CD by Shafran et al.<sup>4</sup> from the University of Central Florida, and Borody et al.<sup>5</sup> from the Centre for Digestive Diseases in Sydney, brings welcome news for people struggling with this miserable condition, and their families.

Shafran et al.<sup>4</sup> used rifabutin and clarithromycin, and Borody et al.<sup>5</sup> triple therapy using these drugs in combination with clofazimine. The selection of these agents to treat CD recognises the long known resistance of clinical infections caused by *Mycobacterium avium* complex (MAC) organisms particularly MAP, to standard drugs used in the treatment of tuberculosis<sup>6,7</sup>. It recognises that the phenotype of MAP in CD is one which does not have a classical mycobacterial ZN-positive mycolic acid-rich cell wall, and, therefore, that drugs like isoniazid, ethambutol and pyrazinamide are unlikely to be of much use<sup>8</sup>. It further recognises that the replication rate of MAP in CD is likely to be extremely slow, a feature which would also reduce the susceptibility of these intracellular pathogens to drugs like ciprofloxacin<sup>9-11</sup>. Finally, it recognises the greater susceptibility of MAC and MAP both in vitro and in vivo, to drugs such as rifabutin and clarithromycin<sup>12-14</sup> which are chemical modifications of natural streptomycetes antibiotics. In their inhibition of RNA polymerisation and of microbial protein synthesis at the level of the ribosome, rifabutin and clarithromycin are likely to act in synergy and may also be potentiated by clofazimine<sup>15</sup>. All three agents have the additional advantage of concentrating in macrophages where MAP in CD is likely to reside<sup>16</sup>.

The present reports bring up to four, the number of independent open clinical studies of the treatment of CD with combinations of drugs with enhanced activity against MAP, including rifabutin and clarithromycin<sup>17,18</sup>. All four studies essentially say the same thing. This is that somewhere between two thirds and three quarters of people with active CD who can tolerate the antibiotics long term, will go into remission with healing of the intestine when treated with these agents. The minority proportion of people with CD who do not respond may be infected with MAP which is already drug-resistant. Geographical variation in response rates may be influenced by strain differences in MAP<sup>19-21</sup> and the ambient use of clarithromycin for other infections. A not uncommon finding has been that a proportion of people who respond, subsequently relapse on treatment. Other responders who have been successfully treated over two or more years may relapse after treatment has stopped. These outcomes are consistent with the known course of other clinical MAC infections in immunocompetent people and the tendency for MAC organisms to develop drug resistance<sup>22-24</sup>. It is also consistent with the ability of mycobacteria in vivo to enter a state of dormancy in which they may be extremely difficult to eradicate<sup>25,26</sup>. The disease has healed but latent infection persists. Borody et al.<sup>5</sup> have found, as I have done, that patients with CD who relapse after healing completely on prolonged treatment, may respond again (but not always) to the same drugs, a finding which emphasises the distinction between drug resistance and dormancy. Despite the risk of relapse, long-term follow-up of CD patients treated with anti-MAP drugs both in London and in the present studies shows that there remains a core group of about 30-35% of people whose inflamed intestine heals and stays healed. Endoscopy and histology may show resolution of previous florid CD, returning to a normal mucosa without microscopical evidence of inflammatory infiltrate. White bands of submucosal scarring on endoscopy may indicate the irreversible damage inflicted by previous long-term severe inflammatory disease. A proportion of people with severe end-stage Crohn's colitis resistant to conventional treatment, who have responded

to drug combinations including rifabutin and clarithromycin, have been rescued from otherwise inevitable panproctocolectomy and are living normal, apparently disease-free, lives.

Several other issues are illuminated by the present valuable contributions from Sydney and Florida. Most patients with CD responding to anti-MAP drug combinations become independent of the need for steroids and conventional immunosuppression. Continuing prednisolone for a few weeks after starting anti-MAP treatment may help mitigate the Jarisch-Herxheimer-type exacerbation of symptoms described by Shafran et al.<sup>4</sup> in some of their patients. Similar responses have been noted shortly after starting treatment for active tuberculosis and leprosy. Drug-related side-effects were not seen in the twelve patients with active CD in Sydney where treatment was introduced in an incremental stepwise dosage and included clofazimine. The release of ileal strictures following anti-MAP treatment described by Borody et al.<sup>5</sup> with a return to apparently normal intestine, is consistent with my own experience and is reminiscent of that seen following the successful drug treatment of some ileal strictures in intestinal tuberculosis<sup>27</sup>. In some other MAP-infected CD patients, complete healing of the gut may result in a dense fibrotic scar requiring limited surgical resection for obstruction<sup>28</sup>. The one patient in the report of Borody et al.<sup>5</sup> with a previous defunctioning ileostomy for a severe pancolitis judged to be CD, responded to anti-MAP treatment with cessation of diarrhoea such that the ileostomy was able to be reversed. On subsequent relapse the condition was re-classified as ulcerative colitis (UC) for which colectomy and ileo-anal anastomosis were required. People with underlying UC who have an inherited or acquired susceptibility to MAP, may develop a MAP superinfection in the UC-ulcerated colon and demonstrate clinico-pathological features characteristic of both diseases. Symptomatic and endoscopic improvement follows treatment of the MAP superinfection, but cessation of treatment and ramp-down of steroids allows the underlying UC to come through. The co-existence of UC and MAP infection is a likely explanation for a proportion of the well-known clinical sub-group of inflammatory bowel disease (IBD) patients whose colitis is indeterminate. Superinfection with MAP in a colon damaged by another condition such as diverticulitis, may explain the Crohn's-like reaction occasionally also seen in a segment previously damaged by other disease<sup>29</sup>.

The principal property of MAP present in the inflamed gut of people with CD, which distinguishes it sharply from all other candidate organisms in respect of disease causation, is the ability of MAP to cause chronic inflammation of the intestine in such a broad range of animals including primates<sup>8</sup>. Just as with tuberculosis<sup>30</sup>

and leprosy, there are differences in the clinico-pathological features of MAP disease between animals, as well as between animals and humans, but the closest match in animals, so far, for CD in humans, is the paucimicrobial form of Johne's disease in sheep<sup>31</sup>. Until recent years, it was this specific chronic enteric pathogenicity of MAP in many diverse species, which provided the best basis for concluding that MAP, in CD, is causative. The availability of a first generation of drugs active against MAP, and the results of anti-MAP treatment in CD from Australia and the United States together with the other work in this field<sup>17,18</sup>, provide us with an important additional insight into the relationship between MAP and Crohn's disease. If MAP in the inflamed gut tissues in Crohn's is not causing the disease and is merely a bystander organism, it would be necessary to accept that despite its broad enteric pathogenicity it is somehow harmless to humans. The responses of a majority proportion of CD patients to effective drug combinations, including rifabutin and clarithromycin, suggest that this is very unlikely to be the case. Furthermore, streptomycetes antibiotics like rifampicin and erythromycin will kill many ordinary gut bacteria, but they are not active against MAP infections, and do not heal CD. The closely related chemically modified antibiotics rifabutin and clarithromycin will also kill many ordinary gut bacteria, but they are much more active against MAP, and can heal CD. Taken together these reflections indicate that when CD patients get better and their inflamed intestine heals on treatment with drug combinations including rifabutin and clarithromycin, it is because these agents are killing the underlying causative organisms.

Contemporary medicine demands a positive outcome in one, or more than one, randomised controlled clinical trial (RCT) before regulatory authorities and professional guidelines will accept a new treatment as able to confer proven benefit. These are expensive and lengthy undertakings and carry their own ethical penalties. Thanks to the initiative of a group of Australian Gastroenterologists co-ordinated by Warwick Selby and supported by the dedication of Chris Bilkey and colleagues at Pharmacia, an RCT of triple therapy with rifabutin, clarithromycin and clofazimine in CD versus placebo, was initiated in September 1999 based on multiple centres throughout Australia. This RCT completed patient accrual in September 2001 and is expected to report in 2003. It is a critically important trial and I predict that it will confirm the indications of the four pathfinding open clinical studies, that anti-MAP treatment can heal CD. In the meantime, the findings of these open clinical studies are sufficiently reproducible to justify an acceptance by Gastroenterologists of treatment with

these drug combinations on compassionate grounds, for people with colonic CD facing proctocolectomy and permanent abdominal stoma, with a lot to gain and nothing to lose.

By the end of 2003, about 50,000 more people in the United States, and at least 50,000 more people in Western Europe, will have developed chronic inflammation of the intestine of the CD type, most of it caused by MAP. In due course, informed public opinion will judge Gastroenterology harshly if a culture of neglect on this issue, and an inadequate understanding and misinterpretation of available scientific information, in the field, occasionally exemplified in contemporary writing<sup>32</sup>, continues to prevail. We should have available the total genome sequences of a bovine, an ovine and a human CD strain of MAP. Comparative genomics and proteomics between these MAP strains and closely related *Mycobacterium avium* subspecies *avium* of lesser pathogenicity for animals and humans together with the use of bioinformatics, could rapidly develop a short list of promising targets for a next generation of pharmaceuticals effective in the treatment of CD. New treatments should include DNA vaccines containing multiple MAP epitopes able to generate populations of antigen-specific CD8+ T-cells to assist in immune-mediated microbial clearance. Experience with leprosy would suggest that therapeutic vaccines would complement rather than compete with drug treatments<sup>33</sup>. Given the prevalence of MAP infection in domestic livestock in many continents together with wildlife reservoirs<sup>34 35</sup>, the existence of hot-spots of CD in areas like Manitoba<sup>36</sup> and North East Scotland, and the emerging ability to identify individuals susceptible to CD genetically<sup>37-40</sup>, we will also need preventative MAP vaccines effective for animals and humans, before we can expect progress towards a global resolution of this complex overall problem, to be achieved.

#### List of abbreviations

CD: Crohn's disease; IBD: inflammatory bowel disease; MAC: Mycobacterium avium complex; MAP: Mycobacterium avium subspecies paratuberculosis; PCR: polymerase chain reaction; RCT: randomised controlled clinical trial; UC: ulcerative colitis.

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