Commentary

The MARVEL trial: a phase 2b randomised placebo-controlled trial of oral MitoQ in moderate ulcerative colitis

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Trials-at-a-glance
Drug: MitoQ (Mitoquinol mesylate)
Target: Mitochondria
Disease: Ulcerative colitis
Mechanism of action: MitoQ can block the effects of mitochondrial-derived reactive oxygen species (mROS). MitoQ is an antioxidant with a mitoquinol component which allows it to migrate to the inner mitochondrial membrane. Here, it can donate a hydrogen atom to reduce mROS and dampen inflammation. MitoQ reduces the leakage and oxidisation of mitochondrial DNA, promotes autophagy and influences energy metabolism, leading to reduced inflammation and improved healing of the gut.
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Summary

Ulcerative colitis (UC) is an inflammatory disease of the large bowel which is characterised by dysregulated immunity and death to epithelial cells in the bowel, leading to prolonged inflammation. This can ultimately lead to surgery to remove the large bowel, with a risk of cancer developing if inflammation persists. Current therapies – which target the incoming immune cells or the cytokines they produce – are improving significantly but they are expensive and are immunosuppressive, leading to risk of infection. Here, we discuss a new trial which targets an early inducer of inflammation – the production of reactive oxygen species (ROS) by mitochondria. Previous work has shown that excessive mitochondrial ROS induces inflammatory signalling through the cGAS-STING pathway, leading to dysregulated immunity and death of epithelial cells. In this MARVEL trial (Mitochondrial Anti-oxidant therapy to Resolve Inflammation in Ulcerative Colitis) individuals with an active UC flare-up will be given a mitochondrial anti-oxidant (MitoQ) or placebo tablet in addition to standard medical treatment, in order to suppress inflammation as it develops. This phase 2b trial will repurpose MitoQ,
which has been previously tested in other large trials in different disease settings, and will measure clinical response and markers of inflammation over 24 weeks. It is hoped that this trial will develop a new target for UC through re-purposing a relatively cheap, non-toxic and well-characterised drug.

Keywords: colitis, mitochondria, DAMP, clinical trial

Ulcerative colitis (UC) is an inflammatory disease of the large bowel that affects around 150 000 patients in the UK; prevalence continues to increase [1, 2]. Individuals with UC can suffer with bloody diarrhoea, uncontrollable bowel habit, dehydration, fever and malnutrition, often with a significant impact on their quality of life, ability to work, and emotional wellbeing. They are at a risk of requiring surgery to remove the large bowel if inflammation persists, and large bowel cancer if UC is poorly treated over time [3]. Dysregulated immunity, microbiota alterations, and epithelial damage combine during the establishment and persistence of UC. Infiltration of innate (neutrophils and macrophages) and adaptive (Th1 and Th17) immune cells into the bowel is critical for development of the disease.

Current therapies for UC have improved significantly in recent years, but they are long term and expensive [e.g. regular infusions of anti-tumour necrosis factor (TNF), anti-α4β7 to block immune cell migration into the bowel, or anti-IL23p40 to block Th17 cell differentiation] [4]. In addition, the current first-line therapies (combined anti-TNF and thiopurines) are effective in only 50% of patients with severe disease [5, 6], are immune-suppressive and have been linked to increased rates of opportunistic infections [7, 8]. Therefore, it is important that we continue to improve our therapeutic options. Exploring options away from downstream immunology to upstream drivers of inflammation – before they trigger the development of the damaging immune response – is an increasing focus of research.

Critical for the development of UC is colonic mucosal barrier dysfunction with increased epithelial death [9]. A persistent inflammatory environment is driven and maintained by a complex inflammatory milieu, with resulting inflammation and further development of damaging immunity [10–12]. Many factors contribute to this maladaptive response, including altered microbiome, genetic susceptibility, and diet, as well as the production of host damage-associated molecular patterns (DAMPs).

Recently, a key role for mitochondrial dysfunction and mitochondrial-released DAMPs (mtDAMPs) in the development of pathogenic bowel inflammation and epithelial death has been established [13, 14].

Release of DNA and reactive oxygen species (ROS) from mitochondria induces production of IL-8, IL-6, IL-1β, and TNF in responding immune cells, triggering the NLRP3 inflammasome and cGAS-STING axis [15]. This inflammation leads to differentiation of, and cytokine production by, other resident and infiltrating immune cells. Subsequent epithelial cell death also occurs. While blocking the latter production of cytokines is well established as a therapeutic option for a number of autoimmune conditions, in this trial, the effects of mtROS on the downstream impact on mtDAMPs will be blocked during an active flare-up of UC.

This trial will test the idea that blocking the effects of mtROS will be important to fully reduce pathogenic inflammation during a UC disease flare and to allow full resolution and complete healing of the inflamed gut mucosa. MitoQ is an antioxidant derivative of coenzyme Q10, which efficiently migrates into the mitochondrial inner membrane and donates a hydrogen atom to combat the radical superoxide species. Previous work by the trial principal investigator Dr. Gwo-Tzer Ho has demonstrated that MitoQ reduces severity and delays onset of colitis in two mouse models: dextran-sulphate sodium (DSS)-induced disease and chronic spontaneous multidrug-resistant 1 (mdr1a−/−) deficient colitis [9, 10]. Other trials using MitoQ in Hepatitis C and Parkinson’s disease have established the drug to be tolerable [16, 17].

Now MARVEL, a randomised phase 2b double blind placebo-controlled multi-centre trial, is starting across participating hospitals in the UK in early 2021. The trial will test the efficacy of MitoQ given as an inflammation-dampening adjunct in addition to usual medical treatment that includes corticosteroids. This study will recruit around 200 adult participants and the participants will have a confirmed diagnosis of UC with a number of features such as blood in the stools which fulfils a set clinical criteria using the Mayo score that indicate active disease. Participants will receive the standard dose of oral prednisolone alongside either MitoQ or placebo for 24 weeks (daily dose). They will be assessed at 12 and 24 weeks with direct examination of the affected colonic mucosa, assessment of their symptom scores and well-being, and with assessment of blood and stool inflammation via calprotectin ELISA. Primary and secondary endpoints of the trial are listed in Table 1. In addition, parallel mechanistic studies will be performed to provide further insights into this clinical intervention in
The combination of experimental studies in clinical trials especially in highly characterised patient cohorts is powerful and recently been endorsed by the NIHR [18].

A further study that is aimed at children with UC (MiniMARVEL) is also set to open in 2021. If the data are supportive, both adults and children may benefit from this. New treatments in children with IBD are often extrapolated from adult studies and there is often a lag period of 3–7 years before new approaches are applied in the younger group. It is uncommon for clinical trials for new treatment to be performed primarily in the younger patient group.

MARVEL aims to re-purpose an existing drug compound to potentially switch off a key factor in gut mucosal inflammation in UC during an active flare-up. There is a huge untapped medicine chest of generic drugs with unexploited uses. Development of new drugs de novo from molecule to clinical use is very expensive, has a high attrition rate and takes a long time (10–15 years). Investigating existing drug compounds in a clinical repurposing trial such as MARVEL will allow considerable saving of time and money.

As such, this approach, which is relatively cheap and non-toxic, may improve the lives of patients with UC. It will also spark further translational research into the role of mitochondria in complex immune-mediated diseases, how the mitochondria intersect with adaptive immunity during pathology; and in the broader sense, how researchers can creatively use drug-repurposing as a route to new treatment approaches. It is important to await the final results of the MARVEL study. This trial, however, provides encouragement and impetus to basic scientists to apply and seek clinical translation of their discoveries where possible.

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Conflict of Interest
The authors declare no conflict of interests.

Data availability
No new data were generated or analysed in support of this research.

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