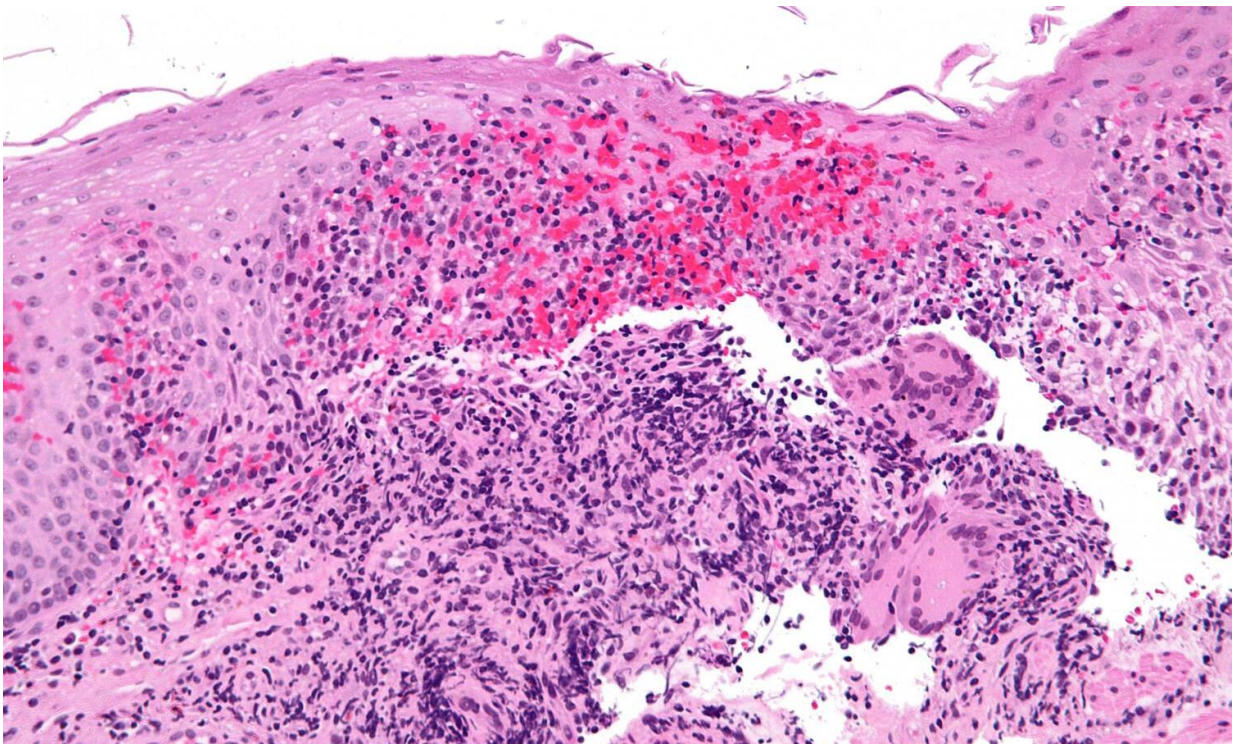
Treating newly-diagnosed Crohn's patients with advanced therapy leads to dramatic improvements in outcomes

February 22 2024



High magnification micrograph of Crohn's disease. Biopsy of esophagus. H&E stain. Credit: Nephron/Wikipedia

A large-scale clinical trial of treatment strategies for Crohn's disease has shown that offering early advanced therapy to all patients promptly after

diagnosis can drastically improve outcomes, including by reducing the number of people requiring urgent abdominal surgery for treatment of their disease by ten-fold.

The PROFILE trial, led by researchers at the University of Cambridge, involved 386 patients with newly-diagnosed active Crohn's disease. Recruiting from 40 hospitals across the UK, it sought to test whether a biomarker—a genetic signature—could predict which patients were at greatest risk of relapses of their condition, and to test two different approaches to treating the disease.

Crohn's disease is a life-long condition characterized by inflammation of the digestive tract. It affects around one in 350 people in the UK. Even at its mildest, it can cause symptoms that have a major impact on quality of life, including stomach pain, diarrhea, weight loss and fatigue.

Typically patients experience "flares" of inflammation, where their condition worsens for a time, producing more symptoms and progressive bowel damage. As many as one in 10 patients will require urgent abdominal surgery to treat their condition within their first year of diagnosis.

The findings of the PROFILE trial are published in *The Lancet Gastroenterology and Hepatology*. While the biomarker did not prove useful in selecting treatments for individual patients, a "top-down" treatment strategy involving use of the drug infliximab straight after diagnosis showed dramatic results.

Infliximab works by blocking a protein found in the body's immune system, TNF (tumor necrosis factor)-alpha, which plays an important role in inflammation. The drug is administered through regular intravenous infusions directly into the bloodstream or injections under the skin. However, due to historical concerns about cost and side

effects—including an increased risk of infection related to immunosuppression—it is currently only offered when patients experience regular flareups that do not respond to less potent treatments.

In the PROFILE trial, patients were assigned at random to one of two treatment groups. Each group was given a different treatment strategy and patients were followed up over the course of a year.

The first group was treated using an "accelerated step-up" approach, which is the conventional treatment strategy used in the UK and across most countries around the world. In this group, patients only started on infliximab if their disease was progressing and not responding to other simpler treatments.

The second group, however, was treated using top-down therapy—that is, they were provided with infliximab as soon as possible after their diagnosis, regardless of the severity of their symptoms.

The results were dramatic: 80% of people receiving the top-down therapy had both symptoms and inflammatory markers controlled throughout the course of the entire year compared to only 15% of people receiving the accelerated step-up therapy.

Two-thirds (67%) of patients in the top-down group had no ulcers seen on their endoscopy camera test at the end of the trial—something known as endoscopic remission. Endoscopic remission is considered very important as this has been consistently associated with decreased risk of later complications in Crohn's disease. Most previous clinical trials of therapies have been considered highly successful based on getting 20 to 30% of patients into endoscopic remission.

As well as these findings, patients in the top-down arm also had higher quality of life scores, less use of steroid medication and lower number of

hospitalizations.

Strikingly, while around one in 20 patients (5%) in the conventional treatment arm of the trial required urgent abdominal surgery for their Crohn's disease, only one in 193 (0.5%) receiving the top-down therapy required such surgery.

Dr. Nuru Noor from the Department of Medicine at the University of Cambridge, one of the study's lead researchers and first author of the trial, said, "Historically, treatment with an advanced therapy like infliximab within two years of diagnosis has been considered 'early' and an 'accelerated step-up' approach therefore 'good enough." But our findings redefine what should be considered early treatment.

"As soon as a patient is diagnosed with Crohn's disease, the clock is ticking—and has likely been ticking for some time—in terms of damage happening to the bowel, so there's a need to start on an advanced therapy such as infliximab as soon as possible. We've shown that by treating earlier, we can achieve better outcomes for patients than have previously been reported."

In fact, say the researchers, the improvements seen among the trial patients receiving top-down therapy might be even more stark compared to usual clinical care. Few patients with Crohn's disease in standard clinical care receive the rapid, accelerated step-up approach provided by the trial protocol, and so the benefits of implementing a top-down approach in standard clinical care might be even more pronounced.

Crucially, the team found no difference in risk of serious infection between treatment strategies, suggesting that infliximab straight after diagnosis was well tolerated, contrary to previous concerns about its safety. In addition, the cost of the drug, which is now an off-patent, generic and "biosimilar" medicine, has fallen considerably from around

£15,000 to around £3,000 per patient per year.

Chief Investigator of the PROFILE trial Professor Miles Parkes, Director of the NIHR Cambridge Biomedical Research Centre, said, "Up until now, the view has been 'Why would you use a more expensive treatment strategy and potentially over-treat people if there's a chance they might do fine anyway?'

"As we've shown, and as previous studies have demonstrated, there's actually a pretty high risk that an individual with Crohn's disease will experience disease flares and complications even in the first year after diagnosis.

"We now know we can prevent the majority of adverse outcomes, including need for urgent surgery, by providing a treatment strategy that is safe and becoming increasingly affordable. If you take a holistic view of safety, including the need for hospitalizations and urgent surgery, then the safest thing from a patient point of view is to offer top-down therapy straight after diagnosis rather than having to wait and use step-up treatment."

The PROFILE team is now actively working on an analysis of the health economics to see whether the benefits of the therapy outweigh its cost.

Professor Parkes added, "It's not just those five percent of people requiring surgery that we need to think about. In the step-up arm lots of people experienced disease flares without necessarily needing surgery. And every time somebody flares, they require several consultations with specialist doctors and nurses, clinical investigations such as scans and colonoscopies, time off work, time out of education and so on—all leading to major impacts on quality of life for individuals."

While there are other anti-TNF drugs, such as adalimumab, that work in

a similar manner to infliximab and are significantly cheaper, more research is required to understand if it would be as clinically effective.

Ruth Wakeman, Director of Services, Advocacy & Evidence at Crohn's & Colitis UK said, "Crohn's Disease affects over 200,000 people in the UK and we know that many of them have symptoms for a long time before they are diagnosed. But diagnosis is not the end of their journey, and the trial and error involved in finding the right treatment can be challenging and distressing.

"This study shows what a dramatic difference early treatment with advanced therapy can make to newly-diagnosed patients. People with Crohn's don't want to be stuck in hospital or having surgery, they want to be out in the world, living their lives. Anything that speeds up the path to remission can only be a good thing."

More information: PROFILE: a multi-centre, randomised, open-label, biomarker-stratified clinical trial of treatment strategies for patients with newly-diagnosed Crohn's disease, *The Lancet Gastroenterology & Hepatology* (2024). DOI: 10.1016/S2468-1253(24)00034-7

Provided by University of Cambridge