

Title of Project

Optimising thiopurine metabolite monitoring to allow personalised thiopurine treatment.

Lay Summary

Azathioprine and 6-mercaptopurine (6-MP) are the most frequent immunosuppressive drugs used in Crohn's disease and ulcerative colitis. Indeed, almost two-thirds of patients with Crohn's disease require this treatment to achieve a steroid free remission or help close fistulas. However, these treatments are not without their problems. Firstly, there is a considerable variation from person to person in response to treatment. Some will find complete relief from their symptoms whilst, despite prolonged courses, others find no benefit. Others may develop side effects resulting in withdrawal of treatment.

We now understand much about how the body handles azathioprine and 6-MP. Once inside the body, a complex network of enzymes acts upon the drugs with the end result being thiogaunine nucleotides (TGNs). These are considered to be the products which lead to the immunosuppressive effects of the drugs. We also know that there is considerable variation between individuals in that some individuals have enzymes missing from this network, putting the whole system out of balance. This can mean that toxic products build up and cause side effects. In other cases people may not be able to make the active end product (TGNs). If this happens the thiopurines will not work.

If we had a way to tell who will benefit from these treatments and who will run into problems this would revolutionise the way in which these drugs are used. So far the most promising technique appears to be monitoring the active end-products of the thiopurines called TGNs. However, whilst promising, these results are not yet accurate enough for use in everyday practice.

The current techniques measure TGNs in red blood cells. However, this is not the best place to take these measurements, both because these cells are not where we need TGNs to be active, but also because red cells don't have some of the important enzymes that handles these drugs. This means that they may deal with thiopurines differently than the rest of the body. We want to measure TGNs in white blood cells (where they are actually working) and platelets instead. Because these cells contain all the enzymes they need to deal with thiopurines, taking measurements here is much more meaningful.

The second complicating factor is that there are three different types of TGN, but the method that is usually used to measure them cannot tell the difference between these types. If only one of these three types is active and important (as recent evidence suggests), production of the others is either harmful or wasteful or both. We propose to

measure each subtype separately to see whether one of these measurements is accurate enough to predict response to treatment.

By combining these two approaches we hope to turn TGN measurements into a clinically useful service predicting those people who will never respond to thiopurines so that they can change over to another type of treatment as soon as possible. In those who are helped by the thiopurines, we will also be able to personalise their treatment, using our measurements to establish the perfect dose for each individual.