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Investigation of the role of ABCB5 in corticosteroid transport and response in IBD

Lay Summary

Steroids (also known as corticosteroids) such as prednisolone are widely used in the treatment of both ulcerative colitis and Crohn's disease. However, some patients do not respond to steroids - these patients can be considered to have "steroid resistance". We do not know why some patients are resistant to steroids.

Recent studies in Edinburgh have shown that steroid resistance may be related to a gene termed ABCB5 (ATP-binding cassette, sub-family B member 5). This is a highly novel finding, and provides us with an important avenue for further investigation.

ABCB5 is a protein present in the gut wall where steroids are absorbed from, and in the white blood cells called lymphocytes, where steroids act in reducing inflammation. ABCB5 pumps drugs out of the cell. Therefore, we would hypothesise that if patients have increased activity of this pump (ABCB5) in the gut wall, it would reduce the absorption of the steroid, while increased activity in lymphocytes would lead to decreased levels of the steroid inside the cell where steroids need to act.

This application aims to evaluate the interaction of steroids with ABCB5. We will do this in several ways:

- using cell lines, determine whether steroids can be pumped out of cells by ABCB5;
- identify other drugs that can inhibit ABCB5
- determine whether the capacity of ABCB5 to pump out different steroids (prednisolone, hydrocortisone, methylprednisolone, dexamethasone and budesonide) varies;
- determine how much ABCB5 is present in the gut wall and lymphocytes, and whether this varies between different individuals; and
- determine whether steroids themselves can increase the level of in cells taken from patients who are known to be sensitive and resistant to steroids, and whether this up-regulation is different between the sensitive and resistant patients.

How will this help patients with steroid resistance? The studies outlined here will lead to more detailed studies which will evaluate how genetic variation in the ABCBS gene results in steroid resistance. The expected outcome from these studies would lead to one or more of the following:

- Better individualisation of therapy so that patients identified as being steroid resistant can be given different drugs rather than the current "trial and error" approach.
- Use of different steroids in different patients depending on how much ABCB5 they possess in their gut wall or lymphocytes.
- Development of inhibitors of ABCB5 so that its activity can be reduced which would allow higher levels of the steroid to be achieved in the cell.