ANTI-ADENOMA THERAPY IN FAP

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BACKGROUND

Familial adenomatous polyposis is caused by a germline mutation on chromosome 5q 21 leading to the development of multiple colorectal and upper gastrointestinal adenomas and an almost certain large bowel cancer risk if left untreated. The average age for cancer development in untreated patients was aged 39 years.

Modern surgical treatment of the large bowel component is either to perform colectomy and ileorectal anastomosis or to perform a pouch. With the former, the rectal remnant needs to be kept under surveillance as the risk of cancer development is high. In one study about 8% of patients developed cancer in the rectum by the age of 50, rising to 29% by the age of 60 (1).

The alternative pouch operation is not itself without risk of adenoma development. In our own series at St Mark’s Hospital 58% of our pouch patients have pouch adenomas and the risk is increased with patients’ age. The later risk of cancer is hard to quantify at this stage of pouch surgery in FAP. Two of our pouch patients have had advanced pouch polyps of large size and villous histology.

I am personally aware of three cases of actual pouch cancer in FAP patients (that is to say, not cancer arising from islands of mucosa left behind after mucosectomy or at the anal component of a stapled anastomosis).

Techniques of Anti-Adenoma Therapy

There are many ways to reduce the adenoma burden: physical, pharmacological/nutrient, photodynamic and experimental gene therapy to name but a few. Straightforward polyp fulguration can be time consuming, but we have found argon plasma coagulation to be safe, effective and well tolerated in the rectum. Experience within the thin-walled duodenum is limited not only by worries of perforation but also by the high argon gas flow rates leading to marked bloating and discomfort.

Early experience with photodynamic therapy was disappointing as each polyp requires prolonged exposure to light of a particular wavelength, the depth of necrosis is very superficial, and patients can become markedly sensitive to sunlight for a prolonged period (3).

Dietary/nutrient trials have focussed on added calcium (4), Vitamin C (5) and resistant fibre (the latter being in the CAPP -Concerted Action in Polyposis Prevention - study). The CAPP study has not yet reported and the effect of calcium and Vitamin C have been disappointing.

Until the emergence of COX2 inhibitors, sulindac was the drug of choice to treat rectal stump polyps, either orally in a standard dose or as a rectal suppository at a much lower dose of 25mg daily (6, 7). But combined COX1/COX2 drug regimens have been disappointing. For example, celecoxib, a COX2 inhibitor, in familial adenomatous polyposis, significantly reduced the number of large bowel polyps (8). A new study will test celecoxib along with difluormethylornithine.

Celecoxib is a COX2 inhibitor shown in a randomised controlled trial significantly to reduce large bowel polyps in FAP by 28% which is now licensed in the USA and a number of other countries, including Australia and Israel, as an adjunct to normal patient management (9). It does seem to have a duodenal effect (10). A new study will test celecoxib with difluormethylornithine.

The sulfinone derivative of sulindac has also been tested in a large randomised controlled trial in FAP patients. Whereas the primary end point in terms of polyp regression was not seen in this study, there are tantalising suggestions of efficacy, particularly on longer term therapy.

Finally, experimentally liposome-mediated APC gene therapy has been tested in MIN mice and has produced a 25% reduction in polyp burden. Locally applied as an enema this might also prove an interesting, albeit currently futuristic, way forward in man.

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Modern surgical treatment of the large bowel component is either to perform colectomy and ileorectal anastomosis or to perform a pouch. With the former the rectal remnant needs to be kept under surveillance every six months because of the cancer risk which seems to be age dependent. In one study about 8% of patients developed cancer in the rectum by the age of 50, rising to 29% by the age of 60 (1).

The alternative pouch operation is not itself without risk of adenoma development. In our own series at St Mark’s Hospital 58% of our pouch patients have pouch adenomas and the risk is increased with patients’ age. The later risk of cancer is hard to quantify at this early stage of pouch surgery in FAP. Two of our pouch patients have had advanced pouch polyps of large size and villous histology. I am personally aware of three cases of actual pouch cancer in untreated, the average age for cancer development in untreated patients being aged 39 years.

In treated FAP patients, upper gastrointestinal cancer is one of the foremost causes of death (2). In our recent experience, about one third of our patients with advanced (Spigelman stage IV) duodenal disease went on to develop duodenal adenocarcinoma and die from their disease over (Spigelman stage IV) duodenal disease went on to develop duodenal adenocarcinoma and die from their disease over this 20-year period. In the same period only 2% of patients with Stages III and II disease developed cancer respectively.

Presently we do not know what to do about pouch polyps. Except in the most advanced stages of duodenal polyposis, prophylactic pylorus preserving and pancreas preserving duodenectomy seems a therapy too far. Not all cases with an ileorectal anastomosis and advanced rectal polyposis are suited to pouch conversion. Some even cannot have the rectum removed because of coincidental desmoid disease. All of these patients are suitable for trials of anti-adenoma therapy.

TECHNIQUES OF ANTI-ADENOMA THERAPY

There are many ways to reduce the adenoma burden: physical, pharmacological/nutrient, photodynamic and experimental gene therapy to name but a few. Straightforward polyp fulguration can be time consuming, but we have found argon plasma coagulation to be safe, effective and well tolerated in the rectum. Experience within the thin-walled duodenum is limited not only by worries of perforation but also by the high argon gas flow rates leading to marked blossoting and discomfort.

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