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REVIEW

Endoscopic and chemopreventive management of familial adenomatous polyposis syndrome

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Abstract

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome predisposing affected individuals to gastrointestinal (GI) cancers through a high burden of polyposis. Colorectal cancer rates reach 100% by the age of 45, making early colectomy a mainstay of treatment. While most patients undergo colectomy at an early age, ongoing screening and surveillance of the upper gastrointestinal tract and rectal pouch must continue throughout adulthood. Endoscopic therapy of gastric, duodenal, ampullary and rectal pouch polyps is critical to reduce morbidity and cancer related mortality. Management of these lesions is not uniform, and is dependent on their location, size, histology, and risk of malignant potential. Medical therapies targeting pathways that reduce the malignant progression of pre-cancerous lesions have been studied for many years. While studies on the use of aspirin and non-steroidal anti-inflammatories (NSAIDs) in chemoprevention have shown encouraging results in Lynch syndrome and primary colorectal cancer, the potential benefits of these medications have not been duplicated in FAP cohorts. While data remains limited on chemoprevention in FAP, a number of randomized trials are currently underway examining targeted therapies with the potential to slow the progression of the disease. This review aims to provide an in-depth review of the literature on current endoscopic options and chemopreventive therapies targeting FAP. While the endoscopic management has robust data for its use, chemoprevention in FAP is still in its infancy. The complementary use of chemopreventive agents and endoscopic therapy for FAP patients is quickly becoming a growing and exciting area of research.

Keywords Familial adenomatous polyposis syndrome · FAP · Hereditary cancer · Endoscopic management · Chemoprevention

Background

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome which predisposes affected individuals to gastrointestinal cancers because of a high burden of gastrointestinal (GI) polyposis. FAP has a prevalence of 1 in 10,000 and is the second most prevalent inherited colorectal cancer syndrome (behind Lynch syndrome) [1]. The risk of developing colorectal cancer (CRC) nears 100% by age 35–45, and thus early identification and management of these patients in the form of colectomy is recommended [1].

Routine surveillance is required for patients with FAP, in the form of both upper and lower endoscopy, as well as consideration of small bowel screening [2–5, 7–11]. The role of endoscopy in the management of hereditary polyposis syndromes is likely to grow with the advancement of endoscopic therapies and endoluminal surgery. Furthermore, research in chemopreventive agents aimed at slowing the

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progression of polyposis in FAP is emerging and provides an exciting outlook on future preventative management of these patients.

This review will aim to outline the current endoscopic and chemopreventive options available in the management of FAP patients. We set out to describe current guideline recommendations and data to support the use of endoscopy in the surveillance and management of FAP, as well as recent research on chemopreventive agents.

Genotype and phenotype

FAP results from a mutation in the adenomatous polyposis coli (APC) gene, with mutations arising in the 5' end of the gene in classic FAP. FAP is diagnosed in those with classic polyposis (> 100 polyps within the colon) and identification of a mutation in the APC gene. FAP severity has been reported to be associated with codon mutation location, with more severe colonic disease found in patients with mutations between codon 1250 and 1464, and higher risk of periampullary adenomas occurring downstream from codon 1051 [5, 6].

Endoscopic management

It is critical for practitioners who manage FAP patients to be well versed in the endoscopic management of the condition. While most patients undergo colectomy at an early age, ongoing screening and surveillance of the upper gastrointestinal tract and rectal pouch must continue throughout adulthood, which has been well described in multiple national and international guidelines [2, 4, 7]. The following section will break down the endoscopic management into the different location in the GI tract affected by FAP: the colon and rectal pouch, duodenum, stomach and small bowel.

Colon

Screening for colonic polyps should begin early in children diagnosed with FAP, with various guideline suggesting initiating colonoscopy between the ages of 10–14, or even earlier depending on the age of colorectal cancer in the proband [5, 7,[11]. As the rates of colon cancer in FAP patients reaches 100% by age 45, regular surveillance is necessary to screen for high-risk lesions [1]. Polyps should be carefully inspected and those with high-risk features removed. High risk features include polyps ≥ 10 mm or evidence of dysplasia based on polyp identification classifications, such as the Kudo or NICE classifications. Early referral for surgery should be made if there is a significant polyp burden that cannot be managed endoscopically, presence of high-grade dysplasia on biopsy or polypectomy, and multiple larger adenomatous polyps (≥ 6 mm or ≥ 10 mm) [2, 4]. Given the low risk of colorectal cancer or high-risk colonic polyps in pediatric patients, a 10 mm cut off is recommended for consideration and discussion on early colectomy [12, 13].

The timing of colectomy in FAP patients requires an in-depth discussion between both patient and care providers. The National Comprehensive Cancer Network (NCCN) recommends surgery be considered in late adolescence or early adulthood, dependent on a multitude of factors including phenotype, genotype and patient involvement [14, 15]. FAP possesses a number of unique challenges in determining the timing of surgery, most importantly the young age at which these patients must participate in shared decision making [16]. Psychosocial considerations include intellectual and educational development of the patient, along with career goals and aspirations, all of which must be weighed against the risk of colorectal cancer development [7]. Changes in quality of life can have a profound impact on the desire and timing of colectomy and a multi-disciplinary, patient centered approach is essential when discussing surgical timing.

There are four accepted surgical options that are recommended in surgical guidelines: total colectomy with ileorectal anastomosis (IRA), proctocolectomy with stapled ileal-pouch anal anastomosis (IPAA), total proctocolectomy with end ileostomy and proctocolectomy with mucosectomy and IPAA [7]. The decision on which surgery to perform is dependent on a number of factors, including expert opinion, the desire to decrease the degree of pelvic dissection in order to preserve fertility, aggressive FAP phenotype (> 1000 adenomas), high risk adenomas (high grade dysplasia or polyps > 30 mm), as well as the presence of rectal adenocarcinoma [7]. Screening of the rectal pouch should be performed in those without total proctocolectomy given the risk of developing ileo-rectal pouch adenomas [17]. Larger adenomas and polyps should be removed using a cold snare or hot cautery (if ≥ 1.5 cm), while smaller diminutive polyps should be removed with biopsy forceps and sent for pathology. Re-referral to a colorectal surgeon who specializes in IPAA surgeries and revisions should be made if there is any indication of high-risk adenomatous polyps, malignancy, or anal canal cancers.

Duodenum

Duodenal adenomas are common in FAP, with the cumulative risk of developing a duodenal adenoma by the age of 70 as high as 90% [18]. The risk of progression to malignancy has been variable in different studies. Campos et al. reported a duodenal malignancy rate of 3.9% in a series of 140 FAP patients; Bulow et al. followed 304 patients with FAP in four Nordic countries (Denmark, Sweden, Finland and the Netherlands) and reported a lifetime risk of duodenal

adenomas of 88%, with 7% developing a duodenal cancer; and Bjork et al. reported a cumulative adenocarcinoma risk of as high as 10% by age 60 in a cohort of 180 patients with FAP [6, 19, 20]. In general, the reported prevalence of duodenal malignancy in FAP patients is approximately 5% [21].

Current guidelines recommend screening for upper gastrointestinal polyps in patients with FAP beginning at age 20–25, with esophagoduodenoscopy (EGD) performed in intervals that vary depending on the Spigelman classification [3, 4, 7, 10]. The Spigelman classification was developed for non-ampullary duodenal adenomas and correlates with risk of progression to duodenal malignancy, with higher stage corresponding to a higher risk of malignancy. The classification criteria take into consideration the number of polyps found, the size of the polyps, the histology of the polyps, and the degree of dysplasia [22]. For Spigelman 0 or I, EGD should be performed every 5 years, every 3 years for Spigelman II, annual with consideration of endoscopic resection for Spigelman III, and every 6–12 months with consideration of endoscopic or surgical intervention for Spigelman IV [2, 23]. It is important, however, to pay careful attention to any duodenal polyp that harbors high risk endoscopic features. These polyps, as with any other duodenal adenoma, should be removed endoscopically and followed up closely.

We recommend a careful examination of the duodenum with a forward viewing scope, followed by a close inspection of the ampulla and periampullary region with a side-viewing duodenoscope, which is also supported by ASGE Guidelines [3]. A distal attachment cap can be used on the forward viewing gastroscope to assist in examining between folds in the second and third part of the duodenum and assists in stabilizing the scope for careful inspection [3]. While the ampulla can, on most occasions, be visualized with a distal attachment cap on a forward viewing gastroscope, the authors suggest proper side-viewing examination of the ampulla if there is any doubt as to adequate visualization of the ampulla with a distal attachment cap. Rates of duodenal adenoma detection increase as much as two-fold when utilizing a side viewing duodenoscope in FAP patients when compared to a standard gastroscope without a distal attachment cap [22]. Roos et al. recently reported the outcomes of duodenal and ampullary adenoma resection in a cohort of 224 FAP patients, of which 67 underwent duodenal interventions. 68 duodenal intervention sessions were performed on 49 patients, with a total of 139 adenomas removed over the study period (mean size 15 mm). Endoscopic mucosal resection was the most common polypectomy method (85%), followed by cold snare polypectomy (11%). Adverse events were minimal: bleeding was the most common event (13%) and were all managed endoscopically. Recurrence rates over 17 month follow up were 23% [24].

An ampulla displaying ulceration, friability, nodularity, or one in which submucosal lifting is unsuccessful warrants surveillance biopsy to assess for dysplasia. Ampullary lesions (in comparison to non-ampullary duodenal lesions) in FAP have been reported to be less aggressive than sporadic ampullary adenomas, however patients with FAP have a 124-fold increased risk of developing these lesions as compared to the general population [25]. One retrospective study examining 95 FAP patients who underwent surveillance for ampullary adenomas reported 12.6% (n = 12) who developed advanced ampullary adenomas, with the remaining showing stable disease. 10 of these patients underwent ampullectomy, and while all had technical success, 30% had residual disease and 10% developed recurrence [26]. Another recent systematic review of 6 studies including 99 patients reported high technical success of ampullectomy in FAP patients, with a pooled rate of 90.3% and an en-bloc resection rate of 60.6%. The success of these findings is, however, limited by a high recurrence rate (25.4%) and adverse events of bleeding (9.2%), pancreatitis (14.7%) and perforation (4%) [27]. Nonetheless, many of these recurrences can be managed endoscopically and avoids another major surgery (pancreaticoduodenectomy) in this patient population, most who have already undergone colectomy.

Recent guidelines on the management of hereditary cancer syndromes published by the joint British Society of Gastroenterology (BSG), Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the United Kingdom Cancer Genetics Group (UKCGG) in 2020 advises against routine ampullectomy in patients with FAP given higher complication and recurrence rates, which is also supported by other European guidelines [2]. Multidisciplinary discussion and careful consideration in consultation with hepatobiliary (HPB) surgery in a dedicated HPB center should be made prior to proceeding with endoscopic ampullectomy.

Stomach

The risk of gastric cancer in patients with FAP has historically been rare, however there has been an increasing incidence in gastric cancer in both Western and Asian populations [28]–[30]. In Japan, the rate of gastric cancer in FAP patients has increased from 2.2% pre-1990 to 2.8% between the years of 1993–2003 [30]. The incidence of gastric cancer has been increasing in the US as well, with one of the largest hereditary cancer registries reporting an incidence of 1.3% between the years of 2006 and 2016. Previously, the registry had no reported cases of gastric cancer in FAP patients dating back to 1979 [29]. This increased risk sheds light on the importance of regular upper endoscopic screening in FAP patients for not only duodenal adenomas and malignancy, but gastric as well. While current guidelines recommend screening with EGD beginning at age 20–25, small studies have reported gastric polyposis with adenomatous

changes in pediatric FAP patients ranging from 40 to 67% [12, 31, 32]. Given the rise of gastric cancer in FAP patients and higher rates of dysplastic changes in gastric polyps in pediatric patients, further large-scale follow up studies are needed to determine the appropriate age to begin screening with EGD.

The most common gastric polyp encountered in FAP are fundic gland polyps (FGP's), which have been reported to be present is as high as 88% of FAP patients [33]. While these polyps are largely benign, Bianchi et al. reported a 41% prevalence of dysplasia, 3% of which were high grade dysplasia (HGD). The FGP's identified as HGD were targeted for biopsy based on their large size (> 10 mm) and irregular appearance, with FGP's > 10 mm having 15.9 (95% CI 1.2, 207.2) greater odds of harboring dysplasia. Furthermore, dysplastic FGP's were associated with degree of duodenal polyposis, with a nearly twofold increase in dysplastic gastric polyps with each increasing Spigelman stage [33]. Mankaney et al. reported similar findings when examining gastric adenocarcinoma in FAP patients, all of which had either carpeting proximal FGP's, thick mounds of polyps or large (> 9 mm) size [29]. One important endoscopic finding for practitioners to be aware of is the proximal white mucosal patch (WMP), first described by Cavalas et al. in 2016 in 3 FAP patients, two of which showed high grade dysplasia and one which showed low grade dysplasia [34]. A follow up study by Das Kannathu et al. found a WMP in 1.8% of the 768 FAP patients and reported its association with other high risk endoscopic features. 14.3% of patients with WMP had proximal gastric adenocarcinoma, with the authors recommending these lesions be excised entirely and patients followed more closely [35].

We agree with the recommended management of these polyps previously suggested by Bianchi and Mankaney [29, 33]. For early Spigleman stage duodenal polyposis (Stage 0-II) with low grade dysplasia in FGP's, EGD should be performed every 3 years, and should be performed annually in Stage III Spigleman patients. Stage IV patients with LGD in FGP should have gastric polyposis surveillance every 3–6 months. If any HGD is found in a gastric FGP, EGD should be performed every 3–6 months with targeted polypectomy for high-risk lesions [33].

Small bowel

Data on routine small intestinal surveillance in FAP patients is not as robust as the colon, duodenum and stomach and has primarily been reported in small trials and observational studies [36–41]. Burke et al. reported 60% small bowel polyp prevalence on 15 FAP patients undergoing video capsule endoscopy (VCE) [40]. Increasing polyp burden was found in those with higher Spigelman stages and older age, and only in those with Spigelman stage III or IV [40]. Iaquinto et al. followed 23 FAP patients in two large Italian referral centers, reporting a small bowel polyp in 7 (30.4%) patients. While they did not look specifically at Spigelman stage, the presence of duodenal polyps was predictive of small bowel polyposis [41]. The use of VCE has been compared to both MR Enterography (MRE) and small bowel follow through (SBFT), both of which were unable to identify polyps distal to the duodenum with the same accuracy as VCE [42]. Therefore, we do not recommend the use of either MRE or SBFT to identify polyposis throughout the small bowel.

The rates of jejunal or ileal cancers in FAP patients are exceedingly low in the reported literature [43]. Prospective evaluation of jejunal polyposis, even in the presence of severe duodenal polyposis, has not shown to yield elevated rates of jejunal carcinomas [44]. While intussusception as a complication of Peutz–Jeghers syndrome is well reported, this has been a case-reportable phenomenon in FAP [45, 46]. Given the uncertainty of the significance of small bowel polyposis, we do not recommend routine video capsule endoscopy in FAP patients in the absence of duodenal polyposis. For those with Spigelman stage III or IV duodenal polyposis, VCE can be considered to screen for high-risk lesions, although this should be done on a case-by-case basis and in discussion with each patient.

Chemoprevention in familial adenomatous polyposis

Significant effort has been made to investigate chemoprevention in hereditary polyposis syndromes, particularly in FAP, for colonic and duodenal polyps. Despite advances in the genetic understanding of FAP, surgical techniques, and endoscopic resection, patients with FAP continue to struggle with significant impacts on their quality of life, including the morbidity of surgery, risk of disease progression, and long term endoscopic surveillance. Furthermore, as surgery and endoscopic surveillance do not completely obviate ongoing polyp growth, the need for adequate chemoprevention is justified as it may forestall a major invasive procedure or slow the development of new polyps. This section will review current literature for chemoprevention in FAP.

Aspirin

Aspirin is non-selective and irreversibly inhibits cyclooxygenase (COX) 1 and COX2. Numerous studies and meta-analyses in the general non-FAP population, including other familial colorectal cancer syndromes, have demonstrated that aspirin decreases the risk of developing advanced adenomas and colorectal cancer [47, 48]. One of the largest studies examining this was the CAPP2 trial, which recently reported results for 10 year follow up in Lynch syndrome

(LS) carriers, showing a significant reduction in colorectal cancer and advanced adenomas [49]. This signal extended to 20 years in English, Finnish and Welsch patients who had data monitoring over a longer period of time. However, as the prolonged use of aspirin increases the risk of gastrointestinal bleeding, it is currently recommended for CRC prevention in select patients with high-risk cardiovascular disease and LS [47]. The data evaluating aspirin chemoprevention in FAP are limited and equivocal [50, 51]. The larger of the two studies evaluating aspirin chemoprevention in FAP was by Burn et al. who evaluated rectosigmoid polyps in 133 patients with FAP aged 10–21 years over a median treatment period of 17 months [52]. Participants were given 600 mg daily and 30 mg starch daily in combination and separately. This multicenter study did not reach statistical significance and reported no reduction in the risk of rectosigmoid polyps. Although there was no decrease in polyp number, it did demonstrate a trend towards smaller polyp diameter ($p = 0.05$) and a significantly decreased polyp diameter if treated for ≥ 1 year ($p = 0.02$). Ultimately, this study was limited by its brief treatment and follow-up period. The second, much smaller Japanese study by Ishikawa et al. randomized 34 FAP patients to 100 mg of aspirin daily or placebo [53]. Unfortunately, recruitment was suspended early, despite the low dose of aspirin, due to the development of severe anastomotic ulceration in a study patient. Although the results were not statistically significant and underpowered to assess the primary endpoint of change in polyp number/burden, the authors found that a higher proportion of patients in the aspirin arm had a reduced polyp burden.

Non-aspirin NSAIDs (celecoxib and sulindac)

Non-aspirin non-steroid anti-inflammatory drugs (NA-NSAIDs) competitively inhibit COX1 and COX2. COX2 is upregulated in colonic adenoma formation and higher COX-2 expression levels are associated with adenoma features predictive of malignant transformation [54]. Furthermore, there are data to suggest that a disrupted *APC* signaling pathway, as in FAP, can drive chronic overexpression of COX2 [55, 56]. Given the close interaction of COX2, the *APC* gene within the Wnt pathway, and development of polyps/malignancy, several medications that inhibit COX2, have been studied as chemoprevention in FAP.

Celecoxib, a selective COX2 inhibitor, was first investigated in 2000 by Steinbach et al. in a randomized controlled trial of 77 FAP patients pre- and post-colectomy who were assigned to one of three treatment arms over 6 months: placebo, celecoxib 100 mg twice daily, or celecoxib 400 mg twice daily [57]. There was a statistically significant decrease in the number of polyps ($p = 0.003$) and polyp burden ($p = 0.001$) in the high-dose celecoxib group compared to placebo with no differences in adverse events. Further analysis of this same cohort demonstrated a significant decrease in duodenal polyposis and area of duodenal disease in the high-dose celecoxib group not seen with the low-dose group [58]. A multicenter, double-blind randomized controlled study by Burke et al. followed 85 children with FAP over 5 years assigned to weight-based celecoxib or placebo [59]. The study was discontinued early due to low occurrence of colorectal polyposis progression in the celecoxib arm. Even in patients who had polyposis progression, it occurred later (2 years vs 1.1 years) in the celecoxib arm than the placebo arm. Ultimately, although celecoxib was the first medication for chemoprevention approved by the United States FDA, its widespread adoption has been limited due to cardiovascular toxicity concerns with long-term, dose-related celecoxib and other COX2 inhibitor use. Further, studies evaluating celecoxib have not shown a reduction in rates of colectomy, colorectal cancer, or death.

Sulindac is another NSAID that also affects non-COX pathways that has been studied in the FAP population for chemoprevention over the last 45 years. Initial studies evaluating sulindac were limited but demonstrated an improvement in rectal adenoma burden, paving the way for the first randomized trial, albeit small, by Giardiello et al. in 1993 demonstrating that sulindac 150 mg twice daily reduces polyp count by 56% and polyp diameter by 65% [60–62]. While initially promising, a "rebound effect" was observed with an increase in polyp size and number shortly after discontinuation of therapy, suggesting the agent did not result in prolonged polyp suppression. Then, in a 2002 randomized study, Giardiello et al. followed 41 teenage children with pathogenic *APC* mutations and no polyps between the anal verge and 20 cm on sigmoidoscopy [63]. The patients were randomized to receive weight-based sulindac or placebo and followed over 4 years with regular endoscopic surveillance. In contrast to their previous study, there was a drop-out rate of 27% due to the progression of polyps and no significant difference in polyp count or diameter between the two groups. Although variations in the dosing of sulindac have been studied, 150 mg twice daily is the most commonly administered dosage. Small trials evaluating sulindac for duodenal adenomas in FAP have shown mixed results with limited benefit [64]. More recently, a long-term retrospective observational study in Germany of 59 FAP patients subdivided by phenotype utilizing sulindac in weight-based dosages twice per day and regular endoscopic surveillance over 7.4 years [range 2–19 years] demonstrated a significant decrease in polyp burden or stable disease enabling endoscopic disease management in 58 patients [65]. Although findings in the upper GI tract were not as robust, there was minimal toxicity. This study supports the further evaluation of sulindac in combination with other medications for chemoprevention.

Combination therapies

To prevent resistance to drug therapy, minimize toxicity, and simultaneously utilize multiple mechanisms of action, significant effort has been employed for combination drug therapy. These trials have studied difluoromethylornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase (ODC), and erlotinib in combination with NSAIDs. Overexpression of ODC has been described in the colorectal mucosal cells of patients with FAP and preclinical trials of DFMO/NSAID in mice produced an additive effect in reducing intestinal tumor number [66, 67]. Based on these findings and a randomized study by Meyskens et al. in the non-FAP population demonstrating a significantly lower risk of developing any adenoma, an advanced adenoma, or multiple adenomas with DFMO/sulindac, Lynch et al. conducted a double-blind, multicenter, randomized trial between 2001 and 2008 of DFMO/celecoxib versus celecoxib with adult FAP patients [68, 69]. Although results (polyp count, polyp burden) in the intention-to-treat analysis were not significant (including the primary endpoint, polyp burden) for combination therapy, analysis of global polyp burden as assessed by video supports the hypothesis that combination therapy can improve overall polyposis versus celecoxib alone. However, it is unknown if this finding will render any clinical benefit due to the short treatment course [51, 70]. To evaluate the clinical benefits of DFMO/NSAID therapy more rigorously, Burke et al. performed a randomized controlled trial of 171 FAP patients who received daily eflornithine (DFMO)/sulindac, eflornithine/placebo, or sulindac/placebo for up to 2 years with regular endoscopic surveillance every 6 months [71]. The results showed that the incidence of disease progression was not significantly lower with combination therapy than with either drug alone. There was also no benefit to duodenal polyposis with combination therapy. Importantly, however, analysis of lower GI tract polyposis showed that no patients in the combination arm, in contrast to those randomized to monotherapy, with an intact colon or post-colectomy with an intact rectum required surgery or complex polyp resection. This critical finding demonstrates that combination therapy may suppress overall colonic polyposis and delay the need for colectomy. Furthermore, combination therapy was not more toxic than either drug alone.

Several studies have evaluated NSAID combination therapy with erlotinib, an epidermal growth factor receptor inhibitor, after successful preclinical data in mouse models with *APC* mutations. The FAPEST trial by Samadder et. al randomized 92 FAP patients with duodenal polyposis to daily erlotinib/sulindac combination therapy or placebo over 6 months with endoscopic evaluation occurring at baseline and at the end of the treatment period [72]. Despite the short treatment time, the results demonstrated a statistically significant decrease in the size and number of duodenal polyps in the treatment arm. A secondary analysis of the FAP patients in this study with a remnant rectum also found a statistically significant decrease in the total colorectal polyp number in the combination therapy group at 6 months [73]. Although the results are promising, long-term erlotinib use is associated with cardiotoxicity, interstitial lung disease, and dermatologic side effects limiting its use as a practical chemopreventive agent [72]. To offset these adverse effects seen with daily erlotinib dosing, a single-arm multicenter trial by Samadder et al. evaluated the safety and efficacy of reducing duodenal adenoma burden with once weekly erlotinib dosing in the FAP population [74]. Of the 46 FAP patients studied over 6 months with weekly erlotinib dosing, duodenal adenoma burden was reduced by 30% ($p < 0.0001$). Lower GI polyp burden was also significantly reduced by a median of 30% ($p = 0.03$). While most patients still reported adverse events, they were lower grade and well-tolerated. At this time, a cost-effectiveness analysis has not been performed on erlotinib for chemoprevention in FAP, however it has been shown to be cost-effective in other non-GI malignancies [75].

Other agents (sirolimus, ascorbic acid, curcumin, fish oil, rapamycin etc.)

Although NSAIDs have been primarily studied for chemoprevention in FAP, several other agents have also been evaluated. Promising preclinical data led Cruz-Correa et al. to conduct a randomized trial of curcumin monotherapy versus placebo for 6 months in 44 FAP patients for lower GI polyposis [76]. Unfortunately, no efficacy in reducing colorectal adenoma count, polyp size, and overall burden was seen. Next, certain free fatty acids have been associated with a reduction in COX2 levels, leading to a study by West et al. evaluating fish oil in controlling FAP progression [77]. 58 FAP patients were randomized to fish oil versus placebo over 6 months. The results showed a statistically significant reduction in polyp size and polyp count with no adverse events. However, as the exact mechanism of action is unclear and consistent results with fish oil have not been demonstrated, this therapy has not yet been widely adopted. Finally, vitamin C, or ascorbic acid, has long been associated with antineoplastic properties. A study by Bussey et al. randomized 49 FAP patients to daily ascorbic acid versus placebo over 18 months with regular endoscopic surveillance every 3 months [78]. There was no difference seen in the number of polyps between groups and significant decrease in polyp area seen at 9 months was lost by 12 months.

Finally, the mammalian target of rapamycin (mTOR) pathway may be a novel target for chemoprevention in FAP, as it plays a critical role in epithelial cell growth. Preclinical studies in *APC* mutant mice have demonstrated decreased epithelial proliferation and tumor growth when mTOR is

inhibited [79]. In particular, treatment with sirolimus in mice has shown polyp regression and increased survival [80]. Roos et al. have recently published a case series of 4 FAP patients treated with sirolimus over 6 months for rectal remnant and ileal pouch polyps [81]. Although there was significant toxicity related adverse events in all patients, even making one patient withdraw from the study, there was marked polyp size and number decrease noted. Although currently limited by toxicity as a chemopreventive agent in FAP, studies of other mTOR inhibitors which are well-tolerated (i.e., encapsulated rapamycin) are being initiated.

Ongoing trials

There are several ongoing trials testing new chemopreventive agents in combination for FAP. These trials include erlotinib monotherapy for duodenal polyposis (NCT02961374), guselkumab on adenoma burden to target the IL-23 pathway (NCT03649971), encapsulated rapamycin (NCT04230499) on adenoma burden, and butyrated high amylose maize starch (HAMSB), among others [70, 82]. Ultimately, the ideal chemopreventive agent or combination of agents for colorectal and duodenal polyposis in FAP has not yet been determined despite the numerous trials described above. While there is no current society or national guideline for routine use of chemoprevention, expert consensus recommends its use only in large tertiary hereditary cancer clinics or as part of ongoing research in a clinical trial setting.

Conclusions

The endoscopic and chemopreventive management of FAP has advanced over the years. While certain areas of endoscopic management have robust (and expanding) data for its use, chemoprevention in FAP is still in its infancy and will be a dynamic area of research with promising new studies on the horizon. As we continue to study outcomes of FAP in the future, a complementary role of endoscopy and chemoprevention in the long-term management of these patients will be critical for improving outcomes.

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