80900_Auto_Edited.docx

WORD COUNT	4743	TIME SUBMITTED	20-DEC-2022 10:27AM
		PAPER ID	94183745

7
Name of Journal: *World Journal of Gastrointestinal Endoscopy*

Manuscript NO: 80900

Manuscript Type: MINIREVIEWS

Endoscopic and chemopreventive management of familial adenomatous polyposis syndrome

Review on familial adenomatous polyposis management

James K Stone, Neal A Mehta, Harminder Singh, Wael El-Matary, Charles N Bernstein

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.

Studies on the use of aspirin and non-steroidal anti-inflammatories (NSAIDs) in chemoprevention have shown only modest results in Lynch syndrome and colorectal cancer. The 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.

This review aims to provide an in-depth review of the literature on current endoscopic options and chemoproventive 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 an growing and exciting area of research.

Key Words: Familial adenomatous polyposis syndrome, FAP, hereditary cancer, endoscopic management, chemoprevention

Stone JK, Mehta NA, Singh H, El-Matary W, Bernstein CN. Endoscopic and chemopreventive management of familial adenomatous polyposis syndrome. *World J Gastrointest Endosc* 2022; In press

Core Tip: 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. While data remains limited on chemoprevention in FAP, a number of randomized trials are currently underway examining targeted therapies.

INTRODUCTION

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 to 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[2–4]. 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 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.

LITERATURE SEARCH STRATEGY

The Reference Citation Analysis (RCA) tool was used to search the available body of literature, using the terms "familial adenomatous polyposis", "FAP", "endoscopic management of FAP", "chemoprevention and FAP" and "management of FAP". A PubMed search was performed using the same search terms.

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. The exact codon location of the mutation plays an important role in the phenotype and severity of FAP. For instance, attenuated FAP (AFAP) is a variant of FAP which presents with a smaller burden of polyposis and a less rapid progression to malignancy, with CRC often not diagnosed until the 6th or 7th decade[5]. Mutations in both the 5′ and 3′ end of the gene have been reported, and as a result these patients display a slightly different phenotype than the traditional FAP patients, often much milder and presenting with fewer than 100 colonic adenomas[5]. In addition, those with AFAP are more likely to be diagnosed with right-sided CRC and have a lower burden of duodenal polyps[5–7].

Mutations in the MutY homologue (MYH) gene results in MYH associated polyposis (MAP), a second phenotypically similar and related condition that presents with less polyposis and later in life[8]. While the risk of developing CRC in MAP is lower and later than FAP, MAP is often classified as a subtype of AFAP given their similarities[7]. FAP severity has also 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[9,10].

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[2–4,11]. 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. The following review is directed towards the management of FAP patients, and not specifically transferrable to management of FAP subtypes, which is out of the scope of this literature review.

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[9,11–15]. 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]. All polyps ≥5mm should be carefully inspected and removed using a cold snare and multiple polyps if not removable biopsied. Early referral for surgery should be made if there is a significant polyp burden resulting in inability to biopsy all, presence of high-grade dysplasia on biopsy or polypectomy, increase in polyp burden, and multiple larger adenomatous polyps (≥6mm or ≥10mm)[2,4]. Given the low risk of colorectal cancer or high-risk colonic polyps in pediatric patients, 10mm cut off is recommended for referral for early colectomy[16,17].

The formation of an ileal-pouch anal anastomosis (IPAA) is the standard of care for FAP patients undergoing colectomy. Annual screening of the rectal pouch should be performed given the risk of developing ileo-rectal pouch adenomas[18]. Larger adenomas and polyps should be removed using a cold snare or hot cautery (if ≥1.5cm), 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%[19]. 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[10,20,21]. In general, the reported prevalence of duodenal malignancy in FAP patients is approximately 5%[22].

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[3,4,11,14]. 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[23]. 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 mo with consideration of endoscopic or surgical intervention for Spigelman IV[2,7].

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[23]. 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 15mm). 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 mo 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 40-67%[16,31,32]. 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 (>10mm) and irregular appearance, with FGP's >10mm 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 2-fold 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 (>9mm) size[29].

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 mo. If any HGD is found in a gastric FGP, EGD should be performed every 3-6 mo with targeted polypectomy for high-risk lesions[33].

Small bowel

Data on routine small intestinal surveillance in FAP patients is not as robust and the colon, duodenum and stomach and has primarily been reported in small trials and observational studies[34–39]. Burke *et al* reported 60% small bowel polyp prevalence on 15 FAP patients undergoing video capsule endoscopy (VCE)[38]. Increasing polyp burden was found in those with higher Spigelman stages and older age, and only in those with

Spigelman stage III or IV[38]. 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[39]. The rates of jejunal or ileal cancers in FAP patients are exceedingly low in the reported literature[40]. Prospective evaluation of jejunal polyposis, even in the presence of severe duodenal polyposis, has not shown to yield elevated rates of jejunal carcinomas[41]. While intussusception as a complication of Peutz-Jeghers syndrome is well reported, this has been a case-reportable phenomenon in FAP[42,43]. 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 familial adenomatous polyposis (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 may moderately decrease the risk of developing advanced adenomas and colorectal cancer, but only after long-term and continuous use[44,45]. 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 Lynch syndrome[44]. The data evaluating aspirin chemoprevention in FAP are limited and equivocal[46,47]. 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 mo[48]. 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[49]. 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[50]. Furthermore, there are data to suggest that a disrupted *APC* signaling pathway, as in FAP, can drive chronic overexpression of COX2[51,52]. Given the close interaction of COX2, the *APC* 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 mo: placebo, celecoxib 100 mg twice daily, or celecoxib 400 mg twice daily[53]. 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[54]. 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[55]. 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%[56–58]. 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[59]. 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[60]. 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[61]. 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[62,63]. 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 2001-2008 of DFMO/celecoxib *vs* celecoxib with adult FAP patients[64,65]. 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 *vs* celecoxib alone.

However, it is unknown if this finding will render any clinical benefit due to the short treatment course[47,66]. 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 mo[67]. 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 mo with endoscopic evaluation occurring at baseline and at the end of the treatment period[68]. 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 mo[69]. Although the results are promising, long-term erlotinib use is associated with cardiotoxicity, interstitial lung disease, and dermatologic side effects limiting is use as a practical chemopreventive agent[68]. 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[70].

Of the 46 FAP patients studied over 6 mo 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.

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 *vs* placebo for 6 mo in 44 FAP patients for lower GI polyposis[71]. 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[72]. 58 FAP patients were randomized to fish oil *vs* placebo over 6 mo. 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 adapted. 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 *vs* placebo over 18 mo with regular endoscopic surveillance every 3 mo[73]. There was no difference seen in the number of polyps between groups and significant decrease in polyp area seen at 9 mo was lost by 12 mo.

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[74]. In particular, treatment with sirolimus in mice has shown polyp regression and increased survival[75]. Roos *et al* have recently published a case series of 4 FAP patients treated with sirolimus over 6 mo for rectal remnant and ileal pouch polyps[76]. 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

Finally, 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, among others[66]. 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.

CONCLUSION

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.

80900_Auto_Edited.docx

ORIGINALITY REPORT

5%
SIMILARITY INDEX

PRIMARY SOURCES

1	link.springer.com Internet	167 words — 3%
2	www.mdpi.com Internet	27 words — 1%
3	www.consultant360.com Internet	18 words — < 1%
4	Kim, B.. "Chemoprevention in familial adenomatous polyposis", Best Practice & Research Clinical Gastroenterology, 201108/10 Crossref	16 words — < 1%
5	James K Stone, Charles N Bernstein, Harminder Singh, Wael El-Matary. "Prevalence of Gastroduodenal Polyps in Children With Familial Adenomatous Polyposis", Journal of the Canadian Association of Gastroenterology, 2020 Crossref	13 words — < 1%
6	Teresa M. Neuhann, Katharina Haub, Verena Steinke-Lange, Monika Morak, Andreas Laner, Melanie Locher, Elke Holinski-Feder. "Long-term chemoprevention in patients with adenomatous polyposis coli: an observational study", Familial Cancer, 2022 Crossref	13 words — < 1%

7 f6publishing.blob.core.windows.net
Internet

12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS