Familial Cancer (2021) 20:23–33
https://doi.org/10.1007/s10689-020-00189-y

REVIEW

Chemoprevention in familial adenomatous polyposis: past, present and future

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Received: 19 February 2020 / Accepted: 18 May 2020 / Published online: 8 June 2020

Abstract
Familial adenomatous polyposis (FAP) is a hereditary colorectal cancer syndrome characterized by colorectal adenomas and a near 100% lifetime risk of colorectal cancer (CRC). Prophylactic colectomy, usually by age 40, is the gold-standard therapy to mitigate this risk. However, colectomy is associated with morbidity and fails to prevent extra-colonic disease manifestations, including gastric polyposis, duodenal polyposis and cancer, thyroid cancer, and desmoid disease. Substantial research has investigated chemoprevention medications in an aim to prevent disease progression, postponing the need for colectomy and temporizing the development of extracolonic disease. An ideal chemoprevention agent should have a biologically plausible mechanism of action, be safe and easily tolerated over a prolonged treatment period, and produce a durable and clinically meaningful effect. To date, no chemoprevention agent tested has fulfilled these criteria. New agents targeting novel pathways in FAP are needed. Substantial preclinical literature exists linking the molecular target of rapamycin (mTOR) pathway to FAP. A single case report of rapamycin, an mTOR inhibitor, used as chemoprevention in FAP patients exists, but no formal clinical studies have been conducted. Here, we review the prior literature on chemoprevention in FAP, discuss the rationale for rapamycin in FAP, and outline a proposed clinical trial testing rapamycin as a chemoprevention agent in patients with FAP.

Keywords Familial adenomatous polyposis · Chemoprevention · Rapamycin · Mammalian target of rapamycin · Colorectal cancer

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary colorectal cancer (CRC) syndrome characterized by the development of innumerable colorectal adenomas. The incidence of this syndrome is approximately 1 in 8300, with onset typically in the second or third decade of life [1]. FAP results from a germline pathogenic variant in the adenomatous polyposis coli (*APC*) tumor suppressor gene on chromosome 5 [2]. *APC* regulates beta-catenin localization and cellular polarity and thus plays a critical role in cell cycle modulation. *APC* also has an important role in the maintenance of T-cell populations in the lamina propria that influence states of chronic inflammation and tumor progression [3, 4]. FAP is characterized by 93% penetrance by age 40 [5], and is associated with a variety of extracolonic manifestations, most notably duodenal polyposis and/or duodenal or periampullary adenocarcinoma [6]. The severity of the colorectal phenotype and the constellation of extracolonic manifestations are governed by the specific *APC* mutation present and can vary significantly [7].

Given the assured progression of colorectal polyposis to carcinoma, pre-symptomatic diagnosis of FAP, endoscopic

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assessment of polyp burden, and subsequent surveillance with colonoscopy and polypectomy are necessary to prevent cancer and help determine the timing and type of surgical intervention. Germline *APC* genetic testing in an affected individual and at-risk relatives (cascade testing) is indicated [8–10]. Once FAP is diagnosed, annual colonoscopy to assess polyposis burden is recommended, usually beginning between the ages of 12–15 [9, 10]. A baseline thyroid exam and ultrasound at time of diagnosis [11, 12] and upper endoscopy beginning between ages 20–25 to assess for the stage of duodenal polyposis are also recommended [8, 10].

Surgical consultation should occur at the time colorectal adenomas are detected. Indications for colectomy include symptomatic polyps, advanced adenomas including CRC, severe or progressive polyposis, a polyp burden that cannot effectively be managed by endoscopy, or when surveillance is otherwise impossible [9]. The surgical options include total abdominal colectomy with ileorectal anastomosis, restorative proctocolectomy with ileoanal pouch formation, and total proctocolectomy with a permanent ileostomy. While considerable surgical advances have been made, these operations are all life-altering and may be associated with morbidity and changes in quality of life [6]. Surgery is not curative of FAP and individuals remain at risk for development of extracolonic manifestations of disease as well as neoplasia in the rectum or ileal pouch which remains following colorectal surgery.

The need for frequent invasive surveillance procedures both pre- and post-operatively, requisite surgical intervention, and continued risk of systemic disease progression has compelled significant research into the role of chemoprevention in chronic management of FAP [13]. Ideal chemoprevention delays or mitigates the need for surgery by stabilizing or reducing polyp burden and delaying or preventing disease progression. An ideal preventive medication has low toxicity, is able to be tolerated indefinitely with durable response, is inexpensive and globally available, and has a reasonable biologic rationale for use. In this review, we will summarize the existing data on chemoprevention for FAP and explore how a novel mTOR inhibitor may be utilized for this purpose.

Medical of disease progression prevention

Celecoxib

Cyclooxygenase (COX), and particularly COX-2, is known to play a critical role in gastrointestinal polyp formation. COX-2 is upregulated in colonic adenomas, and higher COX-2 expression levels are associated with adenoma features predictive of malignant transformation [14]. The interaction between the *APC* gene, the Wnt/ß-catenin signaling pathway, and COX-2 expression is complex. ß-catenin is a transcription factor that upregulates expression of a number of genes involved in cell growth and division, including c-Myc [1]. *APC* prevents uncontrolled cell growth by targeting ß-catenin for degradation [15]. The Wnt/ß-catenin signaling pathway also increases COX-2 expression [16]. *APC* has also been linked to COX-2 activity, as cells taken from *Apc*-mutant zebrafish (which produced a truncated and nonfunctional *Apc* gene product) were found to have elevated levels of COX-2 [17]. In addition, in an $Apc^{\Delta 716}$ mouse model, the addition of a COX-2 knockout mutation produced fewer and smaller gastrointestinal polyps relative to mice with functional COX-2 [18]. In the same mouse model, selective inhibition of COX-2 decreased the number of gastrointestinal polyps in a dose-dependent fashion [18, 19]. COX-2 is initially expressed by subepithelial stromal macrophages and later by epithelial cells, suggesting that a paracrine interaction between the *APC* pathway in the epithelial cells and the surrounding microenvironment drives production of COX-2 and creates a state of chronic overexpression resulting in progression from polyp to adenoma and ultimately malignancy [18, 20]. Thus, *APC*, COX-2, and the polyposis phenotype appear to be closely linked.

Given the close relationship between COX-2 and *APC*, a number of medications known to inhibit the COX-2 pathway have been tested as possible chemotherapeutic preventative agents for patients with FAP. The use of celecoxib, a selective COX-2 inhibitor, was first investigated for use in patients with FAP by Steinbach et al. [21]. In this double-blind, placebo-controlled, randomized trial, 77 patients ages 18–65 with FAP who had already undergone colectomy but had at least five rectal polyps were assigned to one of three treatment arms: placebo, celecoxib 100 mg twice daily (BID), or celecoxib 400 mg BID. Patients were treated for 6 months, with endoscopy performed at baseline and repeated at 6 months to assess the response to treatment. Total number of polyps decreased by 28% in the celecoxib 400 mg BID group compared to 4.5% in the placebo group ($p = 0.003$). Polyp burden (defined as number of polyps and area involved) also decreased in the celecoxib 400 mg BID group relative to the placebo group ($p = 0.001$). No differences between groups in adverse events, including upper gastrointestinal ulceration, were noted. In further analysis of the cohort, Phillips et al. [22] assessed the impact of celecoxib on duodenal polyposis, with EGD performed at baseline and at the 6-month interval. Patients treated with celecoxib 400 mg BID showed a qualitative improvement in duodenal polyposis ($p = 0.033$) and quantitatively decreased area of duodenal disease ($p = 0.049$). Conversely, treatment with celecoxib 100 mg BID did not result in a significant improvement in either EGD findings or area of duodenal disease involvement,

indicating that the higher dose of celecoxib was necessary to produce a clinically evident response.

To address concerns related to the short duration of treatment used in the studies above and to investigate the use of celecoxib in a much younger patient cohort, Burke et al. [23] conducted a multicenter, double-blind, randomized, placebo-controlled trial evaluating celecoxib in children with FAP over a 5-year treatment period. The primary endpoint of this study was the progression of colorectal polyposis to ≥ 20 polyps > 2 mm in size or the diagnosis of colorectal malignancy. Of 106 patients randomized to receive weight-based celecoxib (up to a dose of 16 mg/kg/day) or placebo, 85 patients were still active when the study was discontinued early due to the low occurrence of disease progression observed in the study population. At that time, four patients in the celecoxib group and seven patients in the placebo group had completed the full 5-year treatment course, and the median duration of treatment was 23 months in the celecoxib group versus 25.5 months in the placebo group. On intention-to-treat analysis, fewer patients in the celecoxib group reached the primary endpoint (progression) in comparison to the placebo group (12.7% vs 25.5%). Time to treatment failure, with treatment failure defined as polyposis progression (as described previously), occurred later in the celecoxib group relative to the placebo group (2.0 years vs 1.1 years). There was no difference in number of adverse events between groups. Based on this study, celecoxib appears safe for use in pediatric populations and may slow colorectal polyposis progression.

Though celecoxib ultimately became the first chemoprevention medication approved by the Food and Drug Administration for treatment of colorectal polyps in patients with FAP, a number of important limitations have precluded widespread adoption of celecoxib as a prophylactic agent. Other than the trial by Burke et al. the studies above followed patients for only 6 months, a period of time too abbreviated to evaluate for either a durable treatment effect or a toxicity profile after prolonged treatment. Furthermore, the endpoints of polyp burden and polyp number do not necessarily translate to changes in rates of colorectal cancer, colectomy, or death. Additionally, in other studies, selective COX-2 inhibitors have been shown to have significant toxicities when used over prolonged courses. A study of rofecoxib, a COX-2 inhibitor similar to celecoxib, versus placebo for prevention of colorectal cancer in a general population of patients age ≥ 40 years with a history of ≥ 1 colorectal adenoma removed in the 12 weeks prior to treatment initiation reported a higher rate of thrombotic events with the COX-2 inhibitor (46 in the treatment arm, 26 in the placebo arm, $p = 0.008$) that became apparent only after 18 months of treatment [24]. Celecoxib has also been associated with dose-related increases in death from cardiovascular causes (myocardial infarction, cerebrovascular event, and the development or progression of heart failure) in a similarly designed study testing celecoxib 200 mg BID against placebo for polyp progression in a cohort of patients aged 32–88 years with a history of multiple colorectal adenomas or an adenoma ≥ 0.5 cm in greatest diameter (hazard ratio [HR] 3.4, 95% confidence interval [CI] 1.4–7.8) [25]. Importantly, these studies examine the use of COX-2 inhibitors for a different indication (sporadic polyp formation versus FAP disease progression) and in an older population with more significant comorbidities relative to a population of young patients with FAP. However, given these toxicity concerns with long-term use, selective COX-2 inhibitors do not meet the criteria for an ideal chemoprevention agent.

Sulindac

Sulindac, a less-selective cyclooxygenase inhibitor with additional non-COX pathway effects, has also been used for the clinical management of colorectal polyposis in FAP patients for at least four decades. In 1993, Giardiello et al. [26] performed the first randomized trial using sulindac, randomizing 22 patients to receive sulindac 150 mg twice daily versus placebo for 9 months. Patients enrolled in this study either had not yet undergone colectomy or had an ileorectal anastomosis with remnant rectum that was under surveillance. Flexible sigmoidoscopy was performed to assess polyp burden at 0, 3, 6, 9, and 12 months. In this study, the number of polyps (reported as percentage change from baseline) was significantly lower in the sulindac arm compared to the placebo arm at 3, 6, 9, and 12 months (all $p < 0.05$). The group reported no adverse events and estimated compliance with therapy to be approximately 85%. Despite these promising results, the number and size of colorectal polyps increased in the sulindac group between months 9 and 12, coinciding with the first 3 months following discontinuation of therapy. This rebound effect seen within 3 months of ceasing therapy dampened the positive impact of sulindac on polyp number and size seen in the earlier months of the study.

In 2001, Giardiello et al. [27] published the results of a randomized study in which 41 patients with a pathogenic *APC* mutation and no polyps between the anal verge and 20 cm on sigmoidoscopy received either sulindac or placebo for a period 4 years. The average age of patients involved was 12.9 years in the sulindac arm and 15.8 years in the placebo arm. Dosing of sulindac was weight-based, with subjects ≤ 44 kg receiving 75 mg BID and subjects > 44 kg receiving 150 mg BID. The number and size of rectosigmoid polyps within 20 cm of the anal verge were assessed using flexible sigmoidoscopy at baseline and then at 4-month intervals. Five subjects in the sulindac group and six in the placebo group were withdrawn from the study (drop-out rate of 27%), with progression of polyps (three in sulindac arm,

four in the placebo arm) representing the most common reason for withdrawal. In contrast to the results from their earlier study, the authors found in this trial that, among patients who received therapy for at least 40 months, there were no statistically significant differences between groups in either number of adenomas that developed (5.9 in sulindac arm to 7.5 in placebo arm, p = 0.69) or size of adenomas (0.70 mm in sulindac arm to 1.2 mm in placebo arm, p = 0.17). Levels of prostaglandins D_2, E_2, or F_{2a}, or thromboxane B_2 found in the colorectal mucosa were significantly lower in the sulindac group compared to the placebo arm, suggesting that the drug did produce a physiologic effect, though this effect was insufficient to prevent the mild progression of disease that was observed.

Aspirin

Aspirin is a non-selective COX inhibitor that irreversibly inhibits both COX-1 and COX-2 function. Burn et al. [28] examined the use of aspirin 600 mg daily and starch 30 g daily independently and in combination on recto-sigmoid polyps in 133 patients ages 10–21 years with FAP and an intact colon. After a median treatment interval of 17 months, the authors reported no reduction in risk in number of recto-sigmoid polyps (RR 0.77, 95% CI 0.54–1.10) but a trend towards smaller polyp diameter (p = 0.05) and a significantly decreased polyp diameter in patients treated for ≥ 1 year (p = 0.02). In a much smaller study, Ishikawa et al. [29] randomized 34 FAP patients to receive either aspirin 100 mg daily or placebo. Despite the relatively low dose of aspirin provided in this trial, three severe adverse events occurred: anemia, anastomotic ulcer, and aphtha in the large intestine. Recruitment for the study was stopped following the discovery of an anastomotic ulcer and severe anemia in one patient at the end-of-trial visit and colonoscopy. The study was thus underpowered to assess the primary endpoints of change in polyp number and burden. The authors found that a higher proportion of patients in the aspirin arm had a reduced polyp burden compared with the placebo arm, though this did not meet significance (response ratio of 2.33, 95% CI 0.72–7.55). The side effect profile seen in Ishikawa et al. should be taken in the context of observational data suggesting that Asian populations have a higher bleeding risk on antiplatelet therapy than Caucasian populations [30]. In contrast, no serious adverse events were reported in the Burn et al. study [28] and aspirin is well-tolerated when administered over extended periods of time for treatment or prevention of cardiovascular disease.

While these two studies of aspirin in FAP patients demonstrate no clinical benefit, other studies in non-FAP populations report a protracted delay between treatment initiation and treatment effect. For example, in a blinded, randomized controlled trial evaluating patients with Lynch syndrome, Burn et al. randomized 861 patients with to receive either aspirin 600 mg daily or placebo [31]. While there was no risk reduction seen in the group treated with aspirin on intention-to-treat analysis (HR 0.63, 95% CI 0.35–1.13), patients who remained on aspirin for at least 2 years had a significant reduction in risk of colorectal cancer development (HR 0.41, 95% CI 0.19–0.86). Similarly, in a population-wide study, Cook et al. randomized female health professionals age 45 years or older to receive either aspirin 100 mg every other day or placebo [32]. Patients were treated for 10 years and then followed post-treatment for 8 years. The authors reported a lower rate of colorectal cancer in the group treated with aspirin, but this effect emerged only after 10 years (HR 0.73, 95% CI 0.55–0.95). These studies suggest that aspirin may impact colorectal cancer carcinogenesis, but in a delayed fashion. The failure to reach a statistically significant difference in polyp number in the Burn et al. study among FAP patients [28] may thus be secondary to too brief a treatment and follow-up study period.

While aspirin is relatively well-tolerated over prolonged periods of time, there is no strong evidence that aspirin significantly reduces disease progression among patients with FAP. There is, however, data indicating that aspirin decreases the risk of colorectal cancer development among patients with other familial colorectal cancer disorders as well as among the general population. Further studies regarding this well-tolerated treatment modality, particularly over a longer period of time, are warranted in the future.

Combination therapies utilizing cyclooxygenase inhibitors

Studies have utilized combination chemoprevention agents to modulate multiple pathways involved in the development of neoplasia in FAP. Recently, difluoromethylornithine (DFMO) and erlotinib have been studied in combination with NSAIDs. DFMO is an irreversible inhibitor of polyamine metabolism, and specifically of the enzyme ornithine decarboxylase (ODC). Both overexpression of ODC, the rate-limiting step of polyamine metabolism, and elevated polyamine levels in colorectal mucosal cells have been described in patients with FAP [33] and also linked to increased risk of sporadic CRC [34]. The use of DFMO in combination with an NSAID is supported by a preclinical study in mice with an *Apc* mutation resulting in multiple intestinal neoplasia ($Apc^{Min/+}$) [35]. In this study, mice were treated with DFMO, an NSAID (celecoxib or sulindac), or combination DFMO/NSAID. While treatment with either DFMO or an NSAID alone resulted in a reduction in intestinal tumor number, only treatment with the combination therapy produced a significant reduction in intestinal polyamine levels relative to untreated mice. Thus, DFMO and COX inhibition act through separate pathways to affect

polyposis progression, and the combination of these treatments produce an additive effect.

The first trial to test the DFMO/NSAID combination was conducted in a population of patients with a recent history of sporadic adenoma development rather than FAP. Meyskens et al. [36] conducted a randomized, double-blinded, placebo-controlled trial that randomized 375 patients aged 40–80 with at least one colorectal adenoma resected in the 5 years prior to entering the study to receive either combination DMFO 500 mg/sulindac 150 mg daily or placebo. Patients were followed for 3 years, with colonoscopy performed prior to treatment initiation and at the 3-year time point. Of 375 patients randomized, 267 received a follow-up colonoscopy. Among this group, patients treated with DMFO/sulindac had a significantly lower risk of developing any adenoma (relative risk [RR] 0.30, 95% CI 0.18–0.49), an advanced adenoma (RR 0.085, 95% CI 0.01–0.65), or multiple adenomas (RR 0.06, 95% CI 0.01–0.41). There were no significant increases in cardiovascular or gastrointestinal adverse events or adverse events of grade 3 severity or greater.

Based on these promising results among patients with sporadic colorectal adenomas, Lynch et al. [37] employed DMFO in combination with celecoxib in a cohort of patients with FAP in a double-blinded, multicenter, randomized trial. Patients 18–65 years of age with a clinical diagnosis of FAP, an evaluable colorectal segment, and at least 5 colorectal polyps at baseline were randomized to receive celecoxib 400 mg BID/DMFO 0.5 g/m^2/day or celecoxib 400 mg BID/placebo for 6 months. Colonoscopy at baseline and at 6 months assessed colorectal polyp number, polyp burden at specific sites in the colon (number of polyps multiplied by polyp size), and polyp score as assessed by a video rating of global polyp burden at 6 months relative to baseline. Comparing the combination celecoxib/DMFO therapy to celecoxib monotherapy on intention-to-treat analysis (112 patients total), there was a greater reduction in polyp count (11% versus 1%, $p=0.76$), polyp burden (32% versus 22%, $p=0.17$), and video rating of polyp burden (49% versus 26%, $p=0.13$) among the combination therapy group, though none of these improvements reached statistical significance. However, among patients who completed at least 80% of treatment and had complete polyp counts from both colonoscopies available for analysis (59 patients), the reduction in polyp burden was 18% greater in the combination group ($p=0.08$) and the video ratings of polyp burden improved significantly in this group ($p=0.01$). While the results from the intention-to-treat analysis provide equivocal evidence for the additive effects of celecoxib and DMFO, analyses of polyp burden and global disease as assessed by video demonstrated improvement with combination therapy that was well-tolerated by the study population.

Important limitations to the study by Lynch et al. [37] include relatively low power, a short treatment course of 6 months, and a primary endpoint (polyp counting in prespecified areas of the colon) that standardizes measurement but is less generalizable to a clinical setting. To more rigorously evaluate the potential clinical benefits of combination NSAID/DMFO therapy, Burke et al. [38] performed a phase III randomized, double-blinded, active-controlled trial in adult patients with FAP. 171 patients were randomized to receive CPP-1X (DMFO) 750 mg/sulindac 150 mg daily, CPP-1X 750 mg/placebo daily, or placebo/sulindac 150 mg daily. The primary endpoint of the study was time to occurrence of any colorectal or duodenal excision or progression to advanced duodenal polyposis, cancer, or death. Patients were treated for at least 2 years and observed with both colonoscopy and upper endoscopy at 6-month intervals. The final results of this study have not yet been published [39].

Data examining the role of combination erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, and an NSAID in the prevention of FAP disease progression is more limited. The combination was first investigated in a preclinical model in *Apc*$^{Min/+}$ mice [40]. In this study, treatment with EGFR inhibitors or sulindac individually led to a significant reduction in intestinal polyp number, but the greatest reduction was seen in mice treated with combination EGFR-inhibitor/sulindac therapy. Samadder et al. [41] evaluated this therapy in patients with FAP, comparing combination sulindac 150 mg BID/erlotinib 75 mg daily to placebo in 92 patients with FAP and duodenal polyposis over a 6-month treatment period. The authors found an increase in size and number of duodenal polyps in the placebo arm and a decrease in the size and number of polyps in the treatment arm (both $p<0.001$). A secondary analysis of patients in this study with remnant rectum under regular endoscopic surveillance found that the total colorectal polyp number was 69.4% lower in the combination therapy group relative to placebo at 6 months ($p=0.009$) [42].

To date, the combination studies involving DMFO and erlotinib with an NSAID have provided promising results, but must be taken in the context of important limitations. The combination trials by Lynch et al. [37] and Samadder et al. [41, 42] only treated and followed patients for 6 months and are therefore unable to comment on the durability of each intervention. The study by Burke et al. does involve a more prolonged treatment course (2 years) that will help address issues of treatment durability, but results from this study are not yet available [38]. Prolonged use of erlotinib is associated with severe toxicities, including cardiotoxicity, interstitial lung disease, and acneiform rash, as well as significant expense to the patient, likely precluding long-term administration of this medication [41]. While erlotinib may have a role as an initial medication to halt the progression of disease and induce polyp regression, it is unlikely to be a viable candidate for prolonged chemoprevention.

Fish oil

Certain free fatty acids have also been associated with downregulation of mucosal arachidonic acid levels and reductions in COX-2 expression. Consequently, fish oil has also been proposed as a means of indirectly modulating the COX-2 pathway and impairing polyp progression to malignancy. West et al. [43] investigated the utility of fish oil in controlling FAP disease progression. The authors randomized 58 post-colectomy FAP patients with remnant rectum and ≥ 3 rectal polyps to receive the free fatty acid of eicosapentaenoic acid (EPA-FFA) or placebo for 6 months. The authors found that patients treated with EPA-FFA had a reduction in polyp count by 22.4% ($p = 0.012$) and a 29.8% reduction in polyp size ($p = 0.027$) relative to the placebo group, results similar to those seen in the COX-2 inhibitor trials. The therapy was well-tolerated, with similar rates of AEs occurring in both EPA-FFA and placebo groups and no serious AEs related to study treatment. The authors concluded that EPA-FFA produced antineoplastic activity capable of both promoting regression of existing adenomas and preventing the development of new foci of malignancy. However, while fish oil and COX-2 downregulation appear to be associated, the exact cellular mechanism by which this process occurs is unclear [44]. Although fish oil is well tolerated, the use of fish oil for reliable chemoprevention is limited until the mechanism of action is further delineated and more consistent data is available.

Ascorbic acid

Ascorbic acid, or Vitamin C, has antioxidant properties that have been associated with antineoplastic properties for decades [45]. However, to date, no studies have convincingly demonstrated a clinical benefit to administration of ascorbic acid to reduce colorectal cancer in patients with FAP. Bussey et al. [46] performed a randomized controlled trial ascorbic acid 3 g/day PO versus placebo in 49 patients with FAP who had undergone colectomy with ileorectal anastomosis. Patients were followed for up to 18 months, with proctoscopy performed at baseline and at 3 month intervals thereafter to assess the remnant rectum. Study endpoints were number of polyps and total surface area of polyps. There were no statistically significant differences in number of polyps between groups. There was a significant decrease in polyp area at 9 months in the treatment group ($p < 0.03$), though this was difference was lost by 12 months. Separately, DeCosse et al. [47] randomized 62 patients with FAP who had undergone similar surgical risk-reduction with colectomy and ileorectal anastomosis to one of three groups: ascorbic acid 4 g/day + vitamin E 400 mg/day + fiber 2.2 g/day (multivitamin group), ascorbic acid 4 g/day + vitamin E 400 mg/day + fiber 22.5 g/day (high fiber group), and placebo + fiber 2.2 g/day (control group). The principle endpoint of the study was the ratio of the number of polyps at a particular visit divided by the number of polyps at baseline (= 1: no change; > 1: worsening disease; < 1: improving disease). Patients were followed for 48 months. The authors found that polyp ratios were significantly different only at month 27 and month 33 of treatment, with the high-fiber group having lower polyp ratios. This study is limited in that multiple variables were examined simultaneously (ascorbic acid, vitamin E, and various fiber doses). In combination, though, these two studies suggest a limited effect of ascorbic acid on preventing disease progression in patients with FAP.

Part of the failure of ascorbic acid in the treatment of FAP specifically may be secondary to the proposed mechanism of action of ascorbic acid in non-familial colorectal cancer. Ascorbic acid toxicity to colorectal cancer cells is at least partially mediated through a KRAS or BRAF mutation [48, 49]. In an in vivo model using mice with either an *Apc* mutation or combined *Apc* and *Kras* mutations, Yun et al. [49] demonstrated that ascorbic acid treatment only reduced the number and size of intestinal polyps in mice that also had the *Kras* mutation. Thus, ascorbic acid may be beneficial in patients with FAP, but only after the additional accrual of the *kras* mutation. Further studies would be necessary to determine if the hypotheses generated through these in vivo studies are borne out in clinical practice. Unless this effect in patients with *Kras* mutations can be confirmed in a clinical trial, ascorbic acid likely has limited utility as a chemoprevention agent in patients with FAP.

In summary, no medication tested to date in a randomized controlled trial has convincingly demonstrated the ideals sought for the optimal chemopreventive agent in FAP, including celecoxib [21–23], sulindac [26, 27], aspirin [28, 29], combination sulindac/DFMO, combination celecoxib/DMFO [37], combination sulindac/erlotinib [38], fish oil [43], and ascorbic acid [46, 47]. Further investigation and novel chemoprevention strategies for FAP patients are needed.

The mTOR pathway and rapamycin in FAP

Mammalian target of rapamycin (mTOR) is an intracellular serine/threonine kinase involved in a plethora of cellular processes and may represent a novel target for medical management of FAP patients. mTOR is an integral component of the protein complexes mTORC1 and mTORC2, regulators of protein translation, G1-S phase transition, and cell growth [50, 51]. The cumulative effect of mTOR activity is the accumulation of macromolecules—proteins, lipids, and nucleic acids—to facilitate cell growth and division [50]. In addition to proliferation, mTOR is also implicated in angiogenesis, uncontrolled cellular anabolism, and metastatic

transformation, all of which are components of the progression from benign tissue to malignancy [50].

This central role of mTOR in cell growth and division designates it as a potential target for antitumor medications. Rapamycin, a metabolite initially derived from the bacteria *Streptomyces hygroscopicus*, is a natural inhibitor of mTOR, but the interaction between rapamycin and the mTOR pathways is complex. At high doses, rapamycin has profound immunosuppressive effects through complete mTOR inhibition, which has led to its use as an anti-rejection medication in transplant patients. At lower or more intermittent doses, however, rapamycin acts through the same pathway as an immunomodulator with anti-tumorigenic properties [52].

Rapamycin, along with other mTOR inhibitors, have extensive prior clinical use and well-documented anti-tumorigenic activity. Liver transplant patients undergoing transplant for hepatocellular carcinoma (HCC) had lower rates of recurrent HCC if treated with an mTOR inhibitor rather than a calcineurin inhibitor (8% vs 13.8%, $p < 0.001$) [53]. Similarly, rates of skin cancer in patients after renal transplantation are lower if the immunosuppression regimen contains an mTOR inhibitor, suggesting that mTOR inhibition may be protective against the development of future malignancy [54, 55]. Everolimus, another mTOR inhibitor, has also been used to slow the progression of multiple solid-organ metastatic malignancies, such as hormone receptor-positive breast cancer [56] and renal cell carcinoma [57].

In addition to general anti-tumor activity, there is strong rationale for the use of rapamycin as a chemoprevention agent in FAP. The COX inhibitors indomethacin and nimesulide have been shown to reduce mTOR signaling activity, suggesting that COX and mTOR belong to closely linked pathways of tumorigenesis [58]. Additionally, numerous pre-clinical in vivo studies have demonstrated the role of mTOR in the *Apc* pathway. In an $Apc^{Min/+}$ mouse model, administration of rapamycin blocked proliferation in intestinal polyps but did not affect either apoptosis or proliferation in surrounding normal intestinal epithelium [59]. Separately, in a transgenic mouse model using mice unable to produce a functional Apc protein, rapamycin given in a cyclical fashion (two weeks on therapy, two weeks off therapy) was shown to improve survival relative to a vehicle-treated group (21.5 weeks vs 6.5 weeks, $p = 0.03$) and reduce the colorectal polyp burden defined as the percentage of colon covered in polyps (4.3% vs 56.5%, $p = 0.001$) [60]. Together, these data all suggest that the mTOR pathway is strongly associated with the *APC* pathway and that rapamycin, through mTOR inhibition, can affect tumor progression in *APC*-deficient cells.

The only published data supporting rapamycin use in human patients with FAP is a single case series of two patients [61]. Two male children, ages 13 and 14 and both with strong family histories of FAP, presented with rectal bleeding and were found to have colon polyps on colonoscopy and either periampullary or gastric polyps on EGD. In both cases, each family elected to forego surgical intervention and instead attempted medical management. Both children were started on low-dose rapamycin (doses 0.05–0.1 mg/kg) and surveilled with endoscopy at 6 months, 12 months, and then annually. In the first case, treatment with rapamycin resulted in complete resolution of periampullary polyps, a subjective decrease in colorectal polyp size, and a decrease in degree of dysplasia from high grade to moderate/low grade. In the second case, rapamycin therapy decreased the colonic polyp burden while the gastric polyp burden remained unchanged. In both cases, rapamycin therapy was well-tolerated and no adverse events were reported. This data is obviously limited by the nature of the study design, as a case series is inherently underpowered, nonrandomized, and biased. However, these cases are important as they reflect the potential for mTOR inhibitors as potential chemoprevention agents in FAP patients. In addition to this case series, a single phase II study investigating rapamycin in five patients with FAP post-colectomy has been completed, though the data have not yet been published [62]. Even if this study demonstrates disease response while on rapamycin, a larger trial with longer-term follow up will be necessary.

Encapsulated rapamycin for prevention of FAP disease progression

Classical mTOR inhibitors have a narrow therapeutic window and highly variable absorption and bioavailability rates between patients, which can place patients receiving high-dose oncologic therapy at risk for major toxicities (notably, thrombocytopenia and hyperlipidemia) and necessitates close drug monitoring [63, 64]. To limit the variability in absorption and ameliorate the need for drug monitoring, encapsulated rapamycin (eRapa) was formulated. eRapa consists of sub-micron rapamycin particles incorporated into a pH-sensitive methacrylic acid copolymer, which is expected to provide consistent and predictable oral bioavailability. Recently, a phase Ib trial of eRapa was conducted in patients with low-grade prostate cancer under active surveillance, which demonstrated that the drug is safe, well-tolerated, and produces consistent drug concentrations in the blood within the proposed therapeutic range [65]. The low toxicity and consistent absorption of this medication make it appealing for long-term use. Given these promising phase I results, we plan to initiate a phase IIa trial using eRapa to reduce polyp burden in patients with FAP. The primary objective of the trial will be to determine the efficacy and safety of low-dose eRapa in reducing polyp burden in FAP patients following

risk-reduction surgery. If successful in the treatment of FAP, this therapy may also be beneficial to a broad range of patents with intestinal polyps.

Conclusion

Despite advances in the understanding of the genetic basis of FAP, innovations in surgical technique and endoscopic therapy of polyposis, FAP remains an incurable cancer predisposition syndrome that requires intense endoscopic surveillance and prophylactic colorectal and potentially duodenal surgery to avoid cancer. Even following surgery, patients remain at risk for duodenal, gastric, and thyroid cancer, in addition to desmoid tumors. No single agent or combination of agents has convincingly been shown to delay disease progression or obviate the need for surgery. Research must continue in order to identify appropriate molecular pathways and biologically plausible targets for intervention and medications which are accessible, inexpensive, and well tolerated to prevent polyp progression and hopefully impact the need or timing of surgical intervention. Encapsulated rapamycin used to inhibit signaling through the mTOR pathway represents a potential advance in the treatment of FAP. Based on the known anti-tumorigenic activity of mTOR inhibitors [53–57], the interaction of mTOR with the *APC* pathway demonstrated in pre-clinical models [59, 60, 66], a case report of successful use of rapamycin in two patients with FAP [61], and phase I data indicating that eRapa is well-tolerated, this novel agent warrants further study as a chemoprevention agent in patients with FAP.

Author contributions Conceptualization: GEP, GTC. Literature search: PMKB, JLC, DCE. Writing—original draft: PMKB. Writing—critical review and editing: GM, TJV, RCC, DFH, JLC, ATH, DCE, VS, GTC, GEP, CAB. Supervision: TJV, DFH, GTC, CAB.

Funding There were no internal or external sources of funding for this study.

Compliance with ethical standards

Conflict of interest Dr. George E. Peoples receives consulting fees from Emtora Biosciences, the producers of eRapa. Emtora Biosciences is also the funding sponsor for a phase II study of eRapa in patients with familial adenomatous polyposis. The remaining authors have no conflicts of interest to disclose.

Ethics approval This manuscript is a review article and does not involve any new data, patients, or trials that have not been previously published. No formal ethics review or approval was required to produce this manuscript.

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