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Review

Chemoprevention in hereditary digestive neoplasia: A comprehensive review

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***Abstract*:** Hereditary syndromes, such as familial adenomatous polyposis (FAP), MUTYH polyposis or Lynch syndrome, are particularly predisposing to the development of colorectal cancer. These situations have necessitated the development of adapted prevention strategies based largely on reinforced endoscopic surveillance and the search for complementary prevention strategies. This is the case for chemoprevention, which is the long-term administration of chemical agents limiting carcinogenesis, used as primary or secondary prophylaxis. The aim of this review is to present the available literature and the latest advances in chemoprevention in patients with FAP or MUTYH and other polyposis as well as in patients with Lynch syndrome. The main conclusions of the few available guidelines in these situations are also discussed.

Keywords: adenomatous polyposis, chemoprevention, colorectal cancer, Lynch syndrome

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Introduction

Hereditary syndromes, such as familial adenomatous polyposis (FAP), MUTYH polyposis or Lynch syndrome, are particularly predisposing to the development of colorectal cancer (CCR). These situations have caused the development of adapted prevention strategies based largely on reinforced endoscopic surveillance. Observance of this surveillance remains difficult and despite optimal surveillance, the risk of interval cancer persists. Prophylactic colectomy is therefore still necessary most of the time. This surgery is associated with significant morbidity and an alteration in the quality of the patient's life, and does not decrease the extra-colic neoplasia risk associated with the disease. In these very high-risk situations, complementary prevention strategies have been sought. This is the case for chemoprevention, which is the long-term administration of chemical agents limiting carcinogenesis, used as primary or secondary prophylaxis. The effects of this intervention can be evaluated in experimental *in vitro* or *in vivo* models, which are not presented here. The aim of this review is to present the available literature and the latest advances in chemoprevention in patients with FAP or MUTYH and other polyposis as well as in patients with Lynch syndrome. Some data are only observational case reports, but well-designed and performed randomized control trials are also available. Polyp growth tracking and reporting varies from one study to another and rely on polyps or adenomas count and/or size or gross mucosal surface involvement as well as carcinoma transformation. Some evaluation relies on placebo group and other on pre-post therapy evaluation. Literature search was initially conducted using key words as Chemoprevention OR prevention AND colon cancer in MEDLINE and clinical trial register. Additional search was conducted according to abstract research in conference abstracts sites and literature cited in identified papers. Only human data was considered. The main conclusions of the few available guidelines in these situations are also discussed.

FAP and MUTYH polyposis

In patients with 'florid' FAP, the risk of developing colorectal cancer is estimated to be over 90% at the age of 40 and of almost 100% during life, whereas for patients with 'attenuated' FAP, the risk is estimated to be of about 70%.[1] In the case of MUTYH polyposis, the risk of developing

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colorectal cancer is estimated to be of 80–100% over the course of a lifetime.[2]

Since Waddell and Loughry's observation in 1983 suggesting the efficacy of sulindac on the adenoma growth in patients with FAP,[3] the accumulation of clinical findings and the results of several randomized clinical trials allow consideration of different treatment options. It should be noted that MUTYH polyposis was not identified as such in most of the older studies that considered only the clinical phenotype and is most often not included in the more recent studies with recruitment based on the presence of molecular abnormalities of the APC gene.

Sulindac and sulindac-based combinations

Sulindac is a non-steroidal anti-inflammatory drug that inhibits both cyclooxygenase 1 and 2 (COX-1 and COX-2). Daily use of sulindac at a dose of 150–300 mg results in a decrease in the size and/or number of colorectal adenomas.[4–15] This effect is maintained over time on treatment with, in an initial short series, no advanced adenomas at 64 months.[16] A larger series with an average follow-up of more than 7 years, corresponding to 399 patient-years, showed that the effect of sulindac was rapidly observed in two-thirds of patients, more slowly in 15% and not observed in 15%. In this series, the development of advanced adenomas was observed in only eight patients, on average after 5 years.[17] These initial observations were confirmed by several randomized placebo-controlled trials conducted in the 1990s, all of which showed a reduction in the number and size of colorectal adenomas under oral sulindac therapy in patients with FAP (Table 1).[18–21] Long-term treatment with oral sulindac has also been shown to delay colectomy in some cases of attenuated polyposis.[22–24] Local treatment with sulindac suppositories allows control of the remaining rectal involvement after colectomy in 90% of cases with a follow-up of 33 months.[25–28]

A rapid resumption of growth of colorectal adenomas is observed after stopping sulindac, suggesting a suspensive effect only.[19] Despite an appropriate sulindac therapy observance and endoscopic surveillance, the occurrence of rectal cancer has been reported by several auth ors.[16,18,20,29–32] In a primary prophylaxis situation, a randomized trial in adolescents with APC gene alteration showed no benefit of sulindac prescribed at a dose of 150 or 300 mg per day for 40 months on the occurrence of colorectal adenomas despite a reduction in mucosal levels of prostaglandins D_2, E_2, and F_2 as well as thromboxane B_2 under treatment.[29,31]

Treatment with sulindac 300 mg daily was not associated with a reduction in the number of duodenal adenomas in three series of 22, 8, and 18 adult patients with FAP[20,32,33] despite more encouraging initial preliminary results.[21]

Sulindac sulphone (exisulind) was evaluated in a phase I trial in 18 colectomized patients with FAP with rectum in place. Despite a demonstrated efficacy on polyps growth on the remaining rectum, the poor safety profile with liver involvement prevented its further development.[34,35] Other sulindac analogs are active but have not been evaluated in humans.[36–38]

Sulindac and Erlotinib. The combination of sulindac 300 mg daily and erlotinib, an oral tyrosine kinase inhibitor with anti-EGFR activity, 75 mg daily for 6 months was evaluated *versus* placebo in 92 patients with FAP.[39] This combination reduced the number of colorectal polyps by 70% and the number and mean diameter of duodenal polyps with a 38% decrease in the sum of polyp diameters at the cost of mainly grade I or II skin side effects.[40]

Sulindac and eflornithine. A multicenter randomized trial including 171 adult patients with FAP evaluated sulindac 300 mg daily, eflornithine, a potent inhibitor of polyamines synthesis, 750 mg daily and the combination of the two treatments administered for 48 months.[41] The time to a significant event defined as the need for prophylactic surgery, duodenal polyp excision or duodenal surgery was considered to be the primary endpoint of this study. There was no difference in this endpoint between the groups, but the 'crude' protective effect was higher for the combination of sulindac and eflornithine than for sulindac alone or eflornithine alone.[42] A *post hoc* analysis of this trial showed a significantly longer time to prophylactic or supplementary colectomy or resection of an adenoma larger than 1 cm in the sulindac plus eflornithine group.[43]

Sulindac and other substances. A preliminary study evaluated the effect of sulindac, inulin (prebiotic)

Table 1. Randomized trials testing sulindac in patients with FAP.

Authors	Country (date)	Dosage and duration	Type of study	Population	Targeted site	Primary endpoint	Effect
Labayle *et al.*[18]	France 1991 Multicentric	Sulindac 100 mg × 3/day (4 months) *versus* Placebo 4 months	Randomized, double-blind, crossover controlled (one month washout)	$n = 10$ Colectomy with ileo-rectal anastomosis	Rectum	Number of rectal polyps	Nine with complete or near-complete regression *versus* two partial regression on placebo ($p < 0.01$)
Giardiello *et al.*[19]	USA 1993 Monocentric	Sulindac 150 mg × 2/day *versus* Placebo (9 months)	Randomized, double-blind controlled	$n = 22$ Intact colon ($n = 18$) or ileo-rectal anastomosis ($n = 4$)	Colon Rectum	Number and size of colon and/or rectal polyps	Regression of polyps Number: 56% ($p = 0.014$) Height: 65% ($p < 0.001$)
Nugent *et al.*[20,21]	UK 1993 Monocentric	Sulindac 200 mg × 2/day *versus* Placebo (6 months)	Randomized, double-blind controlled	$n = 24$ Colectomy with ileo-rectal anastomosis Advanced duodenal disease.	Duodenum Rectum	Number and size of polyps in the rectum and duodenum Rectal and duodenal cell proliferation	Regression of rectal polyps in 5 of 7 patients ($p < 0.01$) and duodenal polyps in 5 of 12 patients ($p = 0.12$) Regression of small duodenal polyps (<2 mm) in 9 of 11 patients ($p = 0.02$) Decrease in rectal cell proliferation index 8.5% *versus* 7.4% ($p = 0.018$) and duodenal cell proliferation index 15.8% *versus* 14.4% ($p = 0.003$)
Giardiello *et al.*[29]	USA 2002 Multicentric	Sulindac or 150 mg × 2/day and 75 mg × 2/day if weight < 44 kg (48 months)	Randomized controlled Double blind	$N = 41$ APC mutation without polyp at inclusion	Colon Rectum	Number and size of colon and rectal polyps	No effect

FAP, familial adenomatous polyposis.

plus VSL#3 (probiotic) and the combination of sulindac, inulin and VSL#3 on cell proliferation measured in the rectal reservoir of 17 patients with FAP without showing any significant differences between groups.[44]

Other anti-inflammatory drugs

Indomethacin. In a series of eight colectomized patients with FAP, each with more than 10 polyps in the rectum left in place, a treatment with indomethacin suppository (50 mg) resulted in a regression of more than 50% of the number of polyps in six patients with only a suspensive effect.[45]

COX-2 inhibitors. A randomized placebo-controlled trial in 77 adult patients with FAP, 25 of whom had an intact colon and 52 of whom were colectomized with rectum in place, evaluated the effect of treatment with celecoxib (Celebrex©) 100 mg or 400 mg administered twice daily for 6 months. A 12% ($p = 0.33$) and 28% ($p = 0.003$) reduction in the number of colorectal polyps was observed in each group respectively.[46] An observational cohort of 54 patients with FAP, most often colectomized with polyps in the remaining rectum, suggests that celecoxib protective effect remains over the long term.[47]

A randomized placebo-controlled trial in 83 patients with FAP showed that celecoxib 400 mg twice daily reduced the area of duodenal involvement by 31% in patients who had an initial duodenal mucosa involvement of more than 5%.[48]

The effective dose of celecoxib evaluated in a phase I trial in three groups of six children was 16 mg/kg/day, equivalent to 400 mg per day in adults.[49] A randomized placebo-controlled trial in 106 patients with FAP aged 10–17 years showed a time to progression, defined as the presence of more than 20 polyps greater than 2 mm, lesser with celecoxib 16 mg/kg/day of 2.1 *versus* 1.1 years with placebo.[50]

All these results led to the initial approval of celecoxib for the prevention of neoplastic risk in patients with FAP by both the Food and Drug Administration (FDA) and European Medicines Agency (EMA). This approval was suspended in 2011 due to the potential vascular risk reported in older patients.

A randomized trial in 21 colectomized patients with rectum in place evaluated the effect of rofecoxib 25 mg daily given for 9 months *versus* placebo. Rofecoxib was associated with a decrease in the number of rectal polyps (−10% *versus* placebo) as well as in their size (−16% *versus* placebo).[51] This effect was maintained after an average of 16 months of treatment without any development of advanced adenoma during this period.[52]

A randomized trial in 37 adult patients with FAP compared the effect of celecoxib 400 mg twice daily with the combination of celecoxib and ursodesoxycholic acid 1–2 g daily for 6 months on duodenal involvement.[53] This trial confirmed the protective effect of celecoxib, with the evolution of duodenal involvement considered 'favorable' by a panel of five expert endoscopists. The combination of celecoxib and ursodesoxycholic acid was not associated with any duodenal protective effect.

A more recent trial evaluated the effect of celecoxib 400 mg administered twice daily *versus* a combination of Eflornithine (DFMO) and celecoxib for 6 months in 112 adult patients with FAP, 46 of whom had an intact colon and 66 of whom had been colectomized with their rectum in place. This trial did not show a decrease in the number of colorectal polyps (−1%) compared to the assessment at the moment of inclusion in the 33 patients in the celecoxib alone group but there was a decrease in the sum of polyp diameters of 27%.[54] The protective effect of celecoxib was more pronounced in patients whose celecoxib levels assessed in the polyps correlated with serum levels.[55]

Aspirin. Aspirin is an irreversible, non-selective inhibitor of both COX-1 and COX-2 that is associated with less occurrence and/or recurrence of adenomas and sporadic colorectal cancers. An international randomized trial (CAPP1 trial) conducted in 133 subjects with FAP and intact colon aged 11–20 years found no protective effect of aspirin 600 mg daily for 17 months (1–73 months).[56] However, in patients treated for more than 1 year, the mean size of the largest observed polyp was smaller with aspirin than with placebo (3 mm *versus* 6 mm; $p = 0.02$). A Japanese randomized trial evaluated the effect of aspirin 100 mg daily for 8 months *versus* placebo in 34 patients with FAP and colorectal polyps at inclusion, 20% of whom were colectomized with their rectum in place.[57] This trial suggested a possible protective effect of aspirin on polyp growth, which was significant only when the polyps were initially very small (<2 mm). A more recent Japanese randomized two-by-two factorial design trial (J-FAPP IV) evaluating aspirin and mesalazine was conducted in 104 patients with FAP with a personal history of at least 100 polyps and resection at inclusion of all polyps larger than 5 mm. In this study, the 50 patients treated with aspirin 100 mg daily for 8 months had fewer polyps larger than 5 mm than the non-aspirin group (OR 0.37; 95% CI 0.16–0.86).[58]

Salycilates. Salycilates inhibit colon carcinogenesis *via* COX-2 dependant and independent mechanisms. The Japanese randomized J-FAPP IV trial also considered the effect of mesalazine 2 g daily in 52 patients with FAP with a personal history of at least 100 polyps and an established cleared colon.[58] This trial did not show a significant protective effect of mesalazine.

Other products

Anti-inflammatory diet. A preliminary open trial in 28 colectomized patients with FAP showed the feasibility of an anti-inflammatory diet followed for 6 months with decreased markers of inflammation (calprotectin) and serum growth factor levels (IGF-1).[59] No effect on digestive polyps is yet reported.

Black raspberries. Black raspberries are a species of raspberry initially found in North America and Asia with antiproliferative and immune stimulatory effects. A trial in 24 adult patients with FAP, all colectomized with their rectum in

place, showed that treatment with twice daily suppositories containing 730 mg of freeze-dried black raspberry extract administered for 9 months reduced the polyp burden on the remaining rectum.[60]

Ascorbic acid and vitamin E. Vitamin C may have antioxidant properties that limit colonic carcinogenesis. In a preliminary open series, treatment with ascorbic acid 3 g per day in five colectomized patients with FAP and their rectum in place showed complete regression of rectal involvement in two patients, partial regression in two others and progression in one case observed after 4–13 months.[61] A randomized trial in 49 patients with FAP, all colectomized with their rectum in place, showed in the 19 patients treated with ascorbic acid 3 g per day a non-significant decrease in the number of polyps and a significant decrease in the affected rectal mucosa, but only at the endoscopic check-up carried out at 9 months, with no effect observed on the subsequent check-ups carried out at 12, 15, and 18 months of treatment.[62] Another randomized trial in 58 patients with FAP, all colectomized with their rectum in place, showed in the 16 patients in the ascorbic acid 4 g per day and vitamin E 400 mg per day group no change in the number of polyps or in the area affected on repeat checks every 3 months for 48 months compared with the control group ($n = 22$).[63]

Fibers. A minimum of 50 g of fiber a day minimizes sporadic colon cancer risk. A randomized trial in 58 adult FAP patients, all colectomized with their rectum in place, showed in the 20 patients in the 22.5 g daily cereal fiber supplementation group (11 g per day excess over the control group), a non-significant decrease in the number of polyps and mucosal surface area affected on iterative checks performed every 3 months for 48 months compared to the control group ($n = 22$).[63]

Calcium/vitamin D. Calcium intake is a protective factor against colorectal cancer. An open study of 25 colectomized FAP patients with rectum in place found no protective effect of supplementation with 1500 mg calcium carbonate daily for 6 months.[64] In a study of 18 FAP patients with documented duodenal involvement, a randomized cross-over trial comparing sulindac 300 mg with a combination of calcium carbonate 380 mg and calciferol 500 mg prescribed for 6 months showed no difference in the number and size of duodenal polyps between the groups.[33]

Curcumin. Curcumin is known for its anti-inflammatory action and its usual consumption could be a protective factor against colorectal cancer. An initial open pilot study in five colectomized patients with FAP and rectum in place evaluated the effect of a combination of curcumin 480 mg three times daily and quercetin 20 mg three times daily (a substance chemically similar to aspirin) for 6 months.[65] There was a 60% decrease in the number and 40% decrease in the size of polyps on the remaining rectum or ileal pouch. However, a randomized trial of 44 adult patients with FAP, colectomized or not colectomized, did not show a significant reduction in the number of colonic polyps after 12 months of treatment with curcumin 1500 mg twice daily compared to placebo.[66]

Eicosapentaenoic acid. Eicosapentaenoic acid (EPA) is an *omega-3 polyunsaturated fatty acid* found in fish oil. Daily intake of a purified form of this fatty acid, administered at a dose of 2 g for 6 months, in 55 colectomized FAP patients with at least three polyps on their rectum in place, was associated with a 22% decrease in the number and 30% decrease in the size of the remaining rectal polyps ($n = 28$) compared to the placebo group ($n = 27$).[67]

Metformin. Chronic exposure to metformin could be associated with a lower risk of cancer. A randomized study in 34 Korean patients with FAP, 14 of whom were colectomized with their rectum in place, showed no evidence difference in the number or size of colorectal or duodenal polyps after 7 months treatment with metformin 500 mg or 1500 mg daily compared with the placebo group.[68]

DFMO. Polyamines are major regulators of the cell cycle. In patients with FAP, the activity of ornithine decarboxylase (ODC), a key enzyme in polyamine synthesis, and the mucosal level of polyamines are elevated. Eflornithine (DFMO, CPP-1X) is a potent inhibitor of ODC whose protective effect on colonic carcinogenesis has been characterized in different experimental models.[69] As already mentioned above, a multicenter randomized trial in 171 adult patients with FAP evaluated sulindac 300 mg daily, eflornithine 750 mg daily and the combination of both

treatments administered for 48 months.[41] Progression assessed that the need for prophylactic colorectal surgery, endoscopic treatment of duodenal polyps or duodenal surgery was observed in 22 of 58 (38%) patients in the sulindac group and 23 of 57 (40%) in the eflornithine group with mean times to progression of 24 and 22 months respectively. Duodenal surgery was performed in 14 patients: 5 patients in the sulindac-eflornithine combination group, 6 in the sulindac alone group and 3 in the eflornithine alone group. Eflornithine alone did not provide any significant benefit *versus* sulindac.

Oral contraception. Oral contraception use is associated with a reduced risk of colorectal cancer. An observation in a teenage girl with FAP, regularly followed in a randomized trial with placebo participation, suggests that estrogen-progestin contraception may be associated with a reduction in colonic adenomas.[70]

*Sirolimus. S*irolimus is an mTOR inhibitor. A decrease in duodenal and colorectal involvement was observed at 12 months with low-dose sirolimus (0.05–0.1 mg/kg) in two adolescents aged 13 and 14 years whose parents refused prophylactic colectomy.[71] An open-label pilot study in four patients with FAP, colectomized with rectum left in place ($n=3$) or with ileal pouch ($n=1$), showed that sirolimus prescribed for 6 months at a dose of 2 mg per day with dosage adjusted to achieve a serum concentration between 5 and 8 µg/L was associated with a 25% decrease in the number of polyps and 45–80% decrease in polyp size on the remaining rectum *versus* assessment at inclusion.[72]

Erlotinib. Erlotinib (Tarceva© and generics) is an oral tyrosine kinase inhibitor with anti-EGFR activity. A subsequent prospective multicenter study of 46 mostly colectomized patients with FAP evaluated the effect of erlotinib used alone at a dose of 350 mg once weekly for 6 months.[73] This weekly regimen was associated with a 29% reduction in the sum of duodenal polyp diameters, similar to what had previously been seen with the combination of sulindac and daily erlotinib. This combination reduced the number of colorectal polyps by 30%. Side effects were similar to those of the previous regimen with two cases of grade III toxicity: one skin toxicity and one enterocolitis.

Imatinib. Imatinib is a tyrosine kinase inhibitor that inhibit the BCR-ABL tyrosine kinase. Two patients with attenuated FAP and intact colon, aged 33 and 69 years respectively, treated with imatinib for chronic myeloid leukemia had partial regression of their colonic polyps.[74]

Ongoing clinical studies

Various clinical trials, mostly phase Ib or II, listed on the clinicaltrial.gov website are underway. These trials aim to evaluate the effect of the following products:

- Azithromycin, used for correction of nonsense mutations in the APC gene, 250 mg once daily for 4 months in duodenal and colorectal polyps (open pilot trial, $n=10$, Israel).
- Lithium, used as a regulator of epithelial cell migration in the crypt, 300 mg per day for 6 months on clonal expansion of APC mutated epithelial cells in crypts (open pilot trial, $n=12$, Holland).[75]
- Niclosamide, an anti-helminthic drug which inhibits colon cancer progression, 650 mg once daily for 6 months on colorectal polyps (randomized trial *versus* placebo, $n=72$, Korea).
- Berberine, a plant alkaloid, inhibitor of neoplastic cell proliferation by suppression of the β-catenin pathway, 100 or 300 mg daily orally for 6 months on colorectal polyps (randomized trial *versus* placebo, $n=100$, China).
- Obeticholic acid, bile acid with expected anti-inflammatory effect, 25 mg once daily for 6 months on duodenal polyps (randomized trial *versus* placebo, $n=60$, NCI, USA).
- EPA-FFA, eicosapentanoic acid, 500 mg twice daily for 24 months on rectal polyps (multicenter randomized trial *versus* placebo, $n=214$, SLA Pharma, Liestal, Switzerland).
- Encapsulated sirolimus in different modalities: 0.5 mg daily every other day; 0.5 mg daily every other week; and 0.5 mg daily for 12 months on colorectal polyps (open-label trial, $n=30$, Emtora Biosciences, San Antonio, Texas, USA).
- Gulselkumab (an anti-IL23) 100 and 300 mg monthly subcutaneous injection for 6 months on duodenal, rectal and reservoir

polyps (multicenter randomized trial *versus* placebo, $n=77$, Janssen, part of Johnson & Johnson Innovative Medicine, Pennsylvania, USA).
- Lorpucitinib (a Janus kinase inhibitor) twice daily for 6 months in duodenal and colorectal polyps (open-label pilot trial, $n=40$, Janssen, France, Spain, Germany, Holland, Korea, Puerto Rico, USA)
- REC 4881-201 (dual serine/theonine and tyrosine specific MEK-1 and MEK-2 MAP kinase inhibitor) at doses of 4, 8, or 12 mg once daily orally for 12 months ($n=171$, Recursion Pharmaceuticals, Salt Lke City, Utah, USA).

Experimental animal studies with no available human data or known ongoing clinical trials

Experimental studies conducted in different *in vitro* and/or *in vivo* models have evaluated the possible preventive role of more than 50 pharmacological agents with preclinical effects or on related mechanisms of interest. These studies are not presented here.

Other polyposis

Human data on the value of chemoprevention for digestive cancer risk in other polyposis remain patchy with only a few clinical cases reported. This very low level of evidence does not allow any recommendations for clinical use to be made.

Peutz-Jeghers syndrome

Celecoxib at a dose of 200 mg twice daily for 6 months resulted in a decrease in the number and size of gastric polyps in two out of six treated patients.[76]

The mTOR inhibition pathway has also been evaluated in a few patients. Treatment with everolimus 10 mg daily for 1 year required a reduction in dosage due to stomatitis (one dose every 48 h) with a decrease in polyp burden in the three treated patients.[77] Treatment with everolimus 10 mg daily in a 52-year-old Dutch patient due to a profusion of polyps was discontinued after 7 weeks due to intolerance despite a decrease in the number and size of polyps.[78]

Juvenile polyposis

The risk of colorectal cancer was estimated to be 39–68% in patients with juvenile polyposis. Overexpression of COX-2 in polyps is observed and this overexpression is more intense as the polyps progress.[79,80] However, to our knowledge, there are no data on the effect of COX-2 inhibitor treatment in this situation other than a clinical case reporting a reduction in the number and size of polyps on meloxicam in an 11-year-old child.[81]

Treatment with sirolimus rapidly reduced the number and size of polyps in children aged 14 months, 4 years, 8 years, and 11 years and thus controlled Gastrointestinal bleeding and hypoalbuminemia.[82–85] This effect was also reported in a series of seven children under 2 years of age treated with everolimus or sirolimus, one of whom had also been treated with celecoxib for 8 months, with less use of prophylactic colectomy over the study period [hazard ratio (HR) 0.27 *versus* conventional management].[86] Treatment with sirolimus, one mg daily, resulted in a decrease in the number and size of gastric polyps at 6 months in a 32-year-old adult with no more transfusion requirements.[87]

Cowden's syndrome

In a PTEN-inactivated mouse model mimicking the Cowden syndrome phenotype, inhibition of the mTOR pathway by sirolimus results in a decrease in the number of digestive polyps[88] and an increase in life span.[89] In a series of 14 adult patients treated with sirolimus 2 mg daily for 2 months assessed endoscopically before and after treatment, regression of colonic polyps was noted in only two patients (14%).[90]

Chemoprevention and Lynch syndrome

Lynch syndrome is the most common form of hereditary colorectal neoplasia. It results from germline alterations in the mismatch repair (MMR) genes. The cumulative risk of colorectal cancer at age 70 is 10–13% in patients with PMS2 gene alterations, 42–46% in those with MSH2 gene alterations and 44–53% in those with MLH1 gene alterations.[91] Therefore, from the age of 25 (or 5 years before the earliest index case in the family), regular colonoscopy is recommended, starting only at around 35 year-old in the case of PMS2. The modalities of this surveillance remain debated. Observance of this surveillance remains imperfect and there is a risk of post-colonoscopy interval cancer. Chemoprevention was therefore quickly considered as a way of improving the management of these patients.

Calcium

Low dietary intake of calcium increase colon cancer risk and calcium supplementation could decrease colon carcinogenesis. Calcium could act *via* binding of biliary acids and ionized fatty acids and had a direct action on colon cell proliferation. A randomized study *versus* placebo evaluated the effect of a daily supplementation with 1.5 g calcium carbonate for 3 months in 30 adult patients with Lynch syndrome with evidence of a moderate reduction in the epithelial proliferation index assessed using 5-bromo-2-deoxyuridine incorporation and immunohistochemistry in the treated group.[92]

Sulindac

A randomized, placebo-controlled, crossover study evaluated the effect of sulindac 150 mg taken twice daily for 4 weeks in 22 adult patients with Lynch syndrome.[93] This trial did not show a reduction in the epithelial proliferation index in the treated group.

Aspirin and/or fiber

The randomized CAPP-2 study with a mainly European and Australian enrolment evaluated the effects of insoluble fiber supplementation (Novelose 30 g per day in 2 formulations with 1:1 randomization between these formulations) and those of daily treatment with aspirin 600 mg per day according to a Latin square experimental design.[94] Treatment was initially planned for 2 years and subsequently extended to 4 years. Among 1071 eligible patients, with Lynch syndrome according to Amsterdam criteria I or II or with an identified molecular abnormality over 25 years of age, recruited between 1998 and 2006, 937 patients from 43 centers were included of whom 82% had an identified molecular abnormality: 60% MLH1, 37% MSH2 and 3% MSH6.

Patients intolerant to aspirin were randomized directly to fiber *versus* placebo ($n = 41$ and 35) and those with a history of peptic ulcer disease or those reporting fiber intolerance to aspirin *versus* placebo ($n = 9$ and 10) respectively. Of the 937 patients, 56% had a known history of colonic neoplasia and 15% had at least one adenoma at inclusion colonoscopy (84% with a single adenoma, 13% with two adenomas and 4% with more than two adenomas; 4% with at least one advanced adenoma).

The analysis of the effect of these two supplements was performed in the 746 patients with at least one follow-up colonoscopy. The initial evaluation was performed after a mean follow-up of 29 months (7–74 months) and a mean exposure to the tested supplements of 27 months (compliance assessed at 89% for aspirin and 86% for fiber supplementation) as well as the performance of a mean of three colonoscopies over the period (2–7). During the follow-up, at least one colonic neoplasia was detected in 141 patients (19%). It was an isolated colorectal cancer in 13 patients (1.7%), a colorectal cancer associated with at least one adenoma in 10 patients (1.3%) and only one adenoma in 118 patients (15.8%). Thus 128 patients had at least one adenoma, of which 45 had at least one advanced adenoma. The average size of the largest adenoma was about 10 mm. There was no difference between the different groups in the number of patients with colorectal cancer, with at least one adenoma or with neoplasia, nor in the number or size of adenomas.

A further analysis of the first colonoscopy of 813 patients identified 94 adenomas and 53 hyperplastic polyps with certainty (with obtained histological documentation).[95] The presence of at least one adenoma was found in 10% of patients (18% with more than one adenoma). The prevalence of adenomas increased with age, from 5% before 35 years to 19% after 55 years, with no difference according to the type of molecular alteration identified. The presence of at least one hyperplastic polyp was observed in 5% of patients (24% with more than one hyperplastic polyp). This prevalence did not vary with age and was increased in cases of MSH6 abnormality.

Long-term follow-up of patients randomized to aspirin ($n = 427$) or placebo ($n = 434$) was reported more recently with a mean follow-up of 56 months (1–128): 190 of these patients were followed only during the intervention and 671 had follow-up available beyond the intervention.[96] Of these 671 patients followed up, 40 developed colorectal cancer (6%): 13 of 342 (4%) randomized in the aspirin group and 27 of 329 (11%) randomized in the placebo group. Of the 190 patients with no follow-up information available, eight developed colorectal cancer (4%): 5 of 85 (6%) in the aspirin group and three of 105 (3%) in the placebo group, with an HR of 0.63 (95% CI: 0.35–1.13; $p = 0.12$). Analysis of patients who had definitely taken aspirin ($n = 258$) or placebo ($n = 250$) for at

least 2 years showed a protective effect of aspirin with an HR of 0.41 (95% CI 0.19–0.86; $p = 0.02$). Temporal analysis of the occurrence of colorectal cancer showed that this effect did not occur until about 10 years after exposure.

Follow-up at 10 and sometimes 20 years for some of the patients was carried out passively using data from English, Welsh and Finnish registers.[97] A mean post-intervention follow-up of 7 years was available for 736 patients with 40 (9%) patients randomized in the aspirin group and 58 (13%) patients in the placebo group developing colorectal cancer. Over this period, 74 (17%) patients randomized in the aspirin group and 89 (21%) patients in the placebo group developed at least one cancer on the Lynch syndrome spectrum. The protective effect for the occurrence of colorectal cancer was associated with being randomized in the aspirin group with an HR of 0.65 (95% CI: 0.43–0.97; $p = 0.035$). Proven initial exposure to 2 years of aspirin was associated with a protective effect with an HR of 0.56 (95% CI: 0.34–0.91; $p = 0.02$). These publications do not describe aspirin use after the initial documented exposure. Data on adenomas during follow-up were patchy and showed no difference between groups: 51 (15%) patients in the aspirin group had at least one adenoma *versus* 48 (14.5%) in the placebo group.

Insoluble fiber supplementation maintained for a mean duration of 29 months was not associated with a protective effect on the risk of colorectal cancer with an HR of 1.40 (95% CI: 0.78–2.56; $p = 0.26$),[94,98] a lack of effect confirmed at 10 and 20 years by data from English, Welsh and Finnish registries with an HR of 0.92 (95% CI: 0.62–1.34; $p = 0.63$).[99] Fiber intake level beyond the initial intervention remained unassessed or not reported.

Ongoing aspirin studies

An international randomized trial (CAPP3) is currently evaluating the effect of three doses of aspirin in several thousand patients, taken in an open-label fashion (prescriptions of 100, 300, or 600 mg of aspirin per day), with the aim of finding a minimum effective dose. It should be noted that there is no placebo group in this trial.

The French AAS-Lynch study is a randomized trial conducted in 34 centers that enrolled 424 patients with Lynch syndrome and evaluated the effect of supplementation with aspirin 100 or 300 mg daily *versus* placebo.[100] The primary endpoint is the number of patients who developed at least one colonic adenoma, detected by chromoendoscopy, during the 4-year follow-up, after complete removal of all polyps at the inclusion colonoscopy. This trial includes a nutritional and physical activity questionnaire as well as a 'shotgun' metagenomic microbiota study.

The effect of aspirin 325 mg per day plus atorvastatin 20 mg per day for 6 weeks or omega-3 fatty acids 2 g per day for 12 months are evaluated (COLYNE trial).

Aspirin recommendations

Various recommendations have been issued, based on the results of the CAPP2 trial, in the UK by NICE, the UKCGG and the BSG or by the European Hereditary Tumor Group, advising the prescription of low-dose aspirin in patients with Lynch syndrome.[101,102] The authors of this review consider that there is still insufficient evidence to fully endorse such proposals and prefer to wait for the results of ongoing aspirin studies before proposing a systematic aspirin chemoprevention in Lynch syndrome patients.

Naproxen

Naproxen inhibits colon carcinogenesis and promotes immune activation in Lynch patients. A phase Ib randomized placebo-controlled trial evaluated the effect of Naproxen 220 or 440 mg daily for 6 months in 80 adult patients with Lynch syndrome ($n = 28$ in the placebo group, $n = 27$ in the 220 mg group and $n = 25$ in the 440 mg group).[103] This trial showed a decrease in mucosal PGE2 Prostaglandin E2 levels$_2$ under naproxen treatment.

Other ongoing trials

A phase III randomized placebo-controlled trial is recruiting 260 patients with Lynch syndrome to evaluate the effect of mesalamine 2 g daily for 2 years.

Open trials evaluating the effect of immunotherapies such as Toripalimab 240 mg quarterly parenteral injection for 1 year (anti-PD1) or Nivolumab quarterly parenteral injection for 2 years or specific vaccine therapies (Tri-Ad5 or Nous-209

Vaccines) on the occurrence of adenomas are also planned or yet ongoing.

Conclusion and outlook

The efficacy of chemoprevention in controlling colorectal or duodenal neoplastic risk in certain polyposis has been demonstrated. In adenomatous polyposis patients with colon or at least remaining rectum, sulindac remains the most documented drug and is still the first line therapy to be considered. For duodenal involvement other options could be discussed in specialized centers and no recommendation is available now. Despite existing recommendations on systematic aspirin prescription in Lynch patients, data on the value of aspirin in Lynch syndrome have yet to be consolidated. The risks associated with long-term use of some of these products and the absence of trials of strategies still limit their use to specific situations. Chemoprevention studies, although long and difficult, remain indispensable. These studies, such as the CAPP3 and AAS-Lynch trials currently conducted, should consolidate knowledge and facilitate the implementation of clinical practice recommendations in the near future.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Author contributions

Eugénie Chevalier: Writing – original draft; Writing – review & editing.

Robert Benamouzig: Conceptualization; Project administration; Writing – original draft; Writing – review & editing.

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