Complete Regression of the Adenomatous Polyps in a Patient affected by Familial Adenomatous Polyposis after Prolonged Administration of Phytoestrogens and Sulindac

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Abstract
The chemoprevention of adenomatous polyps that recur after colectomy performed for the familial adenomatous polyposis has been tried several times in the past, but any of the proposed treatments has shown a complete and lasting disappearance of the polyps. A patient with recurrent polyps in the rectal stump after colectomy and ileo-rectal-anastomosis, which required repeated polypectomies, was treated for the first two years with Adipol®, then with both Adipol® and Sulindac (100mg twice/day). After four years, a complete disappearance of the polyps, that was lasting for a year, has been observed without occurrence of side effects. The decrease in polyps was accompanied by an increase of the expression of the estrogen receptor beta. The association of the phytoestrogens to a low dose of Sulindac can obtain a prompt regression of resistant polyps with good tolerability for this chemopreventive choice.

Introduction
Familial Adenomatous Polyposis (FAP) is a hereditary disease characterized by multiple colorectal adenomas. Some of them, with time, can give rise to carcinomas. Prophylactic colectomy is the treatment of choice and is generally undertaken before 20 years of age. Two types of surgical procedures are performed: the total colectomy with ileo-rectal anastomosis (IRA) and the proctocolectomy with Ileal Pouch-anal Anastomosis (IPAA). However, adenomatous polyps can recur after surgery both in the rectal stump and in the ileal pouch and a progression into a cancer is also possible [1,2]. In the last decades, various attempts to control or prevent the growth of these polyps have been tried, but any of the proposed treatments has been accompanied by a complete and lasting disappearance of the polyps [3,4]. The clinical case which we describe in this report shows, for the first time, a complete regression and any regrowth of the adenomatous polyps in the low intestinal tract of a FAP patient operated on by IRA and treated for a long period initially with Adipol® and then with the association of Adipol® and Sulindac.

Case Report
The patient resulted affected by multiple colo-rectal polyposis at the age of 10 years. Also, the father and a brother were affected by colorectal polyposis and were operated on. The deletion of APC gene was found at the codon 437 of the exon 9 in all these familials. In April 1988, at the age of 11 years, the patient was submitted to total colectomy and latero-terminal ileo-rectal anastomosis below the peritoneal reflection. A total of 310 polyps diffuse in all the colon, but prevalent in the sigmoid, was present in the specimen. The dimension of the polyps varies from 1 to 4 mm. The polyps were tubular adenomas with a low grade of dysplasia. The rectal stump was affected by several minute polyps. After surgery, a regular endoscopic control of the rectum was scheduled. The endoscopies were performed after an overnight fast using a flexible video-endoscope (Olympus GIF 165, Tokyo, Japan). Oral administration of PEG was used for the bowel preparation. All the rectal stump from the ileo-rectal anastomosis to the anal verge was accurately inspected quadrant by quadrant, paying attention to use the retroversion in the tract sited over the anal canal and counting...
One year after surgery, rectoscopy showed the presence of about 15 polyps of dimensions around 1-2 mm. Sulindac (100 mg twice/day) was started with a decrease in the number of polyps some months after. However, the onset of epigastric pain advised to suspend the drug. Subsequently, the number of rectal polyps was stabilized around 10 and polypectomies of those with dimensions of 3-5 mm were performed. In the following years, polyps increased in number and dimension and several endoscopic polypectomies with diathermy or cryotherapy were necessary. At the beginning of the year 2000, about 40 polyps were present in the rectal stump and also one adenomatous polyp of 5 mm in diameter grown in the “cul de sac” of the ileum. Polypectomies of the greater polyps (10-20 every six months) were employed for controlling and limiting the increasing proliferation of the rectal mucosa. In 2004, Referecoxib was introduced, but was promptly discontinued after the withdrawal of the drug from the trade. In the following years the endoscopic exams of the low intestinal tract showed the persistence/recurrence of the polyps and the need to remove 15 to 20 of them in each session. In April 2014 the patient began the assumption of 5 g of Adipol® twice a day, at breakfast and dinner times. This patented blend is listed as food supplement in the National Registry of Food Supplements of the Italian Ministry of Health (code: E1041842-Y). Adipol® was chosen for its composition of phytoestrogens (175 mg milk thistle extract, tittered at 70% in silimarin and 30% silibin, 50 mg of flaxseed extract tittered at 40%, secoisolariciresinol) and insoluble and indigestible oat fiber containing cellulose, hemicellulose and lignin. Before the beginning of the treatment and after every 6 months biopsies from macroscopically normal rectal mucosa were taken for the molecular analysis of the expression of Estrogen Receptors (ERs). It has been evaluated the expression of both ERs (ERα and ERβ) genes accordingly with the method previously described [5]. The patient followed the treatment for 2 years. The compliance of the treatment was evaluated collecting the unused sachets every 3 months. During the first year of treatment there were no changes in the number of polyps, in their size (some polyps reached one cm in diameter) and in the need to perform polypectomies. In the following year, however, the number of polyps and the need to perform polypectomies regressed, although the size of the polyps remained constant (Figures 1,2). Tubular adenomas with low-grade dysplasia was found at the pathological examination of the excised polyps except for a tubulovillous polyp with high-grade dysplasia removed during the first 6 months of treatment. In July 2016 Sulindac (100mg twice a day) was started together with Adipol® at the same dosage. In the following months, the number and size of the polyps progressively decreased and, at the last check carried out in February 2018, any polyp was found (Figure 3). The biopsies of the mucosa at the last control showed the absence of adenomatous features and only normal mucosa. The expression evaluation of both estrogen receptors α and β genes during the administration of the dietary supplement with Adipol®, has been evaluated on a treatment time of 6, 12, 18, 24, 36 and also 48 months. The quantitative analysis has demonstrated that in the rectum, ERβ mRNA significantly increased (p<0.01) at 12, 18, 24 months from the beginning of the administration of Adipol®, remaining then constant after 36 months (Figure 4). The biological effect increased with time together with a progressive decrease of the number and size of polyps. On the contrary, ERα mRNA expression was not changed over the months during the treatment. Any side effects were recorded at the clinical controls during all period of the treatment.

Discussion

The glandular mucosa of the intestine in the patients affected by FAP is genetically predisposed to the development of adenomas and to the progression of some of these adenomas versus carcinomas. Carcinomas arise most frequently in the mucosa of the great intestine than in other intestinal tracts. Colectomy with IRA has been proposed by time as a procedure for preventing colonic cancer in patients affected by FAP, but intractable adenomatous polyposis or metachronous cancer in the rectal stump are major concerns. Various medical treatments for avoiding the development of recurrent adenomas in patients with FAP have been proposed [6]. The efficacy of vitamins, drugs and natural products has been tested as potential chemopreventive agents. The most studied and efficacious substances have been the NSAIDs and particularly Sulindac. Sulindac is a non-selective antiCOX that has a rapid effect on the adenomatous polyps. Several clinical trials in FAP patients have shown a reduction of adenoma burden, especially in the rectal stump after IRA. However, prolonging the administration, the positive effect of Sulindac decreases and advanced adenomas or cancer can develop [7,8]. Furthermore, the discontinuation of Sulindac is followed by a prompt recurrence of the polyps. Gastrointestinal toxicity with pain, bleeding or perforation and thrombotic events are complications of the prolonged use of the drug and a limit for its use. Instead of Sulindac, Celecoxib or Rofecoxib, selective COX2 inhibitors, have been employed.
having a lower gastrointestinal toxicity [4,9]. Its efficacy was showed by clinical trials in FAP patients both with intact colon or IRA. However, cardiovascular complications were observed using Celecoxib [10] and this drug, even if available, is employed in USA with black box warning. Instead, Rofecoxib was removed by trade. These drugs inhibit cyclooxygenase and reduce the levels of prostaglandins in the intestinal tissues, but the mechanism of their action in reducing the adenomatous polyps is debated. Sulindac has no effect in normalize the shift of proliferative zone or in reducing mucosal cell proliferation [11], but can induce antineoplastic activities such as apoptosis and suppression of β-catenin-dependent transcription and inhibition of angiogenesis [12].

Another approach in preventing the proliferation of adenomatous polyps in FAP patients is to employ the phytoestrogens. These compounds are present in the food as inactive precursors, are then transformed by the intestinal microbiota into active molecules and structurally and functionally resemble human estrogens. The protective effect of estrogens against the development and progression of colorectal cancer is well known. Evidence of this positive role is suggested by epidemiological data showing a reduced prevalence of adenomatous polyps together with colorectal cancer in women receiving hormone replacement therapy [13]. Interestingly, it was also observed incidentally that colorectal polyps disappeared in a young FAP patient entered into the placebo arm of a chemopreventive trial, when oral contraceptives to treat dysmenorrhea were administered [14]. The high content of phytoestrogens in the eastern diet is considered among factors responsible for the lower colorectal cancer incidence and mortality in western population compared to USA population [15]. It has been also shown that dietary intake of phytoestrogens is inversely related to the colorectal cancer risk [16]. Many types of phytoestrogens have been proposed as protection against colorectal cancer on the basis of their effect either on the cellular cells of colorectal cancer, or in animals or human with adenomatous polyposis. A patented compound of phytoestrogens (silymarin and lignans) and non-starch insoluble fibers is Eviendep® which from 2014 changed name in Adipol®. This blend has been tested both in APC mutated mice and in FAP patients. A significative decrease of the number and the degree of dysplasia of the intestinal polyps was observed in the animals after three months of treatment [17]. The oral supplementation with Adipol® have reduced the adenomatous polyps both at the duodenum and the rectum in FAP patients [5,18]. In particular, the treatment with Adipol® allows to abolish the growth of new adenomatous polyps in the rectal stump of FAP patients and can reduce the number and size of the adenomas observed at the beginning of the treatment. Furthermore, this positive effect is maintained during all the period of supplementation of Adipol® showing that there is not an escape of its effect. Furthermore, the employment for a period longer than 2 years showed a good tolerability of this blend without side effects [5]. The structure of the phytoestrogens allows them to bind to Estrogenic Receptors(ERs). A wide distribution of ERs is present in human colorectal cells. Two subtypes of ERs have been identified: ERα and ERβ. ERβ is the predominant subtype. Interestingly, it has been shown that the presence of ERβ is progressively reduced in the colorectal tumors and its expression is inversely proportional to the degree of the dysplasia and the stage of the cancer [19]. Some months after administration of Adipol®, the expression of ERβ in the rectal mucosa is greatly increased, meanwhile ERα expression remains stable, demonstrating the selective effect of the phytoestrogens on the ERβ [5]. Consequently, we can believe that the protective effect of the estrogens against colorectal carcinogenesis is related to a low ERα/ERβ ratio. It has been shown that the over-expression of ERβ in human colon cancer cells obtained by transfection them with a plasmid inhibits their proliferation by modulation of some key molecular regulators of the cell cycle (decrease in cyclin E and increase in the CDK inhibitor p21C1P1) [20]. Dietary supplement with Adipol® administered for 2 months is able to increase the expression of ERβ in the duodenal and rectal mucosa of patients with FAP. Interestingly, changes of molecular factors which are involved in the carcinogenesis have been observed studying biopsies of the duodenal adenomas of FAP patients. The mRNA expression of oncogenes such as COX-2, PCNA and MUC1 decreases and the mRNA expression of inhibitors genes such as MUC2 increases after Adipol® supplementation [21]. Also, microRNAs are modified after supplementation with Adipol®: in particular the expression of miR-101, which suppresses growth and invasiveness of colorectal cancer, increases after Adipol® supplementation [20]. Employing chemoprevention of FAP adenomas, a combination of agents with different mechanism of action should be desirable either for improving the results or for minimizing the side-effects. There are few information and experimentation about this argument. Lynch et al studied in a clinical randomized trial a combination of a standard dose of Celecoxib and a low dose of difluoromethylornithine, an inhibitor of polyamine synthesis, versus Celecoxib and placebo [22]. The combination of the two drugs was well tolerated, but its efficacy appeared only marginal.
Figure 1: Trend of polyp number for a single patient in a 54 months treatment with Adipol®. Values from 0 to 54 months from the beginning of the supplementation treatment. Adipol® and Sulindac starting treatment points.

Figure 2: Trend of polyp size (mm) for a single patient in a 54 months treatment with Adipol®. Values from 0 to 54 months from the beginning of the supplementation treatment. Adipol® and Sulindac starting treatment points.

Figure 3: Endoscopic Images. Endoscopy of the rectal stump in various periods of the treatment: a) before the beginning of Adipol® treatment; b) 18 months and c) 24 months after the administration of Adipol® and d) 6 months after implementation of Adipol® with Sulindac. There is a regression in number and size of the polyps with their complete disappearance.

Figure 4: Expression of mRNA ERβ (red) and mRNA ERα (blue), evaluated by real-time PCR. mRNA expression was evaluated in rectum biopsies at 6 (T1), 12 (T2), 18 (T3), 24 (T4), 36 (T5), 48 (T6) months after the starting time of the beginning of the treatment with Adipol®. Data are normalized against GAPDH mRNA. Adipol® and Sulindac starting treatment points.

In conclusion, taking in account that surgery reduces dramatically, but does not eliminate the recurrence of adenomatous polyps or risk of cancer in the lower intestinal tract of operated FAP patients, dietary supplementation with phytoestrogens can prevent the formation of new polyps with good tolerability and in absence of side effects. The association of the phytoestrogens to Sulindac can obtain a prompt regression in case of resistant polyps or of great adenoma burden (Figure 4). In the future, it will be necessary a controlled clinical trial of this association to confirm the finding of this isolate case.

References


