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ORIGINAL ARTICLE

Chemoprevention of familial adenomatous polyposis

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Abstract Familial adenomatous polyposis (FAP) has always been first and foremost a surgical disease, whose treatment with colectomy has long been known to reduce risk of premature cancer death. The notion of reducing polyp burden and potentially delaying surgical intervention has spawned a host of "chemoprevention" trials. In this paper I selectively review the findings from these studies, highlighting trial design issues and in particular some of the limitations of historical and existing trial endpoint measures. Nonsteroidal anti-inflammatory agents have been the most commonly employed chemopreventive agents. Sulindac, largely by historical accident, has been the most extensively studied, and is widely considered the standard of care when a clinical decision to intervene medically is made. Newer trials are evaluating combinations of agents in order to take advantage of differing mechanisms of action, in the hope of achieving synergy, as no single agent predictably or completely suppresses adenoma growth. Some of these studies and other single-agent interventions are discussed, though an exploration of the various mechanisms of action is beyond the scope of this paper. It is essential that future trials focus on the issue of "clinical benefit", not simply because the US Food and Drug Administration has insisted on it, but because only real evidence-based advances can improve the standard of medical care for FAP patients. Hence my focus on issues of trial design and clinically relevant endpoints.

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Introduction

Familial adenomatous polyposis is a rare disease, with a frequency of less than 1:10,000. Its natural history involves, in its classic, autosomal dominant form, progression in the number and size of adenomas in the colon and rectum. Onset of adenomas is generally between about the age of 10 and 15 years, though in its most severe manifestations adenomas may occur earlier and in the attenuated form may not develop until age 50 or later. Due to the number of adenomas and inevitability of cancer by age 40 in the usual form, prophylactic colectomy or proctocolectomy is generally undertaken between age 15 and 25, depending on the rate of progression and involvement of the rectum [1]. In about 80 % of patients adenomas of the duodenum occur, but progression is sufficiently slow that cancer occurs in fewer than 10 %. In this article I will review the rationale behind and the history of trials to induce regression of adenomas or to slow the progression of adenomas in FAP. Several reviews on this subject do exist [2, 3].

Rationale

Because prophylactic colectomy, however well accepted it may be, carries appreciable short and long-term complications, there has always been an understandable desire to delay or prevent this intervention through the use of medications. Indeed, the holy grail of FAP chemoprevention

research has to be nothing less than the convert it from a "surgical disease" to a medical one. However, most of the clinical trial efforts to date have dealt with patients that had already undergone prophylactic colectomy and in whom recurrent adenomas in the retained rectum posed a risk of rectal cancer or at least the need for a completion proctectomy.

The amount of effort that has gone into FAP chemoprevention can really best be explained by considering FAP as a natural experiment in the adenoma to carcinoma progression. One key difference between FAP and sporadic adenomas is the fact that a given patient with FAP will commonly have to be followed with at least some adenomas left in situ, thus providing an opportunity to test a drug to see if it will make adenomas regress. In the general population, where a given patient only develops one or several adenomas at a time, mechanical removal of all adenomas is reasonable. Indeed, few sporadic adenoma patients or their clinicians would feel comfortable leaving adenomas in place simply in order to test the effect of a drug. Yet, an agent that proves effective in FAP might very well be considered appropriate for use in average risk patients. In such patients the goal would be to reduce the incidence of new adenomas. So FAP can be considered a proving-ground for drugs of potential benefit in slowing or reversing the adenoma-carcinoma sequence.

History

The first well-documented use of a drug to reduce the adenoma burden in FAP was that of Waddell and Loughry [4]. This followed the observation of improvement in rectal adenoma burden post-colectomy in one patient with both abdominal desmoid and recurrent rectal polyps whose desmoid was being treated with indomethacin and sulindac. Following this anecdotal observation in one patient, four other members of the same family who also had rectal polyps (3 post colectomy and one with intact colon) were treated with sulindac and showed improvement or resolution of adenomas. Part of the historical interest here he approach was the way in which polyps were counted, apparently counts and dimensions assessed in real-time by the endoscopist. In addition, that 3 of the 4 patients with significant rectal polyp burden had undergone subtotal colectomy attests to the typicality of this circumstance prior to the advent of proctocolectomy in patients with extensive rectal polyp burden. Most subsequent trials enrolled patients all or most of whom had also undergone subtotal colectomy with ileorectal anastomosis. With more careful selection of the proper initial surgical procedure based on presurgical rectal polyp burden, colectomy when such burden is low or absent, and proctocolectomy when the burden is high, far fewer patients are currently encountered in whom recurrent rectal polyps is the significant clinical problem that it once was.

Recent studies and current state of the art

Since the original reports by Waddell and colleagues, several trials, with progressively more modern design (randomization, double-blinding, placebo control) have been conducted with sulindac or other nonsteroidal anti-inflammatory drugs (NSAIDs). A few other agents have been employed as well. There is no clear separation between studies that might be considered historical and those considered modern, other than this gradual adoption of standardized clinical trial design features.

An important early trial was that of LaBayle et al. [5]. This occupied a middle-ground between the earlier, uncontrolled studies of Waddell et al. and the later, more commonly cited studies. Ten patients, all postcolectomy and with recurrent rectal adenomas were randomly assigned to sulindac 100 mg TID or to placebo. Treatment was for 4 months, with a one month washout, followed by crossover and an additional 4 months of treatment. Polyp severity was graded at the time of endoscopic assessment: grade 1, no polyp; grade 2, <5 polyps; grade 3, 5–10 polyps: grade 4, 11–20 polyps; grade 5, >20 polyps. A significant regression or down staging was seen while on sulindac, with either no overall change during placebo treatment, or rebound recurrence of adenomas in those initially on sulindac when crossed-over to placebo. Not provided were details as to the method of counting polyps or of quality control in their measure.

The relatively small but important controlled trial by Giardiello et al. [6] is widely regarded and often cited for the proposition that sulindac, at a dose of 150 mg twice a day significant reduces polyp count and diameter. In this study, 22 patients, 18 of whom had not yet undergone colectomy, were treated for 9 months and assessed at intervals of 3 months. A 56 % reduction in adenoma count and a 65 % reduction in average adenoma diameter were observed. No complete regression was observed and substantial regrowth occurred by 3 months following cessation of sulindac dosing.

The method by which polyp counts/diameters was obtained is worthy of comment. In order to achieve reproducibility, a tattoo was placed at 20 cm from anal verge in an area of representative polyp burden and a blinded observer measured the total number of polyps distal to this point, with the diameter of the first five below this tattoo measured with a graduated scale passed through the scope channel. This work is notable for the effort made to achieve reproducibility in the measurement methods and

for the fact that videotaping of findings was carried out. The trial was suspended early due to demonstration of significant treatment effect on interim analysis.

Variations in the use of sulindac

The dosing of sulindac employed in the Giardiello trial probably remains the most commonly employed approach to chemoprevention in FAP. However, several variations in the approach have been employed. In the interest of reducing the side-effects of oral administration, Winde et al. [7] administered sulindac in suppository form to 15 FAP patients who were at least 3 years post colectomy and who had evidence of recurrent rectal polyps. Initially at a dose of 300 mg/day, the dose in this nonrandomized trial was reduced when there was evidence of a major response at follow-up intervals. Commenting on the potential clinical benefit of sulindac administration, Winde offered the possibility that surveillance intervals might be lengthened and the risks of bleeding and perforation from polypectomy reduced.

An important issue remains the long-term effects of sulindac, as none of the randomized controlled trials have employed treatment intervals of more than about 6–9 months. Cruz-Correa et al. [8] enrolled 12 post colectomy patients with IRA and who had at least 5 rectal adenomas, at an average age of about 37 years at enrollment (range 21–52 years). Flexible sigmoidoscopy was done at 4-month intervals and the largest 2 polyps were sampled but not removed. Dosing was started at 150 mg po BID but was adjusted downward if a good response was observed. A majority (7/12) were essentially polyp-free after an average of 77 months of observation. Of the 5 withdrawing early, reasons included one case each of cancer development, progressive dysplasia, increased polyp count, intractable erosions, and noncompliance. Overall a 76 % reduction in polyp count was seen at 1 year and 72 % at last follow-up, with no demographic or clinical features predicting variation in response. That one patient developed an adenocarcinoma of the rectum while undergoing sigmoidoscopy at frequent intervals is distressing and emphasizes the limitations of endoscopic surveillance.

Sulindac has not been shown to have much benefit in the treatment of UGI polyps. In small trials Nugent and Debinski found a mixed response in treating duodenal adenomas [9, 10].

Nugent et al. [10] at St Marks in London treated 24 patients with advanced duodenal adenomatosis (Spigelman stage III or IV), randomized to sulindac 200 mg BID or placebo for a duration of 6 months. All exams were done by the same endoscopist with side-viewing duodenoscope, videotaped, and scored by 2 observers blinded as to treatment arm and order (pre- versus post-treatment). Adenoma burden was described as "better", "same", "worse" than companion video. A trend, not reaching statistical significance ($p = 0.12$) toward improvement in sulindac arm was observed, with better: same: worse ratios of 5:5:1 for sulindac and 2:6:4 for placebo arm. It is distinctly possible that this study was simply underpowered and that a larger sample might have yielded a statistically significant difference favoring sulindac.

The same authors of this sulindac trial of duodenal adenomas then considered the possibility that the lack of significant response might have been due to the advanced stage of disease such that larger adenomas could have lost the capacity to be readily modulated by an agent like sulindac [10]. So they rescored the cases from the same trial, but limited attention to adenomas that were less than 2 mm in diameter. Regression of these smaller polyps was seen in 9 of 11 sulindac-treated patients but in only 4 of 12 in the placebo group ($p = 0.02$) [9].

In a cross-over design, Seow-Choen et al. [11] evaluated 18 patients assigned to calcium (380 mg/day) plus calciferol (500 mg/day) or sulindac (300 mg/day). Treatment was for 6 months, followed by a 2 month wash-out, followed by 6 months of the other drug. Endoscopic assessment was at baseline and following each treatment period. Total number of duodenal adenomas and diameter of largest adenoma were scored. As both duodenal polyps and gastric (fundic gland) polyps were evaluated, only 10 of the 18 patients had duodenal adenomas. No regression in duodenal adenomas was observed in either arm of the trial. Lack of response was attributed, at least in part, to the small sample size and modest polyp burden.

In my own experience, when treating patients with both colorectal and duodenal adenomas, no real regression of duodenal adenomas has been seen. Sulindac may be of marginal benefit in delaying progression of duodenal adenoma but progression of duodenal adenomas appears to be rather indolent in any event [12] such that a carefully conducted long-term assessment would be required to show such a benefit. A somewhat larger trial is underway currently and is comparing sulindac with the combination of sulindac and DFMO.

Use of other NSAIDs

Our own clinical trial experience has focused on the use of selective COX-2 inhibitors. These agents, principally celecoxib and rofecoxib were designed to maintain the salutary anti-inflammatory and potential antineoplastic properties of NSAIDs while minimizing the toxicities most commonly associated with their COX-1 inhibitory properties. Their use in preventing or regressing adenomas in

FAP and in patients with nonfamilial or "sporadic" adenomas is now largely of historic interest, due to an unsatisfactory cardiovascular safety signal observed in sporadic adenoma trials [13, 14]. Rofecoxib was removed from the market altogether and celecoxib's use in arthritis patients probably markedly reduced because of this, though it will likely never be known what the "coxibs" comparative safety or effectiveness is in FAP populations, vis-à-vis sulindac.

In our original, randomized control trial of celecoxib in FAP [15] we observed about a 30 % reduction in colorectal adenoma burden in patients receiving high dose treatment: 400 mg po BID, 4-times the standard antiarthritic dose. The treatment duration was 6 months. The enrolled population was similar in average age to those in the sulindac trials and included both precolectomy and postcolectomy (IRA) patients, with similar responsed seen in both groups. Likely because of the relatively larger sample size that had been seen in the sulindac trials, a significant reduction in duodenal adenomas was observed as well [16]. Rofecoxib trials in FAP, though smaller in scope and with different design, have also shown a positive treatment effect [17].

Aspirin

Given the positive results from trials with sulindac and the coxibs, one would have expected that results at least as dramatic would be seen with aspirin. The one large trial that employed aspirin did not reach statistical significance with its primary endpoint, adenoma count in rectum and sigmoid, though improvement in a secondary endpoint, largest polyp size, was observed [18]. This was a large multicenter trial in which 206 subjects age 10–21 and with intact colons were enrolled. The design was somewhat by the fact that there were in fact four arms in a factorial design: aspirin (600 mg/day), resistant starch, both and neither. The trial may have been compromised by the very large number of enrolling centers and variation in endoscopic technique. Only 133 of the 206 enrolled subjects underwent one or more evaluations after initiation of treatment. Treatment interval was to be at least 1 year, but subjects could elect to remain on study for up to 12 years.

Only one other published study evaluated aspirin in FAP. Ishikawa et al. [19]. In this Japanese randomized controlled trial, 34 subjects post colectomy were treated with low-dose aspirin (100 mg/day) or placebo. Measurements were taken in a field in which at least 4 polyps were present, marked with a tattoo. Regrettably, trial enrollment was suspended after initial treatment follow-up was done in the first 10 subjects when severe anastomotic ulceration was found in one patient assigned to the aspirin arm. Subjects already on study were allowed to finish, though with very close monitoring. Results for the primary endpoint "response ratio" did not reach statistical significance. However, in subset analysis, the proportion of patients whose polyps $\leq$2 mm showed a reduction 5/14 compared was significant compared to the responding proportion on placebo (0/11). The authors conceded that ability to detect a response may have been compromised by the small sample size and by the limited fields in which polyp counting was done.

Combinations of agents [20]

One of the hallmarks of neoplasia is the acquisition of resistance to drug therapy. In order to improve responses and to minimize toxicity, consideration has been given to the potential use of combinations of agents that employ differing mechanisms of action. Such trials are even more difficult to design than single-agent studies, even when the same endpoints are under consideration. Among the design challenges include the number of arms that the trial should include. Even aside from the choice of dose, there is the major issue of choosing the appropriate comparison arm. We undertook to evaluate the combination of celecoxib and difluoromethylornithine (DFMO) an agent that had shown promise in earlier cancer treatment trials but which caused hearing loss at the dose required in such cancer treatment trials. But since work by Gerner and Meyskens [20, 21] had shown promise in experimental systems with lower doses, a trial of "standard" dose celecoxib (400 mg BID) and low dose DFMO was conducted. Since celecoxib had been proven effective and indeed afforded accelerated approval by the US FDA, it was not considered ethical to employ a placebo arm, so celecoxib alone was use as the comparator or control arm of the study. One major consequence of this was the need to employ a substantially larger sample size, in order to potentially detect a synergy. No significant benefit from the combination was detected when using the primary endpoint of % change in adenoma count in a defined region (still photo of reference cluster, with tattoo for localization), though borderline significant benefit was seen when the secondary endpoint of global assessment by video was employed [22].

Other agents

Although most of the drug trials in FAP have utilized NSAIDs in one form or another, a variety of other agents have been employed, with differing mechanistic rationales.

Preclinical support for curcumin (the South Asian spice otherwise known as turmeric) and quercetin (antioxidant flavonoid) led Cruz-Correa et al. [23] to treat 5 patients

post colectomy and who had at least 5 recurrent rectal or ileal pouch polyps [23]. Polyp counts were assessed by sigmoidoscopy at baseline and at 3, 6, and 9 months of treatment. Though not randomized or blinded, a 60 % reduction in polyp count and 50 % reduction in polyp diameters were observed.

In an older study, Bussey et al. [24] evaluated the effect of ascorbic acid. Of 36 evaluable postcolectomy (with IRA) patients, the reduction in polyp area (sum of diameters squared) in patients receiving ascorbate was significant, compared to the placebo group [24]. Considering the positive results, nontoxic agent employed, and the careful trial design, it is a bit surprising that no follow-up trials with ascorbate, alone or in combination, appear to have been undertaken.

The omega-3 fish-oil derivative, eicosapentaenoic acid (EPA) showed favorable results in a recent UK trial of postcolectomy patients with recurrent rectal polyps [25]. After 6 months, the magnitude of favorable EPA effect was very similar to that seen in the Steinbach celecoxib trial. Compared to baseline there was a 22 % decrease in polyp count and a 30 % decrease in polyp burden, with polyp burden measured as the sum of diameters of polyps. The improvement was even more substantial in comparison with the (expected) worsening in the placebo group. As in the Steinbach study, the primary scoring method involved quantitation of polyp counts/diameters in a reference cluster of polyps marked with a tattoo in order to achieve a comparable frame of reference on the pre- and post-treatment exams. A second measure involved a "same, better, worse" assessment by blinded observers of paired videos of the entire rectum.

Trial design challenges and the future

Trial design challenges and the problem of measuring endpoints

In order to conduct useful FAP chemoprevention trials in the next decade, important design issues must be considered. Because there is fairly compelling evidence of adenoma regression with the use of NSAIDs, especially sulindac and celecoxib, it will not really be appropriate to evaluate new agents or combinations of agents against placebo controls. If an NSAID is used as the control arm in randomized control trials, superiority of new agent X will have to be very substantial, will require a very large sample size in order to detect a more modest effect, or will have to be founded on considerations other than efficacy alone, such as a safety advantage.

Achieving clinical trial sample sizes that have adequate power to detect superiority of new agents/combinations against standard of care agents poses special challenges. The largest trials to date have enrolled no more than several hundred subjects, and most have been much smaller. The large trials have required enrollment at numerous institutions, with substantial variation in ability to enroll, evaluate, and retain subjects.

Sponsors face huge expenses in providing drugs and conducting effective monitoring, especially in the face of ever-increasing regulatory requirements.

Even the largest FAP centers do not engage in active clinical surveillance of more than a few hundred patients. As such, eligibility requirements (age range, adenoma burden, freedom from specified coexisting medical comorbidities or drugs, requirement of APC mutation, and others) may markedly limit the number of evaluable patients that a given center can contribute. Under these circumstances, when designing a trial very serious consideration has to be given to each of these important issues.

Age Most trials exclude children under age 18, commonly on the grounds of ethics concerns in "vulnerable" populations. A host of issues exist in pediatric FAP trialing: has the agent in question been properly evaluated for safety in the young? Is the endoscopic evaluation to be conducted by an adult or pediatric gastroenterologist/surgeon? Will the sponsor be able to sustain the cost of propofol anesthesia, the administration of which is rather standard in pediatric endoscopy? Special problems of adherence and monitoring?

Are issues of endpoints and their measures different in children? In several of the trials to date the endpoint has been time to progression of adenomas, an arguable surrogate measure for potential delay in requirement of colectomy. Since the pediatric age group to be considered for a trial will almost invariably have intact colons, the decision of whether to evaluate adenoma burden in the entire colon or an arbitrarily limited distal segment has to be made. If the entire colon is to be evaluated, which is ideal, quality of bowel prep becomes paramount. As important, methods of scoring and of reproducibly scoring adenomas need to be established, as discussed below.

Both of the reported pediatric trials yielded nonsignificant differences between study drug (sulindac [26] or celecoxib [27]) and placebo, using time to progression as the primary endpoint. These results occurred despite using agents that had shown statistically significant adenoma regression in adults. Indeed, in the case of celecoxib, significant regression had even been demonstrated in children [27]. There may be several instructive reasons for these differences. Both studies were underpowered and might well have shown a significant benefit had adequate sample sizes been present. More intriguing, perhaps, are the questions of whether existing measures of adenoma burden are robust enough to detect modest effects and whether the

time-frame of adenoma progression is rapid enough or even well-enough understood as to enable clinical trials to be conducted in time-frame that is doable, given the challenges of retaining adolescents for a period of years.

At the other end of the spectrum, trials commonly exclude patients older than an arbitrary age of 70 years or so. While the number of FAP patients surviving beyond 70 is fairly modest and age-dependent comorbidities might otherwise exclude them anyway, it is always appropriate to re-visit the appropriateness of arbitrary exclusions, including some of the comorbidities that may not in fact really be relevant.

Other common exclusions may or may not make analytic or practical sense. Some trials have insisted that enrollees carry an underlying APC mutation. This may be desirable, but as many as 10–15 % of patients with a clinical picture consistent with FAP will not have a detectable mutation. For purposes of assessing response to an intervention, do we really need to care? If a patient being considered for a drug trial turns out to have biallelic MYH mutations instead of an APC mutation, is there really a practical reason to exclude them from the trial? The answer to this may have to do with how many such patients would be considered for trial, whether issues of stratification by nature of underlying mutation is possible, and so forth.

Endpoint measures

Perhaps the most critical issue in FAP chemoprevention clinical trial design has to do with the question of what is the best measure of adenoma burden, and how to achieve such a measure. If a patient has an intact colon, it is desirable to collect data on the adenoma burden in the entire colon. Any analysis is best when it uses all of the potentially available data. Limiting the polyp information to one small area that can be captured in a photo may appear to lend itself to careful, reproducible measurement. However, this simply begs the question of why we cannot collect information on the total polyp burden with the same or similar degree of care. Arguably, even an imperfect, inadequate measure may be acceptable when the observers are blinded as to treatment arm and the sample size is large—randomization is said to compensate for many sins. Unfortunately in FAP trials the sample size is often regrettably small and in this circumstance the accuracy of endpoint measure is critical.

Technical challenges abound in measuring polyp burden and many key issues arise having to do with quality control in the conduct of the endoscopic assessment of the rectum/ileal pouch in post-colectomy patients, the colorectum in pre-colectomy subjects, and duodenum. Does one measure only polyp number or does diameter (when polyp essentially flat) or even volume (when a polyp is truly "polypoid") become important? Can we be certain that all polyps are truly adenomas, as young patients normally may have very prominent lymphoid "polyps" comingled with adenomas and difficult to distinguish? Do we measure polyps by putting a closed or open forceps adjacent or do we used a special measuring tool and are either of these really practical when the adenoma burden is high. Is the prep quality not only excellent, but comparable from one exam to the next over a series of exams. Regardless of prep quality, is the time devoted to capturing polyp burden adequate? If adequate, is it reproducible from one exam to the next? In performing scope withdrawal from the colon or duodenum, loops and bends in the scope are such that a sudden slippage may occur with many centimeters of gut being overlooked. Although the seasoned endoscopist will simply reinsert the scope, how does one establish, especially in the case of a heavy adenoma burden, that the documentation is resuming exactly where it left off prior to the scope slippage?

One approach that has increasingly been invoked is the placement of a tattoo with India ink or like substance to mark a key landmark or representative cluster of polyps. This does overcome some of the issues of anatomic uncertainty, but the number of such tattoos must be limited, and with attention to quality-control in their placement.

Adenoma burden is really difficult to measure. The relatively straightforward approach involving still photographs of a reference adenomas cluster with a tattoo for reproducibility can be taken as an example of the limitations of current practice. As conducted in the Steinbach celcecoxib [15] and West EPA [25] trials, such a method does carry the ability to reproducibly score a region of polyps. However, the following limitations exist: (a) the relatively few polyps in one photographic field inevitably underestimate the total polyp burden in the colorectum or retained rectum postcolectomy and thus fails to use all of the polyp information available for potential measurement; (b) because only a limited amount of the total polyp burden is assessed in one field of polyps, the effect of any error in their measurement is amplified; (c) one is forced to assume that response to drug in a limited field is representative of the entire polyp burden, and this inference may simply not be the case.

For these reasons, it would certainly be ideal to be able to measure the entire polyp burden in the colorectum. Emphasis is placed on the intact colorectum, as the relative importance of treating the retained rectum postcolectomy is not as great as it may once have been. This is because surgeons are increasingly inclined toward performance of proctocolectomy with ileal J pouch-anal anastomosis (IPAA) in patients with any significant rectal polyp burden. So delaying time to initial surgery becomes an important

objective. This is problematic in classic FAP as it necessarily targets children and adolescents who are routinely excluded from trials. Such exclusions are due to perceived increased risk of any intervention in a "vulnerable" population. Thus, in our undertaking to conduct a celecoxib trial in children age 10–17 we were compelled by anxious collaborators to conduct a preliminary safety study before launching the "main" trial [27]. Though satisfied with the results of this safety study, it did delay the main study by several years. Moreover, the logistics of pediatric trials can be daunting: need for deep sedation, (typically with propofol), territoriality between adult and pediatric endoscopists, generally higher ancillary costs, and problems of adherence to drug on the part of rebellious teens.

I would like to conclude this paper with attention to new issues of importance to designing trials of the future. An overarching issue in this regard has been the pronouncement from the US Food and Drug administration that would require a demonstration of "clinical benefit" as a condition of new drug approval. Guidance has been frankly limited as to what this really means insofar as the determination of proper endpoints. It does appear that endpoints that are relevant to cancer are implicit, such as time to death, progression of disease, or time to surgery. Equally implied is the low likelihood of the FDA accepting the traditionally considered endpoints in FAP trials to date, such as per-cent reduction in adenoma count or similar measure of adenoma burden, as they do not carry with them the requisite "clinical benefit". Consequently, in the past few years investigators and their sponsors have struggled to come up with endpoints that are both realistic and feasible for trials in this rare disease, while at the same time meeting the newly but cryptically articulated FDA standard.

In the interest of developing an endpoint measure acceptable to the FDA and similar regulators demanding a measure of clinical benefit, we have recently proposed a staging system for adenoma burden in the patient with colorectal adenomatosis in the intact colon and for those with rectal adenomas who are post colectomy [28]. The goal of this International Society of Gastrointestinal Hereditary (InSiGHT) polyposis staging system or IPSS was somewhat akin to the Spigelman staging system in the duodenum [29]. For a given stage of severity one could track time to progression to a more advanced stage or, with a favorable response to a chemopreventive agent, regression to a lesser stage. Appropriate levels of surgical/endoscopic intervention that were suited to a given stage were offered. Since a greater or lesser intervention would occur in the case of worsening or improving stage with drug intervention, such a difference in intervention, we argued, would correspond to a clinical benefit meeting the new FDA test. The measure of staging was arbitrary yet showed a high level of interobserver agreement. Good interobserver agreement was also found with respect to stage-specific interventions.

The IPSS awaits further efforts at validation through more rigorous quantification of adenomas in the intact colorectum as well as prospective validation in proposed clinical trials. Such validation against a more strictly quantitative measure of adenoma burden in the colon itself poses significant challenges. On the one hand, high resolution endoscopes multi-terabyte hard drives, and digital videography with easy to use video-editing programs render the capture and management of colonoscopy sessions quite routine. However, the mere counting of adenomas in high polyp-burden cases is not simple. Yet such accurate counting, including estimates of polyp diameter, would be critical to achieving a study endpoint requiring such an endpoint. No study to date has convincingly succeeded in properly scoring colorectal adenoma burden in the intact colon. We have succeeded in achieving a high degree of concordance among scorers using an "electronic abacus" with a "binning" of polyps by diameter [28]. But other issues of quality control in achieving reproducibility in technique between repeat examinations remain relatively unexplored.

A gold standard in colorectal adenoma imaging and quantification remains to be established. CT colonography would likely enable good quantification of adenomas down to a certain diameter, say 2–5 mm [30, 31]. But in any event such an approach would still call for the patient to undergo bowel prep. Concerns of ionizing radiation and cost have also, at least to date, kept use of such an approach from being strongly considered.

Conclusions

This examination of the landscape of FAP clinical chemoprevention trials and of the challenges in trial design has been selective. I have not examined at all the very important issues having to do with mechanisms of action of the drugs employed, much less their mechanistic relevance to the APC gene, mutations in which predispose to adenomas. Neither have I been encyclopedic in even listing all of the trials that have been conducted or are ongoing. I have not even broken down all of the key trials to examine their strengths and weaknesses in assessing their endpoint of polyp burden.

What I have tried to arrive at is some appreciation of the difficulty in even determining the proper subject to consider for trial inclusion. After all, FAP is a rare disease. Further, enrolling the ideal patient, one with a heavy polyp burden whose surgery could be delayed upon exposure to the right dose of the right drug(s), means excluding patients that would ultimately benefit. But the reasons for exclusion are many, and mostly valid.

So what would I consider the ideal trial? Aside from issues of what drug(s) and what dose(s), my preference would be to include patients with all severities of disease. This means operated or not operated, lower and upper GI tract, heavy and minimal adenoma burden. I would not necessarily require an APC mutation be detected, so long as the adenoma burden is clearly consistent with the diagnosis of FAP, and I would allow patients with attenuated FAP, including even those with biallelic MYH mutations. Enrollees in my ideal trial would not be limited be age at either end of the spectrum, nor by comorbid conditions and medications other than those pretty clearly of concern in relation to the study drug. The trial duration should be long enough to involve multiple observations and with endpoints that allow both for time to progression of disease as well as the (likely) regression of disease. I would consider use of something like the IPSS staging system so that we could be convince that a change in burden is significant and thus of "clinical benefit", but would want a rigorous quantification of polyps to accompany and validate it. Following a period of trial intervention, careful assessment of the colon for evidence of rebound would be helpful. The comparison arm could not properly be a placebo, in light of the proven and accepted efficacy of agents such as sulindac.

Is my ideal trial feasible? Probably not. But investigators and sponsors would be well-advised to maintain a check-list of the issues that have been raised. They should also be prepared to give well-reasoned arguments for narrowing the enrollment, given the very rarity of FAP. Our prime directive is of course, "do no harm". Bur remember also, when designing trials, "better is the enemy of good".

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