Early Detection and Prevention of Colorectal Cancer
Author: Karen E. Kim, MS, MS (Editor)
SLACK Incorporated, 2009
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Early Detection and Prevention of Colorectal Cancer edited by Dr. Karen E. Kim is a hardcover book meant to be a comprehensive resource yet useful reference for practicing physicians in adult medicine or gastroenterology, as well as trainees and allied health professionals. The text is easy to read and is comprised of 14 chapters divided into 4 sections that are grouped by (1) epidemiology and mechanisms of carcinogenesis, (2) primary prevention and biomarkers, (3) secondary prevention in high-risk populations with evidence-based guidelines for screening and surveillance, and (4) public health issues, particularly health disparities. Overall, there are 27 contributing authors, most of whom are recognized experts in their fields.

A major strength of the book is its useful algorithms, figures, and comprehensive tables which are used liberally by the authors. The chapters are clearly and succinctly written with consistent style and uniform presentation, all with recent and extensive reference lists. There are some redundancies within the textbook that could have been mitigated with appropriate cross-referencing. For example, the section on Insurance Status in the chapter on Health Disparities and Colorectal Cancer could have been eliminated with a cross-reference, particularly since an entire chapter on the Impact of Insurance Status on Colorectal Cancer Screening directly follows. While difficult to segregate overlapping topics completely, use of the four section areas was a creative means to accomplish this matter. The paper quality is excellent, and the index is thorough and user-friendly. While the reproductions of endoscopic and radiographic images are good, they are limited in number and mostly in black-and-white. The illustrations and tables, although first-rate in content, appear somewhat bland given the lack of color.

Overall, this book successfully combines a review of the basics related to colorectal cancer, with up-to-date content on recent advances in the field. There are substantive discussions on epidemiology, and biology and genetics which are accompanied by practical management recommendations. There is novel insight to the timely issues related to health disparities as they pertain to colorectal cancer related outcomes that are not only unique, but both enlightening and thought provoking. This book proves to be a welcome and valuable addition to the library of any healthcare professional interested in a clear, concise resource on colorectal cancer prevention.

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IL-28B as a Pre-Treatment Predictor of SVR in Genotype I HCV

To confirm the polymorphisms clinical relevance of IL-28B as associated with a two-fold distance in sustained virologic response (VR) to PEG Interferon-Alfa and Ribavirin therapy, intention to treat analysis was carried out on-treatment virologic response SVR.

HCV-1 patients were genotyped as CC, CT, or TT at the polymorphic site, rs12979860. Viral kinetics and rates of RVR (week 4), complete early virologic response (week 12), and SVR were compared by IL-28B type in three self-reported ethnic groups: Caucasians (N = 1171), African American (N = 300), and Hispanics (N = 116).

In Caucasians, the CC IL-28B type was associated with improved early viral kinetics and greater likelihood of RVR (28% vs. 5% and 5%). Complete early virologic response (87% vs. 38% and 28%), and SVR (69% vs. 33% and 27%), compared with CC and TT. A similar association occurred within African Americans and Hispanics. In a multivariable regression model CC, IL-28B type was the strongest predictor of SVR (OR 5.2). RVR was a strong predictor of SVR, regardless of IL-28B type. In non-RVR patients, the CC IL-28B type was associated with a higher rate of SVR (Caucasian 66% vs. 31% and 24%).

It was concluded that in treatment-naive HCV-1 patients treated with pegylated Interferon and Ribavirin, a polymorphism upstream of IL-28B is associated with increased on-treatment and SVR response and effectively predicts treatment outcome. Thompson, A., Muir, A., Sulkowski, M., et al. “Interleukin-28B Polymorphism Improves Viral Kinetics and is the Strongest Pretreatment Predictor of Sustained Virologic Response in Genotype 1 Hepatitis C Virus.” Gastroenterology, 2010; Vol. 139, pp. 120-129.

Lymphocytic Enteropathy and Celiac Disease

A prospective study to determine the clinical, pathologic, and serologic spectrum of celiac disease in a general population was carried out by random sample of an adult general population (N = 1000), analyzed by upper endoscopy, duodenal biopsy, and serologic analysis of tissue transglutaminase (tTg) levels, endomysial antibody (EMA), when tTg was positive.

The cutoff values for diagnosis of celiac disease were villous atrophy with 40 intraepithelial lymphocytes (IELs)/100 enterocytes (ECs).

A total of 33 subjects were tTg-positive and 16 were EMA-positive. Histologic analysis identified 7 (0.7%) with celiac disease. All were tTg-positive and 6 of 7 were EMA-positive. Another 26 subjects were tTg-positive and 7 of 26 were EMA-positive.

This variation was addressed by second quantitative pathology study using a threshold of 25 IELs/100 ECs. All 13 samples that were tTg-positive and EMA-positive had greater than 25 IELs/100 ECs.

In total, 16 subjects (1.6%), had serologic and histologic evidence of gluten-sensitive enteropathy. IELs were quantified at duodenal biopsy samples from seronegative individuals (N = 500); 19 (3.8%) had greater than 25 IELs and lymphocytic duodenitis.

It was concluded that measurement of greater than 25 IELs per 100 ECs correlated with serologic indicators of celiac disease; a higher IEL threshold could miss 50% of cases. Quantification of tTg in the sensitive test for celiac disease as performed, diagnosis can be confirmed by the IELs in duodenal biopsy specimens. Lymphocytic duodenitis and celiac disease is common in the population (5.4%). Walker, M., Murray, J., Ronkainen, J., et al. “Detection of Celiac Disease and Lymphocytic Enteropathy by Parallel Serology and Histopathology at a Population-Based Study.” Gastroenterology, 2010; Vol. 139, pp. 112-119.

Murray H. Cohen, D.O., editor of “From the Literature” is a member of the Editorial Board of Practical Gastroenterology.
Thioketal Nanoparticles: Researchers Develop Oral Delivery System to Treat Inflammatory Bowel Diseases

Researchers at the Georgia Institute of Technology and Emory University have developed a novel approach for delivering small bits of genetic material into the body to improve the treatment of inflammatory bowel diseases. Delivering short strands of RNA into cells has become a popular research area because of its potential therapeutic applications, but how to deliver them into targeted cells in a living organism has been an obstacle.

In the October 10 advance online edition of the journal *Nature Materials*, researchers describe how they encapsulated short pieces of RNA into engineered particles called thioketal nanoparticles and orally delivered the genetic material directly to the inflamed intestines of animals. The research was sponsored by the National Science Foundation and National Institutes of Health.

“The thioketal nanoparticles we designed are stable in both acids and bases and only break open to release the pieces of RNA in the presence of reactive oxygen species, which are found in and around inflamed tissue in the gastrointestinal tract of individuals with inflammatory bowel diseases,” said Niren Murthy, an associate professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University.

This work was done in collaboration with Emory University Division of Digestive Diseases professor Shanthi Sitaraman, associate professor Didier Merlin and postdoctoral fellow Guillaume Dalmasso.

The thioketal nanoparticles protect the small interfering RNAs (siRNAs) from the harsh environment of the gastrointestinal tract and target them directly to the inflamed intestinal tissues. This localized approach is necessary because siRNAs can cause major side-effects if injected systemically.

In the paper, the thioketal nanoparticles were formulated from a new polymer—poly-(1,4-phenyleneacetone dimethylene thioketal) (PPADT)—and engineered to have a diameter of approximately 600 nanometers for optimal oral delivery.

For their experiments, the researchers used a mouse model of ulcerative colitis—a debilitating inflammatory bowel disease in which the digestive tract becomes inflamed, causing severe diarrhea and abdominal pain that can lead to life-threatening complications.

The researchers orally administered thioketal nanoparticles loaded with siRNA that inhibits an inflammation-promoting cytokine called tumor necrosis factor—alpha (TNF-α). The nanoparticles traveled directly to the mouse colons where reactive oxygen species were being produced in excess and decreased the cytokine production levels there.

Tissue samples from the colons treated with siRNA delivered by these thioketal nanoparticles exhibited intact epitheliums, well-defined fingerlike “crypt” structures and lower levels of inflammation—signs that the colon was protected against ulcerative colitis.

“Since ulcerative colitis is restricted to the colon, these results confirm that the siRNA-loaded thioketal nanoparticles remain stable in non-inflamed regions of the gastrointestinal tract while targeting siRNA to inflamed intestinal tissues,” explained the paper’s lead author Scott Wilson, a graduate student in the Georgia Tech School of Chemical & Biomolecular Engineering.

The paper showed that thioketal nanoparticles have the chemical and physical properties needed to overcome the obstacles of gastrointestinal fluids, intestinal mucosa and cellular barriers to provide therapy to inflamed intestinal tissues, he added.

The researchers are currently working on increasing the degradation rate of the nanoparticles and enhancing their reactivity with reactive oxygen species. The team also plans to conduct a biodistribution study to detail how the nanoparticles travel through the body.

“Polymer toxicity is something we’ll have to investigate further, but during this study we discovered that thioketal nanoparticles loaded with siRNA have a cell toxicity profile similar to nanoparticles formulated from the FDA-approved material poly(lactic-co-glycolic acid) (PLGA),” added Murthy.

In the future, thioketal nanoparticles may become a significant player in the treatment of numerous gastrointestinal diseases linked to intestinal inflammation, including gastrointestinal cancers, inflammatory bowel diseases and viral infections, according to Murthy.

(continued on page 46)
This project is supported by the National Science Foundation (NSF) (Award Nos. EEC-9731643 and NSF Career BES-0546962) and the National Institutes of Health (NIH) (Award Nos. U01 HL80711-01, R21 EB006418, RO1 HL096796-01, RO1 DK071594, R01 DK064711 and T32 GM08433). The content is solely the responsibility of the principal investigator and does not necessarily represent the official views of the NSF or NIH.

Merck’s Investigational Medicine Boceprevir Achieved Significantly Higher SVR Rates in Treatment-Failure and Treatment-Naïve Adult Patients with Chronic Hepatitis C Genotype 1 Compared to Control

Merck has reported that final results from two pivotal Phase III studies of boceprevir, its investigational oral hepatitis C protease inhibitor, demonstrated significantly higher sustained virologic response (SVR) rates in adult patients who previously failed treatment (treatment-failure; HCV RESPOND-2) and in adult patients who were new to treatment (treatment-naïve; HCV SPRINT-2) for chronic hepatitis C virus (HCV) genotype 1 compared to control, the primary objective of the studies. The results for the primary endpoints of these studies, which were first reported in a news release in August 2010, and a broad range of further data analyses from these studies are being presented in oral and poster presentations at the 61st Annual Meeting of the American Association for the Study of Liver Diseases (AASLD).

“We are excited by the results of these pivotal studies,” said Dr. Peter S. Kim, Ph.D., president, Merck Research Laboratories. “In these studies, boceprevir substantially increased success rates compared to standard therapy, both for patients who received 48 weeks of treatment and for patients treated with the response-guided therapy approach, many of whom were able to be treated for 28 to 36 weeks,” he added. “Based on these data, Merck has initiated the submission of a New Drug Application (NDA) for boceprevir to the U.S. Food and Drug Administration (FDA) on a rolling basis, and we expect to complete regulatory submissions in the U.S. and E.U. in 2010.”

The HCV RESPOND-2 and HCV SPRINT-2 studies each evaluated two treatment strategies with boceprevir administered in combination with PEGINTRON® (peginterferon alfa-2b) and REBETOL® (ribavirin, USP) (Peg/riba) to assess whether the addition of boceprevir could improve SVR rates and potentially shorten overall treatment duration compared to the use of Peg/riba alone for 48 weeks, which is the current standard duration of therapy. In each study, patients were randomized to three groups:

- Response-guided therapy (RGT), in which total treatment duration was based on certain early response criteria. Treatment-failure patients with undetectable virus (HCV-RNA) at week 8 were eligible to stop all treatment at 36 weeks. Treatment-naïve patients with undetectable virus (HCV-RNA) during weeks 8 through 24 were eligible to stop all treatment at 28 weeks.
- 48 weeks of treatment, in which patients received a 4-week Peg/riba lead-in followed by the addition of boceprevir for 44 weeks.
- Control, in which patients received Peg/riba for 48 weeks.

In both studies, all patients were treated with a 4-week lead-in of PEGINTRON (1.5 mcg/kg/week) and an investigational dose of REBETOL (600–1,400 mg/day), followed by the addition of boceprevir (800 mg three times a day).

In Primary Results, Addition of Boceprevir Significantly Increased SVR Rates Compared to Control

HCV RESPOND-2, which was conducted at U.S. and international sites, included 403 adult patients who had failed prior therapy, including patients who relapsed or were non-responders to prior treatment with peginterferon and ribavirin. HCV SPRINT-2 was conducted in 1,097 treatment-naïve adult patients at U.S. and international sites who were enrolled in two separate cohorts, one with 938 non-African-American/ non-Black patients and the other with 159 African-American/Black patients.
As previously reported, the primary results of these two studies were as follows: In treatment-failure patients in HCV RESPOND-2, boceprevir increased SVR rates to 59 percent for the RGT arm (95/162) and 66 percent for the 48-week treatment arm (107/161) compared to 21 percent for control (17/80). In treatment-naïve patients in HCV SPRINT-2, boceprevir increased SVR rates to 63 percent for the RGT arm (233/368) and 66 percent for the 48-week treatment arm (242/366), compared to 38 percent for control (137/363). (All primary endpoints achieved statistical significance of p<0.0001 based on intent-to-treat analyses.)

Researchers Present New Analyses on Boceprevir Response-Guided Therapy
In secondary analyses presented for the first time at AASLD, researchers reported that nearly half of all patients in the boceprevir RGT arms met early response criteria and received a shorter total duration of therapy:

- In the RGT arm of the treatment-failure study, 46 percent (74/162) of patients met the early response criteria and were eligible to stop all treatment at 36 weeks, which is 12 weeks shorter than current standard therapy. In these patients, the SVR rate was 86 percent (64/74).
- In the RGT arm of the treatment-naïve study, 44 percent of patients (162/368) met the early response criteria and were eligible to stop all treatment at 28 weeks, which is 20 weeks shorter than current standard therapy. In these patients, the SVR rates were 97 percent (143/147) in non-African-American/non-Black treatment-naïve patients and 87 percent (13/15) in African-American/Black treatment-naïve patients.

For the corresponding patients in the boceprevir 48-week treatment arms of these studies, the SVR rates were 88 percent (74/84) in treatment-failure patients, 96 percent (137/142) in non-African-American/non-Black treatment-naïve patients and 95 percent (18/19) in African-American/Black treatment-naïve patients.

Patients in the boceprevir RGT arms of these studies who did not meet the early response criteria and were treated for up to 48 weeks also achieved substantially higher SVR rates compared to control. In these patients, the SVR rates were 40 percent (29/72) in treatment-failure patients, 74 percent (52/70) in non-African-American/non-Black treatment-naïve patients and 58 percent (7/12) in African-American/Black treatment-naïve patients.

“In the study of patients who failed prior treatment, boceprevir combination therapy helped the majority of patients achieve sustained virologic response, the goal of treatment,” said Bruce Bacon, M.D., professor of Internal Medicine, Saint Louis University School of Medicine and co-principal investigator of HCV RESPOND-2. “This is the only study to evaluate a strategy for shorter treatment in these difficult-to-treat patients. We observed that many patients in the boceprevir response-guided therapy arm were able to have their treatment duration reduced by three months compared to current standard duration of treatment.”

“In these studies, boceprevir response-guided therapy provided physicians flexibility in the management of their patients’ HCV therapy, which enabled them to adapt treatment duration based on individual patient response,” said Fred Poordad, M.D., chief of hepatology in the division of gastroenterology at Cedars-Sinai Medical Center, associate professor of medicine at the David Geffen School of Medicine, University of California, Los Angeles (UCLA), and co-principal investigator of the HCV SPRINT-2 study. “These studies were designed with a four-week lead-in strategy that was intended to help physicians identify their patients’ responsiveness to interferon prior to the addition of a protease inhibitor, which provided an early indication of the likelihood of treatment success.”

Merck’s Global Commitment to Advancing Hepatitis Therapy
Merck is committed to building on its strong legacy in the field of viral hepatitis by continuing to discover, develop and deliver vaccines and medicines to help prevent and treat viral hepatitis. Extensive research efforts are underway to develop differentiated oral therapies that bring innovation to viral hepatitis care.


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