

Selected published abstracts of Baylor researchers

ALIMENTARY PHARMACOLOGY AND THERAPEUTICS

Clinical trial: interferon alpha-2b continuous long-term therapy vs repeated 24-week cycles for re-treating chronic hepatitis C

McHutchison JG, Patel K, Schiff ER, Gitlin N, Mur RE, Everson GT, Carithers RL Jr, Davis GL, Marcellin P, Shiffman ML, Harvey J, Albrecht JK; International Hepatitis Interventional Therapy Group

Aliment Pharmacol Ther 2008;27(5):422–432 (see <http://www.blackwellpublishing.com/journal.asp?ref=0269-2813&site=1>). Reprinted with permission from Wiley-Blackwell Ltd.

Background: Treatment options are limited for patients with hepatitis C virus who do not experience sustained viral eradication with pegylated interferon and ribavirin therapy.

Aim: To compare, in an open-label, randomized study, long-term continuous interferon alpha-2b treatment with repeated 24-week courses in patients with chronic hepatitis C virus that relapsed after prior interferon monotherapy.

Methods: A total of 499 patients received 24 weeks of interferon alpha-2b, 3 MIU administered 3 TIW. Responders (normal alanine aminotransferase and negative hepatitis C virus RNA, n = 244) were then randomized to continuous interferon therapy (1, 2, or 3 MIU TIW depending on response) or cyclical therapy (3 MIU TIW for 24 weeks per relapse). Mean Knodell inflammation (I + II + III) and necrosis (IV) scores at baseline vs year 2 were compared.

Results: Patients receiving continuous low-dose therapy vs cycled therapy had larger reductions in inflammation (–3.9 vs –3.1) and fibrosis (–0.49 vs –0.24). Among both groups, the mean change was –3.4 for inflammation and –0.36 for fibrosis. Overall, 73% (95% CI: 67–79) of patients experienced reduced inflammation and 28% (95% CI: 22–34) had reduced fibrosis.

Conclusions: Our results suggest hepatitis C virus patients experiencing viral suppression during long-term maintenance therapy with interferon demonstrate histological improvement. Further prospective trials testing this hypothesis are in progress.

ARCHIVES OF DERMATOLOGY

Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial

Kimball AB, Gordon KB, Langley RG, Menter A, Chartash EK, Valdes J; ABT-874 Psoriasis Study Investigators

Arch Dermatol 2008;144(2):200–207. Copyright © 2008 American Medical Association. All rights reserved.

Objective: To investigate the efficacy and safety of ABT-874, an interleukin 12/23 monoclonal antibody, in psoriasis.

Design: Phase 2, 12-week, multicenter, randomized, double-blind, placebo-controlled trial.

Setting: Outpatient dermatology clinics.

Patients: One hundred eighty patients with clinically stable moderate to severe chronic plaque psoriasis.

Interventions: Patients were randomized in groups of 30 to receive 1 of 6 treatments with ABT-874 provided as a subcutaneous injection: one 200-mg dose at week 0; 100 mg every other week for 12 weeks; 200 mg weekly for 4 weeks; 200 mg every other week for 12 weeks; 200 mg weekly for 12 weeks; or placebo.

Main outcome measure: At least a 75% reduction in the Psoriasis Area and Severity Index.

Results: The percentage of patients achieving a 75% reduction in the Psoriasis Area and Severity Index at week 12 was statistically significantly greater in all of the ABT-874 treatment groups than in the placebo group (200 mg once, 63% [19 of 30]; 100 mg every other week for 12 weeks, 93% [28 of 30]; 200 mg weekly for 4 weeks, 90% [27 of 30]; 200 mg every other week for 12 weeks, 93% [28 of 30]; 200 mg weekly for 12 weeks, 90% [27 of 30]; placebo, 3% [1 of 30]; $P < .001$). Treatment with ABT-874 was well tolerated. The most common adverse event was injection-site reaction, and the most common infectious adverse events were nasopharyngitis and upper respiratory tract infection. There were no serious infectious adverse events.

Conclusions: ABT-874, an interleukin 12/23 monoclonal antibody, was highly effective and well tolerated in the treatment of psoriasis. Longer-term studies are required to confirm these findings.

BIOCHEMICAL PHARMACOLOGY

Curcumin as “*curecumin*”: from kitchen to clinic

Goel A, Kunnumakkara AB, Aggarwal BB

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Although turmeric (*Curcuma longa*; an Indian spice) has been described in Ayurveda as a treatment for inflammatory diseases and is referred by different names in different cultures, the active principle called curcumin or diferuloylmethane, a yellow pigment present in turmeric (curry powder), has been shown to exhibit numerous activities. Extensive research over the last half century has revealed several important functions of curcumin. It binds to a variety of proteins and inhibits the activity of various kinases. By modulating the activation of various transcription factors, curcumin regulates the expression of inflammatory enzymes, cytokines, adhesion molecules, and cell survival proteins. Curcumin also downregulates cyclin D1, cyclin E, and MDM2; and upregulates p21, p27, and p53. Various preclinical cell culture and animal studies suggest that curcumin has potential as an antiproliferative, anti-invasive, and antiangiogenic agent; as a mediator of chemoresistance and radioresistance; as a chemopreventive agent; and as a therapeutic agent in wound healing, diabetes, Alzheimer disease, Parkinson disease, cardiovascular disease, pulmonary disease, and arthritis. Pilot phase I clinical trials have shown curcumin to be safe even when consumed at a daily dose of 12 g for 3 months. Other clinical trials suggest a potential therapeutic role for curcumin in diseases such as familial adenomatous polyposis, inflammatory bowel disease, ulcerative colitis, colon cancer, pancreatic cancer, hypercholesterolemia, atheroscle-

rosis, pancreatitis, psoriasis, chronic anterior uveitis, and arthritis. Thus, curcumin, a spice once relegated to the kitchen shelf, has moved into the clinic and may prove to be "Curecumin."

CANCER

JC virus T-antigen expression in sporadic adenomatous polyps of the colon

Jung WT, Li MS, Goel A, Boland CR

Cancer 2008;112(5):1028–1036. Copyright © 2008, American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Background: JC virus (JCV) has been implicated in the pathogenesis of colorectal cancer; however, its role in premalignant lesions is unknown. The hypothesis that JCV DNA sequences and T-antigen (T-Ag) expression may be present in adenomatous polyps of the colon was tested. Furthermore, an association between JCV and microsatellite instability (MSI) was also sought in these lesions.

Methods: DNA was extracted from 74 paraffin-embedded adenomatous polyps. JCV gene sequences were amplified by polymerase chain reaction (PCR), and the specificity confirmed by DNA sequencing. Immunohistochemical staining was performed to localize T-Ag expression in the adenomas using a monoclonal antibody. For microsatellite instability analysis, 5 mononucleotide repeat markers (BAT-25, BAT-26, NR-21, NR-24, and NR-27) were coamplified in a pentaplex PCR and analyzed for deletion mutations.

Results: JCV T-Ag sequences were found in 82% (61 of 74) of adenomas, and T-Ag protein was expressed in 16% (12 of 74) of these polyps. The T-Ag staining was localized exclusively in the nuclei of adenoma cells, but never in the cytoplasm or the adjacent nonneoplastic cells. The prevalence of MSI-H and non-MSI-H (MSI-L/MSS) in adenomatous polyps was 9.5% (7 of 74) and 90.5% (67 of 74), respectively. Among the 61 adenomas that harbored JCV sequences, 8% (5 of 61) were MSI-H, and similarly among 12 adenomatous polyps expressing T-Ag protein 8% (1 of 12) of the adenomatous polyps were MSI-H.

Conclusions: JCV T-Ag DNA sequences are frequently present in adenomatous polyps of the colon, and T-Ag is expressed specifically in the nuclei of these premalignant lesions. This study indicates that JCV T-Ag is present in the early stage of colonic carcinogenesis. Future studies will be required to determine the molecular mechanism of carcinogenesis in these JCV-infected lesions.

CARCINOGENESIS

Chemopreventive properties of pinoresinol-rich olive oil involve a selective activation of the ATM-p53 cascade in colon cancer cell lines

Fini L, Hotchkiss E, Fogliano V, Graziani G, Romano M, De Vol EB, Qin H, Selgrad M, Boland CR, Ricciardiello L

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The Mediterranean diet is rich in extra virgin olive oil (EVOO) and associated with a lower incidence of colorectal cancer. EVOO contains phenolic extracts with potential anticarcinogenic activity.

Aim: To assess the anticancer properties of EVOO phenolic extracts using in vitro models.

Methods: Phenolic profiles of two different EVOOs (A and B) were determined. RKO and HCT116 (both p53 proficient), SW480 (p53 mutant) and HCT116^{p53-/-} (p53 knocked out) cell lines were treated with EVOO extracts and assessed for cell viability. Apoptosis was determined by terminal deoxynucleotidyl transferase nick end labeling (TUNEL) assay and changes in Bax transcript levels. Cell cycle analysis was determined by flow cytometry and western blots. To confirm the data, analysis of cell viability and cell cycle was performed with purified pinoresinol.

Results: Chemical characterization showed that pinoresinol is the main phenol in EVOO-A, and oleocanthal predominates in EVOO-B. Only EVOO-A affected cell viability, which was significantly more pronounced in p53-proficient cells. At a concentration of 200 nM, p53-proficient cells showed increased apoptosis and G₂/M arrest. In p53-proficient cells, ataxia telangiectasia mutated (ATM) and its downstream-controlled proteins were upregulated after treatment, with a parallel decrease of cyclin B/cdc2. Identical results on cell viability and cell cycle were obtained with purified pinoresinol, but this required a higher concentration than in EVOO-A.

Conclusion: Our results demonstrate that pinoresinol-rich EVOO extracts have potent chemopreventive properties and specifically upregulate the ATM-p53 cascade. This result was achieved at substantially lower concentrations in EVOO than with purified pinoresinol, indicating a possible synergic effect between the various polyphenols in olive oil.

CLINICAL TRANSPLANTATION

Late acute rejection after liver transplantation impacts patient survival

Uemura T, Ikegami T, Sanchez EQ, Jennings LW, Narasimhan G, McKenna GJ, Randall HB, Chinnakotla S, Levy MF, Goldstein RM, Klintmalm GB

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Hepatic allograft rejection still remains an important problem following liver transplantation. Early acute rejection, occurring within 3 months of transplant, is a common event and usually of lesser significance with respect to prognosis than other non-immune-related post-transplant morbidities. However, little is known about late acute rejection (LAR) including factors affecting its occurrence and long-term outcome. In this study, we analyzed LAR including the incidence, clinical risk factors, patient survival, and graft survival. LAR was defined as acute cellular rejection later than 6 months after liver transplant. Adult patients who had a minimum of 24 months of graft survival were included in this study. A total of 1604 case records of consecutive adult patients (over age 18 yr) who underwent liver transplant between 1985 and 2003 were reviewed. Of the 1604 patients, 305 (19.0%) developed LAR. Patients with primary diagnoses of autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis had higher incidences of LAR, while patients with metabolic disease and retransplant had lower incidence of LAR ($P = 0.0024$). The LAR group had more female and younger recipients than the no LAR group ($P = 0.0026$, $P = 0.0131$, respectively). Patient survival as well as graft survival were significantly lower in the LAR group ($P = 0.0083$, $P = 0.0075$, respectively). PTLD was the only significant independent predictor of late rejection. The careful management and treatment of PTLD,

especially immunosuppressive management, is important to prevent LAR, which is related to poorer patient survival.

CYTOKINE AND GROWTH FACTOR REVIEWS

Dendritic cells and cytokines in human inflammatory and autoimmune diseases

Blanco P, Palucka AK, Pascual V, Banchereau J

Cytokine Growth Factor Rev 2008;19(1):41–52. Reprinted with permission from Elsevier.

Dendritic cells (DCs) produce cytokines and are susceptible to cytokine-mediated activation. Thus, interaction of resting immature DCs with TLR ligands, for example nucleic acids, or with microbes leads to a cascade of pro-inflammatory cytokines and skewing of T cell responses. Conversely, several cytokines are able to trigger DC activation (maturation) via autocrine, for example TNF and plasmacytoid DCs, and paracrine, for example type I IFN and myeloid DCs, pathways. By controlling DC activation, cytokines regulate immune homeostasis and the balance between tolerance and immunity. The increased production and/or bioavailability of cytokines and associated alterations in DC homeostasis have been implicated in various human inflammatory and autoimmune diseases. Targeting these cytokines with biological agents as already is the case with TNF and IL-1 represents a success of immunology and the coming years will expand the range of cytokines as therapeutic targets in autoinflammatory and autoimmune pathology.

FAMILIAL CANCER

The biochemical basis of microsatellite instability and abnormal immunohistochemistry and clinical behavior in Lynch syndrome: from bench to bedside

Boland CR, Koi M, Chang DK, Carethers JM

Fam Cancer 2008;7(1):41–52. Reprinted with kind permission from Springer Science+Business Media.

Lynch syndrome is an inherited disease caused by a germline mutation in one of four DNA mismatch repair (MMR) genes. The clinical manifestations can be somewhat variable depending upon which gene is involved and where the mutation occurs. Moreover, the approach to the diagnosis of Lynch syndrome is becoming more complex as more is learned about the disease, and one needs to understand how the DNA MMR proteins function, and what makes them malfunction, to have an optimal appreciation of how to interpret diagnostic studies such as microsatellite instability and immunohistochemistry of the DNA MMR proteins. Finally, an understanding of the role of the DNA MMR system in regulation of the cell cycle and the response to DNA damage helps illuminate the differences in natural history and response to chemotherapeutic agents seen in Lynch syndrome.

INVESTIGATIONAL NEW DRUGS

Phase I study of a 3-drug regimen of gemcitabine/cisplatin/pemetrexed in patients with metastatic transitional cell carcinoma of the urothelium

Hutson TE, Vukelja S, Atienza D, Awasthi S, Delaune R, Deutsch M, Dien PY, Gregory TF, Kolodziej MJ, Muscato JJ, Raju RN, Ruxer RL Jr, Mull S, Ilegbodu D, Hood K, Nicol S, Berry W

Invest New Drugs 2008;26(2):151–158. Reprinted with kind permission from Springer Science+Business Media.

Objectives: Gemcitabine (G) plus cisplatin (C) is standard care for metastatic transitional cell carcinoma (TCC) of the urothelium. Pemetrexed (P), alone or in combination with G, is active in metastatic TCC. However, the safety and efficacy of P combined with GC therapy is unknown. This phase I trial was designed to determine the maximum tolerated dose (MTD) of GC followed by P + G in patients with metastatic TCC.

Methods: Cohorts of 3 to 6 patients received escalating doses 28-day cycles (maximum 6 cycles): G 800–1,000 mg/m² on days 1 and 15; P 400–500 mg/m² on day 15; and C 50–70 mg/m² on day 1. All patients received folic acid, vitamin B₁₂, and full supportive care. The 3 + 3 standard phase I escalation rule was used to determine MTD.

Results: Fifteen patients registered: 13/15 white males; median age 70 years (range, 53–82); 11/15 had KPS ≥90. At dose level 0, 2/4 patients experienced unrelated DLTs, and 1 patient was replaced (completed <1 cycle). Dose escalation proceeded to dose level 1. At level 1, 4/6 patients experienced DLTs; dosing decreased to level 0 and 4/5 patients experienced DLTs. The MTD was not determined. The 2 patients that completed 6 cycles both had partial responses. Grades 3–4 hematologic toxicities included neutropenia (60%), leukopenia (20%), and febrile neutropenia (13%).

Conclusion: Adding P to the standard GC regimen as first-line therapy for metastatic TCC produced no benefit. The MTD exceeded therapeutic gemcitabine and cisplatin doses for urothelial cancer and thus the study was aborted.

SOUTHERN MEDICAL JOURNAL

Four cases of disseminated *Mycobacterium bovis* infection following intravesical BCG instillation for treatment of bladder carcinoma

Nadasy KA, Patel RS, Emmett M, Murillo RA, Tribble MA, Black RD, Sutker WL

South Med J 2008;101(1):91–95. Reprinted with permission from Lippincott Williams & Wilkins.

Intravesical BCG (bacillus Calmette-Guérin) instillation is a first-line treatment for superficial transitional cell carcinoma of the bladder. A rare but severe complication of BCG immunotherapy is the development of disseminated BCG disease, which can result in miliary pneumonia, granulomatous hepatitis, soft tissue infections, bone marrow involvement, and sepsis. Symptoms can present as early as a few hours or as late as several months following the BCG therapy. The key finding in disseminated BCG disease is the formation of caseating granulomas in distant organs; detection of BCG organisms from tissue samples can be difficult. Recommended treatment for disseminated BCG disease includes a combination of antituberculous medications (with the exception of pyrazinamide, to which BCG is typically resistant) and a tapering course of steroids. We present the cases of four patients who developed granulomatous infection consistent with disseminated disease after intravesical BCG treatment and provide a summary of current clinical management recommendations.

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