Resolution of futility by due process: early experience with the Texas Advance Directives Act

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Every US state has developed legal rules to address end-of-life decision making. No law to date has effectively dealt with medical futility—an issue that has engendered significant debate in the medical and legal literature, many court cases, and a formal opinion from the American Medical Association’s Council on Ethical and Judicial Affairs. In 1999, Texas was the first state to adopt a law regulating end-of-life decisions, providing a legislatively sanctioned, extrajudicial, due process mechanism for resolving medical futility disputes and other end-of-life ethical disagreements. After 2 years of practical experience with this law, data collected at a large tertiary care teaching hospital strongly suggest that the law represents a first step toward practical resolution of this controversial area of modern health care. As such, the law may be of interest to practitioners, patients, and legislators elsewhere.

Paget-Schroetter syndrome therapy: failure of intravenous stents

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Background: The purpose of this study is to show that intravenous stents (IS) are contraindicated in patients with thrombosis of the axillary-subclavian vein (Paget-Schroetter syndrome).

Methods: Twenty-two patients had IS placed after balloon dilatation of the venous compression in the thoracic outlet. Each of the patients receiving IS had the diagnosis made <6 weeks after vein occlusion, previous thrombolytic therapy, and poststent anticoagulants. (All were performed in outside hospitals. In no case was surgical decompression of the “externally constricted venous tunnel” performed.) The 22 patients receiving IS were compared with a similar group of 384 patients seen <6 weeks after thrombosis who were treated with “optimal therapy,” i.e., thrombolysis and prompt transaxillary resection of the first rib with venous tunnel decompression.

Results: All 22 patients with IS reoccluded their axillary-subclavian vein from 1 day to 6 weeks after insertion. All were retreated with thrombolytic therapy and first rib resection. Ten remained patent and 7 remained occluded but developed adequate collateral circulation. All 17 were asymptomatic. Five remained occluded with minimal collateral circulation. Attempts were made to reopen them a third time. All 5 are receiving long-term anticoagulants. In contrast, the 384 patients managed with optimal therapy were significantly improved without retreatment or anticoagulants.

Conclusions: From our study, there is no indication for use of IS in patients with Paget-Schroetter syndrome; in fact, from our experience, it is contraindicated when compared with the optimal therapy group. Other authors corroborate this conclusion in recent review articles.

Pilot trial of intravenous infusion of a replication-selective adenovirus (ONYX-015) in combination with chemotherapy or IL-2 treatment in refractory cancer patients

(Cancer Gene Ther 2003;10:341–352)

ONYX-015 is an adenovirus that selectively replicates in p53 dysfunctional or mutated malignant cells. We performed a pilot trial to determine the safety and feasibility of treatment with ONYX-015 delivered intravenously in patients with advanced malignancy. One cohort of 5 patients received ONYX-015 once a week for 6 weeks at a dose of $2 \times 10^{12}$ particles per infusion in combination with weekly infusions of irinotecan (CPT11, 125 mg per week) and 5-fluorouracil (5FU, 500 mg per week). A second cohort of 5 patients received the combination of ONYX-015 at a dose of $2 \times 10^{11}$ particles per week for 6 weeks in combination with interleukin 2 (IL-2, $1.1 \times 10^6$ units daily via subcutaneous injection for 5 days each week for 4 weeks). Toxicity attributable to ONYX-015 was limited to transient fever. All patients demonstrated elevations in neutralizing antibody titers within 4 weeks of the infusion of ONYX-015. Serum levels of IL-6, IL-10, tumor necrosis factor-$\alpha$, and interferon-$\gamma$ increased within 6 hours of viral infusion, suggesting immune activation. This response was more pronounced in the cohort of patients who received $2 \times 10^{12}$ particles per infusion. Two patients demonstrated uptake of viral particles in malignant tissue by quantitative PCR. Electron microscopy confirmed selective cytoplasmic viral particles within malignant cells but not within adjacent normal tissue in a third patient. In conclusion, ONYX-015 can be administered safely in combination with CPT11, 5FU, or low-dose IL-2 and is able to access malignant tissue following intravenous infusion. Further investigation of ONYX-015, possibly with agents that may modulate replication activity, or duration of virus survival, is indicated.

Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin

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Objective: An open-label, parallel-group, randomized, multicenter trial was conducted to compare efficacy and safety of repaglinide versus nateglinide, when used in a combination regimen with metformin for treatment of type 2 diabetes.

Research design and methods: Enrolled patients (n = 192) had HbA1c >7% and ≤12% during previous treatment with a sulfonylurea, metformin, or low-dose Glucovance (glyburide ≤2.5 mg, metformin ≤500 mg). After a 4-week metformin run-in therapy period (doses escalated to 1000 mg b.i.d.), patients were randomized to addition of repaglinide (n = 96) (1 mg/meal, maximum 4 mg/meal) or nateglinide (n = 96) (120 mg/meal, reduced to 60 mg if needed) to the regimen for 16 weeks. Glucose, insulin, and glucagon were assessed after a liquid test meal at baseline and week 16.
lymphoid organs. There, they are activated by antigen-specific T cells. B cells first encounter antigen in the T cell–rich areas of secondary lymphoid organs. Safety assessments were comparable for the 2 regimens.

Conclusions: The addition of repaglinide to metformin therapy resulted in reductions of HbA1c and FPG values that were significantly greater than the reductions observed for addition of nateglinide.

HEPATOLOGY

A model to predict severe HCV-related disease following liver transplantation


(Heptatology 2003;38:34–41) Reprinted with permission from the American Association for the Study of Liver Diseases.

Posttransplantation recurrence is increasing in patients with HCV. Early antiviral therapy may be of benefit in this setting. Thus, accurate and early prediction of progression may help select candidates for treatment. We developed a model based on pre- and/or early posttransplantation variables, which may predict progression to severe disease. Clinical and histologic outcomes were assessed in 554 liver recipients. A total of 1533 biopsy specimens obtained after 1 year (median of 2 biopsies per patient; range, 1–8) were scored. Two outcome measures were used: cumulative probability of developing severe disease (fibrosis 3 and 4) within 5 years and actual progression to severe disease in 2 years. We used Cox proportional hazard survival analysis for the whole cohort. Predictors analyzed included HCV genotype and recipient, donor, and transplant-related variables. The cumulative risk of progressing to fibrosis 3 and 4 was significantly greater in patients transplanted recently (P < 0.001) and was present in all centers. Factors increasing this risk were genotype, induction with mycophenolate, donor age, short course of azathioprine, and prednisone (<12 months). To create a model of prediction, 285 patients with 2-year follow-up were used to create a logistic regression analysis. The estimated probability of being at high risk for severe disease was calculated from a formula that included donor age and recipient therapy as critical variables. In conclusion, we have developed a model that uses early posttransplantation variables to predict severe HCV recurrence. Accuracy of the model is not perfect (c-statistic 0.80), probably reflecting the complexity of HCV in the liver transplant setting.

INTERNATIONAL IMMUNOLOGY

Human germinal center B cells differ from naive and memory B cells by their aggregated MHC class II–rich compartments lacking HLA-DO

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To generate memory B cells bearing high-affinity antibodies, naive B cells first encounter antigen in the T cell–rich areas of secondary lymphoid organs. There, they are activated by antigen-specific T cells and become germinal center (GC) founder B cells. GC founders enter the GC to become centroblasts that proliferate and mutate their BCR. Centroblasts differentiate into centrocytes that undergo selection, which requires both the recognition/capture of antigen on follicular dendritic cells and the presentation of processed antigen to GC T cells. Because at each stage of differentiation B cells act as antigen-presenting cells, we analyzed their content of HLA-DR+–rich compartments (MIIC), as well as their expression of HLA-DM, which catalyzes peptide loading of class II molecules, and HLA-DO, which interacts with HLA-DM and focuses MHC class II peptide loading on antigens internalized by the BCR. Naive and memory B cells concentrate HLA-DR, -DM and -DO into compartments dispersed under the cell surface, which are identified by their expression of lysosome-associated membrane protein (Lamp)-1 as late endosomes/lysosomes. GC founders and GC B cells express larger Lamp-1+ DR+ compartments that are concentrated in the juxta-nuclear region. These compartments express lower levels of HLA-DM and virtually no HLA-DO. Upon induction of a GC founder phenotype through the prolonged (days) coligation of BCR and CD40, the naive B cell's peripheral DR+DM+Lamp-1+ compartments aggregate in a polar fashion close to the nucleus. Furthermore, HLA-DO expression virtually disappears, whereas low levels of HLA-DM remain colocalized with HLA-DR. Anti-κ/λ antibodies, used as surrogate antigens, are promptly (minutes) endocytosed in naive, memory, and GC B cells. Then, naive and memory B cells target the surrogate antigen to their peripheral HLA-DO+ MIIC, while GC B cells target it to their HLA-DO+ MIIC aggregates. Taken together, our results show that human GC B cells differ from naive and memory B cells by their aggregated MIIC that lack HLA-DO.

JOURNAL OF CLINICAL INVESTIGATION

Abnormal passive chloride absorption in cystic fibrosis jejunum functionally opposes the classic chloride secretory defect


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Due to genetic defects in apical membrane chloride channels, the cystic fibrosis (CF) intestine does not secrete chloride normally. Depressed chloride secretion leaves CF intestinal absorptive processes unopposed, which results in net fluid hyperabsorption, dehydration of intestinal contents, and a propensity to inappetant intestinal obstruction. This theory is based primarily on in vitro studies of jejunal mucosa. To determine if CF patients actually hyperabsorb fluid in vivo, we measured electrolyte and water absorption during steady-state perfusion of the jejunum. As expected, chloride secretion was abnormally low in CF, but surprisingly, there was no net hyperabsorption of sodium or water during perfusion of a balanced electrolyte solution. This suggested that fluid absorption processes are reduced in CF jejunum, and further studies revealed that this was due to a marked depression of passive chloride absorption. Although Na+–glucose cotransport was normal in the CF jejunum, absence of passive chloride absorption completely blocked glucose-stimulated net sodium absorption and reduced glucose-stimulated water absorption 66%. This chloride absorptive abnormality acts in physiological opposition to the classic chloride secretory defect in the CF intestine. By increasing the fluidity of intraluminal contents, absence of passive chloride absorption may reduce the incidence and severity of intestinal disease in patients with CF.
Accurate enzymatic measurement of fecal bile acids in patients with malabsorption
Porter JL, Fordtran JS, Santa Ana CA, Emmett M, Hagey LR, Macdonald EA, Hofmann AF

(J Lab Clin Med 2003;141:411–418) Reprinted with permission from Elsevier.

Quantitation of fecal bile acid excretion can help elucidate the cause of diarrhea or steatorrhea. Fecal bile acids can be measured with gas chromatography–mass spectrometry, but this is time-consuming, expensive, and not available for clinical use. Relatively simple enzymatic methods have been described for the measurement of fecal 3α-hydroxy bile acids, but these have not been validated in patients with gastrointestinal disease. We found that an enzymatic method yielded falsely low results in patients with malabsorption syndromes for 2 reasons: First, the preliminary hydrolysis step did not completely deconjugate bile acids, precluding their extraction into diethyl ether for enzymatic assay. Second, long-chain fatty acids inhibited 3α-hydroxysteroid dehydrogenase activity. By increasing the duration of hydrolysis and the concentration of enzyme, we developed a simple, accurate, and reproducible method for measuring fecal 3α-hydroxy bile acids that agreed well with values obtained with the use of gas chromatography-mass spectrometry (R = .95), both in normal subjects and in patients with malabsorption syndromes.

A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity
(Obes Res 2003;11:722–733)

Objective: To evaluate the efficacy and safety of topiramate (TPM) for weight loss in healthy obese subjects.

Research methods and procedures: A randomized, double-blind, placebo-controlled, dose-ranging trial was conducted. Three hundred eighty-five subjects, 18 and 75 years of age, were randomized to receive either placebo or TPM at 64, 96, 192, or 384 mg daily. Dosing began at 16 mg once daily. In week 2, the dose was increased to 16 mg twice daily. Thereafter, the dose was raised every week by 32 mg (16 mg twice daily) until subjects reached their target dose. Twenty-four weeks after beginning treatment, all subjects were tapered off treatment by a dose reduction of 50% per week. All participants received the same lifestyle program.

Results: Mean percent weight loss from baseline to week 24 was −2.6% in placebo-treated patients vs −5.0%, −4.8%, −6.3%, and −6.3% in the 64, 96, 192, and 384 mg/d TPM groups, respectively. Greater percentages of TPM-treated patients lost at least 5% or 10% of body weight compared with placebo. The most frequent adverse events were related to the central or peripheral nervous system, including paresthesia, somnolence, and difficulty with memory, concentration, and attention. Most events were dose related, occurred early in treatment, and usually resolved spontaneously; only 21% receiving TPM withdrew due to adverse events compared with 11% on placebo.

Discussion: TPM produced significantly greater weight loss than placebo at all doses.

Human monoclonal macroglobulins with antibody activity

Assays for specific antigen-binding activity were performed on sera from 172 patients with monoclonal macroglobulinemia defined by immunofixation electrophoresis. The sera were collected between 1970 and 2002. Mean IgM level was 1409 mg/dL with a range from 70 to 6800. Cryoglobulins were identified in 15.3% (26/170 sera: 12 trace, 5 single component, and 9 mixed IgM-IgG). Rheumatoid factor (RF) was detected in 19 of 151 (12.6%) samples with titers ranging from 1:80 to 1:327,680. Among the 9 mixed IgM-IgG cryos, 8 were RF-positive and 6 of 6 displayed positivity for hepatitis C virus. Cold agglutinins (CA) were present in 8.5% (10/117) of sera with anti-I titers between 1:512 and 1:65,536. IgM binding to a series of glycosaminoglycan oligosaccharides, glycolipids, and glycoprotein antigens was found in 75 samples (43%). IgM binding to antigens having known associations to polyneuropathies occurred in 20 patients (12%). Antinuclear antibody (ANA) was documented in 10.7% (18/169) of sera. Anti-DNA activity was absent in all samples tested. Sera from 71% of patients with monoclonal macroglobulinemia in this series exhibited binding to autoantigens. Some of these immune complexes resulted in clinically significant manifestations. Our results suggest that many monoclonal immunoglobulins may be functional antibodies rather than “paraproteins.” Characterization of antigen-binding activities may provide insight into the pathogenesis of monoclonal gammopathies.