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Highlights from Digestive Disease Week 2010

A Review of Selected Topics and Presentations
from Digestive Disease Week
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New Orleans, Louisiana

- **Clinical Updates on the Use of Biologic Agents in Patients With Crohn's Disease**

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- **Clinical Updates on Diagnosis and Prognosis of Pancreatic Insufficiency**

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with Crohn's disease and patients with pancreatic insufficiency.

Statement of Need/Program Overview: As an abundance of new data has recently come to light in the gastroenterology field, there is a distinct educational need in the gastroenterology community for an updated understanding of the treatment of patients with Crohn's disease and pancreatic insufficiency. Throughout the year, various abstracts/posters are presented at major medical meetings that address updates on treatment strategies, comparisons between different therapies, clinical trial data, retrospective data on real-world clinical experience, etc. Unfortunately, physicians at the major meetings cannot attend all of the poster sessions in their therapeutic area. A compendium of abstracts is vital to help disseminate important new treatment/management options.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Summarize the current role of biologic therapies in the treatment of moderate-to-severe Crohn's disease.
2. Discuss emerging data on the use of biologics as they relate to use in clinical practice.
3. Describe new strategies to maximize biologic efficacy and durability of response.
4. Describe new and refined technologies for diagnosis and prognosis of pancreatic insufficiency.

Faculty: Edward V. Loftus, Jr., MD, Professor of Medicine, Department of Gastroenterology and Hepatology, Mayo Clinic

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Overview

Crohn's disease (CD) and ulcerative colitis (UC) are the two chronic diseases grouped together under the rubric of idiopathic inflammatory bowel disease (IBD). Both diseases are characterized by abdominal pain, rectal bleeding, and changes in bowel habits. Whereas UC is associated with inflammation in the colonic mucosa alone, CD is a transmural condition that can manifest in discontinuous patches throughout the length of the gastrointestinal tract, typically grouped into the categories proximal, ileal, ileal-colonic, and colonic only. Extraintestinal manifestations common to UC and IBD include fatigue, anemia, and hypercoagulability. Patients with UC may also experience skin lesions (erythema nodosum, pyoderma gangrenosum) and peripheral and central arthritis. In terms of genetic susceptibility, the etiology of UC has been associated with MHC locus HLA Class II alleles, the interleukin-1 family, and *MDR1*.[1] In contrast, a specific gene has been identified as a factor of genetic susceptibility for CD, *NOD2/CARD15*.[2] Environmental factors are also thought to contribute to UC and CD risk, as well as to pathogenesis.[1,3]

IBD is associated with significant burdens in terms of healthcare expenditures in the United States, and the prevalence of disease has been increasing.[4] For individual patients and their families, IBD is associated with significant effects on quality of life and workplace functionality. Diminished quality of life correlates directly with increased IBD disease severity, regardless of time since diagnosis. In CD, patients self-report great concern regarding the possible need for surgery, the uncertainty regarding symptom onset, and fatigue associated with the disease.[5]

Although patients with UC and CD typically present with mildly to moderately active disease, progression to moderately to severely active disease can generally be expected. In the absence of curative therapy, the goal of treatment is induction and maintenance of clinical and endoscopic remission and avoidance of surgical resection. First-line treatment with corticosteroids (eg, prednisone) has been recommended by practice guidelines for some time. Yet, as IBD is a chronic condition, the high risk of steroid dependence, bone loss, and susceptibility to infections led to the introduction of other maintenance therapies, including the immunomodulators 6-mercaptopurine, methotrexate, and azathioprine. Although these agents are effective, if characterized by slow onset of action, they carry risks of leukopenia, liver toxicity, and infection and other side effects.

Today, based on identification of the critical role of the cytokine tumor necrosis factor alpha (TNF) in the pathogenesis of gut inflammation in IBD, biologic therapies that target cytokines are widely used in the treatment of IBD. The first biologic agent approved for CD was infliximab, a humanized chimeric monoclonal antibody that binds with high affinity to TNF and causes apoptosis of macrophages and activated T lymphocytes. According to currently used guidelines, infliximab is effective in CD patients who are refractory to other treatment options. Infliximab was shown to have a 2-month response rate of 61–69% in patients with UC, compared to 31% for those receiving placebo.[6] Adalimumab is a human anti-TNF monoclonal antibody that demonstrated efficacy in two pivotal CD trials: CLASSIC I and GAIN.[7,8] Adalimumab is effective in patients who are naive to therapy with biologic agents and in those who are no longer responding to infliximab.[9] Another anti-TNF agent, certolizumab pegol, composed of a pegylated Fab' antibody fragment, was shown to be efficacious in the PRECiSE 1 and PRECiSE 2 trials.[10,11] The humanized monoclonal antibody natalizumab targets the cellular adhesion molecule 4-integrin, expressed on leukocytes, which are known to be critical to CD pathogenesis. This agent is effective in patients with moderate-to-severe CD who are refractory to TNF inhibitors and other therapies for CD.[12] Due to its adverse reaction profile and associated increased risk of progressive multifocal leukoencephalopathy (PML), natalizumab is used in patients only after a prior trial of anti-TNF therapy; it may not be used in conjunction with immunosuppressive agents due to the risk of PML. Further research into these and other biologic agents in the setting of IBD is continuing.

Beyond recent findings regarding all aspects of IBD highlighted below, the 2010 Digestive Disease Week, held in New Orleans, La., featured presentations on many other aspects of ongoing clinical research gastroenterology and hepatology, including pancreatitis, hepatitis, gastrointestinal cancer, and other conditions, as well as diagnostic and prognostic tools and technologies. A small sample of these findings, focusing on diagnosis and prognosis of various forms of pancreatic insufficiency, is included herein.

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Clinical Updates on the Use of Biologic Agents in Patients With Crohn's Disease

Extending EXTEND

S1031 Crohn's Disease Mucosal Healing in Adalimumab-treated Patients Is Affected by Disease Duration: Results From EXTEND

WJ Sandborn, R Panaccione, R Thakkar, KG Lomax, N Chen, J Chao, P Mulani, M Yang

Adalimumab is a fully recombinant human IgG1 monoclonal antibody targeting TNF. Its efficacy has been established in multiple trials.[1-3] Nonetheless, beyond the induction of remission that is achievable with this agent, questions remain regarding the correlation between mucosal healing and long-term outcomes. In the EXTEND (EXTend the safety and efficacy of adalimumab through ENDoscopic healing) trial, Rutgeerts and colleagues assessed the efficacy of adalimumab for inducing mucosal healing in patients with CD.[4] The EXTEND trial enrolled 135 patients with moderate-to-severe ileocolonic CD, with a mean disease duration of 10 years. All patients initially received open-label adalimumab induction therapy (160 mg and 80 mg at weeks 0 and 2, respectively). At week 4, patients (n=129) commenced adalimumab maintenance therapy (40 mg every other week) or placebo on a randomized basis through week 52. From week 8, patients who experienced flares or were nonresponsive could receive open-label adalimumab. The primary endpoint of the study was the proportion of patients healing at week 12. Although in the intent-to-treat analysis the primary endpoint was barely missed (27.4% with complete mucosal healing vs 13.1% on placebo, *P*=.056), a statistically significant higher number of patients who received adalimumab maintenance therapy achieved complete mucosal healing compared with patients who received placebo in the per-protocol analysis (27.9% vs 12.5%, *P*=.046). It was concluded that adalimumab maintenance therapy resulted in an improved rate of complete mucosal healing compared with placebo. Adalimumab maintenance therapy also resulted in improved rates of clinical remission at both week 12 (46.9% vs 27.7%, *P*<.05) and week 52 (32.8% vs 9.2%, *P*<.05).

In updated results, Sandborn and colleagues reported a post-hoc analysis of all randomized patients with baseline mucosal ulceration (score of 2 or 3 for ≥1 colonic segments in the Ulcerated Surface subscore of the Simple Endoscopic Score [SES] for CD). Mucosal healing was defined as the absence of mucosal ulceration determined by colonoscopy and multiple secondary endpoints including CD Endoscopic Index of Severity and SES. A total of 123 patients (adalimumab, n=62) were analyzed. Seventeen patients had CD for less than 2 years (13.8%), 24 had CD for 2–5 years (19.5%), and 82 had CD for at least 5 years (66.7%). Rates of mucosal healing at week 12 were observed to be greater for patients who received adalimumab in comparison to placebo, with a greater treatment effect associated with shorter duration of disease. A differential effect was observed on the likelihood of mucosal healing at week 12 in patients with CD for less than 5 years compared to at least 5 years for adalimumab versus placebo (*P*=.029). The interaction between treatment and disease duration was associated with a significant predictive effect on mucosal healing at week 12 (*P*=.044), with shorter disease duration affecting the odds of mucosal healing (odds ratio [OR] for <5 years, 15.27 vs OR for ≥5 years, 1.21). Sandborn and colleagues concluded that increased rates of mucosal healing were achieved in adalimumab-treated patients with early CD as compared to those with longer duration of disease. Adalimumab thus may be most effective when administered early in the disease course, likely due to CD's progressive character.

T1239 Adalimumab Treatment Results in Deep Remission for Patients With Moderate to Severe Ileocolonic Crohn's Disease: Results From EXTEND

J-F Colombel, PJ Rutgeerts, WJ Sandborn, AA Camez, PF Pollack, N Chen, M Yang, P Mulani, J Chao

Further building on previous findings of the EXTEND trial,[4] Colombel and colleagues assessed the efficacy of adalimumab for achieving "deep remission," defined as clinical remission (CD Activity Index [CDAI] <150) and mucosal healing.[5] Two analyses were performed, a prespecified analysis of this endpoint at weeks 12 and 52, and a post-hoc sensitivity analysis of the entire intention-to-

treat population (n=129) using logistic regression analysis, controlling for confounding factors (disease duration, previous anti-TNF therapy, and baseline immunosuppressant use, corticosteroid use, and C-reactive protein [CRP] concentration). It was observed that at week 12 of treatment, a greater number of patients receiving adalimumab versus placebo on a randomized basis achieved deep remission (16.1% vs 9.8%), although in the unadjusted analysis this did not reach statistical significance. Based on the post-hoc sensitivity analysis, it was concluded that patients who received adalimumab were 3.4 times more likely to achieve this clinical result ($P<.05$) after adjusting for the aforementioned factors. The difference in this statistically significant result was even more stark at week 52 and was considered highly significant for the prespecified analysis (19.4% vs 0%; $P<.001$). It was thus concluded that adalimumab is associated with improved likelihood of achieving deep remission in patients with moderate to severe ileocolonic CD and mucosal ulceration at presentation. Due to the study design, in which patients who received placebo had received open-label induction therapy with adalimumab to week 2 and patients with flares who received subsequent open-label adalimumab were considered nonresponders, the authors suggest that the effect of adalimumab at week 12 may be underestimated in this analysis.

Rutgeerts and colleagues reported related findings from a post-hoc analysis of EXTEND regarding the predictive value of endoscopic assessment of early mucosal healing status on 1-year quality-of-life outcomes.[6] This report suggested that early mucosal healing (ie, at week 12 in this study) represents an indicator of sustained improvements in patient quality of life, based on a statistically significant association between early SES and 1-year improvements in Inflammatory Bowel Disease Questionnaire scores.

T1012 Long-Term Maintenance of Clinical Remission with Reduced Dosing Frequency of Adalimumab in Patients with Moderate to Severe Crohn's Disease

R Panaccione, J-F Colombel, WJ Sandborn, A Robinson, J Chao, P Mulani, PF Pollack

Results of the CHARM (Crohn's trial of the Fully Human antibody Adalimumab for Remission Maintenance) trial show that maintenance therapy with adalimumab 40 mg given every other week achieves clinical results similar to those seen with weekly dosing. In CHARM, 854 patients received open-label induction therapy with adalimumab (80 mg at week 0 and 40 mg at week 2). At week 4, 778 patients were randomized to receive adalimumab 40 mg (weekly or every other week) or placebo.[1] Few data, however, exist to clarify how reduction of maintenance treatment from weekly to every other week affects maintenance of remission. An open-label extension of the 56-week CHARM trial, called ADHERE (Additional long-term Dosing with Humira to Evaluate sustained Remission and Efficacy in Crohn's disease), was designed to assess maintenance of clinical remission (CDAI <150) after reduction of adalimumab dosing from 40 mg weekly to every other week in patients with moderate to severe CD. In ADHERE, 75 patients receiving blinded adalimumab 40 mg weekly and who were in remission at the conclusion of CHARM began an every-other-week open-label regimen of adalimumab. If patients did not respond or experienced flare, they had the ability to recommence weekly dosing. Patients were followed for 2 years (1 year in CHARM, 1 year in ADHERE) and remission status was assessed. Panaccione and colleagues reported that 64 of 75 patients in ADHERE (85%) who had reduction in adalimumab dose from 40 mg weekly to every other week were able to maintain the reduced frequency of dosing. At weeks 92 and 116, 54 (84%) and 50 (78%) maintained clinical remission, respectively. It was therefore concluded that a reduction in the frequency of adalimumab dosing from weekly to every other week, which offers benefits in terms of healthcare expenditures and quality of life, was associated with maintenance of long-term clinical remission in a high percentage of patients with moderate to severe CD. In separate findings, adalimumab was associated with long-term maintenance of fistula healing in the 1-year CHARM trial and its 1-year open-label continuation, ADHERE; 22 of 70 (31%) patients with fistulizing disease at baseline of CHARM experienced fistula healing after approximately 2 years of adalimumab therapy.[7]

Putting a Finer Point on PRECiSE

S1035 Certolizumab Pegol Is Effective at Maintaining Response and Remission in Patients With Fistulising Crohn's Disease: 3-year Results from the PRECiSE 3 Study

S Schreiber, IC Lawrance, OO Thomsen, SB Hanauer, R Bloomfield, WJ Sandborn

Certolizumab pegol is a pegylated humanized Fab' fragment of a monoclonal antibody directed against TNF□. An early study of this agent suggested that induction treatment at a subcutaneous dose of 400 mg every 4 weeks would be effective for the treatment of moderate to severe active CD.[8] Based on these results, further trials of certolizumab pegol were conducted: 2 phase III iterations of PRECiSE (Pegylated antibody fRagment Evaluation

in Crohn's disease: Safety and Efficacy).[9,10] PRECiSE 1 comprised a placebo-controlled induction phase, with therapy given at weeks 0, 2, and 4, and a 26-week treatment phase, with therapy given every 4 weeks. In this trial, certolizumab pegol was associated with a modest benefit in terms of response rate but not with a significant improvement in remission. A rapid onset of action was observed. PRECiSE 2 was a 26-week trial of maintenance and withdrawal therapy in patients who previously experienced a response to open-label induction therapy with certolizumab pegol, given at weeks 0, 2, and 4. The results of this trial showed that maintenance therapy consisting of subcutaneously administered certolizumab pegol 400 mg every 4 weeks was superior to placebo in 64% of patients who had a previous response to induction therapy. The combined response rate during the induction and maintenance phases was 40%. The notable difference between PRECiSE 1 and 2 was the administration of 3 doses of certolizumab pegol induction in PRECiSE 2 followed by randomization of responders, in comparison to randomization prior to induction therapy in PRECiSE 1. PRECiSE 3 was an open-label trial designed to study the maintenance of remission in patients who received subcutaneous certolizumab pegol 400 mg in PRECiSE 1 and 2.[11]

Based on the finding, in a post-hoc analysis of PRECiSE 2, that certolizumab pegol was effective at inducing fistula closure, Schreiber and colleagues reported 3-year response and remission findings in the subpopulation of patients in that trial with fistulizing disease who received open-label subcutaneous certolizumab pegol 400 mg every 4 weeks in the PRECiSE 3 extension. Efficacy measures consisted of Harvey-Bradshaw Index (HBI) response (≥3-point decrease from baseline) and remission (HBI ≤4). Only patients with open fistulae at baseline of PRECiSE 2 were included in the analysis, with fistula closure defined as the absence of drainage on gentle compression in at least 50% of open fistulae at any 2 consecutive postbaseline visits at least 3 weeks apart. A total of 58 (13.6%) patients in the intention-to-treat population of PRECiSE 2 responded to induction therapy with certolizumab pegol and had open fistulae at baseline; 30 received placebo and 28 received active therapy on a randomized basis. Of these, 35 patients entered PRECiSE 3 (certolizumab pegol, n=21). Fistula closure was observed in 11 of 21 (52.4%) patients receiving study drug compared with 6 of 14 (42.9%) receiving placebo in PRECiSE 2. Among those receiving active therapy, clinical response and remission rates were numerically better in patients with fistula closure than in patients with open fistula and were maintained through week 154 of PRECiSE 3. It was concluded that there was a carry-over effect from the open-label induction phase of PRECiSE 2, which led to some fistula closure among patients who received placebo on a randomized basis during the maintenance phase of PRECiSE 2. Therefore, when patients who had received placebo began the open-label maintenance therapy with certolizumab pegol in PRECiSE 3, a significant percentage already had experienced fistula closure, likely owing to the previously observed rapid onset of action of certolizumab pegol. Long-term maintenance therapy with certolizumab pegol was considered effective at maintaining clinical response and remission among patients with fistulizing CD.

S1040 Long-term Remission With Certolizumab Pegol in Crohn's Disease: Efficacy Over 4 years in Patients With No Prior TNF-α Inhibitor Exposure (PRECiSE 3 Study)

G Lichtenstein, OO Thomsen, S Schreiber, IC Lawrance, SB Hanauer, R Bloomfield, WJ Sandborn

Lichtenstein and colleagues reported long-term efficacy data for anti-TNFα treatment–naive patients who received certolizumab pegol in PRECiSE 2 and 3. Because CD is a chronic condition that lacks a curative therapy at present, long-term therapy is considered essential for maintenance of remission. Data are currently available for patients who have received a total of 4 years of therapy with certolizumab pegol, based on the 6 months of PRECiSE 2 and the subsequent 3.5 years of PRECiSE 3. This analysis considered the effect of no prior exposure to anti-TNFα therapy (specifically infliximab) on long-term remission rates (remission = HBI score of ≤4) in a subset of patients. Remission rates were calculated using 3 analytics: nonresponder imputation (NRI), observed case (OC), and last observation carried forward (LOCF). Of 141 patients who received active study drug in PRECiSE 2 and in PRECiSE 3, 114 had not received prior therapy with infliximab. At the outset of PRECiSE 3, 105 (75%) and 89 (78%) of the total and infliximab-naive patients had achieved remission, respectively. See Table 1 for remission rates. Continuous administration of certolizumab pegol was associated with long-term remission in patients who responded initially to induction therapy in PRECiSE 2. Moreover, comparable long-term remission rates were observed in the total population of patients receiving certolizumab pegol in PRECiSE 3 and in the infliximab-naive population.

Schreiber and colleagues presented related findings based on a post-hoc analysis of data from PRECiSE 2.[12] The researchers assessed the efficacy of certolizumab pegol in maintaining clinical response and remission based on whether patients had previously received oral immunosuppressants. The analysis included 161 immunosuppressant-naive patients and 264 patients who had previously

Table 1. Long-term Remission With Certolizumab Pegol

		Time since baseline of PRECiSE 2, years			
		1	2	3	4
LOCF	Total, n/N (%)	99/141 (70%)	92/141 (65%)	90/141 (64%)	89/141 (63%)
	Infliximab-naive, n/N (%)	81/114 (71%)	76/114 (67%)	72/114 (63%)	74/114 (65%)
OC*	Total, n/N (%)	84/101 (83%)	54/74 (73%)	44/54 (82%)	29/35 (83%)
	Infliximab-naive, n/N (%)	67/79 (85%)	47/60 (78%)	37/45 (82%)	25/31 (81%)
NRI	Total, n/N (%)	84/141 (60%)	54/141 (38%)	43/141 (31%)	29/141 (21%)
	Infliximab-naive, n/N (%)	67/114 (59%)	47/114 (41%)	36/114 (32%)	25/114 (22%)

*N=Patients completing assessments at years 1, 2, 3, and 4, respectively.

LOCF=last observation carried forward; NRI=nonresponder imputation; OC=observed case.

received oral immunosuppressants at study entry. It was noted that 6.2% of immunosuppressant-naive patients and 35.2% of non–immunosuppressant-naive patients had previously received anti-TNF□ therapy; in addition, approximately one third of patients in both groups were receiving concomitant steroid therapy at study entry. At the end of PRECiSE 2 (week 26), the clinical response rate in immunosuppressant-naive patients (placebo, n=80) was 71.6% for those receiving certolizumab pegol and 43.8% for those receiving placebo (P<.001); for non–immunosuppressant-naive patients (placebo, n=130), the clinical response rate was 57.5% for those receiving certolizumab pegol and 31.5% for those receiving placebo (P<.001). In the immunosuppressant-naive group, 51.9% and 38.8% of those receiving certolizumab pegol and placebo, respectively, achieved remission (P<.05), as compared to 45.5% and 22.3% (P<.001), respectively, among patients who had received oral immunosuppressants. Although certolizumab pegol was considered effective in maintaining response and remission in patients who had or had not received oral immunosuppressants prior to baseline, a tendency was observed toward better response and remission in those who were naive to therapy with oral immunosuppressants.

S1030 Predictors of Response and Remission to Certolizumab Pegol in Patients With Crohn's Disease: Data from the WELCOME Study

WJ Sandborn, MT Abreu, GR D'Haens, J-F Colombel, S Vermeire, K Mitchev, E Ernault, RN Fedorak, M Spehlmann, DC Wolf, SD Lee, PJ Rutgeerts

In relation to the findings and ongoing analysis of the PRECiSE series of trials, the open-label WELCOME (26-Week open-label trial Evaluating the clinical benefit and tolerability of certoLizumab pegol induCtiOn and Maintenance in patients suffering from CD with prior loss of response or intolErance to infliximab) trial was conducted to evaluate the efficacy of certolizumab pegol in patients who had previously responded to anti-TNF□ therapy with infliximab but had lost their response or developed hypersensitivity.[13] Patients with a CDAI score of 220–450 and a history of infliximab failure received open-label induction therapy with certolizumab pegol 400 mg administered subcutaneously at weeks 0, 2, and 4. Those who responded as of week 6 received double-blind maintenance therapy with certolizumab pegol every 2 or 4 weeks or placebo on a randomized basis. The definitions of response and remission were a decrease of at least 100 CDAI points and CDAI score of 150 or lower, respectively. The primary results of this open-label trial have been presented at previous meetings. Sandborn and colleagues conducted a post-hoc analysis to identify predictors of response and remission using multivariate regression analysis with predictors including age, duration of disease, disease location and behavior, resection (yes/no and number), previous exposure to corticosteroids or immunosuppressants, reason for infliximab failure, smoking status, baseline CDAI, CRP level, and levels of anti-infliximab antibodies. The researchers found that disease localization in the colon, no resection performed, and baseline CDAI score below 298 were prognostic factors predictive of remission at week 26. Among those not on corticosteroids at baseline, patients with baseline CDAI under 298 points were over 4 times more likely to achieve remission than those above 298 points at baseline. No predictor was associated with the probability of clinical response at week 26. It was noted, however, that interactions between predictors were associated with predictive value for clinical response: 1) baseline anti-infliximab antibodies or smoking status by CRP level; and 2) reason for previous infliximab failure by resection.

New Directions For Therapy With Infliximab

S2008 Long-term Outcome of Treatment With Infliximab in Paediatric Crohn's Disease: A Population-based Study

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Infliximab was the first anti-TNF chimeric monoclonal antibody introduced. Its safety and efficacy in pediatric patients was determined in the REACH (A Randomized, multicenter, open-label study to Evaluate the safety and efficacy of Anti-TNF CHimeric monoclonal antibody in pediatric subjects with moderate-to-severe Crohn's disease) trial.[14] Crombé and colleagues assessed the long-term clinical safety and efficacy of infliximab in an inception population-based cohort of 537 children younger than 17 years of age with newly diagnosed CD from 1998 to 2004. A total of 120 children (22%; 69 female; median age at diagnosis and infliximab initiation, 14.5 and 18 years, respectively) received infliximab and were included in this analysis. Median follow-up was 111 months (range, 75–161). Patients were divided into 2 groups: those receiving infliximab at last visit and those who stopped receiving the drug while in remission were labeled "IFX efficacy," whereas those who were primary or secondary nonresponders or who discontinued therapy with infliximab due to toxicities were labeled "IFX failure." Long-term effects were defined as the rate of surgical resection and nutritional catch-up, or a continuous variable corresponding to the difference between body-mass index Z scores at most recent follow-up and at baseline diagnosis. Concomitant azathioprine was administered to 96 (80%) patients at outset of therapy and was continued in 57 (60%) patients. Infliximab was administered either on an episodic or a scheduled basis (n=50 [42%] and n=70 [58%], respectively), with 27 patients receiving it on an episodic basis converting to maintenance therapy. It was noted that 39 (32%) patients still received infliximab at final visit, 27 (22%) discontinued while in remission (with 15 [13%] discontinuations due to toxicities), and 39 (32%) were nonresponsive to infliximab therapy. At 1 and 3 years, 77% and 50% of patients, respectively, were likely to be receiving continuous maintenance therapy. Based on the analysis by Crombé and colleagues, 66 (55%) and 54 (45%) patients, respectively, were categorized as IFX efficacy and IFX failure. IFX efficacy was associated with a decreased risk of surgery at 1 and 3 years (6% vs 22% and 13% vs 36%, respectively; P=.009). Moreover, scheduled treatment decreased cumulative risk of surgery in comparison to episodic treatment for patients in the IFX efficacy group. Children categorized as IFX efficacy experienced catch-up of nutritional status (P=.01), whereas those categorized as IFX failure did not achieve catch-up of nutritional status (P=.82). Secondary therapy with adalimumab was administered to 33 of the patients in the IFX failure category. In terms of safety, hypersensitivity reactions were the most common adverse events (n=19), followed by nonsevere infections (n=5). One patient developed undifferentiated colonic adenocarcinoma with liver metastases, which resulted in death. Overall, treatment with infliximab was considered efficacious in 55% of patients in a pediatric population-based cohort. Those who were long-term responders to infliximab experienced a lower rate of surgical resection and improved catch-up of nutritional status.

In related findings from a multicenter retrospective study conducted in The Netherlands, de Bie and colleagues assessed the long-term efficacy of infliximab in pediatric patients who received the anti-TNF agent for more than 3 years.[15] Patients were categorized according to length of therapy: 3–12 months (n=34), 1–3 years (n=74), 3–5 years (n=36), and more than 5 years (n=37). According to this categorization, 88.2%, 60.8%, 69.4%, and 37.8% of patients achieved success of treatment, defined as good clinical response maintained minimally 90 days after conclusion of infliximab administration or when repeated infusions of infliximab were needed to maintain good clinical response. Of 181 total patients, 67 were at some point considered unsuccessfully treated, with 65.7% of them undergoing surgical resection. It was concluded that, although effective, infliximab's therapeutic effect decreases over time, with response lost after 5 years in approximately 60% of pediatric patients. Moreover, greater than 60% of patients require adjustments to the schedule of treatment in order to maintain clinical response after 3–5 years of treatment. As such, a more effective long-term therapy for pediatric patients with CD is still needed in the armamentarium.

T1285 Usefulness of Co-treatment With Immunomodulators in Inflammatory Bowel Disease Patients Treated With Infliximab Maintenance Therapy

H Sokol, P Seksik, I Nion-Larmurier, A Vienne, L Beaugerie, J Cosnes

Debate is ongoing as to whether the use of concomitant immunosuppressants with scheduled infliximab therapy

for IBD is an effective strategy. Sokol and colleagues prospectively assessed 23 patients with UC and 98 patients with CD who received infliximab and at least 6 months of concomitant therapy with azathioprine or methotrexate. For each patient, the infliximab treatment duration was divided into independently analyzed "semesters" (the first semester, however, was excluded from analysis), and IBD activity was assessed using several criteria: IBD flare, perianal complication, abdominal surgical resection, maximal CRP level, infliximab dose/kg/semester, and switch to adalimumab. IBD activity in semesters during which cotreatment was administered was compared to that in semesters during which cotreatment was not administered. A total of 584 semesters were analyzed (265 with immunosuppressants). Semesters with and without cotreatment were similar with regard to patient sex, disease type, age at diagnosis, surgical history, and infliximab indication. Small differences between semesters were noted with regard to smoking habits, with 40% of patients who received immunosuppressants concomitantly as smokers and 38.8% who did not receive immunosuppressants concomitantly as smokers (P=.05). The authors observed fewer IBD flares, perianal complications, and switch to adalimumab in semesters with concomitant administration of immunosuppressants as compared to semesters without cotreatment (19.3% vs 32.0%, P=.003; 4.1% vs 11.8%, P=.03; 1.1% vs 5.3%, P=.006, respectively). Maximal CRP level and infliximab dose/kg/semester were lower in semesters with cotreatment as compared to semesters without cotreatment (8.7 ± 1.1 mg/L vs 10.9 ± 0.8 mg/L, P=.001; 16.0 ± 0.3 mg/kg/semester vs 17.2 ± 0.3 mg/kg/semester, P=.001). Among semesters with cotreatment (azathioprine, n=175 semesters; methotrexate, n=90 semesters), IBD flares and perianal complications were observed less frequently in semesters with azathioprine cotreatment than in those with methotrexate cotreatment (14.3 vs 28.9%, P=.003; 2.3 vs 22.2%, P=.001, respectively). Maximal CRP level and infliximab dose/kg/semester were lower in semesters with azathioprine cotreatment than in those with methotrexate cotreatment (6.8 ± 1.3 mg/L vs 12.2 ± 1.8 mg/L, P<.0001; 15.2 ± 0.2 mg/kg/semester vs 17.6 ± 0.7 mg/kg/semester, P=.04). No statistically significant difference was observed regarding rate of switch to adalimumab among semesters with azathioprine versus methotrexate cotreatment. Sokol and colleagues determined that cotreatment with immunosuppressants is associated with reduction in IBD activity, infliximab dose requirement, and switch to adalimumab dosing. Between azathioprine and methotrexate, the former is considered more beneficial as cotreatment with infliximab. Nonetheless, the authors cautioned that combination therapy carries risks of infection and oncogenesis.

W1259 Adalimumab Vs Infliximab Clinical Comparison: Longitudinal Study

F Zorzi, S Onali, E Calabrese, C Petruzziello, E Lolli, F Pallone, L Biancone

Although infliximab, adalimumab, and certolizumab pegol are all considered safe and effective therapies for CD, no head-to-head double-blind trial of these agents has been undertaken.[16] Infliximab is approved by the US Food and Drug Administration (FDA) for treatment of moderate to severe CD in adults and children who have not responded well to conventional therapies. Adalimumab is also approved by the FDA for treatment of moderate to severe in adults who have not responded well to conventional therapies; it is also indicated for use in those who have lost response to infliximab. Certolizumab pegol, similarly, is approved by the FDA for treatment of moderate to severe in adults who have not responded well to conventional therapies. Zorzi and colleagues evaluated 53 patients in a 6-week longitudinal study to compare the clinical outcome and quality of life associated with infliximab (n=24) and adalimumab (n=29). Patients who received infliximab had refractory disease (n=4), perianal disease (n=5), or severe CD (n=15); patients who received adalimumab had refractory disease (n=8), perianal disease (n=7), or severe CD (n=14). All patients were assessed for CDAI at each infusion, with remission categorized as CDAI score below 150 and response as CDAI score change of over 70; furthermore, patients completed a questionnaire before and after treatment. Infliximab therapy was completed in 16 (67%) patients, with 6 discontinuations due to infusion reactions and 2 due to need for surgical resection. For treatment with either agent, CDAI score was observed to be reduced significantly from baseline to second infusion, at 2 weeks, and to third infusion, at 6 weeks for infliximab or 4 weeks for adalimumab (P<.001). The percentage of reduction of CDAI score from baseline to week 2 and week 6 was 27% and 24%, respectively, with infliximab. The percentage of reduction of CDAI score from baseline to week 2 and week 4 was 23% and 38%, respectively, with adalimumab. Based on responses to the questionnaire, significant improvement in quality of life was achieved with both agents (P<.001), with the increase noted to be 12% with infliximab and 27% with adalimumab. Infliximab was

associated with a greater rate of adverse events in this study, but comparable efficacy in terms of CDAI score and quality of life was achieved with infliximab and adalimumab. A similar single-center experience in the setting of UC, comparing long-term outpatient maintenance therapy with infliximab and adalimumab, was recently reported.[17]

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Commentary

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As can be seen from the selected abstracts, the presentations on biologic therapies in CD at Digestive Disease Week this year were generally not groundbreaking paradigm-changers, but rather attempts to glean additional information from existing datasets.

The study by Sandborn and colleagues on the effect of disease duration on the results of the EXTEND study (S1031) is a post-hoc analysis of a previously presented trial of adalimumab versus placebo for endoscopic healing of CD. Such secondary analyses need to be interpreted with some caution, but the results—that patients with shorter disease duration had higher rates of endoscopic healing and a higher treatment effect compared to placebo—are in keeping with secondary analyses of other treatment trials of biologic therapy. This finding is another piece of evidence suggesting that anti-TNF therapy may be most effective when introduced earlier in the disease course before the deleterious effects of intestinal complications (stricture, fistula, and abscess) have occurred.

Colombel and colleagues used the EXTEND trial results to examine the effect of adalimumab on "deep remission," which encompasses not only clinical remission but also endoscopic improvement (T1239). The unadjusted analysis at week 12 showed no statistically significant differences in deep remission rates, but after adjusting for disease duration, prior anti-TNF exposure, concomitant immunosuppression or corticosteroid exposure, and baseline CRP levels, those receiving adalimumab were over 3 times more likely than those receiving placebo to achieve deep remission, and this result was statistically significant. The concept of deep remission is very appealing, especially given the frequently noted weak correlation between resolution of symptoms and resolution of actual bowel inflammation, but its significance with respect to subsequent outcomes such as hospitalization and surgery needs to be explored in future studies.

In a secondary analysis of the CHARM and ADHERE trials by Panaccione and colleagues (T1012), a subset of patients who were initially randomized to weekly dosing of adalimumab and who were still in remis-

sion at the end of CHARM then received open-label adalimumab every other week. The majority of these 75 patients remained in clinical remission, even over a year after the adalimumab dose was reduced. The applicability of these findings to clinical practice is unclear, as few patients start on weekly dosing. These results do not shed light on the effectiveness of a dose reduction strategy among those patients who had been dose-escalated from every other week to weekly adalimumab because of loss of response or partial response. Nevertheless, the findings are somewhat reassuring.

Schreiber and coworkers performed a post-hoc analysis of CD patients in PRECiSE 2 and PRECiSE 3 who had open fistulae at baseline and had responded to open-label certolizumab pegol (S1035). Just as in the EXTEND trial, the use of an open-label run-in period to identify responders makes the interpretation of the results difficult, as even those randomized to placebo had actually received several doses of active drug upfront. Thus, there is no pure placebo arm. This analysis is also dealing with a relatively small number of patients, and a lack of statistical power may be playing a role here. It appears that we may need a dedicated study of certolizumab pegol in patients with fistulizing disease to definitively answer the question.

The PRECiSE 2/PRECiSE 3 subanalysis by Lichtenstein and colleagues (S1040) suggests that infliximab-naive patients had remission rates on long-term open-label certolizumab pegol broadly similar to the overall population of PRECiSE 2 patients who rolled over into PRECiSE 3. This finding is reassuring in that it shows the benefit of certolizumab pegol as a first-line anti-TNF agent in CD. One might wonder why the infliximab-naive patients did not have higher remission rates than the overall population, as prior anti-TNF exposure seems to be a predictor of a less robust outcome, but I suspect that the anti-TNF–experienced patients who made it into PRECiSE 3 were not representative of the entire anti-TNF–experienced population (many of the latter would have dropped out of PRECiSE 2 before getting a chance to enter PRECiSE 3). On a related note, the secondary analysis of PRECiSE 2 by Schreiber and colleagues examining the effect of baseline immunosuppression on outcomes (S1037) is difficult to interpret, as the patients who were not on immunosuppression at baseline were also more likely to be anti-TNF–naive, which is a known positive predictor of response. The question of monotherapy versus combination therapy can only be answered by dedicated randomized trials (à la SONIC).

The secondary analysis of the WELCOME study (efficacy of certolizumab pegol in infliximab failures) by Sandborn and colleagues sought to identify predictors of clinical remission or response after 6 months of certolizumab pegol (S1030). Colonic extent, no previous surgery, and baseline CDAI score of less than 298 points were predictive of remission. All of these factors have been shown to be either predictive of a milder disease course or of better response to medical therapy in CD. This study reminds us that a significant proportion of patients who had failed infliximab gained clinical response with certolizumab pegol.

Crombé and colleagues reported the results of a retrospective inception cohort of pediatric-onset CD patients from France who had received infliximab (S2008). After a median follow-up of 3 years, roughly one third of patients had no response to infliximab, one third responded and were still on the drug at last follow-up, and approximately one third had discontinued the drug at last follow-up (but most of these had not "failed"). The persistency rate of infliximab was 50% after 3 years, but again it is important to emphasize that over 60% of those who discontinued had done so while in remission. In this "real world" observational experience, patients who had responded to infliximab were significantly less likely to require surgery and more likely to regain normal nutritional status. The Dutch pediatric study by de Bie and colleagues (S2019) is an interesting study, but I would submit that their definition of treatment success (maintenance of good clinical response for at least 90 days after cessation or need for repeated infusions) is too rigorous.

Sokol and coworkers from Paris rigorously examined their observational experience with combination therapy and anti-TNF monotherapy in CD (T1285). Patients on combination therapy were less likely to experience disease flares, perianal disease, and need for a second anti-TNF agent than patients on monotherapy. These results are compatible with the anecdotal experience with many experienced IBD clinicians—although monotherapy may be associated with less toxicity, this possibility is more than outweighed by concerns about increased rates of loss of response among patients on monotherapy. It appears that the pendulum of opinion has swung back towards combination therapy. The risks and benefits of this approach should be discussed with the patient, but all things being equal, many clinicians are opting for combination therapy as their default prescribing preference.

The study by Zorzi and colleagues compared open-label adalimumab to open-label infliximab in 53 CD patients (W1259). Since we lack any head-to-head comparisons of anti-TNF agents in CD, it is tempting to read too much into such studies as these. We are not told if these patients were randomized to the 2 treatment arms, and I suspect that they were not. Efficacy rates were broadly similar and there may have been more adverse events in the infliximab arm, but details are unclear. It is difficult to know how to interpret this open-label, likely nonrandomized, likely underpowered study.

Clinical Updates on Diagnosis and Prognosis of Pancreatic Insufficiency

S1359 Value of the Neutrophil to Lymphocyte Ratio as a Predictive Tool of Disease Severity in Acute Pancreatitis

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Acute pancreatitis remains a disease that is difficult to predict. With an incidence in the United States of approximately 1 in 5,500, the need for prognostic tools with better sensitivity and specificity remains. Currently available scoring systems are considered cumbersome for clinicians and/or burdensome to patients. In an effort to identify a robust but simple-to-calculate system for scoring risk, Azab and colleagues built upon the accepted use of total white blood cell count as a risk factor. In this study, the researchers used the neutrophil to lymphocyte ratio as a predictor of adverse outcomes in acute pancreatitis. A total of 235 patients from a single center with a diagnosis of acute pancreatitis, excluding those older than 80 years of age and those receiving steroidal or chemotherapeutic treatment, were analyzed. The patients' white blood cell parameters, vital signs, and serum levels were assessed (Table 2), with primary outcomes of length of hospital stay and admission to intensive care. The researchers grouped each white blood cell parameter into tertiles. It was found that patients in the highest tertile for white blood cell count in comparison to those in the lowest tertile had greater admissions to intensive care (12.8% vs 7.6%) and longer hospital stays (4.6 vs 6 days). Patients in the highest tertile for neutrophil to lymphocyte ratio had greater admissions to intensive care (17.9% vs 3.8%) and longer hospital stays (4.2 vs 6.5 days). The difference in admission to intensive care between highest and lowest tertiles in neutrophil to lymphocyte ratio model was 14.1% versus 5.2% in the white blood cell count model. Moreover, the neutrophil to lymphocyte ratio was found to correlate with peak amylase and lipase levels more soundly than total white blood cell count (P<.001). As such, neutrophil to lymphocyte ratio was considered a better predictor of severity of acute pancreatitis than total white blood cell count. It was recommended that this parameter be integrated into extant scoring systems in order to refine their sensitivity and specificity.

M1379 Pancreatic Duct Compliance Following Secretin Stimulation: a Novel EUS Diagnostic Tool for Chronic Pancreatitis

TB Gardner, ED Purich, SR Gordon

Endoscopic ultrasound (EUS) is a frequently used tool for morphologic and functional assessment of the pancreas. Chronic pancreatitis is associated with pain, as well as progression to diabetes, exocrine failure, biliary stricture, and pancreatic cancer. In order to refine diagnosis of chronic pancreatitis, Gardner and colleagues combined dynamic EUS with secretin stimulation (sEUS) and duodenal bicarbonate measurement (ePFT) in a single endoscopic procedure. The researchers compared the results of the 2 tests of ductal compliance, defined as the percentage change from baseline to the maximum ductal diameter following secretin stimulation. The use of secretin is considered an aid to the visualization of the pancreatic ductal system that can improve the

Table 2. Predictive Parameters for Length of Hospital Stay and Admission to Intensive Care in Acute Pancreatitis

White blood cell parameters	Vital signs	Serum levels	Correlates
• **Total white blood cell count** • Neutrophil count • Lymphocyte count • Monocyte count • **Neutrophil to lymphocyte ratio**	• Blood pressure • Pulse • Respiratory rate • Temperature	• Creatinine • Blood urea nitrogen • Hematocrit • Aspartate transaminase • Alanine transaminase • Glucose • Peak amylase • Peak lipase	• **Neutrophil to lymphocyte ratio** *versus* • Total white blood cell count *and* • Peak amylase • Peak lipase (P<.001)

diagnostic value of commonly used procedures, particularly in patients with suspected disease or recurrent acute disease lacking an apparent etiology. All patients (n=24) underwent EUS morphologic examination and duodenal fluid bicarbonate measurement at 15, 30, and 45 minutes after secretin stimulation. Pancreatic duct diameter was measured in the head, body, and tail at baseline and 2, 4, 6, 8, and 10 minutes following secretin administration. ePFT result of duodenal fluid less than 80 mEq/L was considered a positive diagnostic result for chronic pancreatitis. No patients experienced complications. A fair correlation was observed between maximal change in ductal diameter and duodenal bicarbonate (r^2=0.29). Ductal measurement in the head, body, and tail independently yielded similar results (r^2=0.21, 0.13, and 0.22, respectively; *P*=.11). Baseline ductal dilation was correlated positively with the diagnostic measurement of bicarbonate level by ePFT in the head, body, and tail (pooled r^2=0.10). The researchers concluded that EUS measurement of ductal compliance following secretin stimulation correlated with duodenal fluid bicarbonate measurement. Further research is needed to prospectively evaluate and confirm the findings that sEUS provides a morphologic and functional assessment of the pancreas.

415g Screening for Familial Pancreatic Neoplasia: A Prospective, Multicenter Blinded Study of EUS, CT, and Secretin-MRCP

MI Canto, RD Schulick, IR Kamel, EK Fishman, MD Topazian, N Takahashi, JH Lee, EP Tamm, R Vikram, S Syngal, JR Saltzman, KJ Mortele, JJ Farrell, D Margolis, Z Zhang, GM Petersen, RH Hruban, MG Goggins

Strong family history of pancreatic cancer and germline mutations are associated with increased risk of developing this disease. Asymptomatic high-risk individuals with these characteristics were evaluated by computed tomography (CT), secretin–magnetic resonance cholangiopancreatography (MRCP), and EUS in order to determine prospectively the prevalence and characteristics of pancreatic neoplasms at screening. A total of 216 high-risk individuals were screened (46% male; mean age= 56 years); 195 had family history of pancreatic cancer, 19 had *BRCA2* mutations, and 2 had Peutz-Jeghers syndrome. All images were interpreted using standardized, blinded techniques, and patients had the option of surgical resection if high-grade cystic neoplasms or progressive lesions were suspected. Of these patients, 77 (36%) had normal pancreas by all screening methods. In comparison, 93 (43%) had at least 1 mass (cystic, n=85; solid, n=3); 6 patients had an isolated dilated main pancreatic duct, and the remaining 40 patients had nonspecific abnormalities. Of the 93 patients with at least 1 mass, 56% had multiple lesions, with 85% of these patients exhibiting lesions in multiple locations. Most lesions (87.5%) were under 1 cm in size (mean = 0.55 cm; range, 0.2–2.3). CT, MRCP, and EUS diagnosed 27%, 81%, and 93% of individuals with at least 1 mass lesion, respectively. The concordance for detection of any neoplastic-type lesion was observed to be higher between EUS and MRI (91%) than EUS and CT (73%). There was a strong correlation between MRCP and EUS for the number (Spearman correlation coefficient=0.82) and moderate agreement for location (κ=0.43) of pancreatic masses. EUS and MRCP detected 229 and 218 lesions, respectively, compared with only 39 lesions detected by CT, of a total of 289. Patients were followed for a mean time of 9.6 months (range, 0–32). Patients were diagnosed with: suspected/confirmed branch duct intraductal papillary mucinous neoplasm (IPMN; n=85), combined IPMN (n=2), endocrine neoplasm (n=4), chronic pancreatitis (defined as >5/9 by EUS criteria; n=44), and indeterminate mass (n=2). Pancreatectomy was performed on 5 patients. It was concluded that screening is useful for the detection of prevalent pancreatic lesions in asymptomatic high-risk patients. EUS and MRCP are superior to CT for detection of small (predominantly cystic) masses.

T1398 Synthetic Human Secretin-Stimulated Exocrine Secretion Increases Endoscopically Collected Yield of DNA Markers for the Detection of Pancreatic Cancer

FR Burton, S Alkaade, NE Choueiri, ED Purich, SD Finkelstein

As the incidence of pancreatic cancer has been increasing, and in consideration of the notable difficulty of early diagnosis of this malignancy and associated poor prognosis, researchers have worked to identify genetic markers of disease. *KRAS2* mutations and mutations, deletions, or hypermethylation of *CDKN2* are the most commonly observed genetic abnormalities in pancreatic adenocarcinoma (>80%). Furthermore, mutations in *p53* and homozygous mutations or deletions of *Smad4* are seen in approximately half of patients. Patients with high-risk precursors, such as chronic pancreatitis, are found to have mutations in *p16* and *KRAS* in some cases. To assess whether an assay of duodenal aspirates after stimulation with secretin could have an increased yield of genetic markers, a randomized, double-blind, placebo-controlled trial was undertaken by Burton and colleagues. Fifty patients received secretin (n=25; 0.2 mcg/kg) or placebo on a randomized basis. A sample of buccal mucosa was taken at the outset of endoscopic analysis for calibration of mutational analysis. At baseline, fluid accumulating in the duodenum was aspirated

for 5 minutes prior to administration of secretin or placebo. After administration, another 5-minute aspiration was taken 10 minutes later. Total volume of fluid, bicarbonate level, and *KRAS2* fluorescence, as well as 8 assessable markers of proteins associated with pancreatic cancer, were measured. At least 3.5 mL of duodenal fluid with bicarbonate concentration of at least 40 mEq/L was required for the sample to be considered adequate for assessment after administration of secretin or placebo. The researchers found that 80% of patients who received secretin stimulation had positive *KRAS2* fluorescence as well as 8 positive results for the markers associated with pancreatic cancer, compared to only 4% of patients who received placebo ($P<.0001$). As such, it was concluded that secretin-stimulated exocrine increased the endoscopically collected yield of markers associated with pancreatic cancer. It was recommended that future studies of diagnostic markers in pancreatic duodenal fluid use secretin stimulation to improve detectability of the markers.

721 Immunological Correlates of Disease Progression, Exocrine and Endocrine Failure in Patients With Chronic Pancreatitis: An Analysis of Pancreatic Juice Cytokines

BS Sandhu, S Sherman, KR Mehta, AJ Sanyal, AM Zfass, D BouHaidar, R Vachhani, PJ Pasricha

In an effort to identify biomarkers of progression of chronic pancreatitis, Sandhu and colleagues conducted a pilot study to compare serum and pancreatic juice in patients with established chronic pancreatitis with control patients undergoing esophagogastroduodenoscopy (EGD) for reflux who do not have pancreatitis. Cytokine analyses of serum and pancreatic juice were performed, including evaluation of 12 cytokines, including the innate immune system (IL-1□, TNF□, IL-6), T helper (Th)1 cells (IFN-□), Th2 cells (IL-4, IL-10, IL-13), and fibrogenic cytokines (TGF-□). Clinical data were recorded, including presence and onset of diabetes and/or exocrine failure, Cambridge disease stage, and type of pain. Pancreatic juice was collected from the duodenum after administration of intravenous human secretin (0.2 mcg/kg). EGD was performed and duodenal fluid collected. The levels of cytokines in serum and pancreatic juice of patients with chronic pancreatitis were compared to those of control patients. A stepwise increase in TNF-□ and IL-1□ was observed in the pancreatic juice from control patients to those with chronic pancreatitis without exocrine failure to those with chronic pancreatitis with exocrine failure ($P=.045$). Levels of IFN-□ in serum were not significantly different, but levels of IFN-□ in pancreatic juice were significantly increased in patients with chronic pancreatitis and diabetes ($P=.043$). IL-13 levels in the pancreatic juice were found to be correlated with varying Cambridge stages of disease, with a small but significant increase in IL-13 in mild and moderate Cambridge stage. Severe Cambridge stage was associated with increased IL-13 in most subjects. It was thus concluded that levels of cytokines in pancreatic juice serve as biomarkers correlated with pancreatic exocrine and endocrine failure, with the former associated with activation of IL-1□, TNF□, IL-6 and the latter associated with Th1. Severe disease by Cambridge stage may be associated with increased activity of Th2 and IL-13.

M1370 Endoscopic Pancreatic Function Testing Using Combined Secretin and Cholecystokinin Stimulation for the Evaluation of Chronic Pancreatitis

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Cholecystokinin (CCK) or secretin is used as a stimulant when ePFT is performed in the evaluation of chronic pancreatitis. Law and colleagues investigated concurrent use of these hormonal stimulants for simultaneous assessment of ductal and acinar cell function. Lipase, amylase, and bicarbonate levels in duodenal fluid samples following concurrent stimulation were measured in healthy volunteers and patients with suspected chronic pancreatitis. Combined EUS and ePFT were performed in 60 patients who received secretin (0.2 mcg/kg) and CCK (40 ng/kg/h). Duodenal fluid was taken in 5-minute samples from 25 to 50 minutes after administration of secretin or CCK. Enzyme output was calculated in proportion to total volume. Patients were stratified based on risk factors (eg, heavy alcohol use and acute pancreatitis) and EUS results: healthy (n=19); EUS normal or indeterminate with no risk factors (n=11); EUS normal or indeterminate with risk factors (n=15); EUS suggestive (n=8); and EUS most consistent with calcifications (n=7). Peak bicarbonate concentration was normal in all patients without chronic pancreatitis and was below 80 mM/L in 30% of patients identified as EUS normal or indeterminate with risk factors or EUS suggestive, as well as in 86% of patients identified as EUS most consistent with calcifications. Amylase output was considered more useful as a parameter than lipase output. The amylase output was at least 40,000 units in 89% of healthy volunteers as compared to 8% of patients who were evaluated for chronic pancreatitis ($P<.001$). It was concluded that combined hormone stimulation with secretin and CCK improves the diagnostic quality of ePFT: peak bicarbonate, which is associated with ductal cell function, has excellent specificity but low sensitivity; amylase output, which is associated with acinar cell function, has high sensitivity for mild and severe chronic disease.


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