

CONFERENCE REPORT

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## Advances in inflammatory bowel diseases 2012

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### The Westin Diplomat, Hollywood, FL, USA 13–15 December 2012

The Crohn’s and Colitis Foundation of America’s (CCFA) Conference, Advances in Inflammatory Bowel Diseases 2012, held in Hollywood (FL, USA), was co-chaired by Richard P MacDermott, from Albany Medical College (NY, USA) and Stephen B Hanauer, from the University of Chicago Medicine (IL, USA). This year’s conference saw a record 1947 total registrants and 1862 in attendance. In addition to the scientific meeting, there were committee meetings for the CCFA and several new events this year, including a ‘meet the experts’ breakfast series, a well-attended fellows workshop and a Scrub Run 5k, which brought in more than 100 runners and was a great way to promote the CCFA’s Team Challenge. Highlights of this year’s conference included presentations on the etiopathogenesis of inflammatory bowel disease (IBD), new approaches to management, as well as new therapies in the pipeline. With clinical, nursing, pediatric and basic science tracks, the sessions included a diverse range of topics and debates that focused on advancing care for individuals with IBD. In addition, there was an emphasis on balancing the risk of adverse events associated with given therapies and optimizing response. The goal of achieving deep remission as a clinical and research end point continues to be debated. Despite the ongoing progress in R&D of new therapies in IBD, there was a call for larger randomized controlled trials that are necessary for comparative effectiveness research. Awards were also granted for the best poster presentations in the conference.

### Clinical update

A number of clinical sessions covered topics on current standards of practice in inflammatory bowel disease (IBD) from making the diagnosis, to monitoring disease activity, to medical and surgical treatment. Various advances at the level of therapy, safety and therapeutic monitoring were brought to light in these sessions.

### ■ Advances in medical therapy

One of the most exciting presentations on emerging therapies is the data on the new alpha 4 beta 7 integrin inhibitor, vedolizumab, which blocks lymphocyte tracking to the gut. Brian Feagan, from London Health Science Center, University Hospital (Ontario, Canada), presented the results of a randomized, placebo-controlled, double-blind trial of vedolizumab in moderate-to-severe ulcerative colitis (UC). For patients who were not responsive to anti-TNF- $\alpha$  therapies, immunomodulator or steroid therapy, the efficacy of vedolizumab in inducing clinical response, clinical remission and mucosal healing was superior to placebo at 6 weeks (increased by 21.7, 11.5 and 40.9%, respectively;  $p < 0.002$ ) [1]. William Sandborn, from the University of California San Diego (CA, USA) also reported on the sustained benefit

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of vedolizumab in UC. After 1 year of therapy, vedolizumab 300 mg intravenous every 8 weeks achieved a durable mucosal healing in 42.6% of patients compared with 17.5% in placebo ( $p < 0.0001$ ) [2]. The benefit was persistent to 52 weeks of maintenance therapy.

The data for vedolizumab in Crohn's disease appears similarly promising. In a Phase III randomized trial, in patients with moderately to severely active Crohn's disease who failed anti-TNF- $\alpha$  therapies, immunomodulators and steroids, vedolizumab 300 mg intravenous at 0, 2 and 6 weeks achieved higher clinical remission rates than placebo at 10 weeks (anti-TNF- $\alpha$  exposed 26.6% vs placebo 12.1%;  $p = 0.0012$ ; overall population 28.7% vs placebo 13.0%;  $p = 0.0001$ ). In addition, subjects in the vedolizumab treatment arm achieved higher CDAI-100 response (reduction of Crohn's disease activity index by at least 100 points; anti-TNF- $\alpha$  exposed 39.2% vs placebo 22.3%;  $p = 0.0011$ ; overall population 39.2% vs placebo 22.7%;  $p = 0.0002$ ) [3].

The duration of combination therapy with anti-TNF- $\alpha$  therapy and an immunomodulator remains an area of controversy in the management of Crohn's disease. The STORI trial provides some guidance for this decision, and was reviewed at this meeting [4]. Bruce E Sands from Mount Sinai School of Medicine (NY, USA) summarized that for Crohn's patients in remission on combination therapy for at least 1 year, withdrawal of infliximab resulted in a relapse rate of 44%. However, in this study, several factors associated with an increased risk of relapse were identified. Risk factors included: male gender, absence of previous surgery, use of steroids within 6–12 months of infliximab withdrawal, hemoglobin level  $\leq 14.5$  g/dl, leukocyte count  $> 6 \times 10^9/l$ , CRP  $\geq 5$  mg/l, fecal calprotectin  $\geq 300$   $\mu\text{g/g}$ , CDEIS  $> 0$  and infliximab trough level  $\geq 2$  mg/l. Patients with fewer than 2 of the identified factors had a 15% risk of relapse within 1 year of discontinuing biologic therapy. A standard approach to this clinical challenge has not yet been defined, but this study certainly provides important information for our Crohn's patients who discontinue their therapy.

At the end of 2012, adalimumab received US FDA approval for the treatment of UC. In patients with moderately to severely active UC in the ULTRA 2 Trial, remission was achieved by 18.5% by week 8, and long-term mucosal healing assessed by the full Mayo score was seen in 40.8% of patients treated with adalimumab compared with 15.4% on placebo after 52 weeks of therapy [5]. The preliminary results of the ongoing extension trial for ULTRA 1 and ULTRA 2 support clinical efficacy of adalimumab for the treatment of moderately to severely active UC with decrease in the partial Mayo score from 5.9 to 1.8 after 2 years of follow up with additional benefit gained with weekly administration [6].

#### ■ Advances in surgical therapy

Optimizing the role and timing of surgery in the treatment of IBD was central to this year's surgical sessions. John Pemberton from the Mayo Clinic (MN, USA), shared data from a recent surgical review demonstrating that 60 months after stricturoplasty, 70.7% (3566/4001) of patients with Crohn's disease remain surgery-free, indicating the efficacy of this surgical intervention (95% CI: 59.8–81.7) [7].

A potential adjunctive effect of the use of biological therapy in reducing the need for repeat stricturoplasty has also been identified. Sands discussed that in low-risk strictures (simplified stricture severity score 0 on enterographic finding), infliximab therapy lowered the requirement for additional intervention by 44% at 1 year.

An emerging role toward minimally invasive surgery using laparoscopic techniques in ileal pouch anal anastomosis was also presented by Pemberton. He described an advantage for higher fecundity rates encountered after laparoscopic procedures than the traditional open laparotomy procedures (70 vs 39%;  $p = 0.023$ ) [8].

#### ■ Advances in safety

The safety of therapy in IBD was a major highlight in the conference. The PIANO registry is a national registry established by Uma Mahadevan at the University of California San Francisco (CA, USA) as part of the Crohn's and Colitis Foundation of America Clinical Alliance to prospectively assess the effects of exposure to immunosuppressant and biologic medications on pregnancy and neonates. To date 1115 women have been enrolled, 896 of whom have delivered. Analysis of this cohort did not reveal an association between congenital malformations and drugs exposure. There was an increased relative risk of spontaneous abortions in the biologic group to 2.56 (95% CI: 1.07–6.12), and for preterm labor in the combination therapy group 1.83 (95% CI: 1.01–3.31). After adjustment for preterm birth, there was no statistically significant difference in the infection rates in the children of these IBD patients at the 4, 9 and 12 months study intervals in the azathioprine group, biologic group or combination-therapy groups [9].

With the known risk of malignancy associated with immunomodulators and their increased use in combination with anti-TNFs, treatment-emergent malignancy determined from long-term studies of adalimumab in Crohn's disease was presented. The incidence of malignancy in adalimumab monotherapy including non-melanoma skin cancer was not elevated compared with expected rates. However, the incidence of malignancy in patients treated with combination adalimumab and immunomodulators was higher than expected with an adjusted odds ratio of 2.91 (95% CI 1.13–7.48) for

malignancies excluding non-melanoma skin cancer, and 4.83 (95% CI: 1.49–15.63) for non-melanoma skin cancer only based on 3050 patient-years of exposure and 1594 patients [10].

#### ■ Advances in therapeutic monitoring

There has been increased interest in mucosal healing as an adjunctive end point to clinical remission in patients with Crohn's disease and UC. In addition to endoscopic assessment of disease activity, other measures, such as drug levels of anti-TNF- $\alpha$  therapies and fecal markers, are being actively studied. In a key presentation, Sands discussed strategies to optimize biologic therapy. For example, in moderate-to-severe Crohn's disease with an elevated baseline CRP ( $\geq 10$ ), increasing adalimumab to weekly dosing has been associated with higher remission rates than every-other-week dosing (56.3 vs 27.5%;  $p < 0.05$ ).

An ongoing project at Brigham and Women's Hospital (MA, USA) was presented by Robert Burakoff. This project implements a standardized clinical assessment and management protocols for patients on infliximab therapy to assess the utility of measuring infliximab and antibody levels in improving remission rates, hospital admission rates and infections rates. More research is ongoing regarding the potential role of therapeutic monitoring for IBD and was discussed in the main sessions and several satellite symposia.

#### Future direction

Jean-Frederic Colombel from Center Hospitalier Universitaire de Lille (Lille, France), discussed several biologic agents in the pipeline for IBD. Golimumab, a subcutaneously administered anti-TNF- $\alpha$  is under investigation for UC. In a randomized Phase III placebo-controlled trial, clinical response assessed by endoscopic Mayo score was higher in the golimumab group than placebo at week 6 (55 vs 29.7%;  $p < 0.0001$ ), and persisted through week 54 on maintenance therapy (50.6 vs 31.4%;  $p < 0.001$ ).

Ustekinumab, is a fully human IgG1K monoclonal antibody that blocks IL-12 and -23 activity, is being studied in Crohn's disease. In a randomized placebo controlled trial, ustekinumab induced clinical response by 6 weeks (36.8 vs 23.5% in placebo;  $p = 0.005$ ) and maintained remission at 22 weeks (41.7 vs 27.4%;  $p = 0.03$ ) in patients with refractory Crohn's disease [11].

Tofacitinib is a novel, oral JAK-inhibitor that modulates signaling for a subset of pro-inflammatory cytokines (IL-2, -4, -7, -9, -15 and -21). A Phase II trial in patients with moderately to severely active UC demonstrated significant benefit in clinical and endoscopic response, as well as remission at 8 weeks. Tofacitinib was also associated with a dose-dependent increases in LDL and HDL cholesterol, and as such requires further evaluation.

#### Nursing update

The Nurses Track provided an overview of IBD drug therapy, prebiologic testing, vaccinations and the nursing implications after surgery. A talk on 'Bones in Crohn's' was presented by Sheri Huffman, Pediatric Gastroenterology and Nutrition, Nemours Children's Clinic (FL, USA). She focused on the fact that poor bone health and reduced bone-mineral density are increasingly reported in children and young adults with IBD. Building a high peak bone mass during growth may be more important to future bone health and prevention of osteoporosis, and reduced fracture risk reduction, than efforts to minimize bone loss later in life.

'Surgical Updates in IBD' by Michele Rubin from the University of Chicago Medicine (IL, USA) reinforced that the discussions about the possibility of surgery need to occur early in the diagnosis, and the timing for surgery needs to be a collaborative discussion between the surgeon and the gastroenterologist. The goal for patients is not to avoid surgery but to be healthy. Staging the ileoanal pouch procedure for UC in patients who are very ill, malnourished and on biologic and steroid therapy is the recommended approach to avoid complications and improve patient outcomes. She also noted that the recently described 'Kono S' anastomosis may be promising surgical technique currently being researched in Crohn's disease to prevent disease recurrence.

#### Pediatric update

The pediatric sessions covered a broad range of topics including; the diagnosis, pathogenesis and management of very early onset IBD (VEOIBD), complications and controversies in the management of pediatric IBD, safety of IBD medications in pediatrics and pregnancy, chronic pain in IBD, surgical management of IBD and immunizations in IBD.

Sessions on VEOIBD by Lee A Denson from Cincinnati Children's Hospital (OH, USA), Ivan Fuss from the National Institutes of Health (MD, USA), and Anne Griffiths from the University of Toronto Hospital for Sick Children (Ontario, Canada) focused on how VEOIBD differs from typical childhood IBD in presentation, genetics, natural history and response to standard therapies. VEOIBD is marked by its UC-like presentation, with more severe and extensive disease, its link to immunodeficiencies, and the difficulty of medical management, often leading to early colectomy. Advances in genetic studies point to defects in the IL-10 receptor as well as polymorphisms in NADPH oxidase in VEOIBD.

Highlights also included Mahadevan's talk, "Long term pediatric consequences of *in utero* IBD medication exposure", which outlined the safety profiles of IBD medications in pregnancy, as well as the pediatric outcomes in pregnant women with IBD. Summarizing

the current literature regarding drug safety during pregnancy, as well as the results from the PIANO registry, no association between fetal anomalies and drug exposure in pregnant women with IBD was shown.

Presentations by James Markowitz from North Shore Long Island Jewish Health System (NY, USA), Anne Griffiths, and Athos Bousvaros from Boston Children's Hospital (MA, USA), focused on the important questions of timing and selection of therapy for pediatric patients with recently diagnosed moderate-to-severe Crohn's disease. Debates over the best approach included immunomodulator monotherapy, anti-TNF- $\alpha$  monotherapy or combination therapy. The panel agreed that due to the lack of pediatric data that a variety of approaches are acceptable and that additional prospective controlled studies are needed.

Presentation of selected pediatric abstracts also covered a number of interesting subjects including: "Inflammation and steroid therapy is associated with white matter microstructure integrity in pediatric Crohn's disease," and "Chronic inflammation and its association with neurobehavioral functions in pediatric Crohn's disease" both by Christine Mrakotsky *et al.*; "Serologic protection to and completion of vaccinations in children with inflammatory bowel disease" by Jennifer de Bruyn *et al.*; and "Early infliximab trough levels predict remission at one year in pediatric IBD patients" by Casey Rosenthal *et al.* The final session selected presentations included: "Trends in hospitalization rates and disease behavior in pediatric inflammatory bowel disease in the United States from 2000 to 2009" by Chaitanya Pant *et al.*; "Long-term outcomes with infliximab treatment in children with Crohn's disease at a single centre" by Peter Church *et al.*; and "Improving oral medication adherence in pediatric IBD by teaching problem solving skills: year 2 results of the PHONE trial" by Rachel Greenley *et al.*

### Basic science update

The basic science track included presentations on the genetics, alterations in the microbiota, infectious triggers, the role of the epithelium and how the microbiota influences the immune system in IBD. Advances in genomics have led to the identification of new loci associated with IBD, bringing the total to 173 loci. Several sessions highlighted research in VEOIBD. Scott B Snapper from Boston Children's Hospital (MA, USA) discussed the genetic mutations identified in children with IBD and how this will provide more insight into the pathogenesis of the disease, as well as elucidate potential therapeutic targets. Maria Abreu of the University of Miami Miller School of Medicine (FL, USA) reviewed the complex interactions between the intestinal microbiota and the

innate immune system, presenting data that builds on current models of disease pathogenesis. Joshua Friedman from the University of Pennsylvania (PA, USA) presented the changes in micro-RNA expression found in children with IBD that could lead to significant therapeutic implications. The influence of microbiota on the regulation of the gastrointestinal immune response and the infectious triggers of IBD were further emphasized.

### Awards

The Crohn's and Colitis Foundation of America awarded three physicians for their exceptional contributions to the field of IBD. The winners of the 2012 Scientific Achievement Awards were:

- Richard J Grand, from Boston Children's Medical Center (MA, USA) was the recipient of the Henry D Janowitz Lifetime Achievement Award;
- Jeffrey S Hyams from Connecticut Children's Medical Center (CT, USA) was the recipient of the Achievement in IBD Clinical Research Award;
- Richard S Blumberg from Brigham and Women's Medical Center (MA, USA), was the recipient of the Achievement in IBD Basic Research Award.

In this year's Advances in Inflammatory Bowel Disease meeting, 265 abstracts were presented in a poster fashion. They were distributed over clinical, pediatric, nursing and basic science poster presentations. At the conclusion of the conference, the following five distinguished posters were awarded:

#### ■ Best overall poster

"Ursodeoxycholic acid and risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a meta-analysis." Siddharth Singh, Sahil Khanna, Darrell Pardi, Edward Loftus and Jayant Talwalkar from Mayo Clinic (MN, USA).

#### ■ Best clinical poster

"Inflammation and steroid therapy is associated with white matter microstructure integrity in pediatric Crohn's disease." Christine Mrakotsky, Christopher Watson, Deborah Waber, Richard Grand, Michael Rivkin from the Department of Psychiatry, Boston Children's Hospital, Harvard Medical School (MA, USA).

#### ■ Best basic science poster

"*In vitro* pharmacology of AVX-470, an oral anti-TNF- $\alpha$  polyclonal antibody for the treatment of IBD." Amy Holdorf, Brenda Lemos, David Keane, Michael Quisenberry, Shawn Clark, Kailash Bhol, Barbara Fox and Daniel Tracey from Avaxia Biologics, Inc., Lexington (MA, USA).

**■ Best nursing poster**

“Creating and implementing a previsit planning tool for IBD visits.” Emmala Ryan Shonce, from Levine Children’s Hospital, Charlotte (NC, USA).

**■ Best young investigator poster**

“Low ultraviolet exposure is associated with increased risk of hospitalization in inflammatory bowel disease.” Berkeley Limketkai, Theodore Bayless, Steven Brant and Susan Hutfless from Johns Hopkins University School of Medicine Baltimore (MD, USA).

**Conclusion**

The largest ever Advances in Inflammatory Bowel Diseases conference, in 2012, provided a unique update on the current standard of care in the management of IBD. Promising emerging therapies were discussed and

will hopefully be available within the coming few years. Valuable safety data particularly pertaining to drug exposure during pregnancy was presented and several therapeutic monitoring strategies were also provided. With its clinical, nursing, pediatric and basic science updates, the conference constitutes a comprehensive overview of the Advances in IBD in the year 2012.

**Financial & competing interests disclosure**

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