INNOVATIONS IN IBD THERAPY AT PENN MEDICINE

Faten Aberra, MD, MSCE; Meenakshi Bewtra, MD, MPH, PhD; Jesse Green, MD; Nabeel Khan, MD; Jan-Michael Klaproth, MD; James D. Lowie, MD, MSCE; Gary R. Lichtenstein, MD; Farzana Rashid, MD; Frank I. Scott, MD, MSCE; Vesselin Tomov, MD, PhD; Gary D. Wu, MD.

Among the largest programs of its kind in the world, the inflammatory bowel disease (IBD) program at Penn Gastroenterology treated more than 3000 patients with ulcerative colitis (UC) and Crohn’s disease (CD) in 2013.

Gastroenterologists at Penn Medicine are pursuing an extensive program of clinical trials to develop a new generation of therapies for inflammatory bowel disease (IBD). The objective of this program is to improve upon the efficacy and safety of the current standards of treatment for moderate-to-severe IBD, including the corticosteroids, immunomodulators and TNF-alpha inhibitors. The current paradigm for the pathophysiology of IBD involves genetic susceptibility to antigenic stimulation by environmental or enteric bacteria, fungi or viruses, leading to an unremitting immune response and chronic inflammation.

One of the strategies now being explored in clinical trials at Penn Gastroenterology and elsewhere involves disruption of the molecules that provoke leukocyte migration and retention, particularly the integrins expressed on the surface of leukocytes.

The integrins represent a large family of transmembrane proteins with potential roles in the inflammatory process in IBD, including leukocyte adhesion and infiltration of the GI tract. A single integrin, alpha-4/beta-7, is expressed by more than 90% of lymphocytes found in the small bowel. Other therapies under investigation at Penn involve the integration of recent advances in our understanding of the microbiology and genetics of gastrointestinal disease.

*For a review of corticosteroid use and increased mortality in patients with IBD authored by Penn gastroenterologists James Lewis, MD, MSCE and Kimberly A. Fonde, MD, et al, see Am J Gastroenterol. 2008;103:1428-1435.
HEPATOLOGY IN LIVING DONOR LIVER TRANSPLANTATION AT PENN MEDICINE

Ranjeeta Bahirwani, MD; Rotonya Carr, MD; Kimberly A. Forde, MD, MHS; David S. Goldberg, MD, MSCE; Maarouf A. Hoteit, MD; Christine Hsu, MD; Vandana Khungar, MD; George A. Makar, MD MSCE; Rajender Reddy, MD; Marina Serper, MD.

Hepatologists at Penn Medicine have a vital role in the management of donor and recipient participating in living donor liver transplantation (LDLT), a successful and accepted standard of care for many patients with end-stage liver disease at the Penn Transplant Institute.

Living donor liver transplantation (LDLT) offers a survival benefit in end-stage liver disease, particularly for patients at risk of disease progression from hepatocellular carcinoma or hepatitis C. Adult-to-adult LDLT involves removing 40% to 60% of the liver from a healthy donor (typically a family member or friend of the recipient) and transplanting it into a patient who has been deemed appropriate for liver transplantation.

For hepatologists, LDLT offers a formidable set of technical complications and a degree of complexity not found with deceased donor transplantation. In LDLT, the whole liver is not transplanted, but split (Figure 1), involving a surgical procedure with unique parameters for venous and biliary continuity, inflow and drainage. Moreover, living donor transplantation involves potential hepatic risks for a healthy donor, and the need for a comprehensive understanding of the regenerative processes in both healthy and compromised persons. Finally, the post-surgical complications and procedures for both donor and recipient (including unique values for immunosuppression in partial heptectomy) are specific to LDLT.

Transplant hepatologists at Penn assess the livers of donor candidates to determine their suitability for LDLT. Pre-existing disease (cirrhosis, hepatitis), hepatic steatosis and inadequate mass are confounding factors. Recipients are evaluated to determine that transplant is justified and to assess survival capacity following a partial graft.

A great benefit for living donation is the potential to make liver transplant available to patients with a lower Model for End Stage Liver Disease (MELD) score than would be possible with deceased donor transplantation. Pennsylvania is in Organ Procurement and Transplantation Network (OPTN) region 2. In 2013, 788 livers were available in the region; as of August 2014, 2,467 people remained on the waiting list. The imposition of a low MELD score usually means years on the waiting list for a deceased donor liver; a time attended by the progressive deterioration of the patient’s health and an increased risk of death, particularly for patients with pre-cancerous conditions. The Penn Transplant Institute performs LDLT in patients with mean MELD scores of 15±5, depending upon blood type. The mean MELD at transplant for deceased donors in region 2 since 2008 has been in the range of 27±7.

- Fig. 1: Penn hepatologists monitor LDLT patients before and after surgery.
Post-transplant outcomes with LDLT at Penn are comparable to deceased donor transplants for patients with end-stage liver disease. Importantly, transplant outcomes for LDLT at Penn are better than national rates, a reflection of both surgical skill and the pre- and post-surgical management of these patients. Between 2002 and 2012, the adult 1-, 3-, and 5-year LDLT recipient survival rates at Penn were 98%, 91%, and 83%, respectively, compared to national rates of 90%, 82% and 78% for the same parameters (Figure 2).

**LDLT Post-Transplant Survival 2002–2012:**

<table>
<thead>
<tr>
<th>Penn Medicine</th>
<th>National LDLT Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year: 98%</td>
<td>90%</td>
</tr>
<tr>
<td>2 years: 91%</td>
<td>82%</td>
</tr>
<tr>
<td>5 years: 83%</td>
<td>78%</td>
</tr>
</tbody>
</table>

![Clostridium difficile](Image 2014 Centers for Disease Control)

**Clostridium difficile**

A hub of research for novel medical approaches to IBD, Penn Medicine is rapidly transitioning from the antibiotics, glucocorticoids and biologic therapies now used to treat UC and CD. New approaches to IBD therapy under investigation at Penn have the objective of improving upon the efficacy and safety of these treatments. All involve the integration of recent advances in our understanding of the physiology, microbiology and genetics of gastrointestinal disease.

**Fecal Microbiome Transfer**

At Penn GI, Gary Wu, MD, is investigating fecal microbiota transplantation (FMT), a biological alternative to antibiotic therapy for patients who have had repeated recurrences of *Clostridium difficile* despite antibiotic therapy. Patients who have three or more recurrences of *C. difficile* are considered to have chronic infection, a course characterized by repeated episodes of treatment followed by disease relapse in which each relapse increases the likelihood of subsequent occurrences.
FMT involves infusing donor fecal microbiota in saline into the small bowel via a nasoduodenal tube. In a recent comparative clinical trial, FMT effectively cured 94% of patients with recurrent *C. difficile* vs. 31% of patients receiving vancomycin 500 mg 4x daily for five days. [1]

Donors for FMT therapy at Penn Medicine are closely screened to avoid exposing recipients to pathogens, transmissible diseases and inflammatory disorders. The Food and Drug Administration currently considers FMA investigational, and its use is restricted to patients with recurrent *C. difficile* infection not responsive to standard therapies.


**AMG-181**

Penn Gastroenterology is involved in a clinical trial of the investigational agent AMG-181, a gut-specific human anti-a4β7 antibody for the treatment of IBD. a4 and β7 are T cell integrin subunits. The α4 integrin is involved in lymphocyte recruitment and infiltration of the gut endothelium during chronic bowel inflammation. The β7 subunit is a component of the adhesion molecule pathway. In the small bowel, >90% of lamina propria T cells express α4β7. AMG-181 acts to block inflammation by antagonizing the β7 subunit.

**METHOTREXATE IN INDUCTION AND MAINTENANCE OF STEROID FREE REMISSION IN ULCERATIVE COLITIS (MERIT-UC) TRIAL**

Penn GI is participating in a multicenter double-blind, placebo controlled, randomized study to investigate the safety and efficacy of 25 mg methotrexate (MTX) applied subcutaneously once weekly in patients with UC who have either failed 5-ASA therapy, or are refractory to, intolerant of, or failing to respond to azathioprine/6-mercaptopurine therapy or infliximab. In patients with Crohn's, subcutaneous methotrexate 25 mg once weekly is an efficient therapy to induce and maintain steroid free remission. Completion of this trial

(Continued on page 5)
SELECTED ENROLLING CLINICAL TRIALS
AT PENN GASTROENTEROLOGY

A phase 3, multicenter, open-label study to investigate the efficacy and safety of SOFOSBUVIR GS-5816 fixed-dose combination in subjects with chronic HCV infection and Child-Pugh Class B cirrhosis.

A phase 3, multicenter, randomized, open-label study to compare the efficacy and safety of SOFOSBUVIR/ GS-5816 fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 24 weeks in subjects with chronic genotype 3 HCV infection.

A phase 2b, multicenter, open-label study to investigate the efficacy and safety of SOFOSBUVIR/ LEDISPASVIR fixed-dose combination and SOFOSBUVIR + RIBAVIRIN for subjects with chronic hepatitis C virus (HCV) and inherited bleeding disorders.

INNOVATIONS IN IBD
(continued from page 4)

will define the therapeutic value of MTX in UC, potentially changing the current therapeutic strategy for the disease.

The specific aims of the trial are to: evaluate the safety and tolerability of the regimen over 48 weeks; evaluate the relapse-free survival of MTX maintenance therapy compared to placebo over 32 weeks; evaluate the efficacy of MTX over 16 weeks to induce steroid-free remission; and establish a DNA, plasma and serum library to enable the evaluation of clinical and pharmacogenomic models to predict response to MTX therapy in patients with UC.

AN EFFICACY AND SAFETY STUDY OF GOLIMUMAB IN PARTICIPANTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

Researchers at Penn GI took part in the multicenter Phase 3 study to evaluate golimumab (Simponi®) in patients with moderately to severe UC. Simponi was approved in March 2014 for the treatment of adults with moderately-to severer active UC to induce and maintain clinical responses, induce clinical remission and achieve and sustain clinical remission in induction responders who have demonstrated corticosteroid dependence or who have had an inadequate response or failed to tolerate prior therapy with oral aminosalicylates, corticosteroids, azathioprine or 6-mercaptopurine.

RESOURCES
Penn GI Division patient website www.pennmedicine.org/GI
Penn GI Division academic website www.med.upenn.edu/gastro
Abramson Cancer Center website www.pennmedicine.org
Penn GI Hepatology Research site www.med.upenn.edu/molecular
Penn Cancer Information www.oncolink.org
Penn Viral Hepatitis Grand Rounds www.viraled.com
"I am delighted to update you on the following exciting developments at the Division of Gastroenterology at Penn Medicine."

Two leading physician-scientists at Penn Gastroenterology, JONATHAN P. KATZ, MD, and BEN Z. STÄNGER, MD, PHD, have been promoted to the position of Associate Professor of Medicine with tenure.

RAJ REDDY, MD, Director of Hepatology and Director of the Viral Hepatitis Center, has co-authored four articles this year in the New England Journal of Medicine on the groundbreaking research now being conducted in HCV therapeutics. The most recent appeared in May. See N Engl J Med. 2014;370:1983-1992.

DAVID GOLDBERG, MD, MSCE, and DAVID KAPLAN, MD, MSc, have authored an article in JAMA on the association between veterans' distance from a transplant center and their access to wait list placement and liver transplantation. See JAMA. 2014;311:1234-1243.

For information about research developments at Penn Gastroenterology, visit: www.med.upenn.edu/gastro/news.shtml