Optimizing inflammatory bowel disease clinical care and research at UTSW

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Internal Medicine Grand Rounds

UT Southwestern Medical Center

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This is to acknowledge that Dr. John Kwon has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program.

Dr. Kwon will not be discussing off-label uses in his presentation

Biographical Information

John Kwon is an Associate Professor in the Division of Digestive and Liver Disease. He is the Director of the Inflammatory Bowel Disease (IBD) Program and the Director of the Clinical and Translational IBD Research Program at UTSW. He received his M.D.-Ph.D. from the Albert Einstein College of Medicine. He completed his Residency in Internal Medicine and Fellowship in Gastroenterology and Hepatology at the Beth Israel Deaconess Medical Center in Boston, MA. Dr. Kwon was previously on faculty at Johns Hopkins University from 2004 to 2010 and the University of Chicago from 2010 to 2015. Dr. Kwon specializes in the care of patients with Crohn's disease (CD) and ulcerative colitis (UC). In addition, his research focus includes translational and basic epigenetic research in IBD and colitis.

Purpose and Overview:

This presentation will provide a general perspective of inflammatory bowel disease (IBD) pathogenesis, epidemiology, diagnosis and treatment. The main purpose is to outline the UTSW IBD Program Mission and the short-term and long-term objectives towards establishing its clinical care and research programs.

Educational Objectives:

At the conclusion of this lecture, the listener should be able to:

1. Understand the high burden of IBD in the United States
2. Recognize the complexities regarding diagnosis and treatment IBD
3. Recognize that further understanding of IBD pathogenesis is necessary for advancement in IBD

IBD Program Mission Statement

The Inflammatory Bowel Disease Program is dedicated to the UTSW Mission of providing excellence in patient care in partnership with the commitment to the advancement of health through the promotion of excellence in basic, translational and clinical science.

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Clinical IBD Team

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Overall Plan For Clinical Care Growth

Provide 24/7 availability.
Facilitated patient access.
Expert and empathetic care.
Comprehensive, coordinated patient care (adult IBD, pediatric IBD, surgery, nutrition, surgery, radiology and pathology).
Expanded IBD specialty presence on inpatient service.
Establishment of IBD specialty presence on Parkland outpatient IBD service.
Incorporation of standard of care protocols for IBD inpatient and outpatient care.

Implement uniform clinical EPIC templates.
Redesign IBD website and marketing materials.
Aggressive referring physician outreach
Aggressive community and CCFA outreach.
Establishment of clinical trials for additional patient choice options.
Establish clinical IBD fellowship.

Overall Plan For Building A Translational Research Core

Establish global IBD IRB registry/repository.
Hire clinical study coordinator for clinical trials and registry management.
Hire database manager for programming infrastructure and data mining.
Hire translational core manager for establishment and maintenance of SOP/BPs.
Hire patient recruiter for patient recruitment and biospecimen recruitment.
Implement uniform clinical EPIC templates for facilitated data mining.
Establish clinical electronic data warehouse.
Implement biospecimen repository software and hardware.
Provide free labor for biospecimen recruitment and processing and storage at cost.
Establish pharma-sponsored clinical trials.
Establish pharm-sponsored investigator initiated studies.
Establish baseline repository of IBD patient DNA, plasma, biopsy-derived FFPE, RNA, protein and DNA.
Initiate epigenetic-based IBD pilot studies.

IBD Strategic Plan: Pre-year 1, year 1, year 2, year 3 and year 5 timeline

Pre-Year 1.

Establish JHK IBD clinic template and initiate scheduling. (Done, initiated Year 1)
Continue Dr. Tasneem Ahmed (TA) IBD clinic, discuss her career goals and needs assessment. (Done)
Discuss with IT regarding options/UTSW standards for EMR data mining. (Done, initiated Year 1)
Establish IBD templates for inpatient and outpatient EMR. (In progress, Initiated Year 1)
Establish specific hardware needs (-80 freezers, -20 freezer, refrigerator, disposables, biobanking software, liquid nitrogen, barcoding, etc) and initiate purchasing. (Done, initiated Year 1)
Initiate global IBD patient registry IRB submission. (Initiated Year 1)

Year 1.

Initiate JHK IBD clinic immediately. (Done)
Continue TA IBD clinic. (Done)
Initiate IBD #3 recruitment (Done)
Institute IBD templates. (In progress)
Initiate community/regional outreach (Done)
Contact CCFA for joint outreach (Done)
Coordinate specific provider visits (Done)
Complete Translational Core infrastructure purchases. (Done)
Obtain global IBD patient registry IRB approval. (In progress)
Recruit Translational Core staff

- Study coordinator (Done)
- Database manager (Done)
- Translational core manager (Done)
- Tissue technician/recruiter (Deferred until recruitment commencement)

Initiate patient registry recruitment (Deferred until IRB approval)
Establish IBD Center organizational meeting (1 hr per month) (Done)
Establish IBD Clinical Case Conference (1 hr per month) (Done)
Establish IBD Translational Core Staff meeting (1 hr per week) (Done)

Year 2.

Complete Translational Core staff recruitment (Deferred, in progress)
Complete IBD registry/EMR interface (Deferred, in progress)
Complete Biospecimen repository software implementation (Deferred, in progress)
Initiate hypothesis-driven Translational Core patient biospecimen recruitment. (On hold until IRB approval)
Establish IBD Research Problems Conference (1 hr per month) (Deferred)
Establish IBD Clinical/Translational Research Studies Meeting (1 hr per month) (Deferred)
Initiate external clinical/translational trials implementation strategic planning.

Plan: Translational collaborative (NIH IBD Consortium) (Communication Initiated)

Plan: Prometheus, Takeda, Abbvie (Biomarker, drug level studies) (Approved, Takeda)

Plan: Clinical trials (Initiated)

Evaluate IBD Center referral status, needs and optimization (End Year 2) (Deferred)
Evaluate IBD Center community outreach efforts (End Year 2) (Deferred)
Evaluate IBD Translational Core performance (End Year 2) (Deferred)

Year 3-4.

Recruit and hire IBD #3 (likely clinical trials director) (Deferred, search in progress)
Recruit tissue technician/recruiter #3 (depending on need) (Deferred)
Initiate IBD external clinical/translational trials (Initiated)
Modify IBD Center community/regional outreach as necessary (Deferred)
Modify IBD Translational Core workflow as necessary (Deferred)
Establish IBD fellowship (Deferred)

Year 5.

By Year 5, the goal of the IBD Center is to have a fully functional, thriving IBD referral center that is the pre-eminent referral center for Dallas and also encompasses the entire Southwest U.S. The goal is to have established a translational core that maintains a stock of well-phenotyped biospecimens and actively obtains study-specific biospecimens for all UTSW and affiliated researchers. The goal is to have established a Pharma/Biotech clinical/translational studies unit that can offset the cost of study coordinators and other IBD Translational Core staff.

Inflammatory Bowel Disease: A Brief Primer

Inflammatory bowel disease is a chronic relapsing and remitting inflammatory disease of the gastrointestinal tract[1]. The two major types of inflammatory bowel disease include Crohn's disease (CD) and ulcerative colitis (UC). UC is characterized by diffuse, continuous, superficial ulcerations that involves the rectum (proctitis) and may progress to include the entire colon. Crohn's disease is characterized by discontinuous, transmural inflammation that can involve any segment of the GI tract. CD can manifest as three main phenotypes presenting as inflammatory, stricturing and fistulizing disease. Both CD and UC are associated with extraintestinal manifestations, including pyoderma gangrenosum, erythema nodosum, ankylosing spondylitis, sacroileitis, uveitis, episcleritis and primary sclerosing cholangitis. The onset of IBD typically occurs in the second and third decades of life with a second peak in the sixth and seventh decade.

Symptoms associated with CD and UC depend on the specific phenotypes. UC is more often associated with bleeding in stools, tenesmus, mucus output, diarrhea and lower abdominal cramping. CD is more often associated with diarrhea, abdominal pain, distention, weight loss, fever and peri-anal disease.

The pharmacologic treatments for CD and UC overlap and include various classes of agents including corticosteroids for induction of remission for CD and UC, 5-aminosalicylates for induction and maintenance of remission for UC, immunomodulators (6-mercaptopurine and azathioprine) for induction and maintenance of remission for CD and UC, anti-tumor necrosis factor antibodies for induction and maintenance of remission for CD and UC, anti-integrin antibodies for induction and maintenance of remission for CD and UC and calcineurin inhibitors (cyclosporine) for induction of remission for UC. Each therapy has different durations of onset, side effect profiles, delivery mechanisms and efficacy rates.

Overall, the IBD specialist will personalized the management for each patient based on disease phenotype, location, severity, presence of extraintestinal manifestations, previous therapies, co-morbid disease and lifestyle impact. In addition, the treatment of the patient focuses on dietary concerns, health care maintenance, treatment of irritable bowel syndrome symptoms, treatment of infectious complications, considerations for surgery, considerations for the risk of cancer and maintenance of compliance.

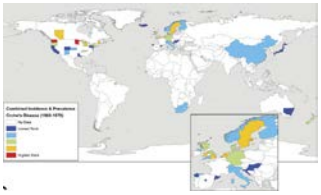
IBD Epidemiology

A recent study examining the worldwide incidence of UC and CD in different regions over time demonstrated an increasing incidence and prevalence of both UC and CD throughout the world [2]. In North America, the incidence of UC and CD are estimated at 19.2 and 20.2 per 100,000 person-years, respectively. Similarly, in North America, the prevalence of UC and CD are estimated at 249 and 319 per 100,000 persons, respectively. Extrapolating this data, using the estimated U.S. census data, it is estimated that 1.8 million people have IBD. The Dallas-Fort Worth area is the fourth largest metropolitan area in the country. Extrapolating this prevalence data, using the estimated Dallas-Fort Worth (DFW) census data, it is estimated that over 37,000 people have IBD in the DFW metropolitan area. Of note, in the entire DFW metropolitan area there are only two non-UTSW-affiliated IBD specialists.

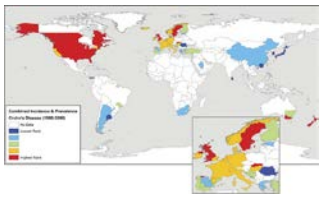
Overall, the care of IBD patients contributes greatly to the overall burden of health care costs [2]. In 2010, IBD diagnoses were the 6th most common lead GI-related diagnoses coded for office visits in the United States, with 2.3 million visits. Similarly, IBD diagnoses accounted for the 10th most common lead GI-related diagnoses coded for all ambulatory visits (office visits, ER and hospital outpatient), with 2.6 million visits. Furthermore, in 2012, IBD diagnoses accounted for 99,140 hospital admissions resulting in $1.0 billion in aggregate costs. The overall health care burden for IBD has been estimated at over $6.3 billion per year [3].

CD Incidence and Prevalence

1960-1979

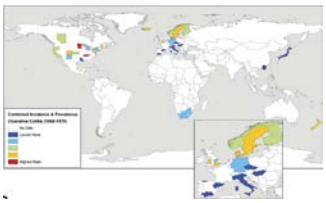


1980-2008

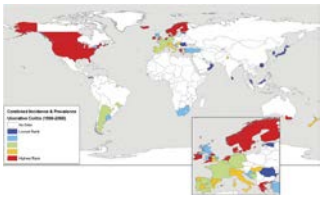


UC Incidence and Prevalence

1960-1979



1980-2008



Ten Remaining Mysteries in IBD

In 2008, a panel of IBD leaders formulated 10 fundamental questions about the epidemiology and clinical course of IBD that remain unanswered despite decades of research in IBD [4].

The 10 remaining mysteries in IBD
What explains the geographical and historical variation in the incidence of inflammatory bowel disease?
Why is appendicitis associated with a reduced risk of ulcerative colitis?
Why does smoking exacerbate Crohn's disease but protects against ulcerative colitis?
Why is the inflammation of Crohn's disease transmural and that of ulcerative colitis confined to the mucosa, and how does it drive cancer?
Are ulcerative colitis and Crohn's disease distinct disorders or part of a continuum?
Why does Crohn's disease have skip lesions down the entire gastrointestinal tract?
What is the role of extraluminal structures (mesenteric fat, vasculature, lymphatics) in Crohn's disease?
What are the factors that determine the timing of the initial attack of inflammatory bowel disease and subsequent relapses?
Why does postoperative recurrence of Crohn's disease usually occur in the neo-terminal ileum?
Why are certain extraintestinal manifestations linked to the evolution of inflammatory bowel disease and some are independent?

These questions reflect the general lack of understanding of the pathogenesis of IBD. We currently lack the understanding of mechanisms of regulation of intestinal inflammation and have yet to identify the environmental influences and key host regulators of IBD. In addition, we don't comprehensively understand the mechanisms by which systemic inflammatory responses are triggered by intestinal inflammation. Without the pathophysiologic understanding of IBD and intestinal inflammatory regulation, the development of new therapies will be hampered. Underlying this dilemma is the general lack of consensus regarding the variability and overall numbers of IBD phenotypes.

IBD Pathogenesis

The pathophysiology of both CD and UC are not completely understood but thought to arise from a dysregulated host immune response arising from environmental stimuli (microbial and other) in genetically predisposed individuals. Despite the discovery of the association of the NOD2 gene with CD in 2001 and the subsequent identification of over 200 additional IBD risk loci, it is estimated that these common variants account for only 26% of the heritability of CD and 19% of the heritability of UC [5]. It is clear that further identification of rare variants is essential for the further elucidation of genes associated with IBD.

In addition to genetics, the microbiota has been clearly associated with IBD. While a single microbe has not been clearly identified, there is growing evidence that IBD is associated with an altered microbiome [6]. In addition, murine models of colitis have been shown to require microbes for the induction and maintenance of colitis. Ongoing studies are being conducted to assess the bacteria, fungal and viral microbiome of IBD and phenotypes such as pouchitis.

IBD is curiously associated with environmental factors. For example, smoking adversely affects CD but is protective with UC. Previous appendectomy is protective in UC. These phenomena indicate that other factors other than genetics are influencing IBD. There is growing evidence that IBD is associated with epigenetic changes. Epigenetics includes mechanisms including histone modification, covalent DNA modification and non-coding RNA [7]. Our laboratory has demonstrated that both microRNA and long non-coding RNAs are differentially-expressed in IBD and regulate intestinal inflammation [8-16]. Our laboratory has also recently utilized techniques assessing DNA hydroxymethylation in intestinal epithelial cells and in colorectal cancer that can be adapted to cell populations associated with IBD [17].

Conclusions

Both CD and UC are complex diseases with a broad spectrum of disease location, phenotype, severity, co-morbid disease, extraintestinal manifestations, health care maintenance and long-term consequences.

Both CD and UC treatments include a spectrum of pharmacotherapies, dietary management issues, side-effect and adverse reaction management issues and surgical approaches.

The DFW area has an extrapolated IBD patient population of 37,000 patients with only four current full-time IBD physicians (2 external, TA and JHK).

The UTSW IBD Program will focus on the establishment of a multi-specialty, collaborative approach towards patient care with standard protocols and patient care templates.

The UTSW IBD Program will establish clinical trials.

The UTSW IBD Program will utilize the clinical templates to facilitate epidemiologic research, well-phenotyped biospecimen recruitment and clinical trial recruitment.

The UTSW IBD Program will establish a biospecimen repository and patient recruitment team to facilitate human tissue-based research.

The establishment of the UTSW IBD program will greatly improve the standard of IBD care, facilitate the establishment and conduct of clinical trials, allow for more comprehensive epidemiology research and facilitate IBD-related basic and translational research efforts.

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