

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Findings from the European Collaborative Inflammatory Bowel Disease Database

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G&H Can you describe the historic evolution of the European Collaborative Study Group on Inflammatory Bowel Disease?

PM In 1988, Dr. Shiva Shivananda, a consulting physician in the Netherlands, called together a conference in Rotterdam of clinicians from 22 centers in 12 countries. This meeting formed the basis for the ongoing European Collaborative Study Group on Inflammatory Bowel Disease (EC-IBD). The initial goal of the study group was to examine the perceived split in IBD incidence between populations in the northern half and the southern half of the continent. Based on the proposed study plan, the European Union provided €1.2 million to help finance the overall venture. Although this was not enough funding to finance all of the participating centers, it did provide a vote of confidence from Brussels, indicating that our plan was worthwhile and considered important in the international medical community.

The first step in creating an international database was to standardize the diagnostic criteria for Crohn's disease (CD) and ulcerative colitis (UC) throughout Europe.

Through discussion and meetings subsequent to the Rotterdam conference, it was found that European doctors, and even histopathologists, were varied in their diagnostic criteria for both diseases. By creating a database of the varying definitions and combining them with the accepted Lennard-Jones criteria, a standardized European diagnostic definition was ultimately agreed upon.

With the standardized diagnosis in place, a protocol was developed to include patients in a recruitment cohort that was initially followed from January 1, 1991 through December 31, 1993. More than 2,000 patients were included in this initial study, and the recorded

results of their ongoing, 2-year follow-up were collected and collated in Amsterdam, again by the group led by Dr. Shivananda. The resulting database contained statistics on disease progression, surgery, cancer, dysplasia, and medical treatment.

G&H What were the initial findings of this first phase of the EC-IBD?

PM The first paper culled from the database was published in *Gut* in 1994, with Dr. Shivananda as first author. It was found that a difference in IBD prevalence between the north and the south of Europe did exist but that it was not as great a difference as originally perceived before the diagnostic criteria had been standardized.

In northern Europe, the incidence of IBD was measured at approximately 8 cases per 100,000 individuals versus only 4 out of 100,000 in the southern European countries.

G&H Were you able to use the database to find a root cause for the north/south difference in IBD prevalence?

PM In phase III of the database analysis, which began in 2000, an examination of genetic factors in the recruited cohort was undertaken in order to consider this question. Unfortunately, environmental factors between north and south could not be compared, as there was no standardized schema available to do as such.

Dr. Lene Riis, practicing here in Copenhagen, published the first of the genetic and biologic marker studies. It was suspected that the known *CARD15* genetic variation would be higher in CD patients in northern Europe compared to those in the south. What was seen in Dr. Riis's paper was actually the opposite. Evidence that high disease incidence would correlate with a higher occurrence of *CARD15* was absolutely negative and ultimately it was found that *CARD15* relates more to disease phenotype in CD and not to the presence of disease. Along with this conclusion, the same data were used to determine that toll-like receptor 4 did not significantly influence described phenotype and that presence of antibodies to *Saccharomyces cerevisiae* (ASCA) and antineutrophil cytoplasmic antibody (ANCA) identify patients with a more severe disease course in terms of recurrence and complications, thus confirming evidence from other studies. A

genetic marker for the north/south split was never identified, but in the process, a tremendous amount of useful evidence was uncovered.

G&H What other issues have been investigated utilizing data from the EC-IBD cohort?

PM Phase II of the program was a protocol developed by Ingrid van der Eijk, a pathologist at the University Hospital Maastricht in the Netherlands. She examined the varying levels of quality of care throughout Europe and how they affect overall quality of life in IBD populations. Her thesis was that quality of care and overall quality of life would correlate. For example, in Scandinavian countries, where patients have a private toilet when admitted to the hospital, as well as easy access to the IBD nurse and medical doctor, patient well-being and overall quality of life are typically higher. The study ultimately showed that quality of care is a determining marker of quality of life in patients with IBD.

van der Eijk also made an analysis of optimum models for quality of life in IBD and found that quality of care was one of these parameters as well as disease activity, psychological status, stressful events, social support, and type of hospital. Another important parameter was the level of disease information provided to the patient, which played a large role. These parameters were compared to scores from the SF36 and Inflammatory Bowel Disease Questionnaire and validated based on how they influenced the accuracy of these indices. It was found that many parameters that affect patient quality of life are not specific to IBD symptoms. The overall efficiency and effectiveness of the health system is a major issue for the patient. Our questionnaire was sent to 827 patients within the EC-IBD cohort, and it was surprising to see that one third of those patients had not received healthcare from a specialist during the past year. IBD quality of healthcare was shown to be a major factor in determining health-related quality of life, particularly as it affected the parameters of cost, providing information to patients, continuity of care, and courtesy to patients.

G&H What associations between IBD and colon cancer have been seen among the EC-IBD cohort?

PM Konstantinos Katsanos from the University Hospital of Ioannina in Greece utilized the database to show that there was no increased risk of colon cancer among IBD patients in the European cohort when looking at 10 years of follow-up. This may not be enough time to show an increased rate of cancer. Further follow-up extending 15–20 years may be required to answer the question completely.

G&H How can these data be applied when evaluating the practice of colonoscopic surveillance for colon cancer?

PM In this European setting, there had been no unified program of colonoscopic surveillance. Some centers monitor patients utilizing the North American guidelines of taking 32 random biopsies after 8 years of disease, and so on, but few centers follow it exactly. Therefore, it is hard to make definite conclusions based on the overall database.

Professor Sylvan Odes of Ben Gurion University in Israel has been using the database to analyze cost effectiveness throughout Europe, and colonoscopic surveillance will factor into this equation. In Denmark, where the colectomy rate in UC is high and we use 5-aminosalicylate (5-ASA) therapy uniformly, our patients have not experienced an increased risk of cancer and surveillance colonoscopy may not prove cost-effective at all.

G&H Could the EC-IBD database be utilized to monitor the safety of biologic and immunosuppressive therapies for IBD?

PM EC-IBD surveillance stopped in 2003, and European use of infliximab (Remicade, Centocor) did not begin until late 1998, so the original database does not provide much information on biologic therapies. We do have the Danish Crohn's Colitis Database, which is following these patients regularly and is in the process of publishing the first 5 years of follow-up data. Similar work has been done in Sweden. Our Danish registry will also follow the newly approved biologic therapy, adalimumab (Humira, Abbott) and the anticipated approval of certolizumab pegol (Cimzia, UCB). With respect to Europe-wide study and the European inception cohort of the EC-IBD, it would be interesting to analyze data on patients diagnosed in 1991 and examine whether eventual use of biologic therapy changed the course of disease. This may be a thesis for future analysis.

G&H What other future plans are under consideration for the EC-IBD?

PM The EC-IBD is now under the umbrella of the European Crohn's Colitis Organization (ECCO). The original database still contains a significant amount of useful information, and at the next ECCO meeting, we will present the protocol for a new inception cohort to measure defensins in IBD patients, in order to develop their prognostic use as a novel biologic marker of disease. This protocol will extend throughout Europe and examine a theorized split between eastern and western

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Europe that may be linked to the presence of defensins. We also hope to measure environmental factors based on the International Organization of Inflammatory Bowel Disease (IOIBD) environmental factor scheme that was validated in Copenhagen.

Suggested Reading

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