

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

Population-based Research in the Natural History of IBD

Morten H. Vatn, MD
 Professor of Clinical Epidemiology
 Institute of Clinical Epidemiology
 and Molecular Biology (EpiGen)
 Akershus University Hospital
 University of Oslo
 Consultant of Gastroenterology
 Rikshospitalet University Hospital
 Oslo, Norway

G&H Can you describe the main patient-related, disease-related, and environmental factors that affect the natural history of inflammatory bowel disease?

MV Patient age at onset of disease has a profound effect on outcomes and the overall course of disease. Patients with pediatric and adolescent onset tend to have more severe disease, greater disease extent, and worse outcomes. Pediatric patients with Crohn's disease (CD) are the most likely to have ileocolonic disease distribution. Those with ulcerative colitis (UC) are most likely to have pancolitis.

Many genetic polymorphisms have recently been related to CD, but the only genetic factor for which we have demonstrated a specific impact on disease prognosis is *NOD2*, which has been related to ileocecal involvement and stenosis. A recent study conducted among twins who are inflammatory bowel disease (IBD) patients has also suggested increased incidence of *NOD2* variation and a corresponding aggravation of *NOD2*-related ileocecal involvement, moreso than among ordinary, affected first-degree relatives of patients with IBD.

From an epidemiologic perspective, our Norwegian cohort had a much lower incidence of *NOD2*-related CD, compared to middle or south European cohorts, but similar to other cohorts in northern Europe. However, during the last decade, we have found an increased incidence of *NOD2* polymorphism among children in Oslo, which may be correlated to the increased incidence

of disease in the population. This relationship has not been fully demonstrated, due to limited material, but the recent incidence rate of *NOD2* was 23% among children with CD in Oslo, whereas the previously published rates for combined adults and children in the IBSEN cohort was 14%. The *NOD2* variation is seen in only 7% of the general population.

Levels of C-reactive protein (CRP), at diagnosis and after 1 year of therapy, have also proven prognostically valuable. Our 5-year follow-up data on CRP, which were published in *Gut* several years ago, demonstrated that CRP after 1 year of treatment was a risk factor for later complicated disease and surgery. There may be other genetic factors associated with the production of CRP as a marker, similar to those that have been found for diabetes and heart conditions.

G&H Have you explored the facility of other serologic markers in predicting disease course?

MV In our latest population-based studies, the only validated data to date are for perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA). Again, as with *NOD2* polymorphism, we have less frequency of ASCA positivity in CD and pANCA positivity in UC in our Norwegian cohorts, when compared to other international studies. Regardless, we have found a strong correlation between complicated disease and ASCA positivity in CD, as well as pANCA positivity associated with extensive UC and the need for surgery. Both of these markers are strongly predictive of a serious disease course in our population, despite the fact that we have lower frequency of serologic markers than has been seen in other cohorts.

G&H Can you describe the ongoing research of familial versus sporadic incidence of IBD and how it may help to characterize disease course?

MV The only data that we currently have making this comparison are from 10 years' follow-up. We now need extended follow-up time to look at increased frequency of familial incidence. In looking at the data from 10 years compared to 5 years, it seems that familial onset and concordance are increasing with prolonged observation.

Concordance of outcomes among relatives with CD, comparing the difference in age at diagnosis for parent and child, was shown to be 15 years in a Johns Hopkins study. Our study showed the likelihood of this difference to be 17 years.

In UC patients, familial outcomes coincide in a much shorter interval, with a difference between age at time of diagnosis for parent and child that is less than 5 years in 64% of the cases. This may indicate that shared environmental factors are more important in determining the time of diagnosis in UC.

For future studies, it will be important to examine unaffected, as well as affected, relatives. Data from the Multiplex Family Study in Europe and the United States are showing strong familial aggregation of genetic disease markers. It is important to look for those markers in familial nonpatients who may become patients in later years. This may reveal how we can predict earlier versus later onset of disease, among other useful information. If we have access to full-genome mapping in complete families, we may be able to determine the markers or combinations that will lead to early versus late onset, versus no disease at all.

G&H How has the relatively recent introduction of immunosuppressive and biologic therapies altered disease course in your population-based studies?

MV In our studies, the number of patients taking both biologic and immunosuppressive therapies is increasing gradually, currently showing a steady increase from the first year to the tenth year of active disease. We are expecting that the use of biologic treatment will increase further and be seen earlier in the disease course more regularly. Immunosuppressives, which were introduced earlier than biologics, have continued to gain use since the 1990s. The rate of azathioprine use at 1-year follow-up in the mid-1990s was 7%, increasing to more than 20% at the 5-year follow-up.

Our latest cohort of patients, who were followed from 2005 to 2007, have no published data in adults as of yet. The emerging data among children, however, indicate an early top-down strategy, with an early start of biologic treatment because of complicated disease, in approximately half of the patients. The results after 1 year are now under review for publication, and the impression thus far is that the results are rather promising, in terms of both efficacy and tolerability. In children, it is of particular importance to avoid both disease progression, hospitalization, and steroid use. Pediatric patients' ability to achieve puberty has also been positively affected by this treatment strategy. We hope to present specific data some time next year.

G&H How has the achievement of mucosal healing as an endpoint affected disease history in your cohorts?

MV One of our analyses, published in 2007, was based on mucosal healing observed in patients before the introduction of biologic therapies. It showed a very high inverse correlation of healed mucosa to later surgery, hospitalization, and the subsequent need for steroids. For both UC and CD, we have seen that mucosal healing is a highly predictive factor even without the use of biologics to achieve it. Given the wide variety of disease course, it is important to remember that many patients do not necessarily need these aggressive drugs during the first year or later, and these mucosal healing data demonstrate this fact.

G&H What other aspects of IBD still require population-based study?

MV Colorectal cancer in patients with UC and Crohn's colitis remains a major question for consideration. We have done some work regarding the risk of cancer and have confirmed the long-term risk, particularly in patients with disease onset at a young age, and particularly with UC. However, controversy remains regarding the preventative properties of 5-aminosalicylic acid agents, both from an observational standpoint and in terms of basic science. The long-term effects of these agents need to be documented, as do the pathways that allow them to prevent carcinogenesis.

Suggested Reading

- Vatn MH. Natural history and complications of IBD. *Curr Gastroenterol Rep*. 2009;11:481-487.
- Vatn MH. Mucosal healing: impact on the natural course or therapeutic strategies. *Dig Dis*. 2009;27:470-475.
- Froesli KF, Jahnsen J, Moum BA, Vatn MH; the IBSEN group. Mucosal healing in inflammatory bowel disease. *Gastroenterology*. 2007;133:412-422.
- Perminow G, Brackmann S, Lyckander LG, Franke A, Borthne A, et al. A characterization in childhood inflammatory bowel disease, a new population based inception cohort from south eastern Norway, 2005-2007, showing increased incidence in Crohn's disease. *Scand J Gastroenterol*. 2009;44:446-456.
- Bengtson MB, Solberg C, Aamodt G, Jahnsen J, Moum B, et al. Clustering in time of familial IBD separates ulcerative colitis from Crohn's disease. *Inflamm Bowel Dis*. 2009;15:1867-1874.
- Solberg IC, Lygren I, Cvancarova M, Jahnsen J, Stray N, et al. Predictive value of serologic markers in a population-based Norwegian cohort with inflammatory bowel disease. *Inflamm Bowel Dis*. 2009;15:406-414.
- Spehlmann ME, Begun AZ, Burghardt J, Lepage P, Raedler A, Schreiber S. Epidemiology of inflammatory bowel disease in a German twin cohort: results of a nationwide study. *Inflamm Bowel Dis*. 2008;14:968-976.
- Henriksen M, Jahnsen J, Lygren I, Stray N, Sauar J, et al. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. *Gut*. 2008;57:1518-1523.