Early Azathioprine in Crohn's Disease

Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977-2009. Am J Gastroenterol. *2012;107:579–588.*

Crohn's disease (CD) is a chronic destructive disease leading to progressive intestinal damage eventually requiring surgery. Till the end of the past century, no significant progress has been made regarding the occurrence of intestinal complications and the need for surgery[1] as 70% to 80% of patients are operated on during their lifetime. However, the widespread use of immunomodulators over the past 20 years and the recent arrival of anti–tumor necrosis factors are expected to change this pessimistic observation. This retrospective population-based study, performed in a province of Hungary, analyzed the evolution and the therapeutic requirements of 506 incident cases of CD diagnosed between 1977 and 2008. The patients were divided into 3 calendar cohorts defined by the year of diagnosis. As expected, azathioprine (AZA) was used more and more over time. In particular, early AZA (defined as started within the 3 years following diagnosis) was given to 4% of patients of the 1977 to 1988 cohort, 25% within the 1989 to 1998 cohort, and 44% within the 1999 to 2008 cohort. Of note, regular maintenance with anti–tumor necrosis factors was not used as it became reimbursed in Hungary only since 2009. The main result of the study was the decrease of the 5-year cumulative probability of resective surgery, which dropped from 0.35 before 1999 to 0.25 afterward. Using multivariate Cox analysis and then matching on propensity scores, the authors demonstrated that the decreased surgical rate was attributable to early AZA use (hazard ratio, 0.42; 95% confidence interval, 0.26–0.67).

COMMENT

In 2005, we published an article showing that in our hands immunomodulators (mainly AZA) had no impact on the need for surgery in CD. This article was used as a demonstration of the failure of immunomodulators for improving the evolution of the disease. This was a misunderstanding of the data. In fact, these data showed that AZA did not modify the need for surgery when prescribed too late.[2] Indeed, the great majority of our patients were put under AZA while already operated on. The take home message of our article should be revised as followed: we should reconsider indications of AZA and prescribe it earlier in the course of the disease. A population-based study from Cardiff[3] used a similar design, comparing different calendar cohorts defined by year of diagnosis. The authors found a marked reduction in surgery rates between 1986 and 2003. Again, multivariate Cox analysis showed that early AZA use (within the first year of diagnosis) was an independent factor associated with the time of surgery. The results of the Hungarian study are somewhat similar, although definition of early use of AZA (within the first 3 years following diagnosis) was less stringent. These 2 results differed from ours, probably because population-based series are quite different from those from referral centers. For a CD of similar severity, we prescribed AZA later than did Welch and Hungarian gastroenterologists. The statistical methodology was also different. However, although propensity scores and multivariate analysis are useful tools to compare retrospective data, they can correct only for the parameters, which have been collected, whereas we are not able retrospectively to catch all the criteria, which led to the decision of starting immunomodulators in 1 individual, particularly 10 to 25 years ago.

Thus, the question of the real impact of immunomodulators on the anatomical course of CD remains unanswered. Although one can estimate that this debate is obsolete in the era of biologics, it should be kept in mind that efficient drugs are still scarce today and the use of biologics may be limited in some countries for financial reasons. Thus, immunomodulators remain the cornerstone of the therapeutic management of CD. In fact, we believe that only prospective randomized study may address this question, and the preliminary results of the 2 controlled trials[4,5] designed to test the efficiency of a very early prescription of AZA are negative. If these disappointing results are confirmed in the long term, the place of immunomodulators in the management of CD may decrease in favor of a larger use of drugs able to modify the anatomical evolution of CD.[6,7]

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