Prognostic factors in Crohn's disease: a systematic review

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Facteurs pronostiques au cours de la maladie de Crohn : revue systématique de la littérature

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R É S U M É

Prérequis : L'histoire naturelle de la maladie de Crohn est associée à plusieurs facteurs affectant le pronostic de cette pathologie.
But : Déterminer les principaux facteurs pronostiques au cours de la maladie de Crohn à travers une revue systématique de la littérature.
Méthodes : Revue de la littérature.
Résultats : Les évènements importants à considérer au cours de la maladie de Crohn et ayant une signification pronostiques sont la nécessité de traitement par immunosuppresseurs, la résection intestinale et la survenue d'une maladie de Crohn invalidante au cours du suivi. Les facteurs associés à ces différents évènements sont l'atteinte iléale, les lésions anopérinéales, et un traitement initial par corticoïdes. D'autres facteurs comme l'âge jeune, le taux de CRP et le tabagisme n'ont pas été retrouvés dans toutes les études. Le rôle protecteur d'un traitement précoce par anti-TNF est très probable, et doit être confirmé par d'autres études.
Conclusion : Chez un sous groupe de patients, caractérisé par la présence de ces facteurs pronostiques, la stratégie « top-down » peut être proposée.

M o t s - c l é s
Maladie de Crohn - Pronostic

S U M M A R Y

Background: The natural history of Crohn's disease is associated with several factors that affect the prognostic of the patients.
Aims: To determine the most prognostic factors in Crohn's disease, based on a systematic review.
Methods: Literature review.
Results: The most important factors to consider in patients with Crohn's disease are the need for immunosuppressive therapy, the need for intestinal resection and disabling disease. Prognostic factors for these events are ileal involvement, perianal disease and initial treatment by corticosteroid. Other factors such young age, CRP level and smoking status, has not been found in all population-based studies. Protective role of anti-TNF drugs is strongly suggested but need to be confirmed in further studies.
Conclusion: In a selected subgroup of patients with Crohn's disease characterized by the presence of these prognostic markers, the "top-down" strategy can be proposed.

K e y - w o r d s
Crohn's disease – Prognosis

Crohn's disease (CD) is characterized by flare-ups alternating with periods of remission. The choice of the treatment in patients with active CD is usually based on severity and the location of the disease (1). Current practice guidelines recommend that most patients with active disease should be treated initially with corticosteroids (2). However, many patients become resistant to or dependent on corticosteroids, and long exposure is associated with several side effects and probably with an increased risk of mortality. The effectiveness of short term infliximab combined with azathioprine or 6-mercaptopurine in patients with active CD was investigated by D'Haens et al. in a large open-label randomized trial (3). This study clearly showed that a greater proportion of patients in the combined immunosuppression group were in remission than were patients given conventional treatment. Patients assigned to early immunosuppression were also exposed to less corticosteroids than were those in the conventional management group (3). More recently, the SONIC trial showed that the proportion of patients in corticosteroid-free clinical remission was greater in the combination therapy group, infliximab and azathioprine, compared to azathioprine group and infliximab group (4). The efficacy of the top down strategy suggested that intensive immunosuppressive approach can be performed in patients with active CD. However, because of side effects of azathioprine and infliximab and cost of biologic treatments, this strategy should be adopted only in a subgroup of patients. For this reason, assessment of prognostic factors in non selected patients with CD is important. In the population based studies, the most studied events in the course of CD were the prescription of azathioprine in patients treated by conventional approach, the need for intestinal resection, and disabiling CD, as previously defined by Beaugerie et al. (5, 6). The aim of this review is to determine the most evaluated prognosis factors in patients with CD, particularly to predict the need for azathioprine therapy, intestinal resection and disabling disease.

PREDICTIVE FACTORS OF AZATHIOPRINE THERAPY REQUIREMENT

In CD patients managed by the conventional therapy, the efficacy of azathioprine has been established for both the induction and the maintenance of disease-free remission, with a clear benefit in steroid sparing, in case of steroid dependency. The efficacy of azathioprine is also established in fistulizing CD, and in prevention of postoperative recurrence (Level A-Class 1) (7). Identification of a subgroup of patients at higher risk of azathioprine requirement can help the clinician to assess the natural history of CD. This subgroup of patients can also be treated initially by azathioprine in association with infliximab, in order to avoid the resistance or the dependency to corticosteroids and to avoid related disease complications or intestinal resection (8). There are very few literature studies evaluating models for predicting outcome and the need for immunosuppressors in CD: In the study of Jacobstein et al, which include 57 children with newly diagnosed Crohn's disease, 59.6% were started on azathioprine, 6 mercaptopurine or methotrexate within one year of diagnosis; and mean serum albumin and hematocrit at diagnosis were lower, and erythrocyte sedimentation rate at diagnosis was higher in patients who required immunomodulators (9). In a retrospective study of non selected hospitalized CD patients, we showed that the cumulative frequency of azathioprine prescription was 11% the first month, 31% at 6 months, 35% at one year and 49% at 6 years. Independent factors associated with azathioprine use in our population were diffuse involvement of the ileum at initial hospitalization, and previous prescription of corticosteroid therapy (Level B – Class 2) (10).

PREDICTIVE FACTORS OF SURGERY IN CROHN'S DISEASE

Retrospective evaluations of the risk of surgery in CD have been made frequently, but problems pertaining to referrals, insufficient numbers of patients and too short follow up period contribute to the lack of consensus so far. In a large Swedish population-based study, the cumulative rate of intestinal resection was 44%, 61% and 71% at 1, 5 and 10 years after diagnosis of CD (11). In this study, the relative risk of surgery was increased in patients with CD involving any part of the small bowel, in those having perianal fistulas and in those who were 45 to 59 of age at diagnosis (11). The phenotypic classification of CD plays an important role in determining the treatment, and may assist in predicting the likely clinical course of disease (12). Using the Vienna classification, it has been shown in clinical-based cohorts that there can be a significant change in disease behavior over time, whereas disease location remains relatively stable. The phenotype of the disease is a dynamic process, and after 10 years, almost 50% of the patients with an inflammatory phenotype at diagnosis develop fibro-stenosing or perforating complications that affect the course of the disease. Other studies confirm the Swedish results, by showing that the presence at diagnosis of perianal lesions is associated with an increased risk of intestinal resection (Level B – Class 2) (13, 14). However, a stricture or intra-abdominal penetrating lesion is associated with an increased risk of surgery (15), and other studies have also shown that abdominal penetrating lesion at the time of first surgery is associated with more rapid recurrence and is an indicator of further surgery (16). In a retrospective study, we also showed that the Montreal classification can predict the need for surgery in patients with CD (17). In our study, the phenotype associated with a higher risk of surgery was the A1L1B3 phenotype, with a Hazard Ratio of 11 and a statistically significant difference compared to other phenotypes (17). In a large European study, phenotype at diagnosis had predictive value for disease recurrence and risk of surgery, with upper gastrointestinal disease being the most important positive predictor, as also shown in Asian population (Level B – Class 2) (18, 19). A phenotypic North-South gradient in CD may be present, illustrated by higher surgery risks in some of the Northern European centers (18). Some serologic and laboratory markers can also be helpful in predicting surgery in CD patients; such as high ASCA levels (20), cumulative reactivity to ASCA, I2 and OmpC (21), increasing amount and level of antibody responses toward gASCA, ALCA, ACCA, AMCA and OmpC (22) and level of CRP only in a subgroup of

patients (23). The role of endoscopy in predicting the course of the disease is also very important; in fact, severe endoscopic lesions predict a more aggressive outcome with increased rates of complications and surgery in CD (Level A – Class 1) (24). Thus, mucosal healing is associated with long term outcome in CD: Data from the IBSEN cohort strongly suggests that mucosal healing predicts a generally favorable outcome of disease based on all types of treatment strategies, except corticosteroids, and is related to treatment efficacy and reduction of frequency of surgical resections (25). In the endoscopic substudy of the ACCENT 1 trial, patients treated with scheduled maintenance therapy with infliximab had superior rates of mucosal healing, and those who maintained complete mucosal healing over one year had a lower rate of hospitalizations and surgery (26), although the study of Nationwide Inpatients sample in USA showed that, during the period of adoption of infliximab as a novel treatment of CD, overall rates of bowel resections have either remained relatively stable or decreased moderately (27). In a recent population-based study from Cardiff, early use of thiopurines, within the first year of diagnosis, as well as year of diagnosis and isolated colonic involvement, were associated with decreased risk of intestinal resection (28).

PREDICTIVE FACTORS OF DISABLING CROHN'S DISEASE

Data from population-based studies showed that, overall, only 1% has a continuously active course, about 10% had prolonged clinical remission, and half of the patients with active disease could expect to have a full year remission within three years. In many of these patients, azathioprine, biologic treatments or surgery are required to achieve remission (5). Important events can occur during the course of the disease, namely corticosteroid therapy, hospitalizations and need for immunosuppressive therapy or surgery. These events usually reflect a bad prognosis related to the disease. Beaugerie et al. arbitrarily defined CD course as disabling during the 5-year period following diagnosis when at least one the following criteria was present in this time interval: more than two steroid courses required and/or dependence on steroids, further hospitalization after diagnosis for flare-up or complication of the disease, presence of disabling chronic symptoms, need for immunosuppressive therapy and intestinal resection or surgical operation for perianal disease. These events were chosen because all that events can interfere with the social, professional and private life of the patients during the 5-year period after diagnosis (6). In the study of Beaugerie et al, independent factors present at diagnosis and significantly associated with subsequent 5-year disabling disease were the initial requirement for corticosteroid use, an age below 40 years, and the presence of perianal disease. The positive predictive value of disabling disease in patients with 2 and 3 predictive factors was 0.91 and 0.93 respectively (6). Loly et al. subsequently used the same markers of disabling disease in a cohort of CD patients from Belgium: In this study, perianal lesions, the need for steroids to treat the first flare of the disease and ileocolonic location, but not age below 40 years, were confirmed as predictive markers, but the predictive performances of the models generate were low (29). Disabling disease can be also defined by the occurrence of complications during the course of the disease: In a population-based cohort study from the Olmsted County, factors associated with development of complications were the presence of ileal involvement and perianal disease (30). Possible explanation for the higher rate of intestinal complications in patients with ileal involvement compared to colonic locations included differences in gut lumen diameter and the intensity of mucosal inflammatory reactions leading to permanent bowel damage (31). Cigarette smoking is also a well known aggravating risk factor for disease progression as evidenced by and increased need for immunosuppressive therapy, surgery, and higher postoperative recurrence rates, but smoking status was not found as prognosis factor in the large population-based studies (Level B – Class 2) (32). Mucosal healing at baseline was associated with less endoscopic disease activity at 5 years and decreased need for subsequent treatment with steroids in a Norwegian population-based study (25). However, mucosal healing within 6 months of diagnosis did not predict a less severe clinical course as defined by relapses, development of complications or surgery (25).

CONCLUSION

The clinical course of CD can be predicted by several clinical, biologic or endoscopic markers. The most important prognostic factors in CD are ileal involvement, treatment of the first flare by corticosteroids and perianal disease. "Top down" strategy can be proposed to this subgroup of patients, in order to avoid complications related to the disease, and to increase their quality of life. Improvement of selection of the patients can be done using the serological markers. The protective role of mucosal healing and biological treatments must be confirmed by further prospective with a long follow up studies.

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