Original Article

Timing of Thiopurine or Anti-TNF Initiation Is Associated with the Risk of Major Abdominal Surgery in Crohn’s Disease: A Retrospective Cohort Study

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Abstract

Introduction: Early stages of Crohn’s disease (CD) are predominantly inflammatory and early treatment could be useful to change the natural history of CD. We aimed to evaluate the impact of early treatment in our cohort of CD patients.

Methods: We retrospectively reviewed clinical records of all CD patients at our centre who have received immunomodulators. Time from diagnosis to first CD-related major abdominal surgery or end of follow-up was considered. Dates of diagnosis, of starting immunomodulators (thiopurines / anti-tumour necrosis factor [TNF]), and of the first CD-related surgery when appropriate were collected.

Results: Of 422 patients who received thiopurines, 189 operated patients started thiopurines after a median of 117 months (interquartile range [IQR] 44–196) since diagnosis; non-operated patients, after a median of 30 months [IQR 6–128], p < 0.005. Odds ratio [OR] for surgery was 1.006 (95% confidence interval [CI] 1.004–1008) for each month of delay in starting thiopurines. Among 272 patients who received anti-TNFs, 137 operated patients started anti-TNFs after a median of 166 months [IQR 90–233] since diagnosis; non-operated patients after a median of 59 months [IQR 14–162]; p < 0.005. OR for surgery was 1.008 [95% CI 1.005–1.010] for each month of delay in starting anti-TNFs. Among 467 patients who received thiopurines and/or anti-TNF, 210 operated patients started any immunomodulator after a median of 120 months [IQR 48–197] since diagnosis and non-operated patients after a median of 30 months [IQR 6–126], p < 0.005. OR for surgery was 1.008 [95% CI 1.005–1.010] for each month of delay in starting immunomodulators.

Conclusions: In our experience, time between diagnosis and thiopurine or anti-TNF initiation was associated with the risk of major abdominal surgery in Crohn’s disease.

Key Words: Crohn’s disease; thiopurines; anti-TNFs
1. Introduction

Crohn’s disease (CD) is a chronic, progressive, and disabling disease that affects the gastrointestinal tract and usually leads to established bowel damage.\textsuperscript{1,2,3,4,5} Conventional step-up approach management is based on the successive introduction of conventional immunosuppressive agents [steroids, thiopurines, or methotrexate] followed by biological monoclonal antibodies in case of toxicity or lack of response. This classic strategy is mainly clinically based and has been scarcely related to a significant modification of the course of the disease.\textsuperscript{6,7,8}

Current knowledge of the disease shows that the disease phenotype is a matter of continuous evolution from predominantly inflammatory forms [that could be successfully managed with anti-inflammatory drugs] to other structuring or penetrating phenotypes, more complex forms that may be related to disabling symptoms or severe complications and may even deserve surgical approach.\textsuperscript{9,10,11,12}

Surgery has been considered the milestone of severe disease in a patient’s life. Improvement in medical therapy may be associated with a decline in surgical rates of CD patients, suggesting a change in natural history of the disease.\textsuperscript{13,14,15} On the other hand, some other studies suggest that surgical rates have not improved despite evolution of medical management.\textsuperscript{5,16,17,18} Two recent prospective and randomised controlled studies failed to demonstrate usefulness of the early introduction of thiopurines,\textsuperscript{19,20} but sub-analysis of other randomised controlled trials showed that anti-tumour necrosis factor alpha [anti-TNFs] drugs were more effective if introduced early.\textsuperscript{21,22} However, there is no universally accepted definition of early CD and an international group of experts recently developed a consensus definition to be used in disease modification trials.\textsuperscript{23} In spite of all of that, early treatment of CD has hardly translated into clinical practice, since clinicians may have additional concerns like costs or safety.\textsuperscript{12}

The aim of this study was to evaluate the impact of early treatment in our own cohort of CD patients.

2. Methods

We retrospectively reviewed the clinical records of all CD patients in our database with a stable follow-up at our centre and who had received either thiopurines or anti-TNFs as maintenance treatment at any point during the follow-up. Demographic data and information about the disease behaviour according to the Montreal Classification,\textsuperscript{24} as well as the smoking status at the end of the follow-up, were collected. Dates of diagnosis, of starting immuno-suppressive therapy [both thiopurines and/or anti-TNFs], and of CD-related first major abdominal surgery when appropriate were collected. Strictureplasties and surgeries for perianal disease were not considered for the analysis. Time from diagnosis to CD-related first major abdominal surgery or the end of the follow-up was considered. Patients lacking any of these data on our database or with no current follow-up at our centre were excluded from the analysis.

2.1. Statistical analysis

Values are reported as percentages or means and standard deviations or, for non-normal distributions, as medians and interquartile ranges. A chi-square test or Fisher’s exact test, as appropriate for sample size, was used to evaluate categorical variables. Differences of means between groups were assessed with the use of Student’s t-test for independent samples if the normal distribution could be assumed, or by the nonparametric Mann–Whitney U-test if normality was not valid. Differences of more than two means were calculated by the analysis of variance [ANOVA] test if the normal distribution could be assumed, or by the nonparametric Kruskal–Wallis test if normality was not valid, using the Scheffé test correction for multiple comparisons. To test for normality, we used either the Shapiro–Wilks test for small samples or the Kolmogorov–Smirnov test with the Lilliefors correction for large samples. Binary logistic regression analysis was used for the calculation of the odds ratios [ORs] and p-values in univariate and multivariate analysis.

A multivariate analysis with logistic binary regression was performed to estimate the effect of the delay in starting immunomodulators on the risk of undergoing surgery, adjusted according to the following variables: Age of diagnosis, Localisation of the disease and Clinical Behaviour, according to the Montreal Classification; Gender [Male or Female]; and Smoking status [never smoked, previous smoker, and current smoker]. Any variable that modified the effect [odds ratio] of the variable of interest [time from diagnosis to initiation of immunomodulators] by more than 10% was considered a confounding variable.

Besides the described multivariate analysis, an additional stratified analysis based on the localisation of the disease [L in the Montreal Classification] was performed, taking into consideration patients with ileal disease [L1] on one hand and the rest of the patients [L2 and L3] on the other hand.

3. Results

At the time of the study, there were 1152 patients followed by our Inflammatory Bowel Diseases Unit; 698 were CD patients, and 554 of them were identified as having received thiopurines or anti-TNFs as maintenance treatment. However, 87 patients were lacking some data or current follow-up and had to be discarded.

We finally considered 467 CD patients for the analysis. Demographic characteristics can be found in Table 1. Among these patients, 210 had undergone at least one CD-related major abdominal surgery during follow-up. Major abdominal surgeries related to CD included ileoceleal resection [63%], small intestine resection [15%], colonic resection [7%], panproctocolectomy [5%], and sub-total colectomy [4%].

We found 422 CD patients who received treatment with thiopurines; 189 patients of this group had undergone at least one major abdominal surgery during follow up, whereas 233 remained free of surgery at the end of the follow-up. Median time from diagnosis to first abdominal surgery was 40 months, inter-quartile range [IQR] 5–101 months, and median time from diagnosis to the end of the follow-up in those non-operated patients was 129 months [IQR 5–101 months, and median time from diagnosis to the end of the follow-up in those non-operated patients was 129 months [IQR 5–101 months]. These operated patients started thiopurines after a median of 48–214 months. These operated patients started anti-TNFs after a median of 166 months [IQR 55–213 months]. The odds ratio for undergoing surgery was 1.006 [95% CI 1.004–1.008] for each 30 months [IQR 6–128 months]; p < 0.001. The odds ratio for undergoing surgery was 1.006 [95% CI 1.004–1.008] for each 30 months [IQR 6–128 months]; p < 0.001. The odds ratio for undergoing surgery was 1.006 [95% CI 1.004–1.008] for each 30 months [IQR 6–128 months]; p < 0.001. The odds ratio for undergoing surgery was 1.006 [95% CI 1.004–1.008] for each 30 months [IQR 6–128 months]; p < 0.001.
patients started thiopurines after a median of 59 months \([IQR 14–162 \text{ months}]\); \(p < 0.001\). The odds ratio for undergoing surgery was 1.008 \([95\% \text{ CI } 1.005–1.010]\) for each month of delay in starting anti-TNFs [Figure 2].

We considered a total of 467 CD patients who received treatment with thiopurines and/or anti-TNFs at any point during their follow-up; 210 patients had undergone at least one major abdominal surgery during follow-up, whereas 257 patients remained free of surgery at the end of the follow-up. Median time from diagnosis to first abdominal surgery was 40.5 months \([IQR 5–107 \text{ months}]\), whereas median time from diagnosis to the end of the follow-up in non-operated patients was 129 months \([IQR 49–213 \text{ months}]\). Operated patients started thiopurines or anti-TNFs after a median of 120 months \([IQR 48–197 \text{ months}]\) since diagnosis, whereas non-operated CD patients started thiopurines or anti-TNFs after a median of 30 months \([IQR 6–126 \text{ months}]\); \(p < 0.001\). The odds ratio for undergoing surgery was 1.008 \([95\% \text{ CI } 1.005–1.010]\) for each month of delay in starting thiopurines or anti-TNFs [Figure 3].

This analysis was repeated after excluding those patients who required surgery within the first year after diagnosis, to exclude those cases with perforating or strictureing disease at baseline that could have biased the results. For this sub-analysis, 405 patients were considered and the results were very similar to the global results: the odds ratio for undergoing surgery in this sub-group of patients was 1.007 \([95\% \text{ CI } 1.004–1.009]\) for each month of delay in starting thiopurines or anti-TNFs.

On the multivariate analysis considering gender, smoking status, and all different categories of the Montreal Classification, delay in the treatment with immunomodulators was associated with higher risk of surgery, with an odds ratio for undergoing surgery of 1.005 \([95\% \text{ CI } 1.003–1.007]\; \(p < 0.001\)\) for each month of delay in starting thiopurines or anti-TNFs.

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Besides the described multivariate analysis and aiming to avoid any kind of bias specifically related to the localisation of the disease, an additional stratified analysis was performed considering

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<th>Table 1. Demographic characteristics.</th>
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Montreal Classification: A [age at diagnosis] 1 [< 16 years], 2 [17–40 years], 3 [> 40 years]; L [Location] 1 [ileal], 2 [colonic], 3 [ileocolonic], 4 [isolated upper digestive tract]; B [Behaviour] 1 [non-stricturing, non-penetrating], 2 [stricturing], 3 [penetrating]; P [perianal disease].
only patients with ileal disease on the one hand [L1 in the Montreal Classification: odds ratio for undergoing surgery 1.007; 95% CI 1.004–1.011; p < 0.001] and the rest of the patients on the other hand [L2 and L3 in the Montreal Classification: odds ratio for undergoing surgery 1.006; 95% CI 1.004–1.009; p < 0.001]. Both results were very similar.

4. Discussion

CD is a progressive disease that, beyond severity of symptoms, may lead to irreversible structural bowel damage including stricture, fistula, or abscess. Early stages of the disease are thought to be a predominantly inflammatory distinct entity. As a matter of fact, in both experimental murine models and humans, cytokine profiles and expression of adhesion molecules in early stages of CD may change during the course of the disease and differ from those in long-standing disease.24,25,27,28,29,30

Current therapeutic goals include more objective and definite endpoints beyond the mere absence of symptoms. Deep remission, that includes mucosal healing, should be considered in clinical practice since it has been associated to positive outcomes and could prevent long-term consequences of the disease like bowel damage, including CD-related surgery and CD-related disability.31,32,33,34 In fact, some evidence suggests that mucosal healing is more easily achievable in early CD and therefore clinicians should be aware of this ‘window of opportunity’ when defining the therapeutic strategy for a CD patient.3,5,35,36,37 A recent retrospective experience showed how progression in CD phenotype might be delayed if therapeutic intervention was initiated before changes in the behaviour of the disease, whereas longer delays between CD diagnosis and beginning immunomodulators were associated with disease progression.38 Moreover, a recently published Canadian experience showed that initiation of immunomodulators at more evolved stages of the disease was associated to treatment failure and subsequent surgery, whereas better outcomes were achieved by treating at early stages.39

Two recent randomised controlled trials showed that early introduction of thiopurines following CD diagnosis failed to reduce CD relapse compared with conventional management.19,20 However, sample sizes were relatively small, follow-up period probably too short and, outstandingly, a high proportion of control subjects eventually required thiopurines, which might have ameliorated the magnitude of the benefit. On the other hand our experience, though retrospective, included an important number of patients followed during a long period of time [more than 10 years of mean follow-up], and suggested that every single month of delay in the beginning of thiopurines from diagnosis might add risk of surgery along the follow-up. A recently published retrospective experience from Australia, which included hundreds of patients followed for decades, also showed how the early use of thiopurines or methotrexate was significantly associated with a reduced need of CD-related surgery.40

Some post-hoc analysis of studies on anti-TNFs have shown that more efficacy is achieved when these drugs are administered in early CD compared with long-standing disease.21,22 In the EXTEND trial, a placebo-controlled trial with adalimumab in moderate to severe CD patients, greater deep remission rates were observed in patients with early CD.23 There are only few randomised controlled trials that enrolled patients with early CD to receive treatment with anti-TNF therapy. D’Haens et al. evaluated the efficacy of early use of combination therapy with infliximab and azathioprine compared with conventional step-up management in treatment-naive CD patients, and showed that a higher proportion of patients in the early combined treatment group were in steroid-free remission at Weeks 26 and 52.44 The SONIC trial compared infliximab monotherapy, azathioprine monotherapy, and combined treatment with both in moderate to severe CD patients who were also naïve to immunomodulators, and showed that a higher percentage of patients in the combination group achieved steroid-free clinical remission at Week 26.45 Trials conducted in a paediatric population are interesting since early CD is more frequently found among these patients. A small and open-label but prospective single-centre study assessed infliximab efficacy in paediatric CD patients and showed that duration of response was greater in early [time from diagnosis < 2 years] than in late disease.46 In another trial, early intervention with anti-TNF therapy [< 3 months] was more effective than conventional immunomodulators after 1 year of follow-up of children with CD.47 Finally, the infliximab pivotal trial in paediatric CD obtained better results than those obtained in the adult trial [ACCENT II], which was mainly related to the duration of the disease [1.6 years in the paediatric population, 7 years in adult patients] and therefore earlier introduction of anti-TNF therapy in paediatric patients was likely to explain the better outcomes.48 Our experience is consistent with all of these data and highlights the clinical relevance of early introduction of anti-TNFs in CD management.

However, there is no universally accepted definition of ‘early CD’, and how early should the therapeutic intervention be to have impact in the natural history of the disease is still to be defined. Even though some previously mentioned studies have considered the time of diagnosis,15,20 some others identified early CD with the 2nd or 3rd year since diagnosis.30,42,44,45 Moreover, an international panel of experts developed a definition of ‘early CD’ and agreed that it should not be longer than 18 months.11 The analysis of our experience highlights the clinical relevance of every single month of delay in starting immunomodulators since diagnosis of CD. Each month of delay was associated to a quantifiable increased risk of surgery, showing that the sooner the treatment was initiated, the better the outcomes achieved: In our experience, each month of delay added approximately 0.5% risk of surgery; if a full year of delay was considered, the risk would rise to 6.2% [95% CI: 3.6% to 8.7%]. Our results suggest that the aforementioned ‘window of opportunity’ begins with the diagnosis of CD and should be considered by clinicians. Moreover, diagnosis delay of CD has not been evaluated in this study but may have additive consequences and should also be taken into account.49

The decision to start immunomodulators may be influenced by many different clinical issues, some of them identified as markers of poor prognosis.35 The importance of the phenotype of the disease has been previously addressed, and current recommendations suggest early immunosuppressive treatment according to the presence of some clinical variables such as perianal disease, ileocolonic disease, the need for steroids to treat the first flare, or age < 40 years at diagnosis.44 In our experience, early treatment was important regardless of other clinically relevant conditions such as the Montreal Classification or the smoking status.

In conclusion, our experience points out the clinical relevance of early treatment of CD and suggests that it could be a key tool to modify the natural history of the disease. Further research is needed to find good predictors to help clinicians to stratify patients and identify the best moment to start immunomodulators in each individual CD patient.

Conflict of Interest

Yago González-Lama, Marta Calvo, María Isabel Vera and Luis Abreu have received personal fees form AbbVie and MSD outside the present work. Yago
González-Lama, Marta Calvo and María Isabel Vera have also received personal fees from Ferring outside the present work. Marta Calvo also received personal fees from Tillots outside the present work. Yago González-Lama have also received personal fees from Olmsted county, Minnesota [1970–2004].

Impact of Early Treatment in Crohn’s Disease