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STEROID-FREE DEEP REMISSION AT ONE YEAR DOES NOT PREVENT CROHN'S DISEASE PROGRESSION: LONG-TERM DATA FROM THE TAILORIX TRIAL

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KEYWORDS : Crohn's Disease ; Deep Remission ; Infliximab ; Endoscopic Remission.

ABBREVIATIONS : CD, Crohn's disease ; CDAI, Crohn's disease activity index ; CRP, C-reactive protein ; HR, hazard ratio ; IQR, interquartile range ; SES-CD, Simple Endoscopic Score for Crohn's disease ; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease ; TAILORIX, Tailored Treatment With Infliximab for Active Crohn's Disease ; TNF, tumor necrosis factor.

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ABSTRACT

BACKGROUND & AIMS :

Crohn's disease (CD) patients included in the Tailored Treatment With Infliximab for Active Crohn's Disease (TAILORIX) trial started infliximab in combination with an immunosuppressant for 1 year. The aim of the present Study was to determine the long-term disease course beyond the study period.

METHODS :

We compared the outcomes of patients who did or did not reach the primary end point of the TAILORIX trial, defined as sustained corticosteroid-free clinical remission from weeks 22 through 54, with no ulcers on ileocolonoscopy at week 54. The primary outcome of this follow-up study was the progression-free survival of CD defined by anal or major abdominal surgery, CD-related hospitalization, or the need for a new systemic CD treatment.

RESULTS :

The 95 patients (median disease duration, 4.5 mo ; interquartile range, 1.0-56.6 mo) analyzed, including 45 (47%) who achieved the primary end point, were followed up for a median duration of 64.2 months (interquartile range, 57.6-69.9 mo) after the end of the study period. There was no significant difference in CD progression-free survival at 1, 3, and 5 years between patients who achieved the TAILORIX primary end point and patients who did not (P = .64). No difference was observed between both groups for each component of CD progression : anal surgery, major abdominal surgery, CD-related hospitalization, or the need for a new systemic CD treatment.

CONCLUSIONS :

Achieving a sustained clinical remission off steroids with complete endoscopic remission in this cohort of 95 patients with early CD was not associated with less disease progression. Prospective trials to define the therapeutic goals that change the natural history of CD and prevent complications are needed.

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Crohn's disease (CD) is a chronic inflammatory bowel disorder, characterized by periods of clinical remission alternating with periods of relapse. Over time, persistent and undertreated inflammation leads to cumulative bowel damage, including the development of Abrostenotic strictures, abscesses, or fistulae.[1] These complications frequently lead to altered intestinal function and represent the main indications for surgical resection, a major contributor to disability.[2] CD therapeutic goals thus have evolved from merely controlling symptoms and improving the quality of life to blocking disease progression and improving long-term disease outcomes by reducing structural damage, disability, and irreversible disease complications.[3-5] As a result, shortterm goals recently were defined by an expert consensus on preferred treatment strategies: the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) 2 program, emphasizing the importance of targeting remission of symptoms with objective resolution of endoscopic inflammation.[6] To improve the natural history of CD, the treatment paradigm recently shifted, promoting early intervention with anti-tumor necrosis factor (TNF) agents in patients with short disease duration because it was associated with a higher clinical response and remission rates in post hoc analyses of clinical trials.[7] The long-term impact that achieving clinical and endoscopic remission may have on the history of CD has been studied in only a few cohorts. Most of them suggested that patients with a single time point achievement of complete endoscopic remission experienced less-severe disease relapse or surgeries than those with remnant mucosal inflammation.[8-13]

According to STRIDE recommendations, the Tailored Treatment With Infliximab for Active Crohn's Disease (TAILORIX) trial aimed to reach corticosteroid-free clinical remission from weeks 22 through 54, with no ulcer on Ileocolonoscopy at week 54 in anti-TNF naïve patients.[14,15] This was achieved in more than one third of the patients form this population with short disease duration (from 4.8 to 12.2 mo). In the present follow-up study, we collected additional data on TAILORIX participants to determine the long-term impact of achieving clinical and endoscopic remission on disease progression in CD patients.

What You Need to Know

BACKGROUND

Crohn's disease therapeutic goals moved from control of symptoms to achieving clinical remission and endoscopic remission off steroids. Data about the long-term impact of achieving an early deep remission on Crohn's disease history remains scarce.

FINDINGS

Achieving clinical and endoscopic remission off steroids was not associated with better disease outcomes in a cohort of patients with early Crohn's disease. When achieved, complete mucosal

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healing remission defined by a Simple Endoscopic Score of Crohn's disease of 0 was not followed by less Crohn's disease progression.

IMPLICATIONS FOR PATIENT CARE

A more flexible approach of the treat-to-target concept should be taken in daily practice for managing Crohn's disease patients.

Methods

INITIAL STUDY DESIGN AND PATIENTS

The TAILORIX trial (European Union Drug Regulating Authorities Clinical Trials Database number 2011003038-14) was a randomized, double-blind, controlled study performed by the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives at 27 centers from Belgium, France, and The Netherlands from July 2012 to September 2015. The aim was to determine if proactive therapeutic drug monitoring targeting infliximab levels greater than 3 µg⁄mL would lead to higher clinical and endoscopic remission rates compared with pure symptom-based dose adaptations. The institutional review board at each center approved the protocol, and all patients provided written informed consent.

Included patients were biologic-naive adults with an active uncomplicated luminal CD defined by a CD activity index (CDAI) greater than 220, associated with a C- reactive protein (CRP) level greater than 5 mg/L and/or a fecal Calprotectin level greater than 250 mg⁄g, with visible endoscopic ulcers having an indication to start anti-TNF therapy in accordance with national guidelines and reimbursement criteria. Patients with the usual contraindications to anti-TNF or immunosuppressants, or other serious concomitant diseases, were excluded. Included patients received induction treatment with infliximab in combination with an immunosuppressant. At week 14 of treatment, patients were assigned randomly to 3 infliximab maintenance groups : dose increases in steps of 2.5 mg/kg based on clinical symptoms and biomarker analysis and/or serum infliximab concentrations, a dose increase from 5 to 10 mg/kg based on the same criteria, or a dose increase to 10 mg/kg based on clinical symptoms alone (controls). The primary end point was corticosteroid-free remission (CDAI, <150) at all visits between weeks 22 and 54 associated with an absence of ulcers on Ileocolonoscopy that was centrally read at week 54 without bowel resection, abscess, or new fistula.[14] Endoscopic activity was scored using the Simple Endoscopic Score for CD (SES-CD).[16] The characteristics of the 122 included patients and the results of the initial study have been published previously in detail.[14]

The study period ended on week 54 for patients who completed the trial. Since the end of the study, patients were treated according to the clinical need judged by their treating physician. Treatments were the usual drugs used for CD, according to licensed or published doses and frequencies.

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DATA UPDATE

The present study was retrospective and observational, collecting data from the end of the study period of TAILORIX until October 2019. All patients randomized in the TAILORIX trial were eligible regardless of randomization arm. Data from patients were updated retrospectively through a standardized form from week 54 in patients who completed the study period and from the date of early termination for the others. Patients with an absence of follow-up data since the end of the original TAILORIX trial were not included in the present study.

The inclusion date of the present study corresponded to week 54 of the TAILORIX trial. The following events and their dates were collected : dose, frequency and duration of infliximab and azathioprine since inclusion, need for a new systemic CD treatment, major abdominal surgery, anal surgery, hospitalization related to CD, occurrence of serious adverse events, and death.

FOLLOW-UP EVALUATION AND OUTCOMES

Follow-up evaluation started at the end of the initial trial. During this follow-up period, the following events and their dates were collected : major abdominal surgery, anal surgery, hospitalization, and/or a need for a new systemic CD treatment (including steroids, immunosuppressants, and biologies). Treatments given at inclusion (infliximab and azathioprine) in the initial study were not considered as new systemic CD treatments given during the follow-up period even if they were discontinued, restarted, and/or optimized. In patients who did not experience any event, follow-up evaluation was censored in October 2019.

Patients were divided into 2 groups if they reached the TAILORIX primary end point or not. The outcomes of both groups were compared. The primary outcome of the present study was to compare rates of progression- free survival in the 2 groups. CD progression was defined by occurrence of the first following event during the follow-up period : major abdominal surgery, anal surgery, hospitalization, or the need for a new systemic CD treatment. We also compared each individual component of the composite primary end point (luminal surgery, anal surgery, hospitalization, and the need for a new systemic CD treatment) between the 2 groups.

Other secondary outcomes were as follows: (1) the proportion of patients still receiving infliximab therapy at the end of the follow-up evaluation; (2) the proportion of patients with infliximab intensification; (3) the rate of adverse events in the whole cohort; and (4) rates of progression-free CD survival between patients who achieved complete mucosal healing at week 54 (defined as SES-CD of 0) compared with those with SES-CD of 1 or higher; and (5) factors associated with CD progression during the follow-up period.

STATISTICAL ANALYSIS

Continuous variables were described using means (±SD) or medians (±interquartile range [IQR]), and categoric variables were described using proportions. The Kaplan-Meier method was used to assess the rates of survival without major adverse CD events in the patients included in the long-term

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follow-up cohort. Cox regression methods were used to compare rates of major adverse CD outcomes between patients who did and did not achieve clinical and endoscopic remission at 1 year. A Cox regression method was conducted for assessing predictive factors of disease-free progression during the follow-up period, including age, sex, smoking status, disease duration, CD location and behavior, achievement of the TAILORIX primary objective, and CRP levels, fecal Calprotectin levels, and SES-CD at inclusion in the follow-up study. For assessing disease-free progression, patient follow-up evaluation was censored on the date of either the first adverse event or of the last follow-up visit in patients with no events (right-censored), A P value less than .05 was considered statistically significant. Statistical analysis was performed using Stata 14 software (StataCorp LP, College Station, TX).

Results

STUDY POPULATION

Follow-up data from 95 of the 122 (78%) patients included in the TAILORIX trial were available and analyzed in the present study. The 27 remaining patients from the original TAILORIX population were not included because of the absence of follow-up data.

The baseline TAILORIX characteristics of the 95 patients included in the present study are provided in Table 1.

Table 1. *Baseline Patient Demographics and Clinical Characteristics of the 95 Patients Included in the TAILORIX Trial With Follow-Up Data Available*

Characteristic	
Female sex, n (%)	59 (62)
Mean age, y (SD)	37.5 (15.5)
Median disease duration at inclusion, *mo* (IQR)	4.2 (1.0-56.6)
Median follow-up duration since the end of the TAILORIX study period, *mo* (IQR)	64.2 (57.6-69.9)
Previous surgery, n (%)	12 (13)
Current smoker, n (%)	25 (26)
CD location[24] at inclusion, n (%)	
L1 (ileal)	22 (23)
L2 (colonic)	17(18)
L3 (ileocolonic)	56 (59)
Perianal	28 (29)
CD phenotype[24] at inclusion, n (%)	
B1 (inflammatory)	71 (75)
B2 (Stricturing)	15 (16)
B3 (penetrating)	9(9)
Mean CDAI score (±SD)	291.7 (±76.5)
Mean CRP level, *mg* (±SD)	29.9 (±34.7)
Mean SES-CD score, *mg* (±SD)	16.1 (±4.2)

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CD, Crohn's disease ; CDAI, Crohn's disease activity index ; CRP, C-reactive protein ; IQR, interquartile range ; SES-CD, simplified endoscopic score of Crohn's disease ; TAILORIX, Tailored Treatment With Infliximab for Active Cron's Disease.

DESCRIPTION OF FOLLOW-UP EVALUATION

Forty-five of the 95 (47%) patients analyzed in the present study achieved the TAILORIX primary end point and 50 (53%) did not. At inclusion in the present follow-up study the mean CDAI score was lower in the 45 patients who achieved the primary end point of the trial than in the 50 patients who did not (65.8; SD, ±60.1; and 161.5; SD, ±96.8; respectively, P < .01) (Table 2), while the mean CRP level, fecal Calprotectin level, and SED-CD scores at week 54 were not significantly different between the 2 groups (Table 2). Complete mucosal healing at week 54, defined by SES-CD of 0, was achieved in 17 of 45 (38%) patients who achieved the TAILORIX primary end point and in 28 of 50 (56%) patients who did not (P = .10).

Overall, 45 (47%) patients had complete mucosal healing at week 54. The mean SES-CD was 4.8 (SD, ±4.9) in the 50 patients with SES-CD greater than 0.

The median follow-up duration since the end of the study period was 64.2 mo (IQR, 57.6-69.9 mo). The flowchart of patients included in the long-term follow-up TAILORIX study is presented in Figure 1. Since week 54 after randomization, infliximab was intensified in 31 (33%) patients, after a median of 13.2 months (IQR, 8.4-21.6 mo). In the 84 (88%) patients still receiving infliximab at the end of the study period, rates of infliximab persistence at 1, 3, and 5 years were 93%, 72%, and 55%, respectively.

Fifteen adverse events were reported in 15 patients during the follow-up evaluation including 8 infections requiring hospitalization (4 respiratory infections, 1 acute cholecystitis, 1 cystitis, 1 erysipelas, and 1 varicella zoster infection), 1 basocellular cancer, and 1 high-grade dysplasia of the cervix. One death occurred from cardiac arrest : a 53-year-old man in whom cardiac arrest occurred in 2016 and infliximab was stopped at this time. The patient received azathioprine as maintenance and died after a second cardiac arrest in 2019.

Table 2. *Crohn's Disease Activity Parameters at Inclusion in the Follow-Up Study According to the TAILORIX Primary End Point*

Characteristic	Patients who reached the study primary end point (n = 45)	Patients who did not reach the study primary end point (n = 50)
Mean CDAI score (±SD)	65.8 (±60.5)	161.5 (±96.8)[a]
Mean CRP level, *mg* (±SD)	3.7 (±3.6)	4.4 (±4.7)
Mean fecal Calprotectin level (±SD)	295.5 (±304.9)	317.2 (±387.8)
Mean SES-CD score, *mg* (±SD)	1.8 (±2.6)	2.9 (±5.1)

CDAI, Crohn's disease activity index ; CRP, C-reactive protein ; SES-CD, simplified endoscopic score of Crohn's disease ; TAILORIX, Tailored Treatment With Infliximab for Active Cron's Disease.
[a] *P* < .01.

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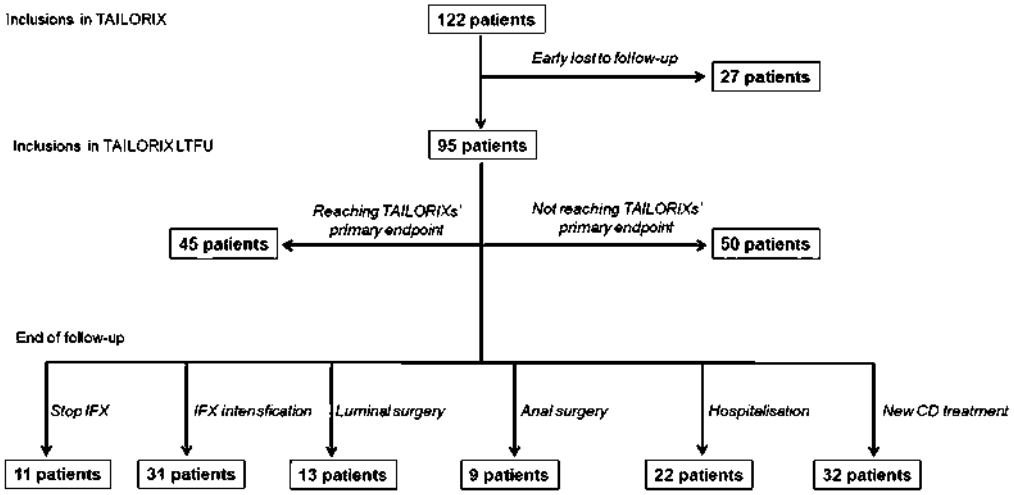
Figure 1. *Flowchart of patients included in the long-term follow-up TAILORIX study. CD, Crohn's disease ; IFX, infliximab; LTFU, long-term follow-up ; TAI- LORIX, Tailored Treatment With Infliximab for Active Cron's Disease.*



CROHN'S DISEASE PROGRESSION

Rates of progression-free survival (defined by any of the following events during follow-up evaluation: luminal surgery, anal surgery, hospitalization related to CD, or the need for a new systemic CD treatment including steroids, immunosuppressants, or biologies) at 1, 3, and 5 years were 82% (95% CI, 88-73), 62% (95% CI, 70-52), and 50% (95% CI, 59-38), respectively.

Progression-free survival rates were similar in patients who achieved the TAILORIX primary end point compared with those who did not: 86% (95% CI, 93-72) and 91% (95% CI, 96-78) at 1 year, 70% (95% CI, 81-55) and 70% (95% CI, 80-55) at 3 years, and 64% (95% CI, 76-48) and 61% (95% CI, 74-45) at 5 years (P = .83), respectively (Figure 2).

Patients with complete mucosal healing (SES-CD, 0) also had similar progression-free survival rates to patients with a SES-CD of 1 or greater (P = .09) (Figure 3). Rates of progression-free survival at 1 and 3 years were 95% (95% CI, 98-82) and 76% (95% CI, 86-60) in patients with SES-CD of 0, and 75% (95% CI, 85-65) and 51% (95% CI, 64-38) in those with SES-CD of 1 or greater, respectively.

Figure 2. *Kaplan-Meier survival curve of Crohn's disease (CD) progression-free survival in patients who reached {black curve) or did not reach {red curve) the TAILORIX primary end point of sustained corticosteroid-free remission (CD activity index, <150) between weeks 22 and 54, associated with an absence of ulcers on Ileocolonoscopy at week 54 without bowel resection, abscess, or new fistula. The median duration of follow-up evaluation was 52 months (IQR 22.2-77.7 mo). SDR, steroid-free deep remission.*

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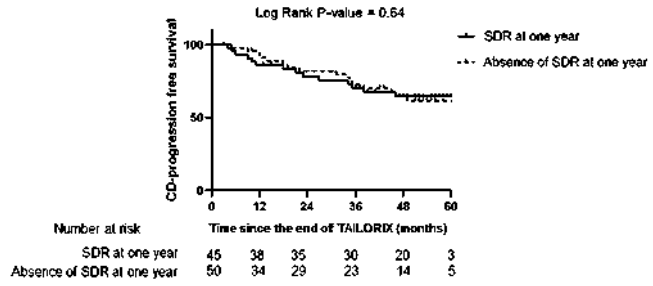
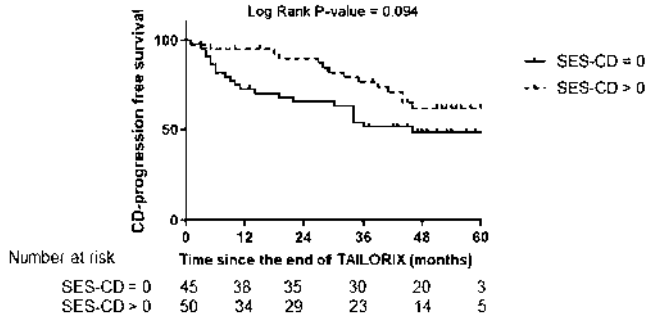


Figure 3. *Kaplan-Meier survival curve of Crohn's disease (CD) progression-free survival in patients with complete mucosal healing (Simple Endoscopic Score for CD [SES-CD], 0 ; black curve) and with a SES-CD of 1 or greater {red curve) at week 54. The median duration of follow-up evaluation was 52 months (IQR 22.2-77.7 mo). TAILORIX, Tailored Treatment With Infliximab for Active Cron's Disease.*



CROHN'S DISEASE-RELATED HOSPITALIZATIONS

Eleven (14%) patients underwent major abdominal surgery, including 2 patients with 2 surgeries, 4 patients underwent ileocecal resection, 3 patients underwent right hemicolectomies, 1 patient underwent a total colectomy with a terminal ileostoma, and 1 patient underwent a segmental enterectomy. This information was not available for 5 patients. Survival rates without major abdominal surgery at 1, 3, and 5 years were 98% (95% Cl, 100-83), 92% (95% Cl, 97-78), and 86% (95% Cl, 93-70), respectively, and were not different between patients who reached the primary end point of the study and those who did not (97%, 93%, and 87%, and 96%, 90%, and 82%, respectively ; P = .42) (Figure 4A).

Nine (9%) patients underwent anal surgery, including 1 patient with 3 surgeries and 2 patients with 2 surgeries. Survival rates without anal surgery were 95% (95% CI, 98-80), 87% (95% CI, 94-70), and 85% (95% CI, 0-74) at 1, 3, and 5 years, respectively, and were similar in patients who reached the primary end point at week 54 and those who did not (93%, 86%, and 86% vs 96%, 88%, and 85%, respectively ; P = .95) (Figure 4B).

Twenty-two (23%) patients were hospitalized during the follow-up evaluation. Hospitalization-free survival rates were 93% (95% CI, 97-78), 83% (95% CI, 90-67), and 75% (95% CI, 92-60) at 1, 3, and 5 years, respectively. Patients who reached the primary end point at week 54 (n = 45; 47%) had similar

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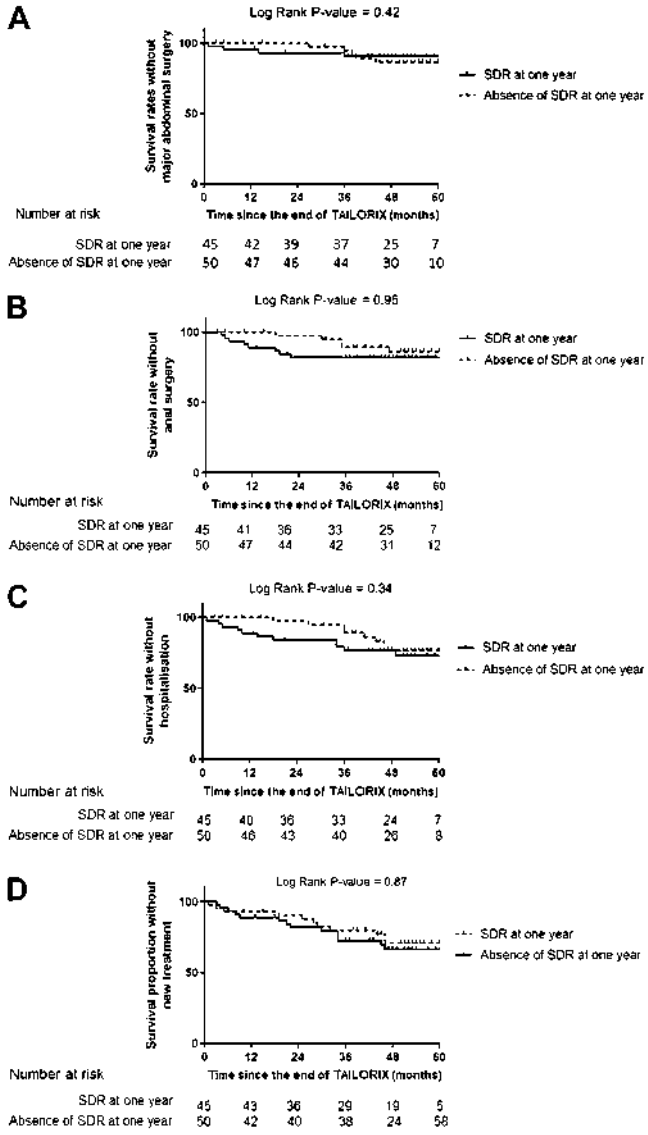
rates of hospitalization-free survival to patients who did not at 1, 3, and 5 years (90%, 81%, and 78% vs 92%, 81%, and 69%, respectively; P = .34) (Figure 4C).

Figure 4. *Kaplan-Meier survival curve of (A) major abdominal surgery-free survival, (B) perineal surgery free-survival, (C) hospitalization-free survival, and (D) systemic Crohn's disease treatment-free survival in patients who reached (black curve) or did not reach (red curve) corticosteroid-free remission between weeks 22 and 54, associated with the absence of ulcers on Ileocolonoscopy at week 54. The median duration of follow-up evaluation was 52 months (IQR 22.2-77.7 mo). SDR, steroid-free deep remission. TAILORIX, Tailored Treatment With Infliximab for Active Cron's Disease.*



FACTORS ASSOCIATED WITH CROHN'S DISEASE PROGRESSION

CD progression during the follow-up period was not associated with a CRP level greater than 5 mg/L (hazard ratio [HR], 2.022; 95% Cl, 0.750-5.449; P = .164), age older than 30 years (HR, 1.522; 95% Cl,

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0.726-3.190; P = .266), active smoking (HR, 0.628; 95% Cl, 0.287-1.378; P = .146), or Bl phenotype (HR, 1.051; 95% Cl, 0.481-2.295; P = .899). Nonachievement of the TAILORIX primary objective was not associated with disease progression (HR, 0.861; 95% Cl, 0.4289-1.7306 ; P = .676).

Discussion

In this prospective cohort of early CD biologic-naive patients who started infliximab in combination therapy, we found that achieving a single time of clinical and endoscopic remission was not associated with better disease outcomes with a follow-up period of longer than 4 years. It was associated with similar rates of surgery, hospitalization, and the need for new systemic treatment than for patients who did not reach this recommended combined end point. Similar results were observed when we compared patients with and without complete mucosal healing, defined by a SES- CD of 0. Importantly, we reported a low rate of luminal surgery in the entire cohort (14% at 5 years after diagnosis), confirming that the early use of combination therapy with anti-TNF and conventional immunosuppressants provides marked improvement of CD activity, with a low rate of significant CD complications.

The STRIDE 2 program recommended deep remission, defined by endoscopic and clinical remission, as the preferred target for the treatment of CD.[6] However, there is no validated or standardized definition of this endoscopic goal. Among the validated endoscopic indices for CD, none have been validated specifically to determine remission. In the systematic review by Khanna et al,[17] which aimed to identify the most appropriate index for defining mucosal healing in clinical trials, the investigators concluded that further validation was needed. A specific score for defining endoscopic remission in CD is currently in development (NCT03498625 and NCT03487900). "

The long-term impact of achieving clinical and endoscopic remission on the history of CD has been studied in a few cohorts. A meta-analysis of 10 studies published in 2016 found that mucosal healing was associated significantly with long-term clinical remission with an odds ratio of 2.80 (95% Cl, 1.91-4.10).[8] In a recent retrospective single-center cohort study including 84 CD patients who received biologic therapy and achieved endoscopic remission defined by a Crohn's disease endoscopic index of severity less than 4, Yzet et al[9] compared the outcomes of patients with complete mucosal healing and those with remnant mucosal inflammation. Treatment failure was lower in patients with no endoscopic lesions compared with the others (P = .045). In the long-term follow-up evaluation of the Effect of Tight Control Management on Crohn's Disease trial with a median duration of 3.02 years, Ungaro et al[10] reported that at the end of the 48-week study period, patients in deep remission had significantly fewer major CD outcomes, defined by the occurrence of new internal fistulas or abscesses, strictures, perianal fistulas or abscesses, hospitalization, or surgery. Unlike the present study, they found that clinical remission was associated with a decreased risk of disease progression on multivariate analysis, suggesting that clinical remission is per se a satisfactory target in CD. It is important to note that these results were limited by missing follow-up data from half the patients originally randomized in the trial.

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Data on the impact of endoscopic remission on the long-term risk of CD major abdominal surgery are conflicting. In the experience from Leuven evaluating infliximab, surgical rates were not different between patients who achieved complete or partial endoscopic remission at a single time point.[18] In a recent meta-analysis, major abdominal surgery-free survival rates at 1 and 5 years after diagnosis were 81.3% and 72%, respectively, with a decreased risk over time.[19] Fewer bowel resections also were observed in the National Swedish registry in the past 2 decades, corresponding to the biologic era.[20] When pooling the 3 studies that included long-term data on surgical outcome, mucosal healing did not influence surgery-free rates (odds ra-tio, 2.22; 95% Cl, 0.86-5.69).[11-13] However, these studies used various definitions of endoscopic remission and had a limited follow-up duration. In the present study, rates of survival without major abdominal surgery at 1 and 5 years were 98% and 86%, suggesting that early combination therapy had a significant impact in biologic-naive early CD patients. In the Risk Stratification and Identification of Immu- nogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease cohort study, including 913 pediatric patients with newly diagnosed CD from 28 sites in North America, it was reported that patients who received early anti-TNFα therapy were less likely to have penetrating complications.[21] In the Randomised Evaluation of an Algorithm for Crohn's Treatment trial, patients treated with early combined immunosuppression had a reduction in major adverse outcomes, such as surgery.[22] These findings suggest a more flexible treat-to-target strategy in CD, recommending endoscopic and clinical remission in early diagnosed patients and less stringent objectives in those with more refractory or advanced disease. Recently, the Selecting End Points for Disease-Modification Trials initiative, involving experts from the International Organization for the Study of Inflammatory Bowel Diseases, proposed goals to achieve in disease-modification trials for preventing disease progression.[23] These future disease-modification trials will evaluate if early use of highly effective treatment in patients with a high risk for disease progression may decrease the impact of CD on the patient's life and the risk of disease complications.

We acknowledge that the present study had several limitations. Follow-up data were collected retrospectively. Because the present study was built on the TAILORIX trial, the sample size could not be changed and was not powered to compare long-term progression-free survival between the 2 groups of patients. Prediction of follow-up evaluation was based on a single endoscopic assessment as well as in cohort studies published to date. Conversely, the present study had several strengths. The present cohort of biologic-naive adults with early active CD who received infliximab in combination with an immuno-suppressant included in a prospective clinical trial was well characterized and homogeneous. Ileocolonos- copies performed at week 54 were read centrally. Finally, the follow-up data collected in 78% of patients for a median duration of at least 4 years were robust, including hospitalizations and surgeries, with limited risk of evaluation bias.

In conclusion, we observed that neither the association of clinical and endoscopic remission nor complete mucosal healing were associated with better disease outcomes. Our data support the early use of powerful treatments to modify the history of CD and also suggest that a more flexible approach of the treat-to-target concept should be taken in daily practice.

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