Improvements in the Long-Term Outcome of Crohn's Disease Over the Past Two Decades and the Relation to Changes in Medical Management

Improvements in the Long-Term Outcome of Crohn's Disease Over the Past Two Decades and the Relation to Changes in Medical Management: Results from the Population-Based IBDSL Cohort

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OBJECTIVES: **Medical treatment options and strategies for Crohn's disease (CD) have changed over the past decades. To assess its impact, we studied the evolution of the long-term disease outcome in the Dutch Inflammatory Bowel Disease South Limburg (IBDSL) cohort.**

METHODS: **In total, 1,162 CD patients were included. Three eras were distinguished: 1991–1998 (*n*=316), 1999–2005 (*n*=387), and 2006–2011 (*n*=459), and patients were followed until 2014. Medication exposure and the rates of hospitalization, surgery, and phenotype progression were estimated using Kaplan–Meier survival analyses and compared between eras by multivariable Cox regression models. Second, propensity score matching was used to assess the relation between medication use and the long-term outcome.**

RESULTS: **Over time, the immunomodulator exposure rate increased from 30.6% in the era 1991–1998 to 70.8% in the era 2006–2011 at 5 years. Similar, biological exposure increased from 3.1% (era 1991–1998) to 41.2% (era 2006–2011). In parallel, the hospitalization rate attenuated from 65.9% to 44.2% and the surgery rate from 42.9% to 17.4% at 5 years, respectively (both *P*<0.01). Progression to a complicated phenotype has not changed over time (21.2% in the era 1991–1998 vs. 21.3% in the era 2006–2011, *P*=0.93). Immunomodulator users had a similar risk of hospitalization, surgery, or phenotype progression as propensity score-matched nonusers (*P*>0.05 for all analyses). Similar results were found for biological users (*P*>0.05 for all analyses).**

CONCLUSIONS: **Between 1991 and 2014, the hospitalization and surgery rates decreased, whereas progression to complicated disease is still common in CD. These improvements were not significantly related to the use of immunomodulators and biologicals.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, characterized by periods of active inflammation, alternated with periods of remission (1–4). The prognosis of CD patients is heterogeneous and hard to predict early in the disease course (2,5). The current goal of CD treatment is to achieve and maintain steroid-free clinical remission and to prevent the development of structural bowel damage in the long term, such as fistulas and abscesses, intestinal strictures, and surgery (6–8).

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The long-term outcome of CD is preferably studied in population-based cohorts, as these comprise an unselected patient population and therefore have good external validity (9–11). Current knowledge about the prognosis of CD is mainly based on data derived from such cohorts. A change in the clinical behavior of CD (i.e., progression from an inflammatory to a stricturing or penetrating phenotype) occurs in 53–62% of the patients within 10 years after initial diagnosis (1,12–14) and surgery is required in ~50% of cases within 10 years (1,2,15,16). These numbers illustrate that a substantial part of the CD population has an unfavorable long-term outcome.

Most outcome data derive from studies that recruited patients several decades ago, in an era in which treatment options and strategies were different from now. Population-based studies have shown that the use of 5-aminosalicylic acid has decreased over the past two decades, whereas immunosuppressive therapy is more often prescribed (17,18). A milestone in CD management was the extension of the therapeutic armamentarium with anti-tumor necrosis factor-α (TNFα) agents. In the Netherlands, infliximab was the first anti-TNFα agent registered in 1999 (19,20), followed by the registration of adalimumab in 2007 (21,22). Randomized-controlled trials and meta-analyses have shown the efficacy of immunomodulators and anti-TNFα agents in inducing and maintaining disease remission (23–26). Whether the adoption of these treatments resulted in an improved long-term outcome of CD in general is important information for clinicians and patients, as well as for health-care planning.

The primary aim of this study was to evaluate changes in the medical management and long-term outcome of CD between 1991 and 2014 in a large, well-characterized Dutch population-based cohort of CD patients. The secondary aim was to assess the relation between the use of immunomodulators and anti-TNFα agents and the long-term disease outcome.

METHODS

Study population and design

The Inflammatory Bowel Disease South Limburg (IBDSL) cohort comprises adult IBD patients who were diagnosed between 1991 and 2011 in the South Limburg area of the Netherlands. The South Limburg area is a well-defined geographic region in the southeast of the Netherlands, bordered by Belgium and Germany and is narrowly connected to the rest of the Netherlands in the north. The relative geographic isolation results in a low net migration rate of 2.1 per 1,000 inhabitants per year (27), favoring population-based research. A recent completeness check showed that over 93% of all eligible IBD patients in the South Limburg area is currently registered in the IBDSL cohort. For detailed information on the IBDSL cohort, we refer to the cohort profile (28).

The present study included all 1,162 CD patients registered in the IBDSL cohort. Patients were followed from the date of diagnosis to the end of data collection (2014), date of emigration, or date of death.

The primary aims of the study were to assess changes in the medical management and long-term outcome of CD between 1991 and 2014. Disease outcome was studied in terms of (i) disease progression from an inflammatory phenotype to either a stricturing or penetrating phenotype (i.e., phenotype progression or change in disease behavior), (ii) hospitalization, (iii) surgery, and (iv) cumulative corticosteroid (CS) use. The latter was assessed as the total number of days and the total dosage of CS use within the first year and first 5 years of the disease course. As a secondary aim, the relation between the use of immunomodulators and anti-TNFα agents and the long-term disease outcome was assessed.

To study the evolution of the aforementioned end points over time, three time cohorts were distinguished, based on the year of CD diagnosis: era '91–'98 (CD diagnosis between 1991 and 1998), era '99–'05 (CD diagnosis between 1999 and 2005), and era '06–'11 (CD diagnosis between 2006 and 2011). Era '91–'98 can be referred to as the "prebiological era", as the first biological agent (infliximab) was registered in 1999 for CD in the Netherlands. The biological era was further equally divided in two subsequent cohorts (eras '99–'05 and '06–'11).

This study was approved by the Medical Ethics Committee of the Maastricht University Medical Centre (NL31636.068.10) and the IBDSL cohort is registered in ClinicalTrial.gov (NCT02130349).

Data collection and definitions

Demographic data, as well as clinical data on the occurrence of phenotype progression, hospitalization, and surgery, were collected from medical records by scrutinizing patient files using a standardized case report form. Phenotype progression was defined as the development of either intestinal strictures (B2) or internal fistulas or abscesses (B3) in patients with an inflammatory phenotype (B1), according to the Montreal consensus (29). To facilitate data comparison with older studies, disease behavior was also classified according to the Vienna consensus (30). Hospitalization was defined as a hospital admission for CD-related complaints, CD-related surgery, or both. Elective admissions for endoscopy procedures or regular drug administration were excluded. Surgery was defined as the resection of a part of the bowel because of intestinal inflammation or a CD-related complication (such as a stenosis, fistula, or perforation). Perianal surgeries were not included in the analyses.

CS treatment was defined as the use of a systemic CS, such as prednisone. CSs that have a local effect, such as budesonide, were not considered in this study. Dates of treatment initiation, cessation, and dose adjustments were retrieved from the medical records. In case no comment on the tapering regimen was specified, and CSs were not used by the patient at the next visit, a standard tapering regimen of 5 mg per week was considered as from the last visit in which CS use was mentioned. The total cumulative dosage and the total number of days were determined including all CS prescriptions within 1 and 5 years after diagnosis. These analyses were performed only in patients having such a long follow-up to avoid extrapolation of the data. Extrapolation could lead to an overestimation of the total CS use in more recently diagnosed patients, as follow-up is shortest in this group and the probability of requiring CS courses attenuates during disease course (31).

Immunomodulators comprised azathioprine, mercaptopurine, tioguanine, and methotrexate, and anti-TNFα agents considered were both agents registered in the Netherlands for CD (infliximab and adalimumab). Dates of treatment initiation and cessation were retrieved from the medical records.

Statistical analyses

Continuous data were presented as means with s.d. in case of parametric data and as medians with interquartile range (IQR) in case of nonparametric data. Data were subsequently compared between eras by one-way analysis of variance or Kruskal–Wallis test, respectively. Dichotomous and nominal data were presented as absolute numbers and percentages and compared by χ^2 tests.

The cumulative probability of event occurrence (phenotype progression, hospitalization, and surgery), as well as the cumulative probability of exposure to immunomodulators and anti-TNFα agents, was estimated by Kaplan–Meier survival statistics to adjust for differences in follow-up between patients. Differences in cumulative probabilities between groups were determined by using the log-rank test. In addition, a multivariable Cox regression analysis was used to model the association between the era of diagnosis and the event of interest, adjusting for known clinical confounders. Age at diagnosis, sex, disease location at diagnosis, disease behavior at diagnosis, and the era of diagnosis were included in all multivariable models. Differences in hazards between eras were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). The proportional hazards assumption was tested for all variables by adding a time-dependent interaction term to the specific model. Time dependency was observed for the outcomes hospitalization and surgery. Therefore, two models were created: one for estimating the outcome risk at diagnosis (defined as within 1 month after diagnosis) and a second model for estimating the outcome risk during follow-up (i.e., beyond 1 month after diagnosis). This approach was used because one model would lead to an underestimation of the early and an overestimation of the late risk (32) and because a difference in outcome risk between diagnosis and follow-up is clinically relevant.

As treatment strategies have changed over time, we subsequently studied the relation between the use of immunomodulators and anti-TNFα agents and the long-term disease outcome. First, we designed propensity score models in which medication users were matched to nonusers. Second, patients were followed as from the date therapy was started (users) or a corresponding matched index date (nonusers). By using this approach, confounding by indication (33) and immune-time bias (34) were minimized, respectively. Separate models were created for immunomodulators and anti-TNFα agents for each outcome (hospitalization risk, phenotype progression risk, and surgery risk). We defined "users" as patients with a first immunomodulator or anti-TNFα prescription within 2 years after CD diagnosis. The period of 2 years was chosen because the temporal changes in the long-term outcome were found to occur within this time span. Users and nonusers were required to have a B1 phenotype at the index date for the analyses on phenotype progression and to be surgery naive for the analyses on surgery risk. First, a propensity score was generated for every patient, using binary logistic regression with start immunomodulator or anti-TNFα therapy within 2 years as dependent variable. Parameters known or suspected to be associated with receiving the specific therapy as well as with the risk of the specific outcome were included, i.e., age at diagnosis, sex, and early course characteristics (i.e., disease location, behavior, hospitalization, CS use, and immunomodulator use (anti-TNFα models only) within 3 months after diagnosis). Subsequently, medication users were matched to nonusers based on the propensity score using a 1:1 neighborhood matching method and a caliper of 0.20. The first 3 months after the index date were censored, as this period is necessary to reach full therapy efficacy and events within this time window are likely the result of reverse causation. Follow-up ended when the event of interest occurred, therapy was stopped (including six months of lag time), or the end of data collection was reached. The cumulative probability of event occurrence was studied by using Kaplan–Meier survival analyses and Cox regression analyses. Results were adjusted for differences in cumulative days of CS use before the index date between users and nonusers by including this parameter in the Cox regression models. In order to evaluate the robustness of the model, sensitivity analyses were conducted in which cutoff values of 6 and 12 months after CD diagnosis were used for the definition of "user". Results of these analyses are presented in **Supplementary Table S1**.

Two-sided *P* values of 0.05 were considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0. (IBM, Armonk, NY).

RESULTS

Patient population

In total, 1,162 CD patients were included in this study. Era '91–'98 comprised 316 patients, era '99–'05 comprised 387 patients, and era '06–'11 comprised 459 patients. These patients were followed for a median of 16.1 (IQR 10.3–19.3), 9.7 (IQR 8.0–11.8), and 4.2 (IQR 2.9–5.6) years, respectively. Patient characteristics are presented in **Table 1**.

Medical therapy

Immunomodulator treatment was ever used by 704 CD patients (60.6%). The cumulative 5-year exposure rate increased from 30.6% (era '91–'98) to 56.7% (era '99–'05) to 70.8% (era '06–'11) ($P<0.01$), see **Figure 1a**. In line, the time to the first prescription decreased, reflected by an increasing number of patients who commenced treatment within the first year of disease: 9.1% (era '91–'98), 31.0% (era '99–'05), and 49.5% (era '06–'11) ($P<0.01$).

Anti-TNFα therapy was ever used by 379 CD patients (32.6%). It became available during the course of patients diagnosed in the era '91–'98, whereas it was available as from diagnosis in patients diagnosed in the eras '99–'05 and '06–'11. The cumulative 5-year exposure to anti-TNFα treatment increased from 3.1% (era '91–'98) to 19.9% (era '99–'05) to 41.2% (era '06–'11) ($P<0.01$), see **Figure 1b**. As with immunomodulators, a decrease in the time to first exposure was observed, reflected by an increase in the

Table 1. Patient characteristics of Crohn's disease patients in the IBDSL cohort

		Era 1991–1998 (*N*=316)	Era 1999–2005 (*N*=387)	Era 2006–2011 (*N*=459)	
Age[a]	Mean (s.d.)	36.2 (15.8)	37.5 (15.8)	38.8 (16.1)	*P*=0.08
Sex, male	*N* (%)	121 (38.3)	137 (35.4)	176 (38.3)	*P*=0.63
Current smoker[a,b]	*N* (%)	141 (55.3)	178 (49.4)	175 (46.3)	*P*=0.09
Disease duration in years	Median (IQR)	16.1 (10.3–19.3)	9.7 (8.0–11.8)	4.2 (2.9–5.6)	*P*<0.01
Disease location[a,c]					*P*=0.04
L1, ileal location	*N* (%)	155 (49.1)	170 (43.9)	175 (38.1)	
L2, colon location	*N* (%)	94 (29.7)	127 (32.8)	150 (32.7)	
L3, ileocolon location	*N* (%)	63 (19.9)	80 (20.7)	124 (27.0)	
L4, only upper GI location	*N* (%)	4 (1.3)	10 (2.6)	10 (2.2)	
Perianal disease (+*p*)[a]	*N* (%)	30 (9.5)	27 (7.0)	37 (8.1)	*P*=0.48
Upper GI location (+*L4*)[a]	*N* (%)	21 (6.6)	43 (11.1)	60 (13.1)	*P*=0.02

GI, gastrointestinal; IBDSL, Inflammatory Bowel Disease South Limburg; IQR, interquartile range.
[a]At diagnosis.
[b]Smoking status was not available in 169 cases.
[c]Disease location according to the Montreal consensus.

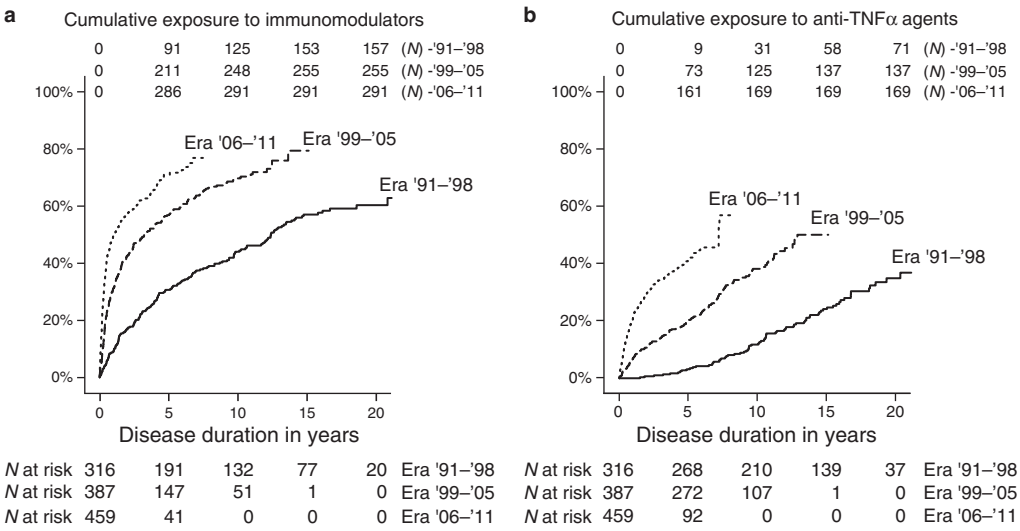

Figure 1. The cumulative exposures to different treatment modalities among the three eras. (**a**) Immunomodulators and (**b**) anti-TNFα agents. The cumulative exposure to immunomodulators (**a**) and anti-tumor necrosis factor-α (TNF-α) agents (**b**) among the three eras. Era '91–'98, patients diagnosed between 1991 and 1998; era '99–'05, patients diagnosed between 1999 and 2005; era '06–'11, patients diagnosed between 2006 and 2011.

number of patients using anti-TNFα therapy within the first year after diagnosis: 0% (era '91–'98), 7.1% (era '99–'05), and 21.2% (era '06–'11) (*P*<0.01). Even within the biological era (eras '99–'05 and era '06–'11), a 3.2-fold increase in the early use of anti-TNFα therapy (i.e., within 1 year) was observed (adjusted HR (aHR) 3.24; 95% CI 2.10–4.99). Many patients exposed to biological therapy were on combination therapy (anti-TNFα+immunomodulator) at the start of the anti-TNFα agent (43.5%) and in 10.8% an immunomodulator was (re)introduced during biological therapy. In 46.1%, the immunomodulator was withdrawn during follow-up.

Disease behavior

In total, 460 patients (39.6%) had a complicated CD behavior, of whom 205 (17.7%) already at diagnosis (**Figure 2a**). Over time, the number of patients with complicated disease at diagnosis decreased from 24.1% (era '91–'98) to 17.1% (era '99–'05) to 13.8% (era '06–'11) (*P*<0.01). The attenuation was most profound for penetrating disease: from 9.5% in the era '91–'98, to 4.5% in the era '99–'05, and to 3.7% in the era '06–'11 (*P*<0.01). The cumulative 5-year risk of having a complicated behavior was 40.2% in the era '91–'98, 35.1% in the era '99–'05, and 32.1% in the era '06–'11 (*P*=0.06). Progression from B1 to either B2/B3 phenotype

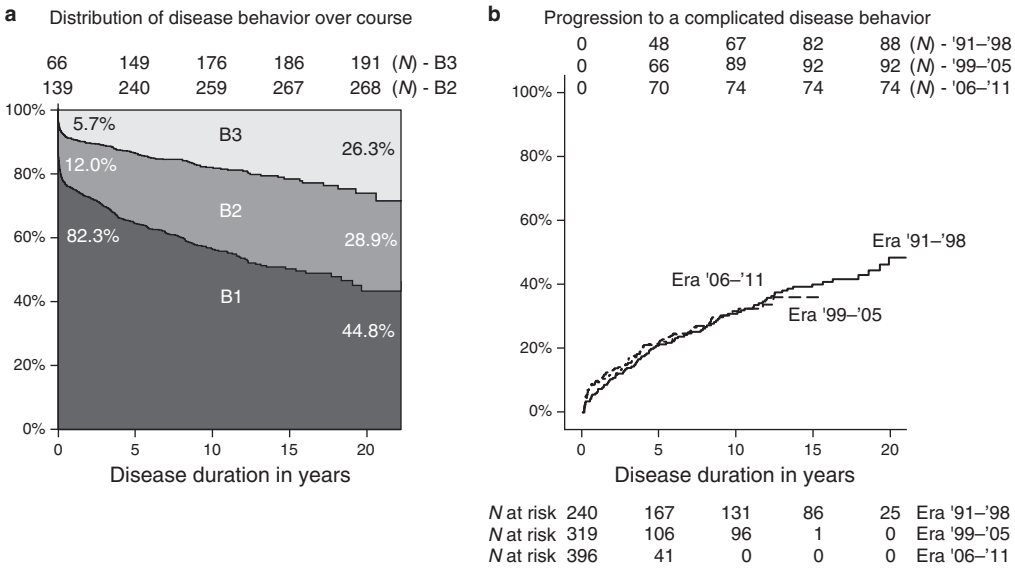

Figure 2. Disease behavior, classified according to the Montreal consensus. (**a**) The distribution of disease behavior over disease course in the full Inflammatory Bowel Disease South Limburg (IBDSL) cohort. (**b**) The cumulative probability of progression from a B1 to either a B2 or B3 behavior in patients with B1 disease at diagnosis, stratified by era of diagnosis. Era '91–'98, patients diagnosed between 1991 and 1998; era '99–'05, patients diagnosed between 1999 and 2005; era '06–'11, patients diagnosed between 2006 and 2011. B1, nonstricturing, nonpenetrating disease; B2, stricturing disease; B3, penetrating disease.

during disease course was observed in 255 patients, corresponding to a cumulative 5-year probability rate of 21.6%. Over time, no change in the progression rate was observed: 21.2% (era '91–'98) vs. 21.7% (era '99–'05) vs. 21.3% (era '06–'11) (P=0.93), see **Figure 2b**. Phenotype progression was found to be associated with an ileal and upper gastrointestinal location of the disease at diagnosis (**Tables 2** and **3**).

In the propensity score model for phenotype progression, 264 immunomodulator users could be matched to 264 nonusers. The cumulative 5-year probability of phenotype progression was 19.0% in users vs. 22.8% in nonusers that did not differ significantly between groups (aHR 1.01; 95% CI 0.60–1.71). For the anti-TNFα analyses, 110 anti-TNFα users could be matched to 110 nonusers, also resulting in a similar cumulative 5-year probability of phenotype progression between groups (21.3% vs. 21.0%, aHR 0.76; 95% CI 0.39–1.48). Results were similar in the sensitivity analyses, with cutoff values of 6 and 12 months for medication use (**Supplementary Table S1**).

Hospitalization

In total, 1221 CD-related hospitalizations took place in 644 patients. Overall, the cumulative 5-year probability of hospitalization attenuated over time, from 65.9% (era '91–'98) to 53.1% (era '99–'05) and to 44.2% (era '06–'11) (P<0.01), see **Figure 3a**. Part of this effect was found to be explained by a decrease in the hospitalization rate at diagnosis: 39.9% in the era '91–'98, 27.0% in the era '99–'05, and 21.2% in the era '06–'11 (P<0.01) (**Table 2**). However, if we only consider patients not hospitalized at diagnosis, the decrease in hospitalization risk remains (**Table 3**). Patients with a complicated phenotype at diagnosis had a higher risk of hospitalization during follow-up. The median number of days admitted per hospitalization decreased from 14.5 days (IQR 10.0–27.0) in the era '91–'98 to 11.0 days (IQR 7.0–18.0) in the era '99–'05 to 8.0 days (IQR 5.0–14.0) in the era '06–'11 (P<0.01). No difference was found in the probability of a rehospitalization within the first 5 years after diagnosis: 34.0% (era '91–'98) vs. 31.5% (era '99–'05) vs. 38.4% (era '06–'11) (P=0.29).

In the propensity score model for hospitalization, 352 immunomodulator users could be matched to 352 nonusers. The cumulative 5-year probability of hospitalization was higher in users than in nonusers (35.6% vs. 27.0%), but did not reach statistical significance (aHR 1.25; 95% CI 0.86–1.80). For anti-TNFα therapy, 168 users could be matched to 168 nonusers and the cumulative 5-year probability of hospitalization was 35.1% in users and 25.1% in nonusers that also did not reach statistical significance (aHR 1.13; 95% CI 0.68–1.87). The sensitivity analyses showed similar results (**Supplementary Table S1**).

Surgery

In total, 361 patients required a total of 456 surgical resections. Surgery type and indication are shown in **Table 4**. Overall, the cumulative 5-year probability of surgery gradually decreased over time, from 42.9% in the era '91–'98 to 26.2% in the era '99–'05, to 17.4% in the era '06–'11 (P<0.01), see **Figure 3b**. Over time, surgeries were less often performed for active, luminal disease, and proportionally more often for stricturing disease (P=0.03). Eighty surgeries were already performed at diagnosis, corresponding to a cumulative probability of 8.0%. Over the past two decades, the probability of undergoing surgery at diagnosis decreased from 17.1% in the era '91–'98 to 7.6% in the era '99–'05 to 2.2% in the era

Table 2. Parameters associated with a complicated phenotype, hospitalization, and surgery at diagnosis

	Risk of having B2 or B3 phenotype at diagnosis		Risk of hospital admission at diagnosis		Risk of surgery at diagnosis	
	Unadjusted hazard ratio	Adjusted hazard ratio	Unadjusted hazard ratio	Adjusted hazard ratio	Unadjusted hazard ratio	Adjusted hazard ratio
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age at diagnosis						
A2, 17–40 years	Ref	Ref	Ref	Ref	Ref	Ref
A3, >40 years	0.92 (0.69–1.23)	0.96 (0.72–1.29)	0.88 (0.70–1.11)	0.97 (0.77–1.22)	1.48 (0.99–2.23)	1.41 (0.93–2.15)
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.88 (0.67–1.17)	0.94 (0.71–1.24)	0.87 (0.70–1.08)	0.90 (0.72–1.12)	0.57 (0.38–0.86)	0.70 (0.47–1.06)
Era						
1991–1998	Ref	Ref	Ref	Ref	Ref	Ref
1999–2005	0.69 (0.50–0.97)	0.71 (0.51–0.98)	0.65 (0.50–0.84)	0.66 (0.51–0.86)	0.43 (0.28–0.68)	0.47 (0.30–0.75)
2006–2011	0.55 (0.40–0.77)	0.56 (0.40–0.79)	0.50 (0.39–0.66)	0.52 (0.40–0.69)	0.12 (0.06–0.24)	0.15 (0.08–0.30)
Disease location at diagnosis						
L1, ileal location	Ref	Ref	Ref	Ref	Ref	Ref
L2, colon location	0.29 (0.19–0.43)	0.30 (0.20–0.46)	0.84 (0.65–1.09)	0.98 (0.75–1.28)	0.12 (0.05–0.25)	0.14 (0.06–0.30)
L3, ileocolon location	0.68 (0.49–0.95)	0.71 (0.51–1.01)	0.94 (0.71–1.24)	1.04 (0.79–1.38)	0.11 (0.05–0.28)	0.15 (0.06–0.37)
L4, only upper GI location	0.65 (0.24–1.76)	0.44 (0.16–1.27)	0.26 (0.06–1.04)	0.25 (0.06–1.05)	0.52 (0.13–2.11)	1.01 (0.20–5.29)
Disease behavior at diagnosis						
B1, inflammatory disease	—	—	Ref	Ref	Ref	Ref
B2, stricturing disease	—	—	1.22 (0.90–1.64)	1.15 (0.85–1.57)	1.58 (0.94–2.64)	1.18 (0.70–2.00)
B3, penetrating disease	—	—	2.20 (1.60–3.04)	1.90 (1.36–2.64)	2.27 (1.25–4.13)	1.26 (0.68–2.33)
Perianal disease at diagnosis						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.24 (0.78–1.97)	1.36 (0.85–2.16)	1.02 (0.69–1.52)	1.01 (0.68–1.50)	0.50 (0.19–1.37)	0.68 (0.25–1.85)
Upper GI location at diagnosis						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.64 (1.13–2.39)	1.68 (1.13–2.50)	1.07 (0.76–1.50)	1.29 (0.90–1.84)	0.67 (0.31–1.46)	0.57 (0.23–1.41)

95% CI, 95% confidence interval; GI, gastrointestinal; HR hazard ratio; Ref, reference category.

'06–'11 (P<0.01). A majority of these surgical resections were performed for inflammatory disease (76.3%), either before or shortly after the diagnosis was established, whereas 17.5% was operated for stricturing disease and 6.3% for penetrating disease at that time. No difference herein was observed between eras (P=0.65). Results regarding the decreasing surgery risk were concordant when only patients were considered who were not operated at diagnosis: the cumulative 5-year probability in these patients was 33.2% in the era '91–'98, 20.8% in the era '99–'05, and 15.9% in the era '06–'11 (P<0.01). Besides era of diagnosis, an ileal disease location was significantly associated with an increased risk of surgery at both diagnosis and during follow-up, and a complicated phenotype at diagnosis was found to be associated with surgery during follow-up (**Tables 2** and **3**).

In the propensity score model for surgery, 315 immunomodulator users could be matched to 315 nonusers and the cumulative 5-year probability of surgery was similar between groups (19.2% vs. 22.8%, aHR 0.72; 95% CI 0.45–1.16, respectively). In the anti-TNFα analyses, 159 users could be matched to 159 nonusers and the cumulative 5-year probability of surgery was also found to be similar between groups (24.3% vs. 21.9%, aHR 1.07; 95% CI 0.56–2.04). Results were concordant in the sensitivity analyses (**Supplementary Table S1**).

Cumulative CS use

CS therapy was ever prescribed to 665 patients (57.2%). The cumulative 5-year exposure was 50.0% in the era '91–'98, 56.2% in the era '99–'05, and 54.8% in the era '06–'11 (P=0.20). Although

Table 3. Parameters associated with a complicated phenotype, hospitalization, and surgery during follow-up

	Risk of progression from B1 to B2 or B3 phenotype		Risk of hospitalization		Risk of surgery	
	Unadjusted hazard ratio	Adjusted hazard ratio	Unadjusted hazard ratio	Adjusted hazard ratio	Unadjusted hazard ratio	Adjusted hazard ratio
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age at diagnosis						
A2, 17–40 years	Ref	Ref	Ref	Ref	Ref	Ref
A3, >40 years	0.85 (0.66–1.11)	0.81 (0.62–1.05)	0.77 (0.61–0.97)	0.95 (0.75–1.22)	0.88 (0.68–1.14)	1.12 (0.86–1.46)
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.95 (0.74–1.23)	0.95 (0.73–1.23)	1.09 (0.86–1.37)	1.10 (0.87–1.40)	0.87 (0.68–1.12)	0.97 (0.76–1.25)
Era						
1991–1998	Ref	Ref	Ref	Ref	Ref	Ref
1999–2005	1.00 (0.74–1.36)	1.04 (0.77–1.41)	0.74 (0.57–0.97)	0.77 (0.59–1.01)	0.57 (0.43–0.75)	0.57 (0.43–0.75)
2006–2011	1.03 (0.74–1.45)	1.07 (0.76–1.50)	0.56 (0.41–0.74)	0.57 (0.42–0.77)	0.43 (0.31–0.59)	0.41 (0.30–0.57)
Disease location at diagnosis						
L1, ileal location	Ref	Ref	Ref	Ref	Ref	Ref
L2, colon location	0.37 (0.27–0.51)	0.38 (0.27–0.52)	0.60 (0.45–0.78)	0.69 (0.52–0.92)	0.22 (0.16–0.32)	0.33 (0.23–0.48)
L3, ileocolon location	0.74 (0.55–1.00)	0.71 (0.52–0.97)	1.08 (0.83–1.40)	1.20 (0.92–1.58)	0.57 (0.42–0.75)	0.69 (0.51–0.93)
L4, only upper GI location	0.51 (0.19–1.37)	0.33 (0.12–0.95)	0.44 (0.18–1.08)	0.42 (0.16–1.11)	0.20 (0.05–0.80)	0.25 (0.06–1.05)
Disease behavior at diagnosis						
B1, inflammatory disease	—	—	Ref	Ref	Ref	Ref
B2, stricturing disease	—	—	2.42 (1.85–3.17)	2.24 (1.70–2.94)	4.39 (3.32–5.79)	3.70 (2.78–4.91)
B3, penetrating disease	—	—	5.11 (3.49–7.48)	4.09 (2.74–6.10)	10.65 (7.70–14.73)	8.15 (5.79–11.46)
Perianal disease at diagnosis						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.79 (0.49–1.27)	0.85 (0.52–1.38)	1.34 (0.94–1.91)	1.39 (0.97–2.00)	0.69 (0.43–1.10)	0.73 (0.46–1.17)
Upper GI location at diagnosis						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.63 (1.14–2.33)	1.66 (1.14–2.43)	1.20 (0.84–1.70)	1.29 (0.87–1.93)	1.41 (0.99–1.99)	1.37 (0.95–1.97)

95% CI, 95% confidence interval; GI, gastrointestinal; HR hazard ratio; Ref, reference category.

the 5-year exposure rate was similar among eras, more patients in the era '06–'11 (48.5%) than in the era '91–'98 (38.5%) had already used CS therapy within the first year of disease (aHR 1.32; 95% CI 1.05–1.65). Colonic and ileocolonic location of the disease at diagnosis were associated with early CS use (aHR 2.73; 95% CI 2.18–3.41 and aHR 2.16; 95% CI 1.71–2.73 as compared with ileal location, respectively). Furthermore, an age at diagnosis of >40 years was associated with a lower need for CS therapy within the first year (aHR 0.69; 95% CI 0.57–0.83).

The cumulative CS use was determined in CD patients who had a first prescription within 5 years after diagnosis and had a follow-up of at least 5 years (n=430) (**Table 5**). Both the total number of days and the total dosage were not different among eras in the first year of disease (P=0.15 and P=0.71, respectively). In contrast, the cumulative use of CS (days and dosage) in the subsequent 4 years of disease decreased over time: from a median of 198 days (IQR 26–653)/2,320 mg (IQR 158–7,487) in the era '91–'98 to a median of 0 days (IQR 0–83)/0 mg (IQR 0–1,260) in the era '06–'11 (P<0.01 for both outcomes). In line, the total cumulative 5-year CS use decreased over time (P<0.01 for both days and dosage analyses), see **Table 5**.

DISCUSSION

In this real-life, population-based, Dutch IBDSL cohort, the long-term outcome of CD has improved over the past two

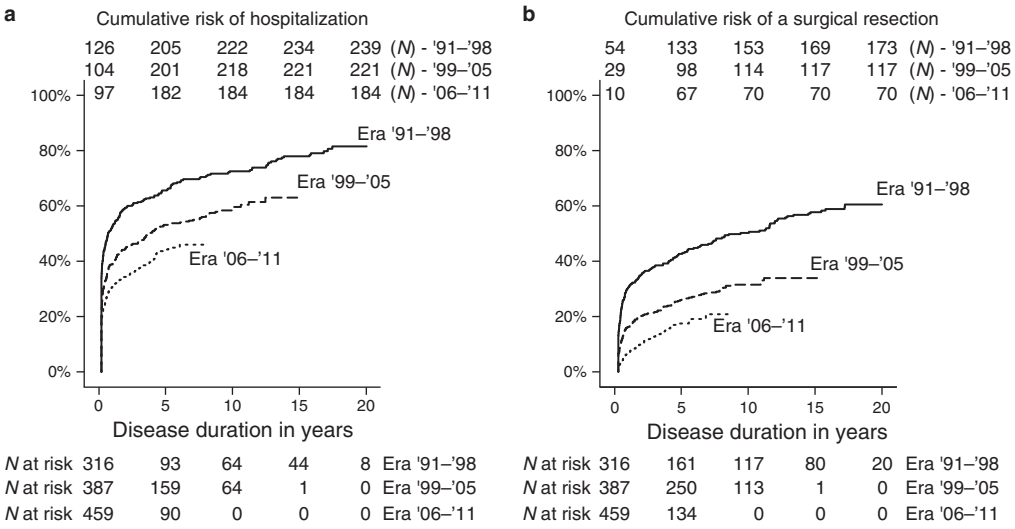

Figure 3. The cumulative risks of long-term outcome measures among the three eras. (**a**) Hospitalization and (**b**) surgical resection. The cumulative risks of hospitalization (**a**) and surgery (**b**) among the three eras. Era '91–'98, patients diagnosed between 1991 and 1998; era '99–'05, patients diagnosed between 1999 and 2005; era '06–'11, patients diagnosed between 2006 and 2011.

Table 4. Characteristics of the first surgical procedure

		Era 1991–1998 (*N*=173)	Era 1999–2005 (*N*=118)	Era 2006–2011 (*N*=70)	
Indication of surgery					*P*=0.03
Active, luminal disease	*N* (%)	79 (45.7)	41 (35.0)	24 (34.3)	
Stricturing disease	*N* (%)	59 (34.1)	44 (37.6)	36 (51.4)	
Penetrating disease	*N* (%)	27 (15.6)	30 (25.6)	8 (11.4)	
Other	*N* (%)	8 (4.6)	3 (2.5)	2 (2.9)	
Type of surgery					*P*=0.27
Ileocecal resection	*N* (%)	135 (78.0)	100 (84.7)	54 (77.1)	
Colonic resection	*N* (%)	19 (11.0)	4 (3.4)	7 (10.0)	
Right hemicolectomy	*N* (%)	15 (8.7)	9 (7.6)	5 (7.1)	
Small-intestine resection	*N* (%)	4 (2.3)	5 (4.2)	4 (5.7)	

decades and, in parallel, marked changes were observed in the medical management. Over time, the use of immunomodulators and anti-TNFα agents increased profoundly and these agents were prescribed earlier after CD diagnosis. The more recently diagnosed CD patients had lower hospitalization and surgery rates, both at diagnosis and on the long-term, and less days of CS exposure during their course. Although fewer patients had complicated CD in more recent eras, the risk of progression from an inflammatory to a stricturing or penetrating phenotype has not changed. The use of immunomodulators or anti-TNFα agents within 2 years after CD diagnosis was not significantly associated with a lower hospitalization, phenotype progression, or surgery rate.

Nowadays, the vast majority (70.8%) of CD patients will ever use immunomodulators and nearly half (49.5%) starts treatment in the first year after CD diagnosis. This is in line with observations in other large cohorts (15,17,18) and with current guidelines that advocate the use of immunomodulators as first-line maintenance therapy and CS sparing agent in CD (6,7). The immunomodulator exposure is rather high in the IBDSL cohort, as compared with other population-based cohorts from the same era, that observed 5-year exposure rates of 45–59% (15,18,35). Nearly one-third of our CD patients diagnosed after the year of anti-TNFα introduction (1999) is exposed to these agents within 5 years after diagnosis that is also high as compared with other cohorts, such as the Copenhagen County cohort (23.3% within 7 years between 2003 and 2011) (36) and the ECCO-EpiCom cohort (19% within 1 year in 2011–2012) (37). Increasing exposure rates of immunomodulators and, in particular, anti-TNFα agents, will inevitably lead to higher medication costs

Table 5. Cumulative corticosteroid use

		Era 1991–1998 (*N*=142)	Era 1999–2005 (*N*=194)	Era 2006–2011 (*N*=93)	
Within first year of disease					
Cumulative number of days	Median (IQR)	107 (35–268)	81 (13–170)	79 (54–160)	*P*=0.15
Cumulative dose	Median (IQR)	2,095 (500–4,189)	1,680 (196–3,460)	1,580 (935–3,133)	*P*=0.71
Between first and fifth year of disease					
Cumulative number of days	Median (IQR)	198 (26–653)	63 (0–173)	0 (0–83)	*P*<0.01
Cumulative dose	Median (IQR)	2,319 (158–7,487)	880 (0–2,680)	0 (0–1,260)	*P*<0.01
Within the first 5 years of disease					
Cumulative number of days	Median (IQR)	366 (107–841)	161 (75–314)	120 (72–211)	*P*<0.01
Cumulative dose	Median (IQR)	4,643 (1,828–10,234)	2,970 (1,508–5,081)	2,180 (1,278–3,715)	*P*<0.01

IQR, interquartile range.
Analyses on the cumulative use of corticosteroids were performed in patients with a corticosteroid prescription within 5 years after diagnosis and a minimum follow-up of 5 years.

and overtreatment looms. Although total costs for IBD care have not increased over time, the Dutch COIN study recently showed that costs for IBD medication have increased and are currently the main cost driver in IBD (38). Future studies that aim to stratify patients in order to select the optimal treatment strategy for each CD patient are warranted to avert under- and overtreatment.

Induction and maintenance of steroid-free clinical remission is the primary treatment goal in CD, but data regarding the cumulative CS use are scarce. A Canadian population-based study (UMIBDED) found no change in cumulative CS use between 1995 and 2010, despite increasing immunomodulator use (31). The present study is the first European study including this important outcome parameter and shows a clear reduction in cumulative CS use in more recently diagnosed CD patients. This discrepancy between studies may be explained by regional differences in prescription policy, but a more profound increase in the cumulative 5-year exposure rates of immunomodulators (UMIBDED: 19.8% (1995–2000) to 31.7% (2005–2009) vs. IBDSL: 30.6% (1991–1998) to 70.8% (2006–2011)) and anti-TNFα agents (UMIBDED: 5.1% (2001–2004) to 12.7% (2005–2009) vs. IBDSL: 19.9% (1999–2005) to 41.2% (2006–2010)) in our area must be acknowledged. Next, we observed that more CD patients in the era '06–'11 than in the era '91–'98 received a CS prescription within the first year after diagnosis. This probably results from a high adherence to recent guidelines that advocate the use of CS for remission induction for all newly diagnosed CD patients, except for patients with limited ileal disease (6,7). The observed cumulative use in the first year of disease in the era '06–'11 (median 79 days (IQR 48–144)/1,580 mg (IQR 840–3,060)) corresponds to approximately one course of CS (63 days, 1,505 mg), assuming a start dose of 40 mg prednisolone and a standard 8–10 weeks of tapering regime as recommended in the Dutch guideline from 2009 (6). Beyond the first year after diagnosis, we observed a clear reduction in the cumulative CS use in more recent eras. This may be the result of more awareness for steroid sparing in more recent years, a milder course of the disease (whether or not because of changes in medical therapy), an earlier diagnosis of the disease (and thus earlier start of treatment), or a combination of these factors.

In all eras, a considerable number of patients suffered from a complicated CD behavior. Over time, a reduction in the number of patients presenting with a complicated behavior was seen in the present study as well as in the cohort from Hungary (15). This may be explained by earlier diagnosis of CD, as strictures and internal fistulas are considered to be the result of longstanding inflammation and subsequent bowel damage (39,40). Regrettably, no data on the time from first symptoms to diagnosis were available for study. The cumulative 5-year probability of having a complicated CD behavior was 35.5% in our cohort, and this is lower than reported in other population-based studies (40–55%) (1,13,14) and lower than in the landmark study from Cosnes *et al.*(12) on this topic (52%). Of note, previous studies often used the Vienna consensus (30) to classify disease behavior, in which perianal fistulas were also considered penetrating disease. When we reclassify disease behavior accordingly (**Supplementary Figure S1**), the proportion of patients with a complicated behavior within 5 years after diagnosis is more alike (43.1%). Progression from B1 to either B2 or B3 disease occurred in 21% within 5 years and was similar among the three eras, despite the earlier and higher exposure to immunomodulators and anti-TNFα agents in more recent eras. This is of relevance, as the prevention of structural bowel damage is currently suggested as a novel therapeutic goal in CD (8,41).

In parallel to an increasing use of immunomodulators and anti-TNFα agents, we observed a considerable drop in the surgery rate, both at diagnosis and during follow-up, even within the biological era. The lower surgery rate at diagnosis may be explained by a combination of improved diagnostics, disease awareness, or a change in treatment policy. A local effect is suspected, as other cohorts did not find such a decrease in the surgery rate at diagnosis (17,18).

The 5-year surgery rate decreased as well, even after correcting for surgeries performed at diagnosis. This observation is in line with Danish data that show a decrease in the surgery rate from 44.7% in 1979–1986 to 19.6% in 2003–2011 (17), and with Cardiff data that show a decrease from 59% in 1986–1991 to 25% in 1998–2003 (18). The present study is the first to include the indication of surgery and shows that the drop in surgery rate is mainly caused by a reduction in surgeries for refractory inflammatory disease rather than complicated disease.

To assess whether the temporal improvements in the long-term outcome of CD are related to the observed changes in the medical management of CD, we compared the long-term outcome of immunomodulator and anti-TNFα users with matched controls. No significant association was found between the use of these agents in the first 2 years of disease and the subsequent hospitalization, surgery, or phenotype progression risk. Results were concordant in the sensitivity analyses in which cutoff values of 6 months and 1 year were used for the definition of "user". Therefore, the results of the present study seem to indicate that the observed improvements in the long-term outcome are mainly caused by other factors than changes in medical management, such as (local) changes in the indications for hospitalization and surgery, or disease monitoring. Referring to the latter, IBD patients are more tightly monitored nowadays: biochemically (e.g., regular checks for blood and fecal inflammation markers), radiologically (e.g., assessment of proximal disease activity and extension), and personally (e.g., easily accessible specialized IBD nurses, adherence coaching). As a result, disease activity or disease-related complications may be recognized and treated at an earlier stage, thereby possibly preventing further progression. Previous studies reflecting on the question of whether medication can alter the natural history of IBD did find an association between the use of azathioprine and/or anti-TNFα and a lower surgery rate (15,42–45). However, not all studies adequately adjusted for confounding by indication or immune time bias. Propensity score matching is commonly used to control for confounding by indication (46), yet its performance depends on the quality of the variables included in the model. In IBD, accurate (clinical) predictors for the disease outcome are currently lacking, limiting the extent to which we can account for such confounding (47). As a result, the findings from the propensity score analyses may therefore be underestimated. Referring to immune time bias (48), Targownik *et al.* (49) postulated that this type of bias may explain the strong beneficial effects of immunomodulators and anti-TNFα agents on surgery risk or phenotype progression that were found in some observational studies. This may explain the discrepancy between the negative findings in the present study and the positive findings in others.

Ultimately, because of the complexity of establishing proper models to study the relation between treatment and outcome and the large number of patients required to measure an effect, our findings should be interpreted with care. Future studies, in particular in cohorts with more patients treated with anti-TNFα agents or combination therapy early in disease course, are needed to further reflect on the question whether specific treatment strategies can change the natural history of CD.

The strengths of this study reside in the prospective registration of newly diagnosed IBD patients in a well-defined geographical area, the large number of CD patients included and high completeness of the cohort (over 93%) (28), the long follow-up time, and the level of detail of the clinical data directly retrieved from patients' files rather than from administrative databases. This enabled us to study time trends in medical management and outcomes in an unselected CD population in real-life clinical practice. Nonetheless, several limitations have to be addressed. First, because of the observational design of the study, no causal relations can be claimed. Second, data on the diagnostic delay would have provided insight into the observed changes in disease presentation, but were not available and are difficult to obtain because of recall bias. Third, hospitalization, surgery, and cumulative CS use were used as proxy measures for a severe disease outcome. Clinical and endoscopic disease activity scores and biochemical markers would have provided additional insight, yet are very hard to collect and interpret in large, observational cohort studies. Finally, data on the cumulative CS use were retrieved from medical records rather than pharmacies, inducing a certain amount of inaccuracy.

In conclusion, the hospitalization and surgery rates decreased over the past two decades, whereas progression to complicated disease is still common in CD. The improvements were not significantly associated with the use of immunomodulators or anti-TNFα agents. Future studies should address whether novel treatment strategies, such as treat to target, can further improve the long-term outcome, in particular the risk of developing structural bowel damage.

CONFLICT OF INTEREST

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Specific author contributions: S.F.G.J.: Study concept and design, data collection, analysis and interpretation of data, drafting of the manuscript, and final approval of the submitted version. T.R.A.v.d.H.: Study concept and design, data collection, analysis and interpretation of data, critical revision of the manuscript, and final approval of the submitted version. L.Y.L.L.: Study concept and design, data collection, analysis and interpretation of data, critical revision of the manuscript, and final approval of the submitted version. M.P.Z., W.H.H., M.J.L.R.-C., L.E.O., A.A.M.M. and D.M.A.E.J.: Study concept and design, analysis and interpretation of data, critical revision of the manuscript, final approval of the submitted version. M.J.P.: Study concept and design, data collection, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, study supervision, and final approval of the submitted version.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The long-term outcome of Crohn's disease varies widely among patients and many have an unfavorable outcome.
- ✓ Over the past decades, treatment options and strategies for Crohn's disease have changed, including a more frequent use of biological therapy.
- ✓ It is currently poorly understood whether the long-term outcome of Crohn's disease has improved and what role medical therapy played herein.

WHAT IS NEW HERE

- ✓ Between 1991 and 2014, the hospitalization and surgery rates have decreased markedly, even within the biological era.
- ✓ Similar, the cumulative corticosteroid use has attenuated, in particular after the first year of disease.
- ✓ The observed improvements in the long-term outcome seem not to be related to the use of immunomodulators and biologicals.
- ✓ Progression to a complicated disease phenotype is still common, illustrating the need for further optimization of the management of Crohn's disease.

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