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The use of 5-aminosalicylates in Crohn's disease: a retrospective study using the UK Clinical Practice Research Datalink

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Abstract

Background There are few recent studies on the use of 5-aminosalicylates (5-ASA) as therapy for Crohn's disease (CD) in routine clinical practice. The aim of this database investigation was to provide real-world evidence on 5-ASA use in CD.

Methods Patients with CD, aged ≥18 years when first prescribed 5-ASA (index date) and having received 5-ASA at any time between 01 January 2006 and 07 May 2018, were included for analysis. Outcomes included treatment patterns and resource use.

Results Of 21,456 patients with CD, 9492 (44.2%) had been prescribed 5-ASA, with the majority (5606; 59.1%) starting on oral 5-ASA as monotherapy. 58.3% (5537) of patients on 5-ASA did not require dose change, 67.6% (6416) did not require supplementary treatment (e.g., corticosteroids, immunosuppressants, etc.), and 4.6% (436) required a switch to another treatment. Resource use was significantly decreased in the year after vs. year before 5-ASA initiation (including: specialist referrals, hospitalizations and hospital days; all P<0.001). Patients remained on 5-ASA for a median of 4.7 years (interquartile range 1.2-10.1). 25.3% (2406) of patients were still on 5-ASA at 10 years. There was a significant correlation between earlier use of 5-ASA following diagnosis and longer 5-ASA retention (P<0.001).

Conclusions 5-ASA is widely used as a long-term treatment for CD, as evidenced by continuation rates extending beyond 10 years in a quarter of patients. CD-related healthcare resource use decreased significantly in the year following 5-ASA initiation. Earlier use was associated with longer retention.

Keywords Inflammatory bowel disease, mesalazine, prescribing, real-world evidence

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Introduction

Crohn's disease (CD) is a highly prevalent form of inflammatory bowel disease (IBD) that affects over 115,000 people in the UK alone [1]. There is no cure for CD, and many patients remain dependent on medication to induce remission during active disease and to maintain remission pre- or post-surgery [2]. 5-aminosalicylates (5-ASA) are widely used in routine clinical practice, with approximately half of all patients with CD in the UK receiving this therapy at some point during the course of their disease [3]. Despite its being an established therapy, there remains ongoing debate about the optimal place in therapy and corresponding benefits of 5-ASA as a treatment for CD [4-6], with many guidelines recommending against its use in these patients [7-10]. The aim of our study was to provide real-world evidence on the initiation, continuation and resource use of 5-ASA in patients with CD, using the Clinical Practice Research Datalink (CPRD) database [11].

Materials and methods

Study design and population

A retrospective, observational, longitudinal cohort study was conducted using data collected from the UK CPRD GOLD database. CPRD collects primary care records from 742 general practices across the UK, with coverage of approximately 15.3 million historic patients [7,12]. There are around 4.4 million active patients, covering around 6.9% of the total UK population [7,8]. The CPRD database has been shown to be broadly representative of the general UK population in terms of age, body mass index, sex and ethnicity [8,13,14].

The study population comprised all patients with CD ≥18 years of age when first treated with 5-ASA between 01 January 2006 and 07 May 2018 (Fig. 1; Supplementary Tables 1, 2, for codings used for CD and 5-ASA). The index date was defined as the earliest date for a patient to have both a 5-ASA prescription and a diagnosis of CD. Follow up ended at patient death, loss to follow up, last date of data collection from the database (07 May 2018), or the discontinuation of 5-ASA treatment (whichever occurred first). Discontinuation was defined as no prescription of 5-ASA for 6 months.

Analyses

The main outcomes of the study were prescribing patterns and management practices, including continuation rates on 5-ASA therapy, and healthcare resource use. A number of different subgroups were established based on prescribing patterns, including those patients prescribed 5-ASA alone at index (monotherapy group), those prescribed a gastrointestinal (GI) treatment (e.g., azathioprine) within 3 months of first prescription of 5-ASA (combination therapy group), those patients that required additional CD treatment to supplement 5-ASA at any time during follow-up ("add-on treatment"), those that required dose optimization (increase/decrease) of 5-ASA during treatment, and those patients that switched from 5-ASA to another therapy. Switch was defined as initiation of another treatment for CD within 3 months of the last prescription of 5-ASA, and add-on was defined as prescription of supplemental medication for CD (e.g., azathioprine) while continuing with 5-ASA. In addition, an analysis based on retention time was conducted to determine whether there was differentiation between these groups in terms of prescribing patterns. The high-retention group was defined as patients who had received 5-ASA for at least 5 years, whereas the low-retention group was comprised of patients who had received 5-ASA for 6 months or less.

The resource use analysis included visits to primary care and specialists, hospitalizations, and GI surgery. Healthcare resource use in the 12 months prior to 5-ASA initiation and the 12 months post 5-ASA initiation was compared. Rates of resource use (per 100 patients) were also compared from 1 year before to 3 years after 5-ASA initiation. The same comparison was done for patients on monotherapy for more than 1 year who had no add-on treatments during the first year after index date.

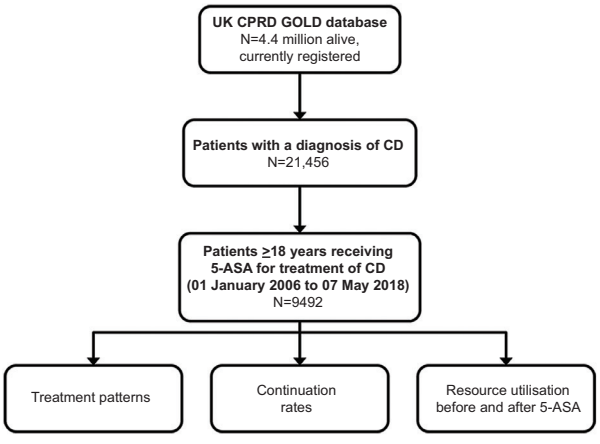

Figure 1 Study flow
CD, Crohn's disease; 5-ASA, 5-aminosalicylate; CPRD, Clinical Practice Research Datalink

Statistical analysis

All available data were used in each analysis. If a specific variable (e.g., information on prescription dates) was missing for a particular patient, then that patient was excluded from that one analysis and the denominator was adjusted accordingly. Descriptive statistics were used to describe baseline characteristics and treatment patterns. Interval data were first analyzed using a Kolmogorov-Smirnov test of normality as a guide for further analyses (*t*-test or ANOVA). The Mann-Whitney *U* test was used for rank or ordinal data. Categorical and dichotomous data were analyzed using the chi-square test. The significance of differences in rates (per 100 patients) of resource use pre and post 5-ASA initiation was assessed using the chi-squared rank test, Friedman test and Kendall's W test. Multivariate Cox regression analysis investigated the strongest associations with duration of 5-ASA treatment. The following covariates were tested: age, added drug, dose optimization, route of administration, initial dose of 5-ASA, hospitalization, and GI surgery. Odds ratios (OR) were derived from Exp(beta) values computed by the Cox regression procedure. All analyses were performed using SPSS for Windows version 15.0 and Microsoft Excel.

Ethics and reporting

Independent Scientific Advisory Committee (ISAC) for MHRA Database Research approval was obtained for this study on 26 April 2018 (protocol 18_065R). General Practitioner (GP) practices consent to patient data being sent to CPRD for public health research and patients have the opportunity to opt

out of contributing their data to CPRD. This study has been reported following the STROBE and RECORD guidelines for reporting of studies conducted using observational, routine-collected health data [15,16].

Results

Initiation of 5-ASA treatment

The total population with CD was 21,456, of whom 9492 (44.2%) were prescribed 5-ASA at some time during the study period. 5-ASA prescriptions peaked in 2006, when 682 patients were started on treatment, with a steady decline thereafter (123 patients started 5-ASA treatment in 2017). Patients (55.8% female) were prescribed 5-ASA within 1.3 months (median) (interquartile range [IQR] 0.0-32.0) after being diagnosed with CD, at a mean age of 42.7 years (standard deviation [SD] 17.2) (Table 1). Less than half (3972; 41.8%) of the patients had received an IBD treatment in the year prior to (index) 5-ASA prescription; the majority of these received prednisolone (3048; 76.7%). Overall, 5977 patients (63.0%) initiated 5-ASA monotherapy at index and 3515 (37.0%) initiated combination therapy. Of those patients starting on combination therapy, the majority were on prednisolone (2570; 73.1%) or azathioprine (713; 20.3%); 496 (14.1%) were on both prednisolone and azathioprine.

5-ASA was started at a median dose of 2.0 g/day, when considering all formulations combined. Overall, 93.5% of patients (8879) were on an oral 5-ASA regimen at index (91.7% [8139] on tablets and 10.9% [971] on granules; some patients received both tablets and granules). The majority of patients were on oral 5-ASA as monotherapy (5606; 63.1%), at a median starting dose of 2.0 g/day (IQR 1.5-2.4; mean 2.2, SD 1.0). The remaining patients, on oral 5-ASA in combination with another therapy (3273; 36.9%), started at a median dose of 2.4 g/day (IQR 1.5-3.0; mean 2.3, SD 1.0). Rectal administration of 5-ASA alone was provided to 466 (4.9%) patients at index (77.3% [360] on suppositories and 59.4% [277] on enemas) and 147 received both oral and rectal 5-ASA treatment.

Dose optimization and treatment changes

Over half of the patients (5537; 58.3%) did not require any dose optimization (increase or decrease in dose) during 5-ASA treatment. For the 2666 patients (28.1%) that required a dose increase, the mean percentage increase was 79.1% (median difference: 1.5 g/day), from a median starting dose of 1.5 g/day (IQR 1.2-2.0) to an increased median dose of 3.0 g/day (IQR 2.4-4.0). Dose reductions were recorded in 1939 patients (20.4%), with a mean percentage reduction of 39.6% (mean difference: 1.0 g/day). The mean dose at index in patients requiring a dose reduction was 2.5 g/day (SD 0.9; median 2.4, IQR 2.0-3.0); after the reduction, the mean dose was 1.5 g/day (SD 0.6; median 1.5, IQR 1.0-2.0). The mean dose at index in patients with a dose reduction was higher than the starting dose for patients requiring a dose increase (mean 2.5 [SD 0.9] vs. 1.7 g/day [SD 0.6], respectively; P<0.0001). Dose reductions and increases occurred at similar rates for those on monotherapy and combination therapy at index (reduction: 19.8% vs. 21.5%, respectively, P=0.051; increase: 28.5% vs. 27.4%, P>0.99). Patients receiving monotherapy and combination therapy experienced dose optimizations at a similar time: dose reductions at a median of 3.5 years (IQR 1.0-6.9) vs. 3.7 years (IQR 1.3-7.7), respectively; and dose increases at a median of 3.7 years (IQR 1.3-7.6) vs. 4.1 years (IQR 1.3-8.1), respectively).

The majority of patients (6416; 67.6%) did not require supplementary IBD treatment in addition to their 5-ASA (monotherapy or combined) therapy (Fig. 2). In those patients who started on monotherapy or combination therapy and then received additional treatment (3076; 32.4%), the majority were prescribed a corticosteroid (2411, 78.4%; mostly prednisolone [2015, 83.6%]) and azathioprine (643; 20.9%). Median time to add-on treatment was 2.2 months (IQR 0.8-8.0; mean 7.9 months, SD 14.2). More patients receiving combination therapy at index date required supplementary treatment compared to those who started on monotherapy (40.3% [1417/5977] vs. 27.8% [1659/3515], respectively; P<0.001). Time to add-on treatment was significantly longer for those who started monotherapy than combination therapy (median [IQR] 4.8 [1.4-13.5] vs. months 1.1 [0.6-2.6], respectively; P<0.001).

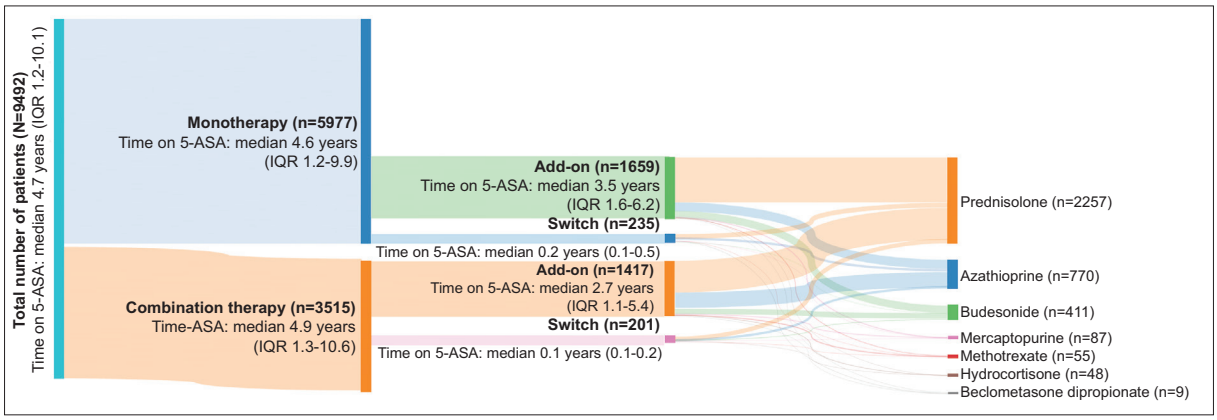

Figure 2 Sankey diagram
IQR, interquartile range; 5-ASA, 5-aminosalicylate

Table 1 Demographics and medication use prior to and at index date

Characteristics	Total population	Monotherapy	Combination therapy
Total	9492	5977	3515
Female, n (%)	5295 (55.8)	3349 (56.0)	1946 (55.4)
Male, n (%)	4197 (44.2)	2628 (44.0)	1569 (44.6)
Age at first recorded CD diagnosis (years)†			
Mean (SD)	40.24 (17.8)	41.23 (17.9)	38.56 (17.5)
Median [IQR]	37 [25-53]	38 (26-54)	35 (24-51)
Age at index date – first prescription of 5-ASA (years)			
Mean (SD)	42.7 (17.2)	43.6 (17.2)	41.2 (17.1)
Median [IQR]	40 [28-55]	41 (29-56)	38 (27-54)
Smoking status			
Never, n (%)	4421 (46.6)	2764 (46.2)	1657 (47.1)
Former, n (%)	1177 (12.4)	781 (13.1)	396 (11.3)
Current, n (%)	3671 (38.7)	2284 (38.2)	1387 (39.5)
Unknown‡, n (%)	223 (2.4)	148 (2.5)	75 (2.1)
Time from diagnosis of CD to 5-ASA prescription (months)			
Mean (SD)	30.9 (89.6)	29.6 (89.3)	33.0 (90.0)
Median [IQR]	1.3 [0.0-32.0]	1.1 (0.0-28.7)	1.5 (0.0-38.0)
5-ASA dose at index (g/day)			
Mean dose, g (SD)	2.2 (1.1)	2.2 (1.0)	2.3 (1.0)
Median dose, g (IQR)	2.0 (1.5-3.0)	2.0 (1.5-2.4)	2.4 (1.5-3.0)
Tablets – median dose, g (IQR)	2.0 (1.5-2.4)	2.0 (1.5-2.4)	2.4 (1.5-2.4)
Granules – median dose, g (IQR)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)
Suppositories – median dose, g (IQR)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Enema – median dose, g (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-1.0)
Medication use in year prior to index date¶, n (%)	3972 (41.8)	457 (7.6)	3515 (100.0)
Immunosuppressants	916 (9.7)	53 (0.9)	863 (24.6)
Azathioprine	794 (8.4)	44 (0.7)	750 (21.3)
Corticosteroids	3679 (38.8)	437 (7.3)	3242 (92.2)
Budesonide	446 (4.7)	41 (0.7)	405 (11.5)
Hydrocortisone	181 (1.9)	9 (0.2)	172 (4.9)
Prednisolone	3048 (32.1)	387 (6.5)	2661 (75.7)
Beclometasone dipropionate	4 (<0.1)	0 (0.0)	4 (0.1)
Anti-TNFs§	3 (<0.1)	1 (<0.1)	2 (<0.1)
Adalimumab	1 (<0.1)	1 (<0.1)	0 (0.0)
Infliximab	2 (<0.1)	0 (0.0)	2 (<0.1)
Combination therapy at index date, with¶, n (%)			
Immunosuppressants	817 (8.6)	-	817 (23.2)
Azathioprine	713 (7.5)	-	713 (20.3)
Mercaptopurine	52 (0.5)	-	52 (1.5)
Methotrexate	52 (0.5)	-	52 (1.5)
Corticosteroids	3105 (32.7)	-	3105 (88.3)
Budesonide	375 (4.0)	-	375 (10.7)
Hydrocortisone	155 (1.6)	-	155 (4.4)
Methylprednisolone	0 (0.0)	-	0 (0.0)
Prednisone	0 (0.0)	-	0 (0.0)
Prednisolone	2570 (27.1)	-	2570 (73.1)
Beclometasone dipropionate	3 (<0.1)	-	3 (0.1)
Anti-TNFs§	2 (<0.1)	-	2 (0.1)
Adalimumab	0 (0.0)	-	0 (0.0)
Infliximab	2 (<0.1)	-	2 (0.1)

†first recorded diagnosis in CPRD GOLD; ‡no smoking status described or conflicting results on the last mention of smoking; §information on anti-TNF therapy not routinely captured in CPRD database; ¶patients can be counted more than once

5-ASA, 5-aminosalicylate; IQR, interquartile range; SD, standard deviation; TNF, tumor necrosis factor

Overall (monotherapy and combination therapy at index), 4.6% of patients (436) required a switch to another treatment. Patients switched most commonly to prednisolone (242; 55.5%), azathioprine (127; 29.1%) and/or budesonide (68; 15.6%). Median time to switch was 1.9 months (IQR 0.9-3.9; mean 5.4 months, SD 12.3). Significantly more patients on

Table 2 Continuation rates on 5-aminosalicylate therapy

Characteristics	n (%)	Continuation rates (%)				P-value
		Year 1	Year 2	Year 5	Year 10	
Total	9492 (100.0)	n=7345	n=6458	n=4594	n=2406	
		77.4	68.0	48.4	25.3	
Sex						
Male	4197 (44.2)	77.8	68.6	48.2	25.4	0.503
Female	5295 (55.8)	77.1	67.6	48.5	25.3	
Monotherapy and combination therapy						
Monotherapy	5977 (62.3)	77.1	67.4	47.9	24.2	0.044
Combination therapy	3515 (37.0)	77.9	69.1	49.3	27.3	
Age bands						
<20 years	453 (4.8)	81.2	72.8	55.0	27.4	<0.001
20-29 years	2130 (22.4)	71.9	61.0	40.9	20.7	
30-39 years	2074 (21.8)	79.7	70.6	50.6	28.6	
40-49 years	1678 (17.7)	78.4	69.1	50.7	27.8	
50-59 years	1320 (13.9)	80.4	72.3	53.5	30.5	
60-69 years	1056 (11.1)	78.5	70.7	52.4	25.6	
≥70 years	781 (8.2)	76.1	65.3	41.2	15.2	

combination therapy at index switched treatment compared to those on monotherapy (5.7% [201/3515] vs. 3.9% [235/5977], respectively; P<0.001). Patients on monotherapy took a significantly longer time to the switch compared to those on combination therapy (median [IQR] 2.7 [1.4-5.8] vs. 1.3 [0.6-2.4] months, respectively; P=0.005).

Continuation rates

Patients remained on 5-ASA for a median of 4.7 years (IQR 1.2-10.1 years; mean 6.4 years; SD 6.1 years) before discontinuation, with a quarter (25.3%) on 5-ASA at 10 years or longer (Table 2). Patients on combination therapy at index stayed on 5-ASA significantly (P=0.044) longer than patients on monotherapy (mean 6.7 years [SD 6.3]; median 4.9 years [IQR 1.3-10.6] vs. mean 6.3 years [SD 6.0]; median 4.6 years [IQR 1.2-9.9]). Patients aged between 50-69 years appeared more likely to persist on 5-ASA therapy than other age groups (all patients, median [IQR] 5.2 [5.0-5.4] years; 50-59 age band median [IQR] 6.6 [6.0-7.2] years; 60-69 age band median [IQR] 6.2 [5.6-6.9] years; P<0.001 difference between age bands). 5-ASA dose optimization increased the median duration of therapy vs. those with no dosage change (increase: 8.8 [IQR 4.1-14.7] years and decrease: 7.9 [IQR 4.0-13.0] years vs. no change: 2.7 [IQR 0.5-7.6] years; both P<0.001). A lower initial dose of oral 5-ASA at index date was significantly correlated with a longer duration of 5-ASA therapy (tablets: P<0.001; granules: P=0.008). Rectal 5-ASA alone was not significantly correlated with continuation time (P=0.142). A shorter time from CD diagnosis to first 5-ASA script was associated with a longer stay on therapy (P<0.001).

Patients who continued on 5-ASA for at least 5 years (high-retention group) had a significantly (P<0.001) shorter time from CD diagnosis to first 5-ASA prescription (median 0.9 months [IQR 0.0-27.8]; mean 22.8 months [SD 92.0]) compared to those receiving 5-ASA for 6 months or less (low-retention group) (median 2.3 months [IQR 0.0-48.3]; mean 35.1 months [SD 86.1]). Patients in the high-retention group also had significantly more add-on treatments prescribed (21.7% vs. 15.9% of patients, respectively; P<0.001).

Multivariate analysis revealed that the most powerful associations with a short duration on 5-ASA therapy was prescription of additional treatment(s) (OR 0.61, 95% confidence interval [CI] 0.58-0.65; P<0.001). On the other hand, dose optimization (increase or decrease in 5-ASA dose) (OR 1.40, 95%CI 1.36-1.43; P<0.001) and GI surgery during treatment with 5-ASA (OR 1.37, 95%CI 1.30-1.45; P<0.001) were associated with a longer time to discontinuation. Neither route of administration (P=0.77) nor any hospitalization (P=0.92) had a significant association with time to discontinuation.

Healthcare resource utilization

Resource use was significantly decreased in the year after 5-ASA initiation compared to the year before index date in terms of specialist referrals (285 vs. 110 [61.4% reduction]; P<0.001), hospitalizations (2475 vs. 1567 [36.7% reduction]; P<0.001) and hospital days (19645 vs. 11574 [41.1% reduction]; P<0.001). GP visits (85279 vs. 84210 [1.3% increase]; P=0.391) and GI surgeries (205 vs. 168 [18.0% reduction]; P=0.104) did not differ in the 12 months before vs. the 12 months after 5-ASA initiation. However, significantly fewer patients required GI surgery during 5-ASA treatment than at any time before index date (7.6% [721] vs. 5.3% [501]; P<0.001). There was a significant and progressive decline in rates of

resource use (referrals, hospitalizations, hospitalization days and surgery; all P<0.001) for at least 3 years following 5-ASA initiation (Table 3).

For patients starting on 5-ASA monotherapy and continuing for more than one year (2203), significant reductions were seen in GP visits (38734 vs. 38217 [1.33%]; P=0.025), specialist referrals (47 vs. 10 [78.7%]; P<0.001), hospitalizations (490 vs. 355 [27.6%]; P<0.001), and hospital days (4298 vs. 2628 [38.9%]; P<0.001), in the 12 months before vs. the 12 months after index. The number of GI surgeries, however, showed no difference between before and after index (36 vs. 34, respectively; P=0.881).

Discussion

This observational study of 9492 patients provides detailed information on the use of 5-ASA for CD in routine clinical practice within the UK. 5-ASA was found to be a widely used, long-term therapy for CD, associated with a significant reduction in healthcare resource use in the 12 months following initiation, compared to the prior 12 months. Overall, 44% of patients with CD were treated with 5-ASA at some point during the course of their disease. A similar prevalence of use was reported in another UK study using The Health Improvement Network (THIN) UK primary care database, which reported that 45% of 12,047 patients with CD had received a prescription of 5-ASA between 2012-2015 [3]. A high prevalence of 5-ASA usage for CD has also been reported in other western countries; for example, 47% of patients in the US (between 2006 and 2010) [17], 59% in Switzerland (2006-2012) [18], and 64% in Denmark (1953-2007) [19]. While the CPRD data show a decline in 5-ASA use over time, perhaps reflecting prescribing in accordance with CD guidelines [7-10], a substantial number of patients were started on 5-ASA treatment in 2017 (n=123), indicating that many clinicians still value it as a useful therapy for some patients with CD.

The vast majority of patients in our study (94%) started on oral 5-ASA at a median dose of 2 g/day. Another study using CPRD data reported that the median dose of oral 5-ASA for CD increased from 1120 mg/day in 1990-1993 to 1740 mg/day in 2006-2010 (P<0.001) [20]. Our results (2006-2018) suggest a continuing trend for increasing doses of oral 5-ASA being used for CD, taking into account that most patients either maintained (58%) or increased (28%) their initial dose over time. 5-ASA was most commonly used as monotherapy (63%), although in over a third of patients (37%) it was used as an adjunct to other IBD treatment, typically prednisolone (73%) and azathioprine (20%), indicating that these were patients with more severe disease. This assertion is strengthened by the fact that significantly more patients on combination therapy than monotherapy required add-on treatment (40% vs. 28%, respectively; P<0.001) and were prescribed this in a shorter time after index (median 1.1 vs. 4.8 months; P<0.001).

During the follow-up period (2006-2018), 5-ASA was found to be a long-term medication for CD, with a median duration of therapy of 4.7 years and 25% of patients still on treatment at 10 years. Multivariate analysis revealed that longer continuance on 5-ASA was associated with dose optimization (OR 1.40, 95%CI 1.36-1.43; P<0.001) and GI surgery during treatment with 5-ASA (OR 1.37, 95%CI 1.30-1.45; P<0.001), and less frequent need for add-on therapy (OR 0.61, 95%CI 0.58-0.65; P<0.001). Optimizing the dose of 5-ASA to match the clinical course of the disease is intuitively a sensible approach and has been greatly facilitated in recent years, as health systems have increased patients' involvement in their care and enabled sharing of data with their IBD team [21,22]. It is perhaps to be expected that the need for additional IBD therapy and a step-up in management, reflective of active disease or increased disease severity, would result in a reduced duration of 5-ASA use.

Interestingly, patients requiring surgery had a greater duration of 5-ASA use, suggesting a role for this therapy postoperatively. Earlier treatment with 5-ASA following diagnosis (P<0.001) and lower initial doses of oral 5-ASA (tablets: P<0.001; granules: P=0.008) were also associated with longer retention on therapy. Likewise, it is well established that earlier treatment with immunosuppressants and/or biologics after diagnosis can result in better outcomes for CD, in terms of mucosal healing, early remission without corticosteroids, and a decrease in the need for surgery and hospitalizations [23-26].

There is a large range in time between diagnosis and initial treatment with 5-ASA. The reason for this is that not all patients were treatment naïve and had been treated with other medications for CD before being prescribed 5-ASA. A key limitation of the CPRD database is that it does not capture a measure of disease activity and severity, such as symptom

Table 3 Rates of resource use, per 100 patients, from 1 year before to 3 years post-index date in all patients

Resource use		Year before index	1st year post-index	2nd year post-index	3rd year post-index	P-value*
	N	9492	9492	7333	6455	
Rate per 100 patients	Referrals	3.003	1.159	0.791	0.697	0.001
	Hospitalizations	26.075	16.509	14.551	12.843	0.001
	Hospitalization days	206.964	121.934	87.195	82.556	0.001
	Surgery	2.160	1.770	1.118	0.899	0.001

*chi-squared rank test, Friedman test, and Kendall's W test (all derived the same P-value)

tools (e.g., CD Activity Index /Harvey Bradshaw Index), patient reported outcomes, and/or endoscopic scoring, etc. The majority of patients in our study had not had any prior medical treatment for CD in the year before index (58.2%), perhaps indicating a population with relatively mild disease. The mean age at diagnosis being 40 years might also be suggestive of a population at the milder end of the disease spectrum. Data from a German study reported a similar mean age for diagnosis of mild CD at 41.1 years, but a younger age for those with moderate disease at 33.9 years [27]. Another salient limitation of the study was the absence of a comparator group. An indication of the effectiveness of 5-ASA as a treatment for CD is that resource use was significantly lower in the year after compared to the year before index, including referrals to a GI specialist, hospitalizations and days in hospital. The fact that two thirds of patients did not require add-on therapy (68%) and the low rate of switching (<5%) also provide some indirect evidence of treatment effectiveness. Other limitations include a lack of information on the use of anti-tumor necrosis factor agents—as these are predominantly prescribed in the secondary care setting and are not indicated for mild CD—as well as nonadherence to medication, which has been reported to be as high as 40-60% for 5-ASA in ulcerative colitis [28,29]. Patients aged between 50-69 years tended to remain on 5-ASA longer in our study, which might be related to adherence, as this age group has been associated with higher adherence rates in studies within other disease areas [30,31].

Our findings demonstrate that 5-ASA remains a widely used, long-term treatment for CD. Hospitalizations, GP visits and specialist referrals are reduced 12 months after initiation of 5-ASA compared to the 12 months before. Earlier use following diagnosis and optimization of dose were key factors linked to a longer duration of 5-ASA therapy.

Summary Box

What is already known:

- Approximately half of all patients with Crohn's disease (CD) receive 5-aminosalicylate (5-ASA) therapy
- Ongoing 5-ASA therapy extends beyond 10 years in a quarter of CD patients
- The optimal place in therapy and corresponding benefits of 5-ASA treatment are currently unknown

What the new findings are:

- CD-related healthcare resource use decreased significantly in the year following 5-ASA initiation
- Newly diagnosed patients with mild CD may benefit from early use of 5-ASA
- 5-ASA remains a viable long-term treatment option for CD

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Supplementary material

Supplementary Table 1 Medical codes for identifying Crohn's disease in CPRD GOLD

Read Code	Read Term
J40..00	Regional enteritis - Crohn's disease
J40..11	Crohn's disease
J40z.11	Crohn's disease NOS
J401z11	Crohn's colitis
J400200	Crohn's disease of the terminal ileum
J400300	Crohn's disease of the ileum unspecified
J400400	Crohn's disease of the ileum NOS
J400500	Exacerbation of Crohn's disease of small intestine
J401200	Exacerbation of Crohn's disease of large intestine
J400z00	Crohn's disease of the small bowel NOS
J401z00	Crohn's disease of the large bowel NOS
J08z900	Orofacial Crohn's disease
Jyu4000	[X]Other Crohn's disease
J40z.00	Regional enteritis NOS
J400000	Regional enteritis of the duodenum
J401.00	Regional enteritis of the large bowel
J400100	Regional enteritis of the jejunum
J401100	Regional enteritis of the rectum
J400.00	Regional enteritis of the small bowel
J401000	Regional enteritis of the colon
ZR3S.00	Crohn's disease activity index
ZR3S.11	CDAI – Crohn's disease activity index
N031100	Arthropathy in Crohn's disease
N045300	Juvenile arthritis in Crohn's disease

Supplementary Table 2 Product codes for identifying 5-ASA in CPRD GOLD

Gemscript code	Product Name
58380020	Asacol mr 400 mg tablet (Procter & Gamble (Health & Beauty Care) Ltd)
32911020	Mezavant XL 1200 mg tablets (Sigma Pharmaceuticals Plc)
72471020	Mesalazine 1 g/100 mL enema
61385020	Asacol 1 g/application foam enema (Allergan Ltd)
85679020	Coltec 400 mg Gastro-resistant tablet (Berk Pharmaceuticals Ltd)
94204020	Mezavant XL 1200 mg tablets (Shire Pharmaceuticals Ltd)
61384020	Asacol 500 mg suppositories (Allergan Ltd)
95765020	Mesalazine 1.5 g gastro-resistant modified-release granules sachets sugar free
511020	Mesalazine 400 mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)
99326020	Salofalk 500 mg gastro-resistant tablets (Dr. Falk Pharma UK Ltd)
504020	Pentasa 500 mg modified-release tablets (Necessity Supplies Ltd)
52476021	Octasa 800 mg MR gastro-resistant tablets (Waymade Healthcare Plc)
72466020	Pentasa Mesalazine 1 g/100 mL enema (Ferring Pharmaceuticals Ltd)
76805020	Ipocol 400 mg gastro-resistant tablets (Sandoz Ltd)
512020	Mesalazine 400 mg gastro-resistant tablets (DE Pharmaceuticals)
94805020	Mesalazine 2 g modified-release granules sachets sugar free
45447020	Octasa 400 mg MR gastro-resistant tablets (Tillotts Pharma Ltd)
99691020	Mesalazine (roi) 1000 mg Modified-release tablet
41199020	Mezavant XL 1200 mg tablets (Waymade Healthcare Plc)
61601020	Mesalazine 500 mg suppositories
20132021	Mesalazine 400 mg gastro-resistant tablets (Waymade Healthcare Plc)
49718020	Mesalazine 250 mg Modified-release tablet
61603020	Mesalazine 2 g/59 mL enema
810021	Mesalazine 3 g gastro-resistant modified-release granules sachets sugar free
98985020	Asacol 400 mg MR gastro-resistant tablets (Allergan Ltd)
99338020	Salofalk 1 g suppositories (Dr. Falk Pharma UK Ltd)
72468020	Pentasa 1 g suppositories (Ferring Pharmaceuticals Ltd)
87039020	Mesalazine 500 mg gastro-resistant modified-release granules sachets sugar free
507020	Pentasa 1 g suppositories (Lexon (UK) Ltd)
40604021	Mesalazine 250 mg suppositories (Ennogen Healthcare Ltd)
87043020	Salofalk 1 g gastro-resistant modified-release granules sachets (Dr. Falk Pharma UK Ltd)
60398020	Mesalazine 400 mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
295021	Mesalazine 1 g modified-release tablets
506020	Pentasa 1 g suppositories (Sigma Pharmaceuticals Plc)
99166020	Octasa 800 mg MR gastro-resistant tablets (Tillotts Pharma Ltd)
49719020	Mesalazine 500 mg modified-release tablets
82438020	Salofalk 2 g/59 mL enema (Dr. Falk Pharma UK Ltd)
505020	Pentasa 1 g suppositories (Waymade Healthcare Plc)
95767020	Salofalk 1.5 g gastro-resistant modified-release granules sachets (Dr. Falk Pharma UK Ltd)
72467020	Pentasa 250 mg Modified-release tablet (Ferring Pharmaceuticals Ltd)
87041020	Salofalk 500 mg gastro-resistant modified-release granules sachets (Dr. Falk Pharma UK Ltd)
72473020	Mesalazine 250 mg suppositories

(*Contd*...)

Supplementary Table 2 (*Continued*)

Gemscript code	Product Name
87332020	Mesren MR 400 mg gastro-resistant tablets (Teva UK Ltd)
49720020	Mesalazine 1 g modified-release granules sachets sugar free
56928020	Salofalk 250 mg gastro-resistant tablets (Dr. Falk Pharma UK Ltd)
293021	Pentasa 1 g modified-release tablets (Ferring Pharmaceuticals Ltd)
75484020	Pentasa 1 g modified-release granules sachets (Ferring Pharmaceuticals Ltd)
44834021	Mesalazine 4 g modified-release granules sachets sugar free
76808020	Salofalk 1 g/application foam enema (Dr. Falk Pharma UK Ltd)
21680021	Asacol 400 mg MR gastro-resistant tablets (Waymade Healthcare Plc)
64436020	Mesalazine 400 mg gastro-resistant tablets
61602020	Mesalazine 1 g suppositories
72472020	Mesalazine 1 g/application foam enema
35131020	Pentasa 2 g modified-release granules sachets (Mawdsley-Brooks & Company Ltd)
61383020	Asacol 250 mg suppositories (Allergan Ltd)
94364020	Asacol 800 mg MR gastro-resistant tablets (Allergan Ltd)
75483020	Pentasa 500 mg modified-release tablets (Ferring Pharmaceuticals Ltd)
513020	Asacol 400 mg MR gastro-resistant tablets (Sigma Pharmaceuticals Plc)
94202020	Mesalazine 1.2 g gastro-resistant modified-release tablets
94661020	Mesalazine 1 g gastro-resistant modified-release granules sachets sugar free
502020	Pentasa 500 mg modified-release tablets (Waymade Healthcare Plc)
95290020	Pentasa 2 g modified-release granules sachets (Ferring Pharmaceuticals Ltd)
64437020	Mesalazine 250 mg gastro-resistant tablets
67523020	Mesalazine mr 400mg Tablet (IVAX Pharmaceuticals UK Ltd)
82437020	Salofalk 500 mg suppositories (Dr. Falk Pharma UK Ltd)
812021	Salofalk 3 g gastro-resistant modified-release granules sachets (Dr. Falk Pharma UK Ltd)
91690020	Mesalazine 800 mg gastro-resistant tablets
44835021	Pentasa 4 g modified-release granules sachets (Ferring Pharmaceuticals Ltd)
99324020	Mesalazine 500 mg gastro-resistant tablets
39414020	Mesalazine 3 g gastro-resistant modified-release granules sachets sugar free
46086020	Mesalazine 800 mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
23575021	Pentasa 1 g modified-release tablets (Waymade Healthcare Plc)