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ORIGINAL ARTICLE

Clinical and endoscopic outcomes of patients with colonic Crohn's disease treated with 5-aminosalicylates as monotherapy

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KEYWORDS
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Abstract
Background: In spite of the lack of evidence regarding the clinical benefits of oral 5-aminosalicylic acid (5-ASA) compounds in Crohn's disease (CD), these drugs are frequently used in daily clinical practice, particularly for colonic CD. Our aim is to assess the use and clinical outcomes of 5-ASA of those patients with colonic CD treated with 5-ASA as monotherapy.
Methods: Patients diagnosed with isolated colonic CD and treated with 5-ASA but never exposed to immunosuppressants or biologicals were identified from the local databases of five referral centres. A retrospective review of clinical and endoscopic outcomes was performed.
Results: Out of 545 patients with isolated colonic CD, 106 (19%) were treated with oral 5-ASA in monotherapy as maintenance therapy. The median follow-up was 144 months (interquartile range [IQR], 48–234). Almost all of the patients (92%) presented an inflammatory pattern and 11% developed perianal disease. Half of the patients had already received 5-ASA at diagnosis, and the median duration of 5-ASA treatment was 107 months (IQR 22.5–187). Endoscopic remission, as defined by the absence of ulcers at the last complete colonoscopy, was observed in 65% of those patients undergoing at least one colonoscopy during follow-up. Male gender and extraintestinal manifestations were associated with a lower likelihood of achieving endoscopic remission. Nine patients required colectomy, but mostly soon after CD diagnosis.

Abbreviations: CD, Crohn's disease; 5-ASA, 5-aminosalicylic acid compounds; IBD, inflammatory bowel disease; IQR, interquartile range.

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Conclusions: 5-ASA seems to be of benefit in the long-term in one fifth of patients with colonic CD as the only maintenance therapy and should be considered in fragile patients with Crohn's colitis.

PALABRAS CLAVE
Enfermedad de Crohn;
Colitis;
Mesalazina;
5-ASA;
Enfermedad inflamatoria intestinal;
Endoscopia

Resultados clínicos y endoscópicos de pacientes con enfermedad de Crohn colónica tratados con 5-aminosalicilatos como monoterapia

Resumen
Antecedentes: A pesar de la falta de evidencia sobre los beneficios clínicos de los 5-aminosalicíilatos (5-ASA) orales en la enfermedad de Crohn (EC), estos medicamentos se utilizan con frecuencia en la práctica clínica diaria, particularmente para la EC cólica. Nuestro objetivo es evaluar el uso y los resultados clínicos del 5-ASA en aquellos pacientes con EC cólica tratados con 5-ASA en monoterapia.
Métodos: Los pacientes diagnosticados con EC cólica aislada y tratados con 5-ASA pero nunca expuestos a inmunosupresores o agentes biológicos fueron identificados a partir de las bases de datos locales de 5 centros de referencia. Se realizó una revisión retrospectiva de los resultados clínicos y endoscópicos.
Resultados: De 545 pacientes con EC cólica aislada, 106 (19%) fueron tratados con 5-ASA oral en monoterapia como terapia de mantenimiento. La mediana de seguimiento fue de 144 meses (rango intercuartílico: 48-234). Casi todos los pacientes (92%) presentaban un patrón inflamatorio y un 11% desarrollaron enfermedad perianal. La mitad de los pacientes ya habían recibido 5-ASA en el momento del diagnóstico y la mediana de duración del tratamiento con 5-ASA fue de 107 meses (rango intercuartílico: 22,5-187). La remisión endoscópica, definida por la ausencia de úlceras en la última colonoscopia completa, se observó en el 65% de los pacientes a los que se les realizó al menos una colonoscopia durante el seguimiento. El género masculino y las manifestaciones extraintestinales se asociaron con una menor probabilidad de lograr la remisión endoscópica. Nueve pacientes requirieron colectomía, pero en su mayoría poco después del diagnóstico de EC.
Conclusiones: Los 5-ASA parecen ser beneficiosos a largo plazo en una quinta parte de los pacientes con EC cólica como única terapia de mantenimiento y deben considerarse en pacientes frágiles con EC con afectación exclusiva del colon.

Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract of unknown aetiology. CD is characterised by a transmural chronic inflammation that causes cumulative tissue damage and eventually leads to the development of intestinal strictures, enteric fistulae or intraabdominal abscesses. CD is classified phenotypically according to the Montreal classification in terms of age at diagnosis, location and disease behaviour, which are known to determine surgical and medical requirements, as well as disease prognosis.[1,2] Isolated colonic CD, also known as Crohn's colitis, was first described as a separate entity in 1952.[3] Crohn's colitis accounts for approximately one third of CD patients in population-based studies. Of note, anatomical disease location is unlikely to change over time in CD.[4] Crohn's colitis is often perceived as a subtype of CD due to certain peculiarities. Robust data suggest that Crohn's colitis is genetically separable from small intestine CD and ulcerative colitis,[5] that it has a higher prevalence of perianal disease (ranging from 41% to 92% depending on rectal involvement) and a lower prevalence of strictures and intraabdominal penetrating complications as compared with ileal CD, leading to lower rates of surgical intestinal resections.[4,6–9]

Two early trials comparing sulphasalazine with placebo for the induction of clinical remission in mild-to-moderate CD suggested that the efficacy of the drug was limited to patients with colonic CD.[10,11] Since then, two meta-analyses of randomised controlled trials have agreed in showing no benefits of 5-aminosalicylic acid compounds (5-ASA) over placebo either in the induction of remission or the maintenance of medically induced remission in CD.[12,13] However, specific meta-analyses and randomised controlled trials focussing on isolated colonic CD are not available and, furthermore, two recent network meta-analyses focusing on the efficacy of high doses of 5-ASA for the induction of clinical remission in CD reported conflicting results.[14,15] The latest guidelines of the European Crohn's and Colitis Organisation for the medical treatment of CD based on the

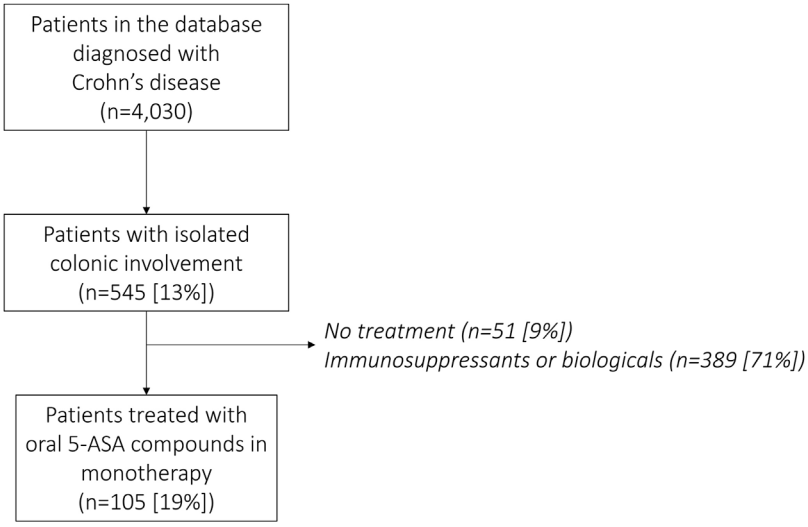

Figure 1 Treatment scheme.

GRADE workflow recommended against the use of 5-ASA for either the induction or maintenance of remission in CD.[16] Nevertheless, the authors of the guidelines also stated that there is a gap in our knowledge regarding how to treat mild-to-moderate CD localised in different parts of the gastrointestinal tract other than the ileum and right colon. The same applies to maintenance treatment in patients in whom remission has not been induced by biological agents or who do not meet the criteria for steroid-dependency. Nonetheless, 5-ASA are still commonly used in daily clinical practice, particularly in Crohn's colitis, probably due to its milder course, the theoretical preventive effect of 5-ASA compounds on dysplasia and their good safety profile, demonstrating a significant gap between clinical practice and evidence-based recommendations.[17]

Our aim was to assess the use of 5-ASA in monotherapy in patients with isolated colonic CD, describe their clinical features, and assess their clinical outcomes in 5-ASA therapy.

Methods

This is a retrospective, multicentre study performed at five Spanish referral centres for inflammatory bowel disease (IBD). All adult CD patients with isolated colonic involvement were identified from the local ENEIDA registry database of each participating centre. ENEIDA is a prospectively maintained registry promoted by the Spanish Working Group in Crohn's and Colitis (GETECCU), which includes patients with IBD.[18] The database includes clinical characteristics, outcomes and treatments. The registry was approved by the local Ethics Committees of all the participating centres, and all patients gave their signed informed consent.

Patients were included if they were exposed to treatment with 5-ASA at any time during the disease course. Exclusion criteria were exposure to immunosuppressants or biological agents and any involvement of the gastrointestinal tract in addition to the colon and rectum. Patients were followed-up from CD diagnosis to death, loss of follow-up, or last visit before data collection, whichever occurred first.

Collected data included demographic characteristics, age at diagnosis and onset of 5-ASA, disease behaviour at diagnosis and during the follow-up period in accordance with the Montreal classification, development of perianal disease or any extra-intestinal manifestation, dose and duration of 5-ASA therapy, and use of steroids (including the number of steroid courses). Findings at all the colonoscopies performed after diagnosis were reviewed and registered. Finally, we registered the presence of dysplasia or neoplasia and the necessity of segmental or total colectomy.

Statistical analysis

Continuous variables are expressed as median and interquartile range (IQR) and compared using the Student's *t* test. Categorical variables are expressed as proportions and compared by means of the Chi-square test.

Results

Among a total of 545 patients with isolated colonic CD, 105 (19%) received treatment with 5-ASA and were never exposed to immunosuppressants or biologicals (Fig. 1). These patients' characteristics are summarised in Table 1. Median age at disease diagnosis was 42 years (range, 11–82) and median follow-up was 153 months (range, 12–432). Seven patients were initially diagnosed with ulcerative colitis ($n = 4$) or inflammatory bowel disease unclassified ($n = 3$), but this diagnosis was later changed to CD. More than 90% of patients had at least two colonic segments involved, and 19% had pancolitis (rectal plus all colonic segments involved) and it is noteworthy that 60% had rectal involvement. CD showed an inflammatory pattern in almost all patients (90%), though 10% developed both stenosing and penetrating disease-related complications. In addition, perianal disease developed in 12% of patients and extra-intestinal manifestations in 20% (mostly (10%) dermatological and rheumatological (9%)). Seventy-one patients (68%) were diagnosed after 2000, when biological agents became available.

Table 1 Patients' characteristics ($n = 105$).

Female gender	59 (56)
Colonic involvement	
Cecum	59 (56)
Ascending colon	63 (60)
Transverse colon	69 (66)
Descending colon	72 (69)
Sigmoid colon	70 (67)
Rectum	63 (60)
Disease behaviour	
Inflammatory	95 (90)
Stricturing	0 (0)
Penetrating	0 (0)
Stricturing and penetrating	10 (10)
Perianal disease	12 (12)
Extraintestinal manifestations	21 (20)

Regarding the use of therapeutic resources, 62 patients (59%) had received systemic corticosteroids at any time during the course of the disease. Half of the patients started oral 5-ASA at the time of disease diagnosis (range, 0–324 months), and 75% started within the first year after diagnosis. The median duration of treatment was 107 months (range, 0–414); the median maximal dose of 5-ASA was 3 grams/day (range, 1.5–6) and the minimal dose was 2 g/day (range, 0.5–4), with a median individual variation in the 5-ASA dose of 0.8 g/day.

Seventy-five patients (71%) underwent at least one complete colonoscopy during the follow-up after a median time from diagnosis of 108 months, and 49 patients (46%) underwent at least two colonoscopies. Endoscopic remission (as defined by the absence of ulcers at the last complete colonoscopy) was observed in 49 (65%) of these patients. Moreover, 43 patients on whom one or more colonoscopies were performed (57%) were in endoscopic remission in all the examinations.

Nine patients required a total ($n = 4$) or segmental ($n = 5$) colectomy during follow-up (four for refractoriness, two for dysplasia, two for colonic strictures and one for colonic perforation). Table 2 summarises the main features of the patients who underwent surgery. Five out of nine had pancolitis with or without rectal involvement, and only two were females. Interestingly, seven out of these nine patients underwent surgery either at the time of or within the first year after diagnosis. In two patients who were operated on for colonic cancer, CD diagnosis was made at the time the cancer was detected. Of note, six out of nine patients underwent surgery at over 60 years of age and three before the era of biological agents.

In the univariate analysis, male gender ($p = 0.007$) and extraintestinal manifestations ($p = 0.033$) were associated with a lower likelihood of being in endoscopic remission at the last endoscopic assessment.

Discussion

Several recent population-based studies have confirmed the extensive use of 5-ASA in patients with CD regardless of the current recommendations in American and European guidelines and the widespread availability of biological agents. Schoepfer et al. observed that 59% of CD patients from the Swiss IBD cohort were prescribed 5-ASA (for half of them as monotherapy) already in the era of biologicals; moreover, they found that the use of 5-ASA was significantly more frequent among patients with colonic disease.[17] Hart et al. assessed the prescription of 5-ASA among more than 21,000 CD patients between 2006 and 2018 using the UK Clinical Practice Research Datalink database. They found that 5-ASA was prescribed in 44% of patients, in 63% of the cases as monotherapy.[19] Van Deen et al., in a 2010–2012 insurance claims analysis encompassing more than 500,000 CD patients in the United States, reported that 5-ASA had been prescribed to 42% of patients, 79% of whom underwent the treatment as monotherapy.[20] Finally, Rubin et al., in another retrospective analysis of commercial US insurance claims from 2006 to 2010 including more than 13,000 CD patients, observed that 5-ASA was the most commonly prescribed therapeutic drug group (47%) and was used as monotherapy in almost half of the patients.[21] From a different perspective, a recent systematic review of all randomised, placebo-controlled induction and maintenance trials in adults with CD found a pooled proportion of concomitant use of 5-ASA at inclusion in the placebo arms of 44% (95% CI 39–49%) for induction trials and 49% (95% CI 35–69%) for maintenance trials.[22] However, none of these studies focused on Crohn's colitis, despite it being the phenotypic form of CD in which 5-ASA compounds are preferentially used and might be most beneficial. In order to assess the potential clinical benefits of 5-ASA in CD, we decided to include only patients with Crohn's colitis and we found a rate of 5-ASA use of 19%. This figure is markedly lower than that reported in the Swiss cohort, in which 68% of patients with Crohn's colitis used 5-ASA. However, there are a number of reasons that may explain this difference with regard to previous studies. Firstly, our data come from five referral centres whereas large insurance or administrative databases often include private practices and small centres that may account for milder cases or be more prone to following careful step-up therapeutic approaches. Second, all the above-mentioned studies also included patients treated with 5-ASA in combination with other drugs whereas we only included patients treated in monotherapy and never exposed to any immunosuppressant or biological agents. In fact, when considering only patients in monotherapy, their figures are closer to ours than those of the aforementioned studies.[17,19–21]

Most of the available studies on the use of 5-ASA in CD lack a direct evaluation of disease evolution while on 5-ASA or only searched for surrogate parameters such as clinical effectiveness as perceived by the physician,[17] treatment discontinuation, dose titration or switching.[21,22] Using these indirect parameters of therapeutic efficiency, approximately half of the patients seemed to benefit from 5-ASA, as expressed by the 48% rate of treatment continuation[21] or 67% rate of patients not needing additional drug therapies.[19] We also observed a relatively low rate of steroid requirements (less than two thirds), with a median of only one steroid course. Furthermore, one of the strengths of our study is the assessment of endoscopic remission during follow-up, the currently recommended target in the long-term for any therapy in inflammatory bowel diseases.[23] Most of

Table 2 Main characteristics of the patients undergoing colectomy.

Case	1	2	3	4	5	6	7	8	9
Gender	M	M	M	M	F	M	M	F	M
Year of diagnosis	1988	1994	1996	1998	1994	2003	2005	2005	2010
Age at colectomy	26	62	52	64	67	80	49	83	73
Year of colectomy	1988	1994	1996	2001	2002	2003	2005	2006	2010
Affected segments	Pancolitis with rectal sparing	Ascending & transverse colon	Pancolitis	Pancolitis with rectal sparing	Pancolitis with rectal sparing	Pancolitis	Left colon & rectum	Left colon with rectal sparing	Transverse colon & rectum
Rectal involvement	No	No	Yes	No	Yes	Yes	Yes	No	Yes
Disease behaviour	Inflammatory	Inflammatory	Inflammatory	Inflammatory	Stricturing & penetrating	Inflammatory	Inflammatory	Inflammatory	Inflammatory
Indication for surgery	Refractory disease	Refractory disease	Stenosis	Perforation	Stenosis	Refractory disease	Colonic cancer	Refractory disease	Colonic cancer
Type of colectomy	Total	Segmental	Segmental	Total	Segmental	Total	Segmental	Total	Segmental
Months from diagnosis to the beginning of 5-ASA	324	0	12	0	0	0	0	12	0
Follow-up colonoscopies	Rectal persistent lesions in 2010, 2012, 2015	Endoscopic remission 2011, 2017	Endoscopic remission 2008 and 2014	Rectal endoscopic remission 2011, 2013, 2015	Endoscopic remission 2005	Not applicable	Endoscopic remission in 2008, 2010, 2011	Not applicable	Not applicable

our patients had at least one follow-up colonoscopy and, strikingly, two thirds showed endoscopic remission at the last endoscopic assessment while on 5-ASA therapy. We are aware that we do not have a control group for purposes of comparison and it can even be considered that some milder forms of Crohn's colitis (aphtous colitis) may remain stable or even heal over time, as recently reported.[24] However, the rate of endoscopic remission is high enough to consider a certain therapeutic role of 5-ASA. Moreover, although nine patients underwent segmental or total colectomies, most of them were indicated at the time of CD diagnosis or in the following months. Our efficacy data, together with the known safety profile of 5-ASA compounds, support the use of these drugs in those patients with colonic CD in whom immunosuppressants are contraindicated or should be avoided, such as the elderly, as some authors have also recently suggested.[25] In fact, elderly-onset CD tends to be predominantly colonic in distribution, with an inflammatory and indolent behaviour, making it the optimal target for this therapeutic strategy.[26,27]

Its retrospective design, the lack of periodical faecal calprotectin determinations and outcomes such as CD-related hospitalizations are additional limitations of our study. However, this is counterbalanced by the availability of endoscopic assessment during follow-up and the number of steroid courses. Finally, the exclusion of those patients who were exposed at any time to immunosuppressants or biologicals might have introduced a selection bias, which may provide an alternative explanation of our good results, than attributing them to the effects of 5-ASA.

In conclusion, 5-ASA compounds are still used for CD, particularly for Crohn's colitis, and even at referral centres. Our data suggest that they induce endoscopic remission in the majority of patients and should be considered a therapeutic option in fragile patients with Crohn's colitis.

Conflicts of interest

LM has served as a speaker, or has received research or education funding or advisory fees from Takeda, Janssen, Pfizer and Tillots; MC has served as a speaker, or has received research or education funding or advisory fees from Takeda, Janssen, Faes Farma, Gilead, Pfizer and MSD; CG-M has received education funding fees from Jansen, Kern, Faes, Tillots Pharma, Takeda; FC has served as a speaker, or has received research or education funding or advisory fees from Takeda, Janssen, MSD, and Ferring; JG has served as a speaker, or has received research or education funding or advisory fees Roche, MSD, AbbVie, Kern Pharma, Takeda, Janssen, Pfizer, Ferring and GE Healthcare; EG-P has served as a speaker, or has received research or education funding or advisory fees from MSD, Abbvie, Kern, Gebro, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Faes, Tillotts Pharma, Pfizer; MM has served as a speaker, or has received research or education funding or advisory fees from FAES, Ferring MSD, AbbVie, Takeda and Janssen; ED has served as a speaker and has received research and educational funding and advisory fees from AbbVie, Adacyte Therapeutics, Biogen, Celltrion, Gilead, Janssen, Kern Pharma, MSD, Pfizer, Roche, Samsung, Takeda, Tillotts, Thermofisher. The remaining authors declared no conflicts of interest.

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