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Effect of 5-aminosalicylates on renal function in patients with inflammatory bowel disease: 4-year follow-up study

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ABSTRACT

OBJECTIVE: Nephrotoxicity has been described in some patients with inflammatory bowel disease (IBD) treated with 5-aminosalicylates (5-ASA). Our aim was to conduct a retrospective study of IBD patients, both with and without 5-ASA treatment, who underwent regular evaluation of renal function over a 4-year period.

METHODS: Serum creatinine was measured before the start of 5-ASA therapy, and thereafter yearly up to 4 years. Creatinine clearance (Cl_{Cr}) was estimated from serum creatinine (Cockroft & Gault formula). The influence of 5-ASA treatment on renal function was assessed by univariate and multivariate analysis.

RESULTS: A total of 150 IBD patients (ulcerative colitis in 45%, Crohn's disease in 55%) were included. Sixty-two patients were receiving 5-ASAs (95% coated mesalazine, mean dose 1.9 ± 0.8 g/day). Both serum creatinine levels and Cl_{Cr} were similar in patients with and without 5-ASA treatment, and remained stable throughout the 4-year follow-up in patients taking 5-ASAs. In the multivariate analysis, 5-ASA treatment (or its dose) was not correlated with serum creatinine levels or Cl_{Cr}. No interstitial nephritis was reported during follow-up.

CONCLUSION: 5-ASA-related renal disease was not found in our series, suggesting that the occurrence of renal impairment in IBD patients receiving these drugs is exceptional. Our results do not support the recommendation of serum creatinine monitoring in patients receiving 5-ASA treatment.

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EFECTO DE LOS 5-AMINOSALICILATOS EN LA FUNCIÓN RENAL A LO LARGO DE 4 AÑOS EN PACIENTES CON ENFERMEDAD INFLAMATORIA INTESTINAL

OBJETIVO: Se han descrito algunos casos de nefrotoxicidad en pacientes con enfermedad inflamatoria intestinal (EII) tratados con 5-aminosalicilatos (5-ASA). Nuestro objetivo fue realizar un estudio retrospectivo de un grupo de pacientes con EII, con y sin tratamiento con 5-ASA, en los que se evaluaba la función renal regularmente durante un período de 4 años.

MÉTODOS: Se determinaba la creatinina sérica antes de comenzar el tratamiento con 5-ASA y posteriormente se efectuaba un control analítico anual durante 4 años. Se estimó el aclaramiento de creatinina (Cl_{Cr}) a partir de la creatinina sérica (fórmula de Cockroft-Gault). La influencia del tratamiento con 5-ASA en la función renal se valoró mediante análisis multivariante.

RESULTADOS: Se incluyeron 150 pacientes con EII (un 45% con colitis ulcerosa y un 55% con enfermedad de Crohn). Los valores séricos de creatinina a los 0, 1, 2, 3 y 4 años en los pacientes que recibían 5-ASA permanecieron estables. Asimismo, el Cl_{Cr} no se modificó durante los 4 años de seguimiento en los pacientes tratados con 5-ASA. Más aún, los valores tanto de creatinina sérica como de Cl_{Cr} fueron similares en los pacientes con y sin tratamiento con 5-ASA. Finalmente, el tratamiento con 5-ASA no se correlacionó con los valores séricos de creatinina ni con el Cl_{Cr} en el estudio multivariante. No se describió ningún caso de nefritis intersticial durante el seguimiento.

CONCLUSIÓN: No hemos constatado ningún caso de nefrotoxicidad en nuestra serie de pacientes tratados con 5-ASA, lo que indica que la incidencia de alteraciones de la función renal en los pacientes con EII que reciben estos fármacos es excepcional. Nuestros resultados no apoyan la recomendación de registrar regularmente las cifras de creatinina sérica en los pacientes con EII que reciben tratamiento con 5-ASA.

INTRODUCTION

In mild to moderate active ulcerative colitis, both sulfasalazine and 5-aminosalicylic acid (5-ASA) have proven efficacy in inducing and maintaining clinical remission[1,2]. Considerations of long-term toxicity are important as lifetime maintenance treatment is usually recommended for ulcerative colitis. The introduction of 5-ASA into the treatment of patients with inflammatory bowel disease (IBD) has offered the opportunity of increasing dosages much further than had been possible with sulphonamide carrier compounds such as sulfasalazine, as a major advantage of 5-ASA agents is the safety profile[2]. However, a number of cases have been reported with 5-ASA-related toxicity[3,4]. In particular, nephrotoxicity, which may be potentially irreversible, has been described in some patients with IBD treated with 5-ASA[3-5]. In this respect, both acetylsalicylic acid and phenacetin, which have been implicated in the occurrence of non-steroidal anti-inflammatory drug induced nephropathy, share structural similarities with 5-ASA[6,7]. Furthermore, it has been demonstrated that 5-ASA may cause lesions to kidney tubular epithelial cells in animals when fed in high doses[6,7].

The actual incidence of nephrotoxicity in IBD patients receiving 5-ASA therapy has not been determined, but it has been suggested that renal impairment may occur in up to 1 in 100 patients treated with 5-ASA, although clinically important interstitial nephritis would occur in only 1 in 500 patients[8]. However, data regarding potential of renal impairment by 5-ASA therapy are contradictory, with some studies reporting an incidence > 1% of interstitial nephritis, and others suggesting that 5-ASA treatment has no effect on renal function[5]. Nevertheless, these data are based on a relatively low number of patients and with a limited follow-up.

Consequently, despite increasing recognition of the potential for this serious adverse event (nephrotoxicity), guidelines for monitoring renal function in patients prescribed 5-ASA preparations are not widely employed[3]. Furthermore, no evidence exists to date that either the test, or the frequency of testing, is effective in identifying these patients at risk of developing 5-ASA-related renal impairment, and therefore there are no firm recommendations for renal function monitoring in IBD patients treated with these drugs.

Our aim was to conduct a retrospective study of IBD patients, both with and without 5-ASA treatment, evaluating parameters of renal function regularly analyzed during 4 years, to assess whether long-term use of these drugs has detrimental effects on renal function.

PATIENTS AND METHODS

Patient population

Consecutive patients with the diagnosis of IBD at the Gastroenterology Unit from the Hospital Universitario de la Princesa (Madrid, Spain) and followed-up for at least 4 years, were included in this retrospective study. Diagnoses of Crohn's disease and ulcerative colitis were established by standard clinical, radiological, histological, and endoscopic criteria[9]. The Vienna classification of Crohn's disease based on Age at Diagnosis –under 40 years (A1), equal to or over 40 years (A2)], Location [terminal ileum (L1), colon (L2), ileocolon (L3), upper gastrointestinal (L4)], and Behaviour [nonstricturing nonpenetrating (B1), stricturing (B2), penetrating (B3)–, was used. For ulcerative colitis, a classification based on the location and extension of the disease was used: proctitis, left-side colitis (up to the splenic flexure), and extensive colitis/pancolitis. Exclusion criteria were: pre-existing renal disease, cardiac or hepatic failure, hypertension, diabetes mellitus, patients treated with diuretics or antihypertensive drugs, and the history of chronic ingestion of aspirin or non-steroidal anti-inflammatory drugs.

Data collection

Medical records from these patients were reviewed for the study. At baseline, the following variables were prospectively extracted in a predefined data extraction form: age, sex, smoking habit, body weight, type of IBD, site of involvement, history of bowel resections, and use of medication since the diagnosis (mainly with 5-ASA, but also with other drugs used for the treatment of IBD, and with non-steroidal anti-inflammatory drugs). With respect to the use of 5-ASAs, patients were divided into the following subgroups: patients without a history of 5-ASA treatment, with a history of sulfasalazine, with a history of mesalazine, or with a history of both compounds. 5-ASA dosage was categorized as: low (less than 1.5 g/day), intermediate (more than 1.5 but less than 3 g/day) and high (more than 3 g/day). All data obtained were collected in an anonymous database for the analysis, which was approved by the local Medical Ethical Committee.

Assessment of renal function

Patients were reviewed in our out-patient clinic every 6 months for clinical evaluation of disease activity. Analytical controls (including complete blood count and biochemistry including creatinine) were performed every 12 months in all patients. Renal function was monitored by measuring levels of serum creatinine in all patients (both with and without 5-ASA treatment). In patients taking 5-ASAs, serum creatinine was measured before starting 5-ASA therapy, and thereafter yearly up to 4 years (patients were taking the drug at a stable dose for the 4-year period of study). Because creatinine excretion was not regularly measured, we were unable to calculate endogenous creatinine clearance (Cl_{Cr}). Therefore, Cl_{Cr} was estimated from serum creatinine with the Cockroft and Gault formula, which takes into account age, weight and sex[10,11]. The Cl_{Cr} (in ml/min) was calculated by the following formula: (140 – age [in years] × body weight [in kg]/72 × serum creatinine [in mg/100 ml]); because of differences in body composition, a correction factor of 0.85 was used for women. Based on the estimated glomerular filtration rate, patients were classified as having: normal renal function (Cl_{Cr} > 60 ml/min), moderate impairment (Cl_{Cr} 30-59), severe impairment (Cl_{Cr} 15-29), and advanced renal failure (Cl_{Cr} < 15)[11].

Statistical analysis

For continuous variables, mean and standard deviation were calculated. For categorical variables, percentages and corresponding 95% confidence intervals (95% CI) were provided. Categorical variables were compared with the χ^2 test, and quantitative variables with the Student t test. A p value < 0.05 was considered statistically significant. The influence of 5-ASA treatment on renal function was assessed by multivariate analysis (multiple linear regression analysis). The dependent variable was Cl_{Cr}, and the independent variables were: age (categorized as higher or lower than 42 years, which was the median value), sex (male/female), smoking (smokers/non-smokers), weight (categorized as higher or lower than 67 kg, which was the median value), type of IBD (ulcerative colitis or Crohn's disease), and treatment with 5-ASAs or steroids.

RESULTS

One-hundred and fifty patients (45% with ulcerative colitis and 55% with Crohn's disease) were included in the study. Mean age was 45 ± 15 years, 45% were males, and 30% were smokers. Vienna classification of Crohn's disease patients was as follows: age at diagnosis (A1, 79%;

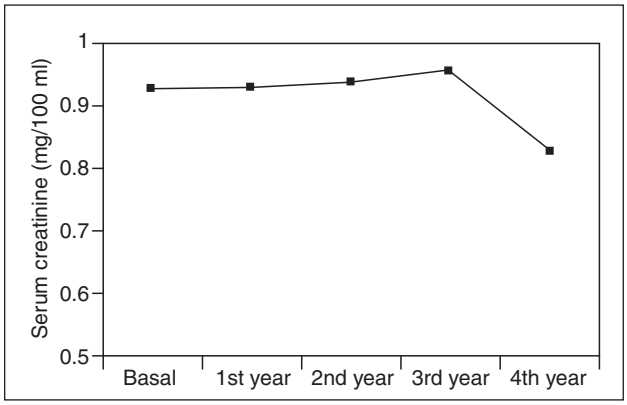

Fig. 1. Serum creatinine levels during follow-up in patients treated with 5-aminosalicylic acid.

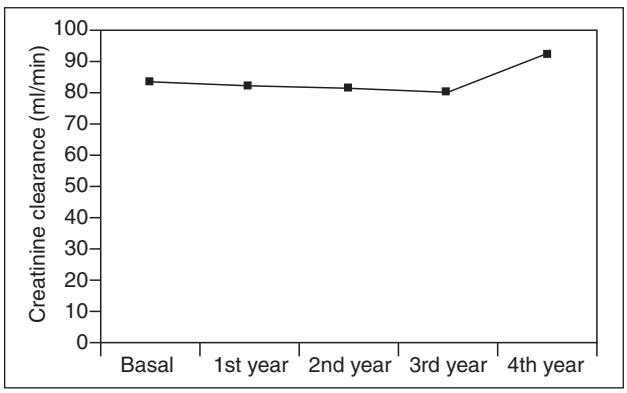

Fig. 2. Creatinine clearance during follow-up in patients treated with 5-aminosalicylic acid.

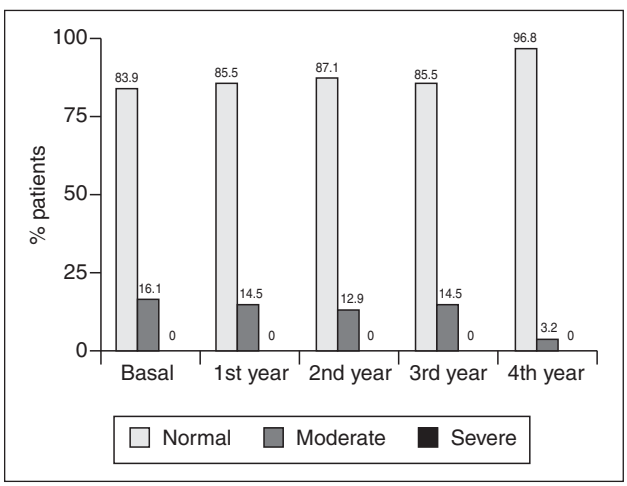

Fig. 3. Percentage of patients with mild, moderate, and severe impairment of the estimated glomerular filtration rate during follow-up in patients treated with 5-aminosalicylic acid.

A2, 21%), location (L1, 25%; L2, 20%; L3, 51%; and L4, 4%), and behaviour (B1, 43%; B2, 21%; and B3, 36%). Ulcerative colitis location distribution was as follows: proctitis (25%), left-side colitis (43%), and extensive colitis/pancolitis (32%).

TABLE I. **Values of serum creatinine (Cr) and creatinine clearance (Cl_{Cr}) in patients with and without 5-aminosalicylic acid (5-ASA) treatment**

	With 5-ASA treatment (n = 62)	Without 5-ASA treatment (n = 88)
Cr basal	0.93 ± 0.2	0.94 ± 0.2
Cr 1st yr	0.93 ± 0.2	0.93 ± 0.1
Cr 2nd yr	0.94 ± 0.2	0.95 ± 0.2
Cr 3rd yr	0.96 ± 0.2	0.94 ± 0.2
Cr 4th yr	0.83 ± 0.2	0.86 ± 0.2
Cl_{Cr} basal	84 ± 26	89 ± 19
Cl_{Cr} 1st yr	83 ± 26	89 ± 20
Cl_{Cr} 2nd yr	82 ± 23	88 ± 20
Cl_{Cr} 3rd yr	81 ± 25	89 ± 21
Cl_{Cr} 4th yr	93 ± 25	99 ± 28

Sixty-two patients (46 with ulcerative colitis, 16 with Crohn's disease) were receiving 5-ASA treatment: 59 patients (95%) received coated mesalazine (Claversal® or Lixacol®), 1 patient (1.6%) received prolonged release mesalazine (Pentasa®), and 2 patients (3.2%) received sulfasalazine. Mean dose of mesalazine was 1.9 ± 0.8 g/day (range, 0.5-4), and most patients were receiving between 1 and 3 g/day (< 1 g/day, 4 patients; 1-2 g/day, 21 patients; 2-3 g, 22 patients; and 3-4 g/day, 8 patients). Sixty-three patients were receiving azathioprine or mercaptopurine, and 3 patients were treated with infliximab.

Serum creatinine levels at 0, 1, 2, 3, and 4 years in patients taking 5-ASAs remained stable (0.93 ± 0.2, 0.93 ± 0.2, 0.94 ± 0.2, 0.96 ± 0.2, and 0.83 ± 0.2 mg/100 ml) (fig. 1). Similarly, Cl_{Cr} did not change for the 4-year follow-up in 5-ASA treated patients (84 ± 26, 83 ± 26, 82 ± 23, 81 ± 25, and 93 ± 25 ml/min) (fig. 2). Furthermore, values of both serum creatinine and Cl_{Cr} were similar in patients with and without 5-ASA treatment (non-statistically significant differences at any time from 1 to 4 years) (table I).

The percentage of patients with moderate impairment of the estimated glomerular filtration rate at 0, 1, 2, 3, and 4 years was: 16.1% (95% CI, 9-27), 14.5% (7.8-25%), 12.9% (6.7-23%), 14.5% (7.8-25%), and 3.2% (0.9-11) (fig. 3); while the corresponding figure for severe impairment of the estimated glomerular filtration rate was 0% at all control times (fig. 3).

Finally, in the multivariate analysis, 5-ASA treatment (yes/no) did not correlate with serum creatinine levels or Cl_{Cr}. Dose of 5-ASA was not predictive for change in renal function. No interstitial nephritis was reported during follow-up.

DISCUSSION

5-ASA-related renal disease was not reported in our series, which suggests that the incidence of renal impairment in IBD patients receiving these drugs is exceptional. Furthermore, values of both serum creatinine and Cl_{Cr} were similar in patients with and without 5-ASA treatment. Several studies have investigated the epidemiology of nephrotoxicity associated with 5-ASA use in patients with IBD. As an example, in the Dutch Pentasa study per-

formed in 1995, two patients (1.3%) developed modest, reversible renal impairment, only one of whom had biopsy proven interstitial nephritis (which represents a rate of clinically significant interstitial nephritis of approximately 1 in 150[12]). In 1996, a review of eight published clinical trials of 5-ASA therapy in IBD concluded that renal impairment, defined as any increase in serum creatinine, may occur in up to 1 in 100 patients treated with this drug, but that the incidence of clinically significant interstitial nephritis was less than 1 in every 500 patients treated[8]. This same year, Marteau et al[13] presented the safety reports on the use of Pentasa in France: spontaneous reports of adverse effects, submitted to a pharmaceutical manufacturer over a 2-year period, included 2 cases of renal impairment in approximately 45,000 patient-years of therapy[13]. One year later, Walker et al[14] reviewed a large computerized database drawn from general practices in the UK; renal complications of 5-ASA therapy were extremely rare (0 and 0.2 cases per 100 patient-years for high-dose users of sulfasalazine and 5-ASA, respectively).

In 2002, Ransford and Langman[15] evaluated serious adverse reactions reported to the Committee on Safety of Medicines of the UK in 1991-1998, noting 11.1 reports per million of prescriptions of interstitial nephritis associated with 5-ASA. This same year, a review of the literature included 18 clinical trials assessing the efficacy of 5-ASA preparations in the treatment of IBD for 6 months or more, and reported a prevalence of deterioration in renal function of only 0.06%[16]. In 2003, Logan et al[17], in a large epidemiological study in the UK, included almost 40,000 patients and found that the overall incidence of renal damage was rare in patients taking 5-ASA drugs, but was increased relative to control patients (general population). More recently, data from the UK General Practice Research Database showed an incidence rate of 0.17 cases per 100 patients per year[18]. At the same time, in 2004, in a large European registry containing more than 1,500 patients with IBD, reported during a follow-up of 1 year, the incidence of renal failure was not increased in patients using 5-ASA[19]. Finally, a detailed postal questionnaire sent in 2004 to members of the British Society of Gastroenterology and the Renal Association[20], calculated an incidence of 5-ASA nephrotoxicity of 1 in 4,000 patients/year only.

The renal impairment associated to 5-ASA use may be diagnosed at any interval after starting treatment. Thus, several studies have concluded that there is no relationship between duration of 5-ASA treatment and the risk of renal disease[15,21], and that nephrotoxicity may appear from less than 1 month to more than 80 months after starting 5-ASA treatment[5]. However, most studies have included a relatively low number of patients and with a limited follow-up (of only several months). In our study, serum creatinine levels remained stable in patients taking 5-ASAs during the 4-year follow-up. Similarly, Cl_{Cr} did not change in these 4 years in 5-ASA treated patients, and no interstitial nephritis was reported during follow-up. Studies with 5-ASA treatment in which serum creatinine or Cl_{Cr} was measured regularly are summarized in table II[12,21-51] –including a total of 2,671 patients receiving 5-ASA treatment during a total of 3,070 years of follow-up–, where it is shown that nephrotoxicity was exceptional, being reported in only a few studies[12,22,43] (giving a mean annual nephrotoxicity rate of only 0.26% per patient-year of follow-up)[5].

TABLE II. **Studies with 5-aminosalicylic acid (5-ASA) treatment in which serum creatinine or creatinine clearance was measured regularly**

Autor (reference)	#Patients	Duration of 5-ASA treatment (months)	Patients with nephro-toxicity (%)
Birdetvedt et al[22]	32	28	2 (6%)
Birdetvedt et al[22]	59	38	3 (5%)
Courtney et al[23]	49	12	0 (0%)
Courtney et al[23]	50	12	0 (0%)
De Jong et al[24]	56	46	0 (0%)
Diener et al[25]	9	–	0 (0%)
Fockens et al[12]	150	12	1 (0.7%)
Fraser et al[26]	21	12	0 (0%)
Gendre et al[27]	80	24	0 (0%)
Giaffer et al[28]	65	12	0 (0%)
Green et al[29]	108	12	0 (0%)
Green et al[30]	49	12	0 (0%)
Green et al[30]	46	12	0 (0%)
Hawkey et al[31]	99	6	0 (0%)
Ireland et al[32]	82	6	0 (0%)
Kiilerich et al[33]	114	12	0 (0%)
Kruis et al[34]	108	6	0 (0%)
Mahmud et al[35]	40	9	0 (0%)
McIntyre et al[36]	41	6	0 (0%)
Mesalamine Study Group[37]	126	6	0 (0%)
Monteleone et al[38]	36	–	0 (0%)
Mulder et al[39]	41	12	0 (0%)
Poulou et al[40]	86	29	0 (0%)
Rachmilewitz et al[41]	115	2	0 (0%)
Rijk et al[42]	23	48	0 (0%)
Riley et al[43]	40	48	2 (5%)
Riley et al[44]	50	12	0 (0%)
Riley et al[21]	34	35	0 (0%)
Rutgeerts et al[45]	131	12	0 (0%)
Sandberg-Gertzen et al[46]	160	6	0 (0%)
Schreiber et al[47]	185	32	0 (0%)
Schroeder et al[48]	49	1.5	0 (0%)
Singleton et al[49]	230	4	0 (0%)
Siveke et al[50]	39	> 6	0 (0%)
Thomson et al[51]	68	12	0 (0%)

There have been several case reports of renal disease associated with 5-ASA treatment in patients with IBD (table III)[8,52-83]. The actual development of 5-ASA-related renal disease seems rare, as only 46 patients with this complication have been reported[5]. Thus, although the association between 5-ASA therapy and tubulo-interstitial nephritis is clearly described in several case reports, our study and other studies came to the reassuring conclusion that renal impairment in IBD patients is not frequently observed and is rarely associated with 5-ASA therapy. In the study by Elseviers et al[19], all IBD patients seen at the outpatient clinic of 27 European centres of gastroenterology during 1 year were registered and screened for renal impairment controlling for a possible association with 5-ASA therapy. Renal screening (calculated Cl_{Cr}) was performed at baseline, after 6 and 12 months. Decreased Cl_{Cr} was observed in 34 patients, among which 13 presented chronic renal impairment. Comparing patients with and

TABLE III. **Case reports of patients with inflammatory bowel disease and renal disease associated with 5-aminosalicylic acid (5-ASA) treatment**

Autor (reference)	Inflammatory bowel disease	Dose (g/day)	Duration (months)[a]	Type of nephrotoxicity
Agharazii et al[51]	UC	3.6	-	Interstitial nephritis
Agharazii et al[51]	UC	6.0	-	Interstitial nephritis
Arend et al[52]	UC	1.2	18	Interstitial nephritis
Behrens et al[53]	CD	-	-	Interstitial nephritis
Bonet et al[54]	UC	1.6	36	Interstitial nephritis
Brouillard et al[55]	CD	-	-	Interstitial nephritis
Brouillard et al[55]	CD	-	-	Interstitial nephritis
Brouillard et al[55]	UC	-	-	Interstitial nephritis
Calvino et al[56]	CD	1.2	12	Interstitial nephritis
Colombel et al[57]	CD	4	6	Interstitial nephritis
De Broe et al[58]	UC	1.5	28	Interstitial nephritis
Fornaciari et al[59]	UC	-	-	Minimal change nephropathy
Frandsen et al[60]	UC	-	10	Interstitial nephritis
Garcia-Diaz et al[61]	CD	-	1	Interstitial nephritis
Haas et al[62]	CD	2.4	12	Interstitial nephritis
Hamling et al[63]	CD	3	72	Interstitial nephritis
Henning et al[64]	UC	0.5	36	Interstitial nephritis
Howard et al[65]	UC	-	36	Interstitial nephritis
Laboudi et al[66]	CD	-	84	Interstitial nephritis
Maeda et al[67]	UC	-	-	Interstitial nephritis
Manenti et al[68]	UC	-	12	Interstitial nephritis
Margetts et al[69]	UC	-	24	Interstitial nephritis
Margetts et al[69]	CD	-	36	Interstitial nephritis
Masson et al[70]	UC	1.2	10	No renal biopsy
Mehta et al[71]	UC	2.4	7	Interstitial nephritis
Musil et al[72]	UC	-	1	Interstitial nephritis
Novis et al[73]	UC	2.4	5	Minimal change nephropathy
Ohya et al[74]	UC	-	12	Interstitial nephritis
Popoola et al[75]	UC	1.6	12	Interstitial nephritis
Popoola et al[75]	UC	1.6-2.4	60	Interstitial nephritis
Ruf-Ballauf et al[76]	UC	1.5	7	Interstitial nephritis
Smilde et al[77,b]	UC	3	24	Interstitial nephritis
Smilde et al[77,b]	UC	1.5-2	10	Interstitial nephritis
Smilde et al[77]	UC	1.5	36	Interstitial nephritis
Smilde et al[77]	CD	1.5	6	Interstitial nephritis
Smilde et al[77]	CD	1.5	8	Interstitial nephritis
Tadic et al[78]	UC	1.5	48	Interstitial nephritis
Thuluvath et al[79]	UC	1.2	24	Interstitial nephritis
Thuluvath et al[79]	UC	2.4	36	Interstitial nephritis
Von Muhlendahl et al[80]	UC	0.75	36	No renal biopsy
Wilcox et al[81]	CD	-	10	Interstitial nephritis
Witte et al[82]	CD	-	24	Interstitial nephritis
World et al[8]	UC	2.4	2	Interstitial nephritis
World et al[8]	-	-	8	Interstitial nephritis
World et al[8]	UC	1.6	3	Interstitial nephritis
World et al[8]	CD	4.2	42	Interstitial nephritis

CD: Crohn's disease; UC: ulcerative colitis.
[a]From starting 5-ASA treatment to nephrotoxicity development.
[b]The patient had already impaired renal function before starting treatment with 5-ASA.

without renal impairment, no difference could be observed in 5-ASA consumption.

In our study, dosage of 5-ASA was not predictive for change in renal function. In pre-clinical studies in animals nephrotoxicity appeared to be dose-related[3]. However, interstitial nephritis has been reported in patients taking doses of 5-ASA as low as 0.75 g/day[81] or even 0.5 g/day[65]. Most of the cases of nephrotoxicity reported in the literature occurred in patients taking doses from 1.2 to 2.4 g/day, being relatively low[5]. Furthermore, several studies have concluded that there is no relationship between 5-ASA dose and the risk of renal disease[15,18,19,21,24]. Finally, some authors have evaluated urinary enzymes as markers of renal tubular damage in patients with IBD, and could not demonstrate a correlation between the enzymuria and the cumulative doses of 5-ASA[84]. Moreover, they showed normalization of these urinary enzymes with successful medical therapy (directed to IBD) despite increasing cumulative doses of 5-ASA[84]. In this respect, in a point prevalence study no clear distinction between the influence of disease activity and drug treatment can be made, if increased dosage of the anti-inflammatory drug used correlates highly with disease activity[47]. The low overall incidence of renal disease during 5-ASA treatment reported in the literature, together with the absence of a clear relationship between 5-ASA dose and the risk of nephrotoxicity, suggest that the renal reactions may be idiosyncratic rather than dose related in nature.

Our study has several methodological limitations. Firstly, its retrospective design, although the study variables were prospectively extracted in a predefined data extraction form. Secondly, renal function was monitored by measuring levels of serum creatinine. The shortcomings of serum creatinine as a marker of renal function are well-known, and this parameter is a poor marker of renal function despite its universal use for this purpose. It is significantly af-

fected by a range of factors unrelated to glomerular filtration rate (e.g. sex, muscle mass and dietary meat intake)[85]. Furthermore, significant loss of functioning renal mass may occur before any rise in serum creatinine is apparent[85]. Therefore, more studies are necessary to determine whether serum creatinine gives sufficient warning of nephrotoxicity or whether more elaborate tests of renal function are required[20]. Because creatinine excretion was not regularly measured, we were unable to calculate endogenous Cl_{Cr}. However, in coincidence with other studies[19,24], Cl_{Cr} in our patients was estimated from serum creatinine with the Cockroft and Gault formula, which takes into account age, weight, and sex[10,11]. The above formula gives a correlation coefficient between predicted and mean measured Cl_{Cr} of 0.83, a figure that, although relatively high, is not perfect[10]. With this formula, the mean Cl_{Cr} may be estimated reliably in groups of patients. However, in higher ranges of Cl_{Cr}, the formula seems to underestimate Cl_{Cr}, whereas Cl_{Cr} seems to be overestimated in lower ranges[3,11]. Finally, due to the low incidence of 5-ASA related nephrotoxicity, thousands of patients would be needed to observe any significant difference between exposed and non-exposed subjects[86]. Thus, analytical epidemiological research (prospective cohort study or case-control study) needs the inclusion of a very large number of IBD patients. It has been emphasized the need for timely recognition of renal impairment and prompt discontinuation of 5-ASA treatment of affected patients. By not doing so, patients are placed, in theory, at risk for developing irreversible kidney damage. Thus, despite a lack of evidence that monitoring of serum creatinine is necessary or effective in patients receiving 5-ASA treatment, it has been suggested that there is a need for this analytical control. However, the optimal monitoring schedule remains to be established as there is no evidence to date that either the test, or the frequency of testing, is effective in identifying these patients at risk of developing 5-ASA-related renal impairment. Therefore, there are no firm recommendations, supported by medical evidence, for renal function monitoring (type and frequency) in IBD patients treated with these drugs[5]. Consequently, the «recommendations» regarding systematic screening for renal impairment should be considered as being «suggestions» and not as medically necessary based upon the review of the literature, as there is presently no evidence that such screening or monitoring improves patient outcomes[5].

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