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High risk of drug-induced microscopic colitis with concomitant use of NSAIDs and proton pump inhibitors

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SUMMARY

Background
Microscopic colitis (MC) is a chronic bowel disorder characterised by watery diarrhoea. Nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs) and statins have been associated with MC. However, underlying mechanisms remain unclear.

Aim
To study the association between exposure to these drugs and MC, with attention to time of exposure, duration, dosage and combined exposure, and to test hypotheses on underlying pharmacological mechanisms.

Methods
A case–control study was conducted using the British Clinical Practice Research Datalink. MC cases (1992–2013) were matched to MC-naive controls on age, sex and GP practice. Drug exposure was stratified according to time of exposure, duration of exposure or dosage. Conditional logistic regression analysis was applied to calculate adjusted odds ratios (AORs).

Results
In total, 1211 cases with MC were matched to 6041 controls. Mean age was 63.4 years, with 73.2% being female. Current use of NSAIDs (AOR 1.86, 95% CI 1.39–2.49), PPIs (AOR 3.37, 95% CI 2.77–4.09) or SSRIs (AOR 2.03, 95% CI 1.58–2.61) was associated with MC compared to never or past use. Continuous use for 4–12 months further increased the risk of MC. Strongest associations (fivefold increased risk) were observed for concomitant use of PPIs and NSAIDs. Statins were not associated with MC.

Conclusions
Current exposure to NSAIDs, PPIs or SSRIs and prolonged use for 4–12 months increased the risk of MC. Concomitant use of NSAIDs and PPIs showed the highest risk of MC. Acid suppression related dysbiosis may contribute to the PPI effect, which may be exacerbated by NSAID-related side-effects.

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INTRODUCTION

Microscopic colitis (MC) is a chronic disorder of the large intestine, characterised by watery, nonbloody diarrhoea. MC is used as an umbrella term for lymphocytic colitis (LC), collagenous colitis (CC) and incomplete MC. Strict histological criteria are applied to diagnose these subtypes.[1] MC is diagnosed in 10–30% of cases presenting with chronic diarrhoea[2], and recent epidemiological studies have reported increased incidence rates over the last decade.[3, 4] Treatment with oral budesonide is successful in 81% of cases.[5] However, after cessation of treatment a relapse of symptoms occurs in over 60% of patients, often implying a chronic, intermittent disease course.[6] This contributes to the high impact of MC on patient's quality of life.[7] In order to enable improvement of treatment strategies in future, more insight in the aetiology of MC is warranted.

The exact cause of MC is still to be elucidated, although positive associations with auto-immune diseases, bile acid malabsorption and smoking have been reported. There is increasing evidence that exposure to various drug classes is associated with MC. Studies have reported an elevated risk of MC with use of nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs) and statins.[8–12] Only one study addressed the dosage and recency of drug exposure, and generally found stronger associations with current use of NSAIDs or PPIs than with past use.[12] The observed association between NSAIDs and MC appeared to be dose dependent. Furthermore, NSAIDs and PPIs are often used concomitantly. To date, no studies addressed the effect of duration of continuous use or concomitant use of MC associated drugs on the risk of MC. Such detailed analyses are relevant in order to explore why only a minority of users of the abovementioned drug classes develops MC. Moreover, these data could aid to identify subjects at risk of MC and could provide insight in possible pharmacological mechanisms underlying MC. Although previous observational research speculated on underlying mechanisms,[10–13] no analyses were performed to more specifically test these hypotheses. Therefore, the aim of this study was to evaluate the association between NSAID, PPI, SSRI and statin use and MC, with attention to the effect of recency of use, duration of continuous use, average daily dose and concomitant use. In addition, the data will be used to indirectly test possible pharmacological mechanisms underlying medication-induced MC.

MATERIALS AND METHODS

Source population

The British Clinical Practice Research Datalink (CPRD) is a longitudinal research database containing active computerised medical records from over 4.4 million inhabitants from 674 primary health care practices in the UK. The CPRD represents about 7% of the UK population.[14] Data recorded by general practitioners include drug prescriptions, clinical data and information on demographics, lifestyle parameters, medical history, laboratory results and treatment outcomes. Use of the CPRD as a reliable data source has been well validated.[15, 16]

Study population

A case–control study was performed using the CPRD. All patients aged 18 years or older, with a record for MC (undefined), CC or LC between 1 January 1992 and 31 December 2013, were selected (CPRD Medical Codes 30678, 39119 and 35424). The index date of the cases was defined as the date of the first record of MC, CC or LC. Each case was matched with up to five MC-naive controls by year of birth, gender and GP-practice, using the incidence density sampling technique.[17] Controls were assigned the same index date as their matched case. A minimum period of 12 months of valid data collection prior to the index date was required for each subject upon inclusion. MC cases and their matched controls were excluded in case of a pre-diagnostic colectomy or a history of inflammatory bowel disease (IBD) or gastrointestinal cancer.

Exposure

To study the association between the recency of use and the risk of MC, patients were categorised into current, recent, past or never users of PPIs, SSRIs, NSAIDs or statins based on the date of the last prescription before the index date. A latency period (lag time) of 60 days was taken into account. This was considered the minimal period required for an established diagnosis of MC. All prescriptions and events within the latency period were ignored in order to reduce reverse causation. Current, recent and past users received their last dispensing 61–90, 91–150 and >150 days before the index date, respectively.

For the main analyses, subjects were stratified according to recency of exposure. These analyses were performed for the whole study population and for CC and LC separately. Subsequently, the duration of continuous

use and the average daily dose were calculated for current users. The duration of continuous use was based on the prescribed drug supply and prescribed daily dose. In case of an overlap between two dispensings or a repeated dispensing within 30 days after discontinuation of the previous period, the duration of continuous use was extended with the time of the last dispensing. In case of any missing data on prescribed drug supply or daily dose, medians were applied. Duration of continuous use was classified into ≤3, 4–12, 13–24 and >24 months of continuous use. The average daily dose was calculated by dividing the cumulative dose by the total treatment time, applying WHO defined daily doses (DDD),[18] and was classified as <0.75, 0.75–1.25 and >1.25 DDDs.

Consistent with other studies,[9, 12] crude analyses were adjusted for relevant covariates, i.e. in the NSAID group: presence of auto-immune arthritis, irritable bowel syndrome (IBS), PPI use and SSRI use; in the PPI group: presence of auto-immune arthritis, IBS, NSAID use and SSRI use; in the SSRI group: presence of IBD, NSAID use and PPI use; and in the statin group: smoking status. Here, PPI, SSRI and NSAID use was defined as any exposure to these drugs in the 6 months prior to index date. A variable was considered a confounding factor when an independent relationship between this variable and both the outcome (MC) as well as the exposure (drug class) was expected.

Statistical analysis

Conditional logistic regression analysis was performed in order to estimate the associations between drug exposure and MC (SAS version 9.3, PHREG procedure; SAS Inc. Cary, NC, USA). Adjusted odds ratios (AOR) for MC were estimated by comparing current, recent or past use of a drug class with never use. Analyses were stratified for recency of use (i.e. current, recent or past use). All analyses were statistically adjusted for potential confounders (e.g. concomitant drug use in the 6 months before index date).

A sensitivity analysis was performed by extending the lag time to 90 days, to investigate data robustness. In addition, smoothing spline regression plots were drafted to visualise the association between duration of continuous use and MC.[19]

Additional analyses were performed to test hypotheses on pharmacological mechanisms that might underlie drug-induced MC. Amongst others, the association between MC and concomitant use of NSAIDs and PPIs was studied, as well as single NSAID or PPI use without any co-exposure. Furthermore, the NSAIDs were analysed as total group, as well as for the subgroup of cyclooxygenase (COX) 2 selective NSAIDs separately. Inhibition of the arachidonic acid pathway, leading to an impaired mucosal barrier defence, might be a mechanism involved in the pathophysiology of MC.[11] Separate analyses for individual PPIs were performed in order to test for a drug specific effect, considering a possible association between MC and lansoprazole, specifically.[20] Because acid suppression is assumed a key mechanism in the pathogenesis of PPI-induced MC,[13] analyses were performed to test the association between exposure to histamine-2 receptor antagonists (H2RA) and MC. All additional analyses were stratified by recency of use (i.e. current, recent or past use), and exposure definitions were similar as those of the primary analyses.

Ethics/approval

The study protocol was approved by the Independent Scientific Advisory Committee for MHRA Database Research (protocol 14_059R2A). The approved protocol was made available to the reviewers of this journal.

RESULTS

Population characteristics

A total number of 1323 cases with a first diagnosis of MC (undefined), CC or LC between 1992 and 2013 were selected. Of those, 112 patients fulfilled one or more exclusion criteria (prior colectomy: $n = 12$, IBD: $n = 94$; gastrointestinal malignancy: $n = 11$). The remaining 1211 cases consisted of 394 CC (32.5%), 292 LC (24.1%) and 525 (43.4%) unspecified MC cases. In total, 6.041 case-matched controls were included. The average time of valid data collection before the index date was 10.3 ± 5.6 years. Further subject characteristics are listed in Table 1.

Risk of MC stratified to recency of use

Table 2 shows that current use of NSAIDs (AOR 1.86, 95% CI 1.39–2.49), PPIs (AOR 3.37, 95% CI 2.77–4.09) or SSRIs (AOR 2.03, 95% CI 1.58–2.61) was significantly associated with MC when compared to never use. No association was found with current statin use (AOR 1.13, 95% CI 0.94–1.36). Stratification to MC subtypes showed that current use of PPIs (AOR 5.35, 95% CI 3.79–7.54) and NSAIDs (AOR 2.32, 95% CI 1.46–3.68) was significantly associated with CC, whereas current use of PPIs (AOR 2.06, 95% CI 1.36–3.13) or SSRIs (AOR 2.28, 95% 1.43–3.63) was associated with LC (Table S1).

Table 1 | Baseline characteristics of cases and controls

	Cases		Controls		Crude
	n = 1211	%	*n* = 6041	%	OR (95% CI)
Female	886	73.2	4423	73.2	1.00
Mean age at diagnosis (s.d.)	63.3	14.1	63.2	14.1	1.00
No drug use (6 months before index date)	429	35.4	3408	56.4	0.38 (0.33–0.44)**
Drug use (6 months before index date)					
NSAIDs	250	20.6	679	11.2	2.09 (1.78–2.46)**
PPIs	506	41.8	1054	17.5	3.79 (3.29–4.37)**
SSRIs	186	15.4	451	7.5	2.27 (1.88–2.72)**
Statins	327	27.0	1431	23.7	1.23 (1.06–1.43)*
H2RAs	56	4.6	119	2.0	2.40 (1.73–3.31)**
Presence of (before index date)					
Auto-immune related arthritis	37	3.1	135	2.2	1.37 (0.95–2.00)
Coeliac disease	37	3.1	15	0.2	9.00 (4.79–16.92)*
Irritable bowel syndrome	255	21.1	458	7.6	3.36 (2.83–3.99)**
Smoking status					
Never	400	33.0	2392	39.5	0.74 (0.64–0.84)**
Current	259	21.4	962	15.9	1.47 (1.26–1.73)**
Former	547	45.2	2541	42.1	1.15 (1.01–1.31)*
Unknown	5	0.4	146	2.4	0.16 (0.07–0.40)**

OR, odds ratio; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drug; PPIs, proton pump inhibitor; SSRIs, selective serotonin reuptake inhibitor; H2RAs, histamine-2 receptor antagonist.

*$P < 0.05$, **$P < 0.01$.

A two to fourfold risk of MC was found with recent use of NSAIDs (AOR 2.09, 95% CI 1.56–2.80) or PPIs (AOR 4.00, 95% CI 3.19–5.02) when compared to never use. These associations were not statistically different from current use. After discontinuation of NSAID and PPI use for more than 3 months, the risk of MC dropped to baseline levels (Table 2).

Risk of MC and use of PPIs

Current users were stratified for average daily dose and duration of continuous use. Continuous exposure for 4–12 months was associated with the highest risk of MC (AOR 4.69, 95% CI 3.58–6.13). As visualised in Figure 1 and Table S2, the risk of MC decreased after more than 1 year of continuous use. Although a dose-related effect appeared to exist, differences between dosages were not statistically significant (Table 2). When any concomitant NSAID use was excluded, a two to threefold significantly increased risk of MC was still observed for PPI use alone (Table 3).

Separate analyses for individual PPIs were performed to test for a specific drug effect, rather than a class effect. Table S3 shows that beside omeprazole, especially current and recent use of lansoprazole was associated with an increased risk of MC. No or weak associations were found for esomeprazole, pantoprazole or rabeprazole.

To test the hypothesis of an acid suppression related aetiology, a regression analysis on H2RA exposure was performed. Results showed a statistically significant risk of MC in recent and past users of H2RAs, compared to never use (Table S3).

Risk of MC and use of NSAIDs

Current users were stratified for average daily dose and duration of continuous use. Continuous exposure for 4–12 months yielded the highest AOR in current NSAID users, i.e. 3.86 (95% CI 2.28–6.50), and prolonged exposure attenuated this association towards baseline (Figure 1, Table S2). Although a medium average daily dose (0.75–1.25 DDD) showed the strongest association with MC, this was not statistically different from low or high daily doses (Table 2).

To test the hypothesis that COX inhibition might be a mechanism leading to mucosal barrier dysfunction, NSAIDs were divided into selective COX-2 inhibitors and other NSAIDs. However, the associations between MC and these two groups were not statistically different from each other (Table S3).

When any concomitant PPI use was excluded in the total group of NSAID users, a 30% increased, but statistically nonsignificant risk of MC was found for recent and current NSAID use (Table 3).

Table 2 | Use of NSAIDs, PPIs, SSRIs or statins, and the risk of MC, by average daily dose

	Cases		Controls		Crude	Adjusted†
	n = 1211	%	*n* = 6041	%	OR (95% CI)	OR (95% CI)
NSAID use before index date						
Never	308	25.4	2264	37.5	1.00	1.00
Past use	716	59.1	3297	54.5	1.65 (1.42–1.91)**	1.39 (1.19–1.62)**
Recent use	94	7.8	229	3.8	3.10 (2.36–4.06)**	2.09 (1.56–2.80)**
Current use	93	7.7	251	4.2	2.84 (2.16–3.73)**	1.86 (1.39–2.49)**
By average daily dose						
One prescription only	4	4.3	10	4.0	3.17 (0.96–10.48)	1.59 (0.43–5.79)
Low (<0.75 DDDs)	62	66.7	177	70.5	2.67 (1.95–3.67)**	1.78 (1.27–2.49)**
Medium (0.75–1.25 DDDs)	21	22.6	45	17.9	3.62 (2.11–6.20)**	2.30 (1.30–4.07)**
High (>1.25 DDDs)	6	6.5	19	7.6	2.46 (0.97–6.21)	1.67 (0.61–4.55)
PPI use before index date						
Never	476	39.3	3945	65.3	1.00	1.00
Past use	304	25.1	1175	19.5	2.32 (1.97–2.73)**	1.97 (1.67–2.34)**
Recent use	172	14.2	328	5.4	4.95 (3.98–6.16)**	4.00 (3.19–5.02)**
Current use	259	21.4	593	9.8	4.19 (3.47–5.05)**	3.37 (2.77–4.09)**
By average daily dose						
One prescription only	9	3.5	17	2.9	4.69 (2.04–10.74)*	4.09 (1.75–9.53)**
Low (<0.75 DDDs)	179	69.1	444	74.9	3.85 (3.13–4.75)**	3.05 (2.45–3.79)**
Medium (0.75–1.25 DDDs)	51	19.7	104	17.5	4.85 (3.39–6.96)**	3.90 (2.69–5.66)**
High (>1.25 DDDs)	20	7.7	28	4.7	7.22 (4.01–13.01)**	6.58 (3.61–11.99)**
SSRI use before index date						
Never	821	67.8	4729	78.3	1.00	1.00
Past use	221	18.2	918	15.2	1.43 (1.21–1.70)**	1.10 (0.92–1.32)
Recent use	48	4.0	150	2.5	1.87 (1.34–2.62)**	1.39 (0.97–1.98)
Current use	121	10.0	244	4.0	2.91 (2.31–3.68)**	2.03 (1.58–2.61)**
By average daily dose						
One prescription only	2	1.7	8	3.3	1.42 (0.30–6.72)	1.02 (0.21–4.97)
Low (<0.75 DDDs)	53	43.8	98	40.2	3.25 (2.30–4.59)**	2.25 (1.55–3.28)**
Medium (0.75–1.25 DDDs)	37	30.6	99	40.6	2.15 (1.46–3.16)**	1.36 (0.90–2.05)
High (>1.25 DDDs)	29	24.0	39	16.0	4.53 (2.76–7.44)**	3.89 (2.26–6.68)**
Statin use before index date						
Never	824	68.0	4356	72.1	1.00	1.00
Past use	82	6.8	315	5.2	1.43 (1.10–1.86)**	1.36 (1.05–1.77)*
Recent use	107	8.8	465	7.7	1.27 (1.00–1.61)*	1.20 (0.95–1.52)
Current use	198	16.4	905	15.0	1.21 (1.00–1.45)*	1.13 (0.94–1.36)
By average daily dose						
One prescription only	2	1.0	10	1.1	1.13 (0.25–5.15)	1.10 (0.24–5.07)
Low (<0.75 DDDs)	98	49.5	483	53.4	1.12 (0.88–1.42)	1.04 (0.82–1.33)
Medium (0.75–1.25 DDDs)	73	36.9	325	35.9	1.25 (0.95–1.64)	1.18 (0.89–1.55)
High (>1.25 DDDs)	24	12.6	87	9.6	1.59 (1.01–2.51)*	1.29 (0.93–2.33)

OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; DDD, defined daily dose.

Recency of use was defined as the last prescription 61–90 (current use), 91–150 (recent use), >150 (past use) days before index date.

PPI, SSRI and NSAID use was defined as any exposure to these drugs in the 6 months prior to index date.

† Adjusted for [NSAIDs] presence of auto-immune arthritis, irritable bowel syndrome (IBS), PPI use, SSRI use; [PPIs] presence of auto-immune arthritis, IBS, NSAID use, SSRI use; [SSRI] presence of IBS, NSAID use, PPI use; [statins] smoking status.

*$P < 0.05$, **$P < 0.01$.

Concomitant use of NSAIDs and PPIs

Nonsteroidal anti-inflammatory drugs and PPIs are frequently prescribed in combination. Table 3 shows that current concomitant use of both NSAIDs and PPIs yielded a higher risk of MC (AOR 3.61, 95% CI 2.46–5.29) than current use of NSAIDs (AOR 1.29, 95% CI 0.90–1.86) or

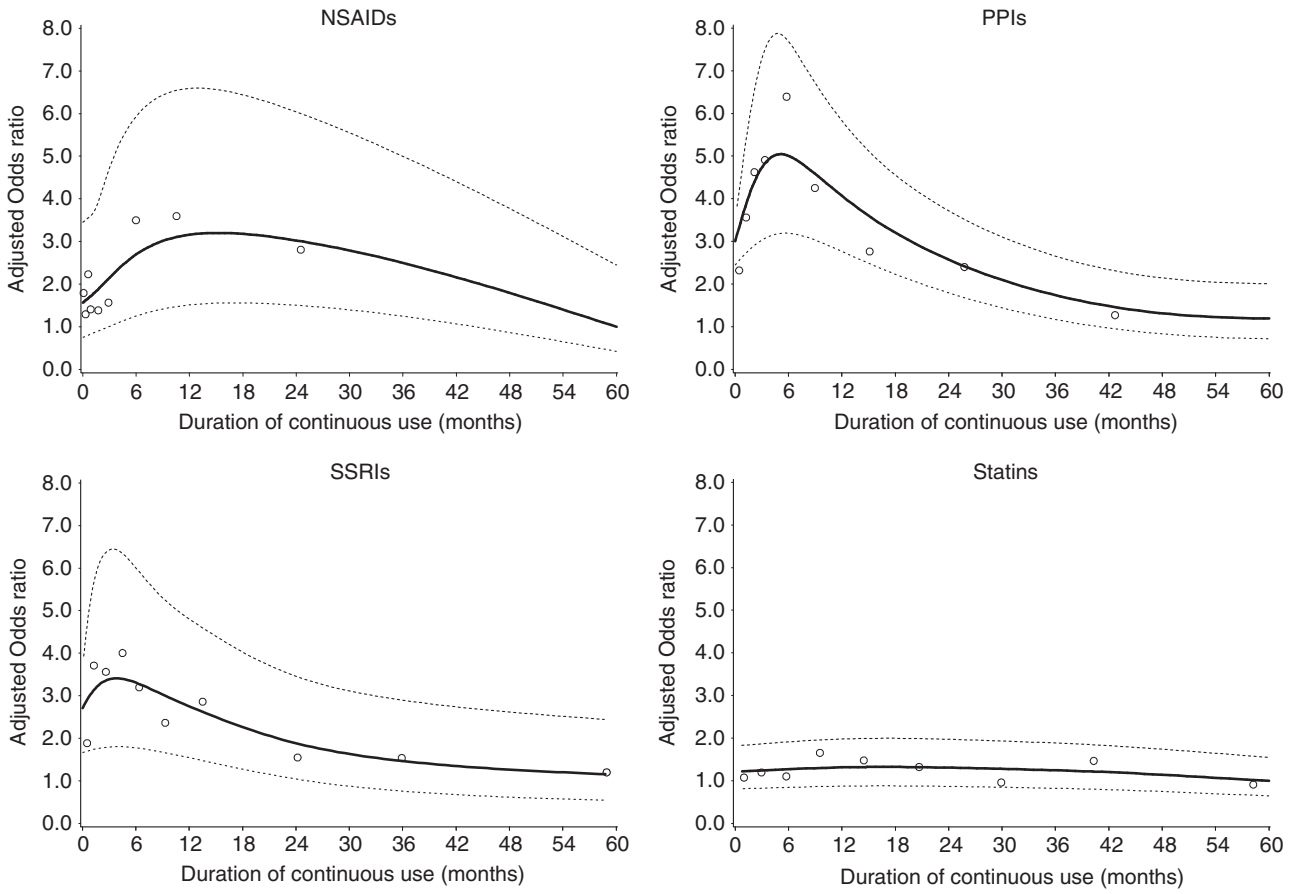

Figure 1 | Risk of microscopic colitis and duration of continuous use of non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs) or statins. *Solid lines* Adjusted Odds ratio, *dashed lines* 95% confidence bands. Adjusted for the same confounders as listed under Table 2.

PPIs (AOR 2.41, 95% CI 1.98–2.92) alone. This was also the case for recent concomitant use (AOR 5.40, 95% CI 3.46–8.42).

Risk of MC and use of SSRIs or statins

In current SSRI users, 4–12 months of continuous exposure was associated with the highest risk of MC (AOR 2.68, 95% CI 1.83–3.83) (Figure 1 and Table S2). Dose dependency was not observed. No associations were observed between statin use and MC.

Sensitivity analysis

In a sensitivity analysis, the latency period was extended from 60 to 90 days. Associations between MC and current use of NSAIDs, PPIs or SSRIs were stronger than those for recent and past use, when compared to the primary analyses (Table S4). This was also the case for the concomitant and single use analyses from Table 3. However, in all cases current use was again not statistically different from recent use. No significant changes were observed with regard to the average daily dose and duration of use analyses. The sensitivity analysis results did not change the main findings of this study.

DISCUSSION

The results of this case–control study showed that current and recent use of NSAIDs and PPIs were associated with an increased risk of MC, when compared to never and past use, especially in case of continuous exposure for 4–12 months. However, concomitant use of NSAIDs and PPIs was associated with the highest risks of MC, whereas the associations between NSAIDs or PPIs and MC weakened when any co-exposure to the other drug class was excluded. Only the association between MC and PPI use only remained significant. A positive association was also found with current, but not recent, SSRI exposure. No statistically significant associations were observed with statin use.

Proton pump inhibitors and microscopic colitis

The finding that PPI exposure yielded the highest risk of MC, compared to other drug classes, was consistent with

Table 3 | Use of NSAIDs or PPIs alone or concomitant use and the risk of MC

	Cases		Controls		Adjusted†
	n	%	*n*	%	OR (95% CI)
NSAID use alone					
Never	124	10.2	492	8.1	1.00
Past use	500	41.3	2497	41.3	0.91 (0.80–1.06)
Recent use	50	4.1	189	3.1	1.31 (0.93–1.86)
Current use	44	3.6	177	2.9	1.29 (0.90–1.86)
PPI use alone					
Never	292	24.1	2173	36.0	1.00
Past use	88	7.3	375	6.2	1.15 (0.89–1.48)
Recent use	128	10.6	288	4.8	2.73 (2.15–3.46)**
Current use	210	17.3	519	8.6	2.41 (1.98–2.92)**
Concomitant NSAID and PPI use					
Never	184	15.2	1772	29.3	1.00
Past use	216	17.8	800	13.2	1.42 (1.19–1.69)**
Recent use	44	3.6	40	0.7	5.40 (3.46–8.42)**
Current use	49	4.1	74	1.2	3.61 (2.46–5.29)**

OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Recency of use was defined as the last prescription 61–90 (current use), 91–150 (recent use), >150 (past use) days before index date.

PPI, SSRI and NSAID use was defined as any exposure to these drugs in the 6 months prior to index date.

† Adjusted for [NSAID use alone] presence of auto-immune arthritis, irritable bowel syndrome (IBS), PPI use, selective serotonin reuptake inhibitor (SSRI) use; [PPI use alone] presence of auto-immune arthritis, IBS, NSAID use and SSRI use; [Concomitant NSAID and PPI use] presence of auto-immune arthritis, IBS, SSRI use.

**$P < 0.01$.

other observational studies.[9, 12, 21] Especially current and recent exposure were associated with MC, which was reported by one other study.[12] The observed association remained present after exclusion of any concomitant NSAID use (Table 3).

Although it has been established that exposure to PPIs could lead to colonic intra-epithelial lymphocytosis,[22] the exact pathophysiological mechanism of PPI-induced MC is yet unrevealed. Several hypotheses on the underlying mechanisms have been postulated. One of them is an idiosyncratic drug reaction.[13] However, the observed association with recent use and dosage in our study do not support this, as a rapid and dose-independent onset of symptoms would then be expected.

Acid suppression related colonic dysbiosis could contribute to impaired intestinal barrier function and is another hypothesised mechanism on PPI-induced MC. Imhann *et al.* recently reported that any exposure to PPIs could induce intestinal dysbiosis in humans.[23] A dysbiosis with clinical implications will take some time to develop. Our finding that 4–12 month continuous exposure to PPIs was significantly associated with MC might support this hypothesis. Because restitution of the normal microbiota composition is expected after discontinuation of exposure, the observed decline in AOR between current and past use is supportive as well. Furthermore, stronger acid suppression is expected to result in a more pronounced alteration in the intestinal microbiota and thus an increased risk of MC. The observed trend towards a dose-dependent effect for PPIs supports this, as does the statistically significant, albeit less pronounced association with the less potent H2RAs.

A variant of the gastric H^+/K^+-ATPase is reported to be present in colonic tissue.[24, 25] Inhibition of this pump by PPIs is also suggested as a potential mechanism of PPI-induced MC.[13] In theory, inhibition of this colonic proton pump might lead to an electrolyte disbalance, altering colonic barrier function. However, binding of PPIs to this colonic proton pump and their subsequent activation is unlikely to play a major role *in vivo*. PPIs are pharmacologically designed to be rapidly absorbed in the upper gastrointestinal tract and targeted to be activated in the highly acidic environment of the gastric canaliculus.[26]

A remarkable finding of this study was the strong association between lansoprazole exposure and MC. It is tempting to assume lansoprazole specifically to be related to MC, considering the number of case series on MC related to the use of lansoprazole.[20] An explanation could be sought in the specific binding of lansoprazole to the cysteine 321 residue of the proton pump.[27] However, it has never been elucidated how this specific binding could lead to an impaired barrier function and/or MC. In this study, 95–98% of all subjects were never exposed to pantoprazole, esomeprazole or rabeprazole. But despite underpowered calculations, recent use of these PPIs was statistically significantly associated with MC (Table 3). A drug-class effect instead of a drug-specific effect can therefore not be excluded.

Nonsteroidal anti-inflammatory drugs and microscopic colitis

In the main analysis (Table 2), statistical correction for PPI co-exposure in the last 6 months before index date was applied, showing a positive association between current and recent NSAID use and MC. This was consistent with other case–control studies.[9, 10, 12, 21, 28–31] However, the statistically significant association between NSAID

use and MC was not observed when any concomitant PPI use was excluded. Therefore, our results suggest that the association between NSAIDs and MC as reported in the main analysis of this and other studies is likely to be based on residual co-exposure to PPIs. Nevertheless, in PPI users, co-exposure to NSAIDs did strengthen the association with MC (Table 3).

Animal models have shown that concomitant use of PPIs in NSAID exposed rats significantly aggravated intestinal damage.[32] Pharmacologically, a dysbiosis due to PPI-induced gastric acid suppression, in combination with NSAID related effects, could be the underlying mechanism. Their effect on colonic mucosal barrier function by COX inhibition might be attributive herein. The impaired prostaglandin synthesis can increase gut permeability, enhancing the chance for luminal toxins and bacteria to translocate,[30] especially in case of an altered microbiota composition due to gastric acid suppression. As COX-2 is not present in colonic epithelial cells under normal circumstances,[30] exposure to selective COX-2 inhibitors was expected to yield a lower risk of MC when compared to nonselective NSAIDs. This could however not be confirmed by our results (Table S3), probably due to insufficient statistical power. Therefore, this hypothesis needs further study.

Another explanation for the reported associations might be sought in the interaction of NSAIDs with bile. NSAIDs are able to increase bile salt cytotoxicity.[33] Animal models in which bile duct ligation was performed showed no intraluminal NSAIDs and no signs of gastrointestinal toxicity.[34]

SSRIs and statins and MC

An association was also found between current SSRI use and MC. Consistent with other studies, this was mainly explained by the association with LC.[9, 10]

Serotonin is a relevant substance for gastrointestinal motility, secretion and perception. Increased 5-HT levels are found in diarrhoea predominant IBS.[35] Serotonin is also found to exhibit pro-inflammatory effects in colitis.[36] In MC patients, an increased density of serotonin producing cells has been reported and increased serotonin concentrations have been found.[37, 38] Findings from a study on serotonin transporter gene polymorphisms were contradictive, indicating these polymorphisms to be but one factor contributing to the higher serotonin levels in MC.[38, 39] Administration of SSRIs increases serotonin levels.[40, 41] It might therefore lead to luxation or aggravation of colitis symptoms by interference with the gastrointestinal motility and secretion. However, the relation between SSRI exposure and colonic inflammation remains a black box.

According to the results of the present study, statin use is not associated with an increased risk of MC. Weak associations with MC have been reported, but these studies had methodological shortcomings regarding, e.g. exposure definition and confounder correction.[9, 10] The scarce literature on statins and colitis remains disputable about their presumed anti-inflammatory effect.[42, 43]

Cause or bias?

There is a lack of large prospective longitudinal studies that prove causal relationships on drug-induced MC.[44] It is therefore tempting to assume that the general phenomenon of drug-induced MC is based on false associations due to methodological biases or confounding by indication. After all, drugs found to be most associated with MC are prescribed for unspecific abdominal complaints as well. However in MC, abdominal pain is present in only 25–40% of the patients and often mild of nature.[45, 46] It is therefore unlikely that PPIs, NSAIDs, the combination of both, or SSRIs will be frequently prescribed for these complaints, and if so, the prescription period will be short. By contrast, 50–70% of the current users in the present study were continuously exposed for more than 3 months.

We acknowledge that PPI with or without NSAID, and SSRI exposure is associated with an increased risk of diarrhoea, especially in the elderly,[47] which could lead to a diagnostic bias and reverse causation. However, the incidence of diarrhoea due to drug use is about 1% for NSAIDs[48] and 2–4% for PPIs,[49] and often mild, self-limiting and dose independent.[50] Moreover, studies with the ability to correct for confounding by indication still reported on an increased risk of MC in NSAID and PPI users.[9, 12] Therefore, drug exposure is likely to play a causative role in the development of MC in a selection of patients.

Strengths and limitations

Some limitations of this study have to be acknowledged. First, this was a retrospective study and reliable data on the onset of symptoms relative to the time of first exposure were not available. This hindered proving any causality between NSAID, PPI or SSRI exposure and MC. Second, we were unable to match our cases with a group of MC-negative controls with chronic diarrhoea. Therefore, the reported associations could be an overestimation of the true associations due to confounding by

indication. Third, information on over-the-counter medication was lacking. However, misclassification of exposure was assumed nondifferential, because a random distribution of exposure to nonprescribed drugs in case and control group might be assumed. Fourth, no information on the histology supporting the MC diagnosis was available. Because MC is a histology-based diagnosis, we assumed that established diagnoses will be recorded by GPs in the CPRD database. Nevertheless, some undiagnosed cases might be missed.

Despite these limitations, the strength of this study resides in its data source. The CPRD provides reliable and detailed data on patient characteristics, comorbidities and first-line and clinical drug prescriptions. Furthermore, our methodology allowed for stratification on recency of use, duration of continuous use and average daily dose and enabled the performance of additional analyses to gain more insight in potential pathophysiological mechanism of drug-induced MC.

CONCLUSION

In conclusion, this study showed that current and recent use of NSAIDs and PPIs and current use of SSRIs was associated with MC. Concomitant use of PPIs and NSAIDs, however, was associated with the highest risk of MC and turned out to be responsible for the observed association between MC and NSAID use as such. Additional analyses indicated that acid suppression related dysbiosis may contribute to the increased risk of PPI use. The strong association for concomitant PPI and NSAID use indicated that gastrointestinal effects of NSAIDs might aggravate or luxate PPI-related MC.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Use of NSAIDs, PPIs, SSRIs or statins and the risk of MC, by average daily dose.

Table S2. Current use of NSAIDs, PPIs, SSRIs or statins and the risk of MC, by duration of continuous use.

Table S3. Use of selective COX-2 inhibitors, nonselective NSAIDs, individual PPIs or H2RAs and the risk of MC.

Table S4. Use of NSAIDs, PPIs, SSRIs or statins and the risk of MC, by average daily dose, with a lag time of 90 days.

AUTHORSHIP

Guarantor of the article: Frank de Vries takes responsibility for the integrity of the work as a whole, from inception to published article.
Author contributions: BV and FV designed the work and performed the data analyses and data interpretation. PS performed the data acquisition. DJ contributed to the data analyses and data interpretation. All authors participated in the draft and/or revision of the manuscript. All read and approved the final draft submitted.

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