

Colites microscopiques

Focus sur les IPP

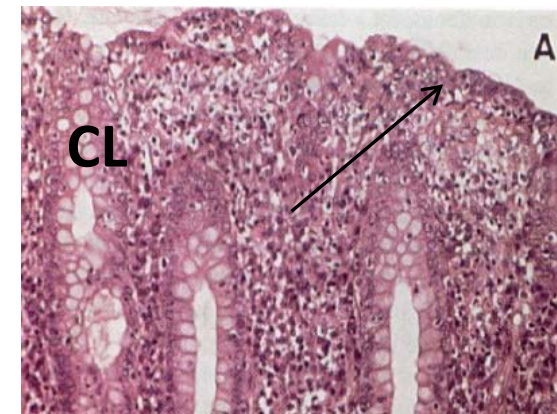
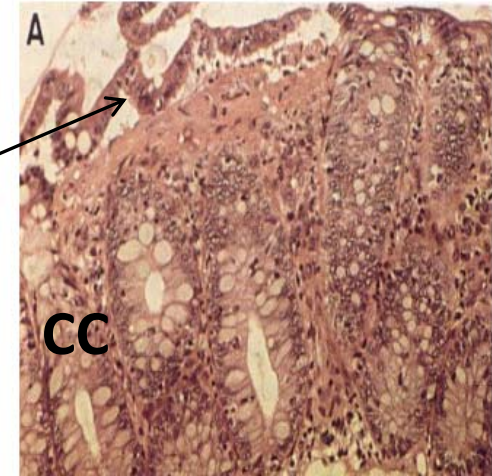
VIGIMED

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Colites microscopiques

- **Définition**
 - diarrhée (aqueuse) en général chronique
 - aspect normal de la muqueuse colique
 - inflammation particulière (microscopie)
 - colite lymphocytaire (CL)
 - colite collagène (CC)



Colites microscopiques

- **Incidence en augmentation** : 2 à 4 cas pour 100 000 hab./ an (pour chaque sous-type)
- Femmes entre 50 et 65 ans +++
- Association avec **maladies immunes** (thyroïdite, PR, etc.)
- **Complications**
 - liées à la diarrhée : anomalies hydro-électrolytiques et métaboliques (hypokaliémie), déshydratation, perte de poids, fatigue, carence vitaminique
 - retentissement psychologique

Physiopathologie

- Mécanismes non élucidés, multifactoriel
 - Réponse immune de la muqueuses contre des agents luminaux
 - Prédisposition génétique
 - Métabolisme du collagène anormal ? Fonction de la barrière épithéliale altérée?
 - Diarrhée → inflammation de la muqueuse
- Parfois médicamenteux
 - **IPP**, antidépresseurs (IRSS), AINS, veinotoniques (CYCLO3), *etc.*

IPP

- Omé*, panto*, ésomé*, lanso**, rabé –**prazole**
- 3 indications principales
 - RGO et oesophagite par RGO
 - **lésions gastroduodénales dues aux AINS** et leur **prévention chez les patients à risque** (> 65 ans, antécédents d'ulcère gastroduodéal, traités par antiagrégant plaquettaire, anticoagulant ou corticoïde)
 - **éradication d'Helicobacter pylori** et le traitement des ulcères gastroduodénaux
- Etude ANSM (données SNIIRAM 2015) → important mésusage ¹
 - dans 80% des cas, **aucun facteur de risque** justifiant l'utilisation systématique d'un IPP en association avec un AINS n'était identifié

* Forme parentérale disponible, ** forme Lyoc disponible

IPP et CM

- Effet de classe 2-6
- **Lansoprazole ?** 7-8

	Numbers exposed		Crude OR (95% CI)	OR_adjusted (95% CI)
	Cases	Controls		
Collagenous colitis				
Nonlansoprazole PPI	758	4165	1.00 (ref)	1.00 (ref)
Lansoprazole	1712	1923	4.94 (4.24-5.76)	5.04 (4.31-5.90)
Lymphocytic colitis				
Nonlansoprazole PPI	608	2557	1.00 (ref)	1.00 (ref)
Lansoprazole	659	1234	2.26 (1.84-2.77)	2.38 (1.93-2.94)

	Numbers exposed		Crude OR (95% CI)	Adjusted OR (95% CI)
	Cases	Controls		
Collagenous colitis				
Never use of PPI	2040	40 533	1.00 (ref)	1.00 (ref)
Omeprazole	285	1528	4.23 (3.61-4.96)	3.14 (2.66-3.70)
Pantoprazole	359	1764	4.33 (3.75-5.00)	3.01 (2.58-3.50)
Lansoprazole	1712	1923	20.64 (18.59-22.92)	15.74 (14.12-17.55)
Esomeprazole	257	1020	5.22 (4.40-6.20)	3.75 (3.13-4.49)
Any PPI	2470	6088	9.17 (8.52-9.88)	6.98 (6.45-7.55)
Lymphocytic colitis				
Never use of PPI	1980	28760	1.00 (ref)	1.00 (ref)
Omeprazole	208	882	3.84 (3.20-4.61)	3.01 (2.49-3.63)
Pantoprazole	310	1166	3.97 (3.40-4.62)	2.60 (2.21-3.06)
Lansoprazole	659	1234	8.92 (7.84-10.15)	6.87 (6.00-7.86)
Esomeprazole	175	602	4.30 (3.52-5.24)	2.93 (2.37-3.62)
Any PPI	1267	3791	5.24 (4.80-5.72)	3.95 (3.60-4.33)

Bonderup O *et al.* Significant association between the use of different proton pump inhibitors and microscopic colitis: a nationwide Danish case-control study. *Aliment Pharmacol Ther.* 2018

Agier et al. 2019

Etude BNPV

- Incidence CM x10 avec lansoprazole vs autres IPP
- Symptômes : 64 j (médian) (20–365)
- Resolution complète en quelques jours après arrêt de IPP

CO-005

Proton pump inhibitor-induced microscopic colitis: a specific side effect of lansoprazole?

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Introduction: Microscopic colitis (MC) is a cause of diarrhea characterized by normal-looking colonic mucosa but abnormal histopathology. Many drugs have been associated with the development of MC, such as anti-acid drugs for which case series of MC are specifically linked to lansoprazole use. The aim of this study was to confirm that the risk of MC is higher with lansoprazole compared to other proton pump inhibitors (PPI).

Material and methods: We analyzed all cases of colitis/diarrhea notified to the French Pharmacovigilance Regional Centers (FPRC) from 2008 to 2017 for which a PPI was coded “suspect”. Cases of colitis were then classified in 4 groups: 1/ “Certain” (MC confirmed at the colonoscopy and highest imputability for the PPI and favorable outcome after stop); 2/ “Probable” (other drug suspects); 3/ “Possible” (colonoscopy not performed); 4/ “Excluded” (unknown outcome and/or colonoscopy not performed and/or other drugs suspects). To approximate the incidence of “certain” and “probable” MC for each PPI, we reported the number of cases to the number of treated patient-year using data of reimbursement (Medic’AM 2008–2017) and PPI’s utilization (National Health Data System- ANSM).

Results: During study period, 256 cases of colitis/diarrhea were reported to the FPRC; 22 cases were classified as “certain” MC, 16 as “probable” and 97 as “possible”. Median age of patients was 74 years [Q1–Q3: 63–82] with a sex ratio (M/F) of 0.60. Symptoms of MC started within few months after the start of PPI (median 64 days; range 20–365), and a complete resolution after PPI discontinuation was observed within few days. Incidence of “certain” and “probable” MC was 1.3.10⁻⁶ patient-year (P.Y) for all PPIs, but 6.8.10⁻⁶ P.Y for lansoprazole, 0.73.10⁻⁶ P.Y for esomeprazole, and 0.5.10⁻⁶ P.Y or less for omeprazole, pantoprazole and rabeprazole.

Discussion/Conclusion: Although studies have shown that the incidence of diarrhea did not differ among PPIs, incidence of MC reported with lansoprazole in our study was more than 10 times higher than that with other PPIs. Most patients were female older than 60 years, which is in accordance with studies investigating the epidemiology of MC. The mechanism by which lansoprazole may cause MC is unknown but may be linked either with an inappropriate immune reaction or with direct toxicity; some authors hypothesize that a specific affinity of lansoprazole for colonic cells might exist. Despite several limitations of this study, we confirmed that MC reported with PPI seems to be mainly due to lansoprazole.

Facteurs de risques

Période de l'exposition : OUI

- Pour les 2 sous-types : **CC** et **CL**
- Risque accru (vs non utilisateurs)
 - patients **en cours d'utilisation (3 mois)** **x7** et **x4**
 - **utilisateurs récents (3 mois-1 an)** **x5** et **x2,3**

Dose : NON

- Pas effet dose retrouvé

Physiopathologie

- pompes à protons présentes au niveau de la muqueuse colique. Inhibition → réponse immune → CM
- IPPs : même capacité intrinsèque à réduire la sécrétion acide
 - mais sites de liaison différent selon IPP
 - **Lansoprazole** : Résidu cystéine321 → changements spécifiques dans les colonies des pompe à protons coliques ?
 - Toxicité directe ?

Conclusion

- **Respect des indications +++**
- Déprescription ⁹
- Devant une colite microscopique → penser à une cause iatrogène
- Effet indésirable à prendre en compte pour choix IPP au marché

Références

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