2025

Thèse

pour le

Diplôme d'État de Docteur en Pharmacie

Impact des maladies inflammatoires chroniques de l'intestin sur les étapes de la pharmacocinétique et pertinence clinique

--

Impact of Inflammatory bowel disease on pharmacokinetics phases and clinical relevance

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Né le 25/08/1999 au Mans (72)

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Soutenue publiquement le :
19 mai 2025

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REMERCIEMENTS

Aux membres de mon jury

A Flavien BESSAGUET,
Merci à toi d'avoir accepté de diriger cette thèse. Ton soutien sans faille, tes précieux conseils et ta disponibilité m'ont permis aujourd'hui d'aboutir à la fin de ce chapitre universitaire. C'était un plaisir d'échanger avec toi, merci pour tout !

A Nicolas CLERE
Merci à vous d'avoir accepté la présidence de cette thèse et pour l'ensemble de vos enseignements qui m'ont transmis la passion de la pharmacologie et la rigueur scientifique.

A Louis-Maxime MAIN,
Merci à toi d'avoir accepté d'être membre de ce jury, merci pour tes conseils, ta gentillesse quand j'étais étudiant et maintenant dans l'élaboration des entretiens pharmaceutiques, tu fait partie des pharmaciens qui m'inspirent au quotidien.

Aux pharmaciens titulaires et équipes officinales

A l'équipe de la pharmacie d'Aliénor, merci à vous tous et tout particulièrement à JT, Nadia et Phillipe pour m'avoir accueilli à deux reprises dans la bienveillance dans cette pharmacie pleine de bonne humeur. Vous m'avez fait grandir en tant que futur pharmacien, grâce à vos conseils, échanges et connaissances. Merci !

A l'équipe de la pharmacie des Prés : Mélanie, Vitaline, Marlène, Florine, merci pour votre gentillesse votre rigueur, votre compétence, vous êtes géniaux et ça a été un plaisir de partager ces 4 mois à vos côtés. Merci !

To the FV hospital pharmacy team (Song, Ai…)
Thank you for everything and those wonderful memories during my hospital internship, where my thesis was born

A ma famille

A toi Maman,
Je te l'avais promis avant que tu partes il y 8 ans, un jour je serais pharmacien. Aujourd'hui tu n'es plus là pour me voir mais ça y est, aujourd'hui je deviens pharmacien, merci pour tous ces beaux souvenirs à tes côtés.
Je t'aimais, je t'aime et j'aimerais

A toi Papa,
Merci pour ton soutien, tout au long de mes études et de cette thèse. Merci d'avoir soutenu tous mes projets, merci pour l'amour et la fierté que je lis dans tes yeux et que tu me communiques, m'a porté pendant ces 7 ans. Malgré toutes les épreuves de la vie que tu as traversées, tu restes debout. Tu es un exemple de résilience et gentillesse qui me porte au quotidien.
Je t'aime Papa !

A toi Kevin,
Merci frero, pour ton soutien et ta volonté de toujours comprendre ce que je faisais. Tu es un exemple de combativité, de détermination dont je suis fier et que j'admire. Aujourd'hui tu es ingénieur et aujourd'hui je deviens docteur en pharmacien, on l'a fait ! On a traversé les épreuves ensembles et on est toujours debout.
Je t'aime Fréro !

A toi Nathalie,
Merci pour ton soutien et d'être présent dans la vie de mon papa. Je ne pourrais rêver mieux pour lui, merci pour tout !

A l'ensemble de ma famille,
Merci à vous tous pour votre gentillesse et votre intérêt tout au long de mes études. Merci pour tous ces souvenirs que nous créons lorsque nous nous réunissons. On reste unis et solidaires dans les épreuves qui traversent notre famille et c'est notre plus grande force !

REMERCIEMENTS

A mes meilleur.e.s ami.e.s

A toi Emy,
Mille mercis ne suffiraient pas à exprimer toute la gratitude que j'ai pour ce que tu m'as apporté depuis qu'on se connait. Partager, échanger, pleurer, rire, se voir grandir, traverser des épreuves qui nous construisent, est un honneur de le faire à tes côtés. Tu as toujours été un soutien à chaque moment et pour tout ça merci, merci, merci ! Ta gentillesse, tes valeurs, ta bonne humeur communicative, me rendent heureux lorsque je suis avec toi, merci pour tout, merci d'être toi !
Je t'aime Emy !

A toi Lou-Anne,
Lou, on s'est rencontrés il y a 15 ans, sans le savoir à cette époque que je tu serais parmi mes meilleures amies aujourd'hui. Après avoir traversé ensemble le lycée, puis la première année à tes côtés, on s'est soutenu et on a vécu cette année ensemble qui nous a définitivement rapprochées. Merci d'être qui tu es, d'être là depuis tout ce temps, je chéris notre amitié et toutes les épreuves et souvenirs partagés à tes côtés me rendent pleins de gratitude. Aujourd'hui un nouvel arc narratif s'ouvre dans ma vie avec mon départ à la Réunion et ça sera un plaisir de créer de nouveaux souvenirs avec toi sur cette île de l'océan Indien.
Je t'aime Lou-Anne !

A toi Brice,
Merci à toi ! Au début intimidé à tes côtés, on a su tisser notre amitié au fur et à mesure se solidifiant avec les épreuves, j'ai toujours appris à tes côtés et je suis heureux de te compter parmi mes meilleurs amis. Ta curiosité, passion de ce que tu aimes est une source d'inspiration pour moi. Petit génie du groupe tu m'impressionnes dans tous tes projets. Pour tous ces souvenirs partagés à tes côtes qui ne sont que le début, merci ! Te voir épanoui et heureux aujourd'hui est un plaisir à voir !
Je t'aime Brice

A toi Warren,
Merci pour ta bonne humeur, nos discussions au bout de la nuit, ton pas de danse légendaire et ta curiosité sur mes études. Parti trop tôt, je penserai toujours à toi !

To u Krista,
Thank you for everything! You are my soulmate of Erasmus, we have created an unbreakable link that binds us forever. For 5 years now I have known you, you've helped me grow as man and pharmacist, nowadays. We went through tough moment in our lives and you've always been here even from 2581km away. Travelling and creating new memories with you is always a pleasure. I'm so glad to have met you and to have you as part of my life. Never forget that you are Awésome Krista !
Love u!

A toi Pierro

Merci pour qui tu es ! A toutes nos soirées à l'appart et avec les copains, tu es un gars fantastique avec une vision de la vie unique et c'est toujours un plaisir de partager des soirées discussions, big deal et méditation avec toi.

A vous : Marie, Manon :
Merci à vous, d'avoir partagé ces dernières années à mes côtés, c'était un plaisir d'aller en sortie myco avec vous, de partager nos discussions, nos rires, nos danses, nos créations culinaires et suivre ce DU avec toi Marie.
Merci d'avoir toujours été présent !

A vous la team CRPV : Amélie, Hilary, Agate :
Merci pour ces moments partagés à vos côtés et de notre team crée pendant ce stage, vous êtes géniaux, merci d'être qui vous êtes !

A tous mes autres ami.e.s : Pep, Sabrine, Elise, Marie, Léa-Eden, Lise, Anne, Théo
Merci à vous tous pour ces moments joyeux partagés à vos côtés en France et aux quatre coins du monde, pour nos échanges, nos rire et les souvenirs crées ensemble !

Plan

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TABLE DES MATIÈRES

TABLE DES ILLUSTRATIONS

Abbreviations

5-ASA	5-aminosalicylic acid
^{51}CrEDTA	51Cr-labelled ethylenediaminetetraacetic acid
6-TGN	6-Thioguanine nucleotide
AAG	Alpha-1-acid Glycoprotein
ABC	ATP-binding cassette
ANOVA	Analysis of Variance
ASBT	Apical sodium dependent bile acid transporter
AUC	Area under curve
AZA	Azathioprine
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutical classes
CD	Cronh's disease
CDAI	Crohn's disease activity index
Cmax	maximal Concentration
COM-T	Catechol O-methyl transferase
CYP	Cytochrome
DMEs	Drugs metabolizing enzymes
DoE	Design of experiment
DP	Duodenal pathology
DSS	Dextran sulfate sodium
EFCCA	European Federation of Crohn's and Ulcerative Colitis Association
GITT	Gastro-intestinal transit times
GST	Glutathione S-transferase
HC	Healthy control
HPLC	High performance liquid chromatography
HSA	Human serum albumin
IBD	Inflammatory bowel disease
IL	Interleukin
KO	Knockout
LBS	Lipid based formulation
MDR1	Multidrug resistance-1
MICI	Maladies inflammatoires chroniques de l'intestin
MMES	Modified mayo endoscopic score

MV	Mesenteric vein
NOD2	Nucleotide-binding oligomerization domain 2
mRNA	messenger ribonucleic acid
NSAIDs	Non-steroidal anti-inflammatory agents
pH	Potential of hydrogen
OATP	Organic anion transporter
OCTN-2	Organic cation transporter novel
OR	Odds ratio
PCR	Polymerase chain reaction
P-gP	P-glycoprotein
PKPB	Physiologically based pharmacokinetic
PV	Portal vein
PXR	Pregnane X Receptor
RAG	Recombination-activating genes
RR	Relative risk
RT-PCR	Reverse Transcription- PCR
SB-VCE	Small bowel video capsule endoscopy
SITT	Small intestinal transit times
SLC	Solute carrier proteins
SMA	Superior mesenteric artery
Th1/Th17	T-helper type 1
TIM-1	TNO Gastro-Intestinal model
TNF	Tumor necrosis factor
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis
UC-DAI	Ulcerative colitis -disease activity index
UGTs	UDP-glucuronosyltransferases
UPLC-MS	Ultra-performance liquid chromatography–mass spectrometry
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
WT	Wild type
XOD	Xanthine oxydase

Introduction

La prévalence des maladies inflammatoires chroniques de l'intestin (MICI) a augmenté considérablement depuis plusieurs décennies. Ces pathologies sont devenues une problématique de santé mondiale. Selon la Fédération européenne des associations des patients atteints de maladie de Crohn ou rectocolite hémorragique, 10 millions de patients sont concernés par ces maladies. D'autre part, aux États-Unis, la prévalence est estimée supérieure avec 721 cas pour 100 000 habitants.(1). L'étiologie des MICI est une complexe interaction entre facteurs génétiques et environnementaux, la dérégulation de la réponse immunitaire et l'altération du microbiote intestinale (2).

Les MICI sont divisés en deux grandes pathologies : la maladie de Crohn et la rectocolite hémorragique. Ces pathologies sont associées à une inflammation chronique du tractus digestif. Il est donc légitime de s'interroger de l'impact des MICI sur les étapes de la pharmacocinétique, du devenir du médicament et ces répercussions cliniques.

Les études scientifiques de la base de données PubMed a été consultée entre mai 2022 et février 2025. Les principaux mots clés de recherche ont été maladie de Crohn, rectocolite hémorragique, ainsi que des termes additionnels : maladies inflammatoires chroniques inflammatoires de l'intestin ; pharmacocinétique ; métabolisme ; absorption ; distribution ; élimination ; biodisponibilité ; transporteurs d'efflux ; P-gP ; cytochrome ; pH ; temps de transit intestinal ; longueurs des villosités ; soit seul ou combinés. Les études in vitro et in vivo publiées entre 1985 et 2024 ont été inclues. En raison de la différence de microbiote dans les populations asiatiques, nous avons exclu les publications menées dans ces populations (3).

Impact of inflammatory bowel disease on pharmacokinetics phases and clinical relevance

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Introduction

Inflammatory bowel disease (IBD) increased substantially over the decades and has become a global health issue. According to the European Federation of Crohn's and Ulcerative Colitis Association (EFFCA), IBD is affecting 10million people around the world. On the other hand, in the United states of America (USA), the prevalence of IBD is estimated to be higher (721 per 100 000) (1). The etiology of IBD is a complex interplay with genetics, environmental factors, dysregulation of immune response and altered gut microbiota (2).

IBD is mainly divided in two diseases : Crohn's disease (CD) and Ulcerative colitis (UC). Associated with chronic inflammation of intestinal tract it is justified to question the impact of IBD on pharmacokinetics steps, the fate of the drug and the clinical relevance.

Relevant literature from the PubMed database, accessed between May 2022 and February 2025. The main search terms were Crohn's disease and ulcerative colitis, along with additional terms like inflammatory bowel disease, pharmacokinetics, metabolism, absorption, distribution, elimination, bioavailability, efflux transporter, P-gP, cytochrome, pH, transit times, and villous length, either on their own or combined. In vitro and in vivo studies published between 1985 and 2024 were included. On account of the difference in

the microbiota in Asians populations we excluded all the scientific research according to this topic from Asian countries (3).

Overview of Inflammatory Bowel Disease

1.1. Crohn's disease

Crohn's disease is a chronic inflammatory affection of the gastrointestinal tract that can impact any part of the digestive system and cause bowel damage. Depending on CD type, repercussion can be observed from the esophagus to the anus but most commonly affecting terminal ileum and proximal colon (4). CD is a relapsing and remitting pathology and has an impact of the patients' quality of life with gastrointestinal spectrum like chronic diarrhea, fatigue, abdominal pain and weight loss (2,4,5).

1.1.1. Epidemiology

CD affects women and men equally. Even though, CD can occur at any age, the onset of the disease and diagnosis are commonly between the age of 18 and 35. Incidence is higher in developed countries (4). Systematic reviews from 1990 to 2016 shows that the incidence of adult Crohn's disease remained stable or decreased in most high-income countries (Canada 23,82 per 100 000 persons; USA 13,9 per 100 000 persons; Europe 15,4 per 100 000 persons). However, for pediatric CD, the incidence continues to rise. Prevalence rates are 322 per 100 000 persons in Europe and 319 per 100 000 persons in Canada.

Nevertheless in the newly industrialized countries in Asia, South America or sub-Saharan Africa, this incidence and prevalence rise, likely due to pollution exposure and change in the diet and lifestyle (4,6).

1.1.2. Pathophysiology

The exact causes of the onset of CD are still unknown. However, several pathogenic key factors could explain the origins of disease. One of them is the Nucleotide-binding oligomerization domain 2 (NOD2) gene expression which controls stability of microbiota and epithelium function. NOD2 is found in Paneth cells, cells from small intestine epithelium, releasing antimicrobial factors in healthy patients. In CD conditions, a function impairment of NOD2 is observed causing loss of barrier integrity (7,8). The mucin production impairment, a key protein of epithelium protection, causes the formation of a thinner layer of the intestinal mucosal.

Moreover, disruption of intestinal barrier characterized by discontinuous, segmental and transmural lesion occurs and antigens can easily cross the intestinal barrier in a result of T-helper type 1 and 17 (Th1/Th17) activation causing the release of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) , interleukins (IL-6, IL-12, and IL-23…) and dysregulation of T-cell response leading to chronic inflammation associated with reduction of gut microbiota (4,9).

1.1.3. Diagnosis

CD diagnosis is based on the anamnesis of the patient and physical examination (10,11). Furthermore, serum and stool test are also performed to support the diagnosis. The presence of calprotectin in stool test is a sign of intestine inflammation as well predicting disease activity. C-reactive protein (CRP) in serum manifest body inflammation and severity of disease (12,13). Additionally, transabdominal ultrasound, computed tomography , magnetic resonance imaging can be performed to screen intestinal lesion (10,14,15). Non-invasive methods are used to exclude differential diagnosis (irritable bowel syndrome, enterocolitis, intestinal tuberculosis) (4,10,11). These features are supported by endoscopy (identify lesion, inflammation), histopathology, cross sectional imaging to determine transmural extent (affecting multiples epithelium layer). To assess CD degree of illness, Crohn disease activity index (CDAI) has been developed. CDAI is a

complex score gathering different settings (symptoms, stool number, complications…). The score can range from 0 to 600, under 150 is consider to be in remission, 150 to 219 : midly active, 220 to 450 : moderately active, above 450 to be severe activity (16,17).

1.1.4. Risk factors

Genetics (as instance NOD2 mutation) with a first degree relative affected by CD is the strongest risk factor to develop this pathology even if environmental factors are also fundamental. Indeed for monozygotic twins, the concordance for Crohn's disease reaches 50% (18). Therefore, environmental factors are essential to explain CD development. Smoking is significantly identified as a risk factor (increased the risk of CD by 2-fold) but the physiopathological mechanisms are still unclear (19,20). Drugs exposure (contraceptive pill, antibiotics, non-steroidal anti-inflammatory agents (NSAIDs)) could also be a trigger for CD (20,21). Antibiotics intake, especially fluoroquinolones and metronidazole, induces the disruption of gut microbiota and the initiation of the disease even more in childhood (4,22). The use of NSAIDs presents a paradoxal effect. On the one hand, it promotes the onset of CD by cyclooxygenase-2 inhibition. On the other hand, it is used as a medication to relieve symptoms (19,20,23).

The impact of vaccination on the disease initiation is not yet established. Some studies showed a protective effect with rotavirus vaccination in Asian countries but not in USA. Meta-analysis of childhood vaccination (diphteria, tetanus, smallpox, poliomyelitis, measles-containing vaccines) or papillomavirus vaccine have no effect on CD (20,24,25). The ultra-processed food intake is also associated with a significant higher risk to develop CD but the result of the studies are based on questionary (4,26).

High physical activity is associated with a 37% reduction of the risk to develop CD by highest autophagy and reducing the pro-inflammatory cytokines (27,28). Furthermore a 10 g/day fiber intake is a protective factor promoting intestinal barrier function and microbiota (4,20,27).

1.1.5. Management of the pathology

Different forms and intensity of the pathology exist, and the treatment moves toward personalized medicine. The aim of the treatment is to induce remission and to maintain a quiescent state (2). Therapeutics strategies have evolved over the past few decades. A change in the paradigm from the escalation use of corticosteroids, 5-aminosalicylates, thiopurines drugs occurred due to treatment failure. The transition to biotherapies discovery, reduces drastically the intestinal resection and colostomy, treatment adverse effect and co-morbidities and improves patients' quality of life (2,4).

CD treatment is complex, choices are guided by several factors (severity of the inflammation, lesion location or extra-intestinal manifestation) (29). Nowadays, biological drugs such as anti-TNFα (infliximab; adalimumab; certolizumab pegol) are the most effective to induce and maintain quiescent state (2,4,29). As well, anti-integrin agents (natalizumab; vedolizumab), anti-interleukin 12/23p40 (Ustekinumab) are new biological drugs emerging with effective CD management (4,10,29).

1.2. Ulcerative colitis

UC is a long-lasting inflammation affecting colon and rectum mediated by the immune system. The disease is commonly described as rectal bleeding and persistent diarrhea, fecal incontinence, weight loss and fatigue. UC is a relapsing and remitting disease. One quarter of the patient experience extra intestinal manifestation, especially immune disease such as arthritis, polyarthritis, ankylosing spondylitis (9,30). Different types of UC based on the extent of the disease are described: proctitis (30-60%), left-sided colitis (16-45%), extensive colitis (14-35%). Each one is specific associated with characteristics symptoms (31,32).

1.2.1. Epidemiology

This subtype of IBD is estimated to affect more than 5 million people around the world. There is no sex distribution and can occur at any age but the diagnosis is commonly in people aged 18 to 35 years (4,9,30,32). Since the end of the 20th century, the incidence

increases especially in newly industrialized countries like Africa, South America and Asia(32,33). The highest prevalence worldwide is in Europe with 505 per 100 000 in Norway (33).

1.2.2. Pathophysiology

UC results from multifactorial factors, an interplay of genetic predisposition, environmental factors, dysregulation of immune system and epithelial barriers defect (31,32,34). Healthy sigmoid colon is made of inner mucus layer that is impermeable to bacteria (35). Unlike heathy patient in UC, well-designed observational studies showed depletion of goblet cells that secrete mucus, providing protective effect. Therefore, there is a lack of core mucus that is likely to contribute to UC (33,36). Additionally, epithelial barrier defect occurs due to the dysregulation of claudin-2, essential component of tight junctions that controls paracellular permeability (32,37). Increasing paracellular permeability allows antigens from virus and bacteria to cross inner colon mucus layer and epithelial cells (32).

In parallel to CD in UC, there is an abnormal response against antigens due to a dysregulation of adaptive and innate immune system resulting in hyper-release of pro-inflammatory cytokines (TNF, IL-6, Interferon-γ (IFN-γ),…) (32,38). Moreover, in UC, dysbiosis is implicated in pathogenesis, with a depletion of butyrate producer's bacteria such as Firmicutes phylum. As a key source of energy for colonocytes, butyrate provides anti-inflammatory effect promoting healthy microbiome (32,39,40).

1.2.3. Diagnosis

The diagnosis is a combination of clinical symptoms (rectal bleeding, tenesmus, diarrhea or constipation…), endoscopic and histological features. There is no gold standard as CD diagnosis. A combination of markers in blood test indicates colonic inflammation with CRP, complete blood count, erythrocyte sedimentation rate but are not specific for ulcerative colitis. To establish the diagnosis, endoscopy with biopsies is highly reliable with his particularly precision and sensitivity (32,41).

Mayo score ulcerative colitis-disease activity index (UC-DAI) is used to classify ulcerative colitis severity. This score is based closely to CDAI with 4 degrees to appreciate disease activity with stool frequency, blood in the stool, symptoms and endoscopic lesion. From a score below 2 for quiescent UC to a score above 11 for severe cases, Mayo score is used in clinical practice. However modified mayo endoscopic score (MMES) is currently used because mucosal inflammation is also evaluated (42,43).

1.2.4. Risk factors

First, genetic predisposition with risk alleles (such as IL23R single nucleotide polymorphism; rs80174646) is involved in intestinal barrier defect pathway or T-cell immunity. Second, oral contraceptive pills have been showed to increase the risk by 30%. Interestingly, this risk was limited to women with history smoking but mechanism is not clear (20,21,44). Finally, a meta-analysis found out that the consumption of soft drinks could increase the risk of UC but these result remains controversial (20,45).

Surprisingly for UC, a meta-analysis found out that smoking is a protective factor against the development of UC. Some hypotheses are based on the immune system regulation, alteration of microbiota, and mucus thickness. Furthermore, the exact mechanism due to the numerous and complexity of chemicals in tobacco remains difficult to identify (20,46).
Despite antibiotic exposure in the protective factors have been identified for CD such as fiber intake, physical activity; antibiotics intake limitation, none of them are linked to lower risk for UC development (27).

1.2.5. Management of this pathology

The management strategy is to obtain a rapid clinical response by symptoms reduction and biomarkers normalization such as C-reactive protein or cytokines (47). On the other hand, treatments improve the quality life of the patient preventing the relapsing of the

disease (30,32). To manage UC, therapeutic choice is based on severity and extent of the disease (32).

The empiric treatment is based on 5-aminosalicylic acid (5-ASA) in all types of UC (32,48). Corticosteroid therapy could be used in combination with 5-ASA or in monotherapy (48). Maintenance therapy for mild to severe UC is made up of novels therapies. To reach quiescent state, immunosuppressants drugs (azathioprine), biologics drugs (infliximab, adalimumab) or anti-janus kinase inhibitors (Upadacitinib) can be used (31,32,48,49).

Even though, new therapeutics exist but the remission rates do not exceed one third of the patient in induction clinical trials and 30 to 60% in real life conditions (31,32). Surgery could be requested, in some refractory acute severe UC to have colectomy. Although needing surgery decreased over past decades it's still represent more than 15% risk at 15 years post-diagnosis (32).

Overview of pharmacokinetics

1. Absorption

1.1. Order absorption model

1.1.1. Zero-order kinetics

Drug rate elimination is independent of plasma concentration and remains constant due to saturable process used by the drug, half-life is not constant and constant clearance per unit of time. Salicylate, omeprazole or fluoxetine, cisplatin follow zero order kinetics (50,51).

1.1.2. First order kinetics

Rate elimination is directly proportional to drug concentration. This is a non-saturable process (50). Thus, half-life is constant, and a steady percentage of drug concentration is eliminated per unit of time, considering as the linear process. Drugs among them are ibuprofen, amoxicillin (51,52).

1.1.3. Non-linear kinetics

The relationship between drug dose and plasma concentration is not proportional due to saturable enzymatic processes. Some medications such as ethanol or phenytoin follow first order-kinetics at low concentration but zero-order kinetics at high concentration (53,54).

1.2. Bioavailability

Bioavailability is a value referring to the amount of drug that reaches the bloodstream to be available on the action site, influenced by pharmacokinetics steps. Understanding bioavailability is essential to ensure therapeutical efficiency (51).

1.2.1. Area under the curve

To assess bioavailability of the drugs, area under the curve (AUC) is used to reflect drug body exposure in the systemic circulation after administration and first past effect. As reference, the AUC with intravenous administration is 100%. *per os* drug bioavailability is expressed as the ratio of AUC *per os*/AUC intravenous. On first-order pharmacokinetic, AUC is proportional to drug dosage (55,56).

1.3. Potential of hydrogen (pH)

Gastric pH is primordial for drug absorption. Absorption phase is mainly a balance of dissolution and ionization degree of the drugs. To be absorbed, weak acids or weak bases have to be non-ionized to easily cross biological barriers but soluble in water to be dissolved. pH change induces drug degree-ionization modification thus impacting absorption and bioavailability. For example, weak acids absorption is reduced when pH increases due to elevation of ionization degree and conversely for weak bases (57–59).

1.4. Solubility, permeability

Intestinal permeability and aqueous solubility are key settings to explore performance of the drugs. BCS is subdivided in four classes, class 1: High solubility-high permeability drugs (acetaminophen, verapamil, propranolol…). Class 2: Low solubility-high

permeability drugs (carbamazepine, naproxen, nifedipine…). Class 3 : High solubility-low permeability drugs (metformin, atenolol, cimetidine…) and Class 4 : Low solubility-low permeability drugs (furosemide, ciclosporin, ritonavir…). According to this classification, drugs absorption and bioavailability can be predicted. Moreover, based on this two settings it allows to predict bioequivalence of drugs and excipient bypassing and surrogating in vivo studies that is crucial to develop new generics (59,60).

1.5. Gastro-intestinal transit times (GITT)

Gastric emptying refers to the process when the stomach releases gastric content into the upper part of intestine. Influenced by the presence of nutrients, gastric emptying has a major impact on drug absorption. Delayed or fasted gastric emptying can significantly impact bioavailability (61,62).

Major part of drug absorption is mediated by duodenum, the upper part of small intestine. Small intestinal transit times (SITT) has big influence on drug absorption thanks to villi and microvilli, which increase drastically surface absorption to 30m² out of 32m² for gastrointestinal tract (63). High inter-individual absorption difference is noticed for BCS class 3 according to GITT (64).

1.6. Intestinal transporters enzymes

To cross intestine barrier, drugs must pass through influx transporters of enterocytes but could be rejected by efflux transporters multidrug resistance like P-glycoprotein (MDR1/P-gp) associated with drug absorption reduction. Moreover, drugs metabolizing enzymes (DMEs) such as cytochrome P450 family (CYP450), expressed in enterocytes, have impacts on drugs absorption and bioavailability (65,66).

2. Distribution

This phase defines the process of the drugs going from the bloodstream to the tissue and organs to be active or transform by them. Involving several parameters such as blood flow with volume of distribution, active transporter organic anion transporter (OATP), tissue permeability, protein binding, thus any modification can impact the fate of the

drug (51). Moreover, solute carrier proteins superfamily (SLC) is part of active transporter and has a major role for the drug to cross cell membrane (67).

3. Metabolization

First pass effect occurs on enteral administration primordially in the liver and therefore reducing bioavailability (68).

3.1. Phase 1 enzymes

3.1.1. CYP450

Cytochromes are major isoenzyme superfamily involved in metabolization. To identify all different types of cytochromes, a specific nomenclature is used to describe them respectively by clans (CYP450), families (2), subfamilies (D) and isoenzymes (6). By adding hydrophilic group on the drugs, renal excretion is improved. CYP450 induction or inhibition are a major source of drug-drug-interaction. High genetic polymorphism is also found to promote or decrease effectiveness of CYP450. The most representative case is CYP2D6. It exists poor, rapid and ultrarapid metabolizers influencing by ethnicities and interindividual diversity. As instance 5 up to 10 % are poor metabolizers in Caucasians contrary to 1 % in Africans and Asians unlike ultrarapid phenotypes concerning up to 11% in Middle Eastern populations often leading to contraindication for many drugs, such as codein (51,69–76).

3.2. Phase 2 enzymes

Several enzyme groups belong to phase 2 enzymes are implicated in drug metabolism, among them UDP-glucuronosyltransferases (UGTs), glutathione S-transferase (GST), catechol O-methyl transferase (COMT) therefore increasing drug hydrophilicity and promoting kidney excretion (51,77).

UDP-glucuronosyltransferases (UGTs) are major enzymes group of metabolization. Through a glucuronidation reaction, UGTs transform xenobiotics into a more soluble compounds to be excreted in the urine. NSAIDs, anticonvulsants drugs, opioids analgesics are some of the family drugs metabolized by UGT (78–80).

4. Elimination

Xenobiotic is excreted throughout different system, mainly by the kidney with the urine and the liver with biliary and feces elimination (81). Several settings determine the elimination rate: clearance, half-life, efflux transporter. Clearance is defined as the rate of elimination per unit of time, in fact the ability to excrete the drugs (51).

Crohn's disease

1. Absorption

1.1. In vitro

a) Solubility

Analytic laboratory test solutions reproducing gastrointestinal fluids based on design of experiment (DoE) approach representing CD conditions in fed and fasted state (CD-FaSSIF, CD-FaSSCoF, CD-FeSSIF, CD-FeSSCoF), investigate drugs solubilization of budesonide, sulfasalazine, azathioprine, loperamide, celecoxib, dipyridamole comparing result to HC.

These drugs show acid or base characteristics. In CD models, an altered solubility is highlighted, weak acid solubility could be enhanced by the elevation of gastric pH. CD characteristics by increasing osmolality, gastric pH and bile salt reduction could explain the difference (figure 1) (82).

To investigate lipase activity and bile acid composition in CD drugs absorption, a TNO gastro-intestinal multi-compartmental model (TIM-1) was performed in three different conditions miming HC, CD, using ciprofloxacin as drug reference to compare with lipid-based formulation (LBS) of ciprofloxacin. No difference between CD and HC model is observed for ciprofloxacin, but for LBS of ciprofloxacin, a reduction and delay dissolution of LBS are observed, suggesting an altered drug performance in high lipophilic drugs in CD (figure 1) (83).

1.2. In vivo

1.2.1. Human

a) Gastric intestinal time

Small intestinal transit time (SITT) can be measured by small bowel video capsule endoscopy (SB-VCE). SITT is prolonged in active CD compared to HC and quiescent CD respectively (median of active CD: 253 min vs 216 min). No difference is observed between quiescent CD and HC in SITT. In active CD, prolongation of SITT could alter drug pharmacokinetics profile but further studies need to be performed toward a personalize medicine (figure 1) (84).

b) pH

A study conducted in HC and CD (active and quiescent) evaluated CD state impact on gastrointestinal pH by radiotelemetry approach. Data analysis suggests a similar gastrointestinal pH in active and quiescent CD. One significant difference in median stomach pH values showed higher pH in CD compared to HC (85). Nevertheless, all of the studies are limited by the small number of patients (figure 1) (86).

c) Bioavailability

An overview of clinical study rated pharmacokinetics of Upadacitinib between CD and HC by liquid chromatography, and tandem mass spectrometric detection methods. At least one plasma concentration was analyzed up to 30h following single or multiple administration. Area under the curve (AUC) was significantly higher by 21% in CD without clinical relevance (figure 1) (87).

To assess absorption and bioavailability of vitamin D, a clinical study including patients with CD and HC was conducted. Two groups ingested a single dose of 50 000 UI vitamin D2. Twelve hours later, a bioavailability test with blood samples analyzed by High Performance Liquid Chromatography (HPLC) was performed. A reduction of 30% on the ability to absorb vitamin D2 in all the types of CD was confirmed (figure 1) (88).

F. Sanaee et al administered a single oral dose of 80mg verapamil in CD (active and quiescent) and HC conditions. After 8h, a quantification by HPLC and clinicals measures (blood pressure, heart rate) was performed and only plasma-S-verapamil was significantly higher (AUC 9 to 14-fold higher) in active CD compared to HC. Surprisingly, a strong significant negative correlation was observed in drug potency, with small or no response to verapamil or toxicity (figure 1) (89).

In a pediatric pool of CD with duodenal pathology (DP), azathioprine (AZA) bioavailability of major active metabolite 6-Thioguanine nucleotide (6-TGN) has been investigated after excluding interindividual role of thiopurine methyltransferase (TPMT). Sub-therapeutic level of 6-TGN was observed in DP compared to non-DP, despite a higher median dose of AZA evaluated in CD with DP. Up regulation of xanthine oxidase (XOD) activity in CD with DP could be responsible, transforming azathioprine into inactive metabolite without statistical significance (90).

To emphasize about the impact of CD on bioavailability further studies are highly recommended to evaluate possible clinical impact of CD on drug disposition (88–90).

d) Intestinal permeability

In quiescent CD and HC, Vilela et al. performed intestinal permeability test by collecting urinary excretion after oral administration 6g of lactulose and 3g of mannitol. HPLC system analyzed urinary excretion collection over a period of 6h. Lactulose excretion and lactulose/mannitol ratio was significantly higher respectively in quiescent CD compared to HC (91).

2. Distribution

2.1. In vivo

2.1.1. Animals

After the induction of chronic intestinal inflammation in RAG knockout (KO) C57BL/6 mice by transferring CD4+ T cells from IL-10 KO mice, colonic and ilea blood flow rate was assessed. These genetic models were used to simulate IBD in active and mild

inflammation state. Blood flow rates and arterioles diameter were determined by dopplers. Higher inflammation was found to elevate blood flow in contrast to mild state that was reaching one third of ileal and colonic blood flow of active IBD. Severe inflammation could promote loss of capillary density thus increasing hypoxia promoting angiogenesis by an elevation of vascular endothelial growth factor (VEGF) (figure 1) (92).

2.1.2. Human

A study conducted in 2009 on CD biopsies evaluated messenger ribonucleic acid (mRNA) expression level of SLC compared to a previous HC study. The measure and interpretation were made respectively by spectrophotometer and reverse transcription polymerase chain reaction (RT-PCR). Across colon, a significant decrease of mRNA expression was observed for organic cation transporter novel (OCTN2) compared to HC. As well in terminal ileum for apical sodium dependent bile acid transporter (ASBT) vs HC. This result is in accordance with another study on ABST mRNA expression CD (figure 1) (67,93).

Among CD (active and quiescent) and HC patients, intestinal blood flow and diameters were measured by doppler ultrasound across splanchnic area. Results were similar between active CD and quiescent CD, all significantly superior to HC. For example, active CD Portal vein (PV) blood flow (1519,2 ± 350 ml/sec) was significantly higher compared to HC (1014 ± 187 ml/sec). Comparable results were observed with mesenteric vein (MV) and superior mesenteric vein (SMA) (figure 1) (94).
Terminal ileum (TI) and duodenum from children biopsies with active and quiescent CD were compared to HC. A 2-fold reduction of villous length in duodenum and TI was noticed in active CD compared to HC and CD in remission. In quiescent state, a significant reduction in terminal ileum was highlighted compared to HC. Another study showed similar results comparing duodenal villous length (µm) biopsies of pediatric CD. A significant reduction was found respectively in CD with duodenal pathology compared to CD without duodenal pathology (figure 1) (90,95).

a) Protein drug binding

A lower human serum albumin (HSA) level compared to healthy controls was found, while alpha-1-acid glycoprotein (AAG) levels were higher in CD than in HC (figure 1) (96).

3. Metabolization

3.1. In vitro

Flow-through cell model was used as reference to conduct in vitro release study testing budesonide performance. Biorelevant media miming CD characteristics was used based on physiologically pharmacokinetic (PKPB) modeling, simulating fed and fasted conditions compared to previous HC data. After collection of samples every 30 minutes, results were analyzed by HPLC-UV. Higher budesonide exposure was found in CD cell model in agreement with PKPB model prediction. Alteration of CYP3A4 was demonstrated to be the major setting impacting budesonide exposure (figure 1) (97).

3.2. In vivo

3.2.1. Human

a) CYP450, Pg-P

To evaluate the impact of CD in metabolization, midazolam, a major substrate of CYP3A4, was given 100µg per os and 8 hours after 50µg IV in 8 active CD. Intestinal and hepatic CYP3A4 activity was compared to previous control group study. According to the data using ultra-performance liquid chromatography-mass spectrometry (UPLC-MS/MS), midazolam has 5-fold higher AUC in CD than previous HC, suggesting a significant reduction of intestinal and liver CYP3A4 activity (figure 1) (98).

mRNA expression of P-gP and CYP3A4 have been assessed on CD children and controls biopsies. P-gP and CYP3A4 mRNA expression analyzed by RT-PCR highlighted a wide interindividual difference among them. Despite this difference, a significant alteration was established in both settings P-gP and CYP3A4 between CD and HC. In fact, a substantial range of CYP3A4/vilin and PgP/vilin ratio was found in CD (figure 1) (99).

In contrast, Wilson et al. evaluated biopsies of CD and HC CYP3A4 and P-gP expressions in ileal and colon by western blot. A decrease colonic and ileal expression of CYP3A4 and a reduction of P-gP expression in colon were demonstrated. However, this study showed significant interindividual difference (figure 1) (100).

Another study evaluated the impact of inflammation on MDR1 and P-gp expression on biopsies of CD (inflamed and non-inflamed) using RT-PCR and immunohistochemistry. A significant reduction (>10 fold) of MDR1 mRNA expression and proteins levels in inflamed ileum and colon tissue of CD patients was found independently of pregnane X receptor (PXR) expression, the main transcription factor that modulates metabolism enzymes expression (figure 1) (101) . Similar result was obtained in a study on children's biopsies of CD (active and unactive) and HC. A significant reduction of CYP3A4 mRNA expression (analyzed by RT-PCR) in ileal tissue was observed in active CD compared to HC. No significant difference was found between unactive CD and controls (95). Comparable result was obtained in children with active (inflamed) CD positively correlated with a decreased of PXR expression (figure 1) (102).

4. Elimination

4.1. In vivo

4.1.1. Human

Among CD patients and HC, a single dose of 500 mg of methyldopa was given to evaluate the elimination phase. Despite half-life of elimination, the rate of absorption and elimination was not statistically abnormal. A significant reduction was observed in urine excretion. Only one half of the dose was absorbed and excreted within 48h with a correlation in clinical and AUC data (figure 1) (103).

Another study assessed elimination settings in CD by analyzing urinary excretion of alendronate. A dose of 10mg of the drug was given for 6 months with a check in at 3 and 6 months by HPLC analysis (104). No significant difference was found in alendronate excretion compared to previous HC studies using a method on an interval of 36h collection with dosage from 5 to 80mg (105).

Ulcerative colitis

To put in perspective data from studies, altered pharmacokinetics in UC is not well established due to a lack of in vitro and in vivo models. Few studies have evaluated the impact of UC on metabolism pathway.

1. Absorption

1.1. In vitro

a) Solubility

Effinger et al. conducted a study to characterize drugs solubility in UC. Analytic laboratory test solutions simulating gastrointestinal fluids based on design of experiment (DoE) miming UC conditions was produced. Solubility of 6 drugs with different physical properties was assessed (Azathioprine, Budesonide, Celecoxib, Dipyridamole, Loperamide and Sulfasalazine). Compared to HC biorelevant media, an altered solubility was found (figure 1) (106).

1.2. In vivo

1.2.1. Human

a) Gastric intestinal time

A pool of UC patients in remission active phases ingested electronic capsule (3D Transit-system) to analyze GITT. Data was compared to HC from previous studies. GITT was significantly longer in severe UC especially in proximal colon. Paradoxically, an inverse relationship was found with GITT and stool frequency in severe UC due to colonic inflammation that induces urgency defecation (107). Comparable result with radiopaque markers was found in a study with UC and HC (108). This dysmotility could affect fate of the drug (figure 1) (107).

Based on small bowel video capsule endoscopy (SB-VCE) in UC (active and quiescent) and HC, SITT in UC was significantly longer independently of disease stage. Prolongated SITT could impact drug release especially in colon drug delivery (figure 1) (84).

b) pH

Fallinborg et al. investigated gastrointestinal pH in active UC by radiotransmitting capsules ingested. Patients with active and highest severity of the disease presented a low intraluminal pH compared to HC. No difference was observed for HC in stomach comparing previous results (figure 1) (109).

In contrast, another research measured pH by radiotelemetry capsule after 24h in UC and HC. A significant pH elevation was observed in stomach, terminal ileum, caecum and in the right colon (figure 1) (85).

Further studies must be conducted to properly assess colonic pH, due to unpredictable and doubtful result due to data loss from the compact feces (85,109).

c) Bioavailability

On CD and HC, combined Phase 1 and Phase 2 clinical studies assessed Upadacitinib pharmacokinetic by HPLC and tandem mass spectrometry. A single or multidose of Upadacitinib was given. Within 30h after administration, at least one plasma concentration was recorded. AUC was 21% higher in UC compared to HC but no clinical pertinence was reported (figure 1) (87).

After a daily oral dose of cyclosporin microemulsion for seven days, a measurement of drug concentration through time was performed. Pharmacokinetic profiles are broadly similar to the previous study on HC with no correlation with disease severity. However, the peak concentration (Cmax) emerged to be higher by 22% in UC compared to CD. The assumption is that peak concentration is higher in UC because the site of absorption is not inflamed unlike in CD were small intestine is inflamed which delays absorption (figure 1) (110).

d) Intestinal permeability

Urinary excretion of 51Cr-labelled ethylenediaminetetraacetic acid (^{51}CrEDTA) after oral administration is assimilated to retrieve intestinal permeability in UC (active and quiescent) and HC patients. After 24h, urinary excretion of ^{51}CrEDTA was significantly increased in UC (6.72%) compared to HC (0.93%). A significant correlation was linked with disease activity and increased permeability at 24 h (111). Close result was observed in another study with ^{51}CrEDTA method (figure 1) (112).

2. Distribution

2.1. In vivo

2.1.1. Animals

Chronic intestinal inflammation was obtained on C57BL/6 mice RAG knockout (KO) by transferring CD4+ T cells from IL-10 KO mice.

This mice model mimics IBD and was used to assess colonic and ileal blood flow. A measurement of arterioles diameter and flow rates was performed by dopplers. Mild inflammation of IBD was found to reduce significantly blood flow whereas a slight increase of the blood flow was observed for severe inflammation on IBD mice. Cells dysfunction in severe inflammation could cause hypoxia, promoting VEGF elevation thus increasing intestinal blood flow (figure 1) (92).

mRNA expression of SLC transporter from intestine biopsies of UC was quantified by spectrophotometer and RT-PCR and compared to previous HC study (113). A significant dysregulation of mRNA SLC expression was observed in terminal ileum and colon despite a high interindividual difference. Moreover, OATP2B1 mRNA expression was significantly upregulated in UC colon vs HC and OCTN2 mRNA expression was significantly dowregulated in colon compared to HC (figure 1) (67).

2.1.2. Human

To investigate blood flow in UC, a study in 24 UC (active and quiescent) and HC patients was conducted in portal vein, superior mesenteric artery, mesenteric vein (PV, SMA, MV)

and resistance index. In active UC, a significant higher PV and MV blood flow was demonstrated and a lower resistance index of SMA meaning a superior blood flow than HC was observed (figure 1) (94).

a) Efflux transporters

A study evaluated efflux transporters (breast cancer resistance protein (BCRP) and P-gP) mRNA expression by PCR in UC based on colonic and rectal biopsies under active and quiescent UC compared to HC. In active UC patients, BCRP mRNA expression and P-gP from villi were reduced in colon (BCRP by 89% and P-gP by 78%) and rectum (BCRP by 84% and PgP by 66%) (figure 1) (114).

The inflammation in UC modulated efflux transporters expression with an significant up-regulation of ABCA1 (>10 fold) and ABCA3 (>19 fold) , and a significant down-regulation of ABCC4 (<27fold) and a down regulation of ABCF2, ABCC6 and ABCB8 linked to epithelial damage (figure 1) (115).

3. Metabolization

3.1. In vivo

3.1.1. Animals

a) CYP450

In 2015, a study led in active UC male ICR mice by the intake of 3,5% dextran sulfate sodium (DSS) for 10 days and then stop for 40 days. A significant reduction of CYP expression by 70% of CYP3A4, CYP1A2, CYP2C9, CYP2E1 compared to controls was demonstrated. On day 50, CYP expression brought back to physiological level apart from mRNA CYP2D9 that remained 70% lower than control mice (116). Similar results were observed on mice C57BL/6 model (figure 1) (117).

3.1.2. Human

On HC and UC biopsies, Langmann et al. analyzed mRNA expression of efflux transporters by RT-PCR. MDR1 and PXR mRNA expression in colon were significantly reduced but not

in ileum. Moreover, a 12,1-fold reduction of mRNA expression CYP3A4 was observed in colon of UC (figure 1) (118).

4. Elimination

4.1. In vivo

4.1.1. Animal

P-gP expression was determined on 8 weeks old colitis mice (Balb/c) using 7% DSS for 5-7days. Colitis was assimilated to UC in rodents. To estimate the P-gP function, rhodamine123 was used as a specific substrate of P-gP using the everted sac method and its expression was analyzed by RT-PCR. An assessment of rhodamine 123 efflux was conducted 20 minutes after injection into large intestine. mRNA expression and function reduction of P-gP in large intestine of mice with colitis compared to mice HC were demonstrated (figure 1) (119).

4.1.2. Human

Blokzijl et al investigated the inflammation's impact on MDR1 and P-gP expression in UC compared to HC using RT-PCR and immunochemistry. A significant decrease by 10 folds in MDR1 mRNA and protein levels in inflamed tissues, independent of PXR expression was found (figure 1) (101).

Resume of pharmacokinetics alterations in Crohn's disease and Ulcerative Colitis

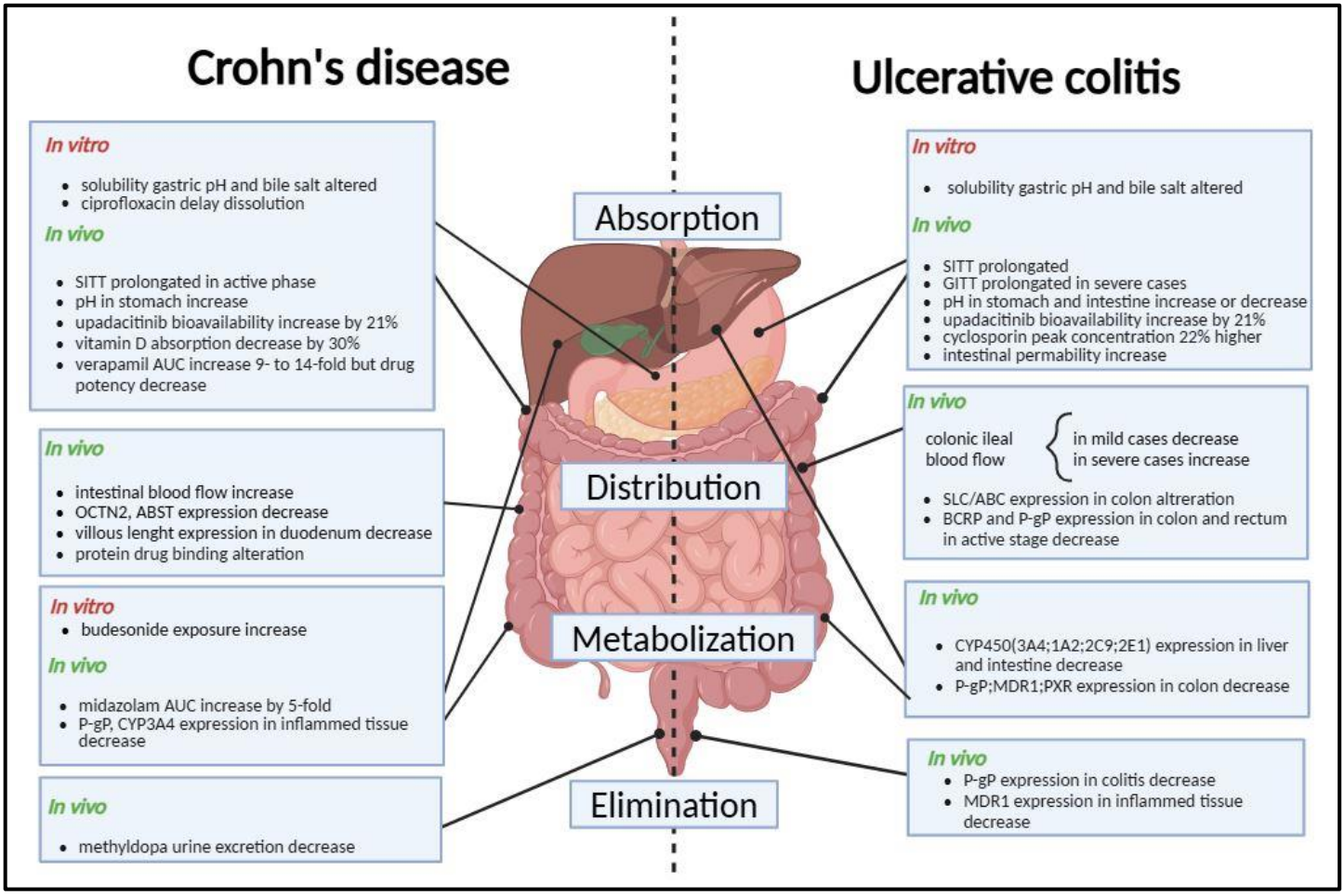

Figure 1 : Pharmacokinetic modification in a context of Crohn's disease and Ulcerative colitis.

AUC: area under the curve
ABC: ATP-binding cassette
ABST: apical sodium dependent bile acid transporter
BCRP: breast cancer resistance protein
CYP: cytochrome P450
GITT: gastro-intestinal transit time
MDR1: multidrug resistance mutation
OCTN2: organic cation transporter novel
P-gP: P-glycoprotein
pH: potential of hydrogen
PXR: pregnane X receptor
SITT: small-intestinal transit time
SLC : solute carrier

CONCLUSION AND PERSPECTIVE

Data collection and analysis through this review *in vitro* and *in vivo* highlight a variable impact. IBD is not only concerned with inflammation of gastrointestinal tract but also with physiological alterations impacting pharmacokinetics. In the absorption phase UC and CD presents solubility alteration due to elevation of gastric pH. Moreover, in severe CD and UC, dysmotility is described with a paradoxical elevation. Referring to bioavailability, multiple changes are found in both UC and CD with a variable clinical relevance. A representative case is verapamil in active CD. AUC increases at least by 9 fold whereas drug potency decreases. Distribution phase presents an elevation/reduction of intestinal blood flow rely on disease activity. Intestinal efflux transporters are dysregulated for both CD and UC that could be associated with epithelial damage. In metabolism phase, various cytochrome activities are modified, especially CYP3A4 which metabolizes half of medication and could be linked to drug interaction. A decrease in intestinal and hepatic CYP3A4 activity is settled in CD and UC, thus enhancing the potency of most of the drugs. As instance, midazolam AUC is increased by 5-fold in CD. Moreover, active CD has the widest influence on the alteration whereas quiescent state appears to be closer of HC. P-gp mRNA expression in inflamed tissues also decreases in IBD. For elimination phase, MDR1 and P-gP expression decreases in active UC and CD. Abnormal urine excretion related to elimination is found for methyldopa with lack of strong evidence.

Even though IBD has substantially increased over the decades, this review highlights a high variability of pool patient; method; reproducibility and a lack of studies on clinical relevance. Several alterations of pharmacokinetics steps are found but need drug-dose adjustment. However, to obtain and have reliable conclusions, further investigations must be conducted. Within this approach and to aware health care providers, this review should be published in scientific journal.

CONCLUSION ET PERSPECTIVE

Les études in vitro et in vivo étudiées dans cette thèse ont montré un impact variable des MICI sur la pharmacocinétique. En effet, en plus de l'inflammation du tractus gastro-intestinale, des altérations physiologiques sont mise en évidence pouvant impacter les étapes de la pharmacocinétique. Lors de la phase d'absorption, la rectocolite hémorragique et la maladie de Crohn présentent des altérations de la solubilité dues à une élévation du pH gastrique. Une élévation paradoxale du temps de transit intestinale a été décrite dans les cas sévères de MICI. Concernant la biodisponibilité, de nombreux changement sont observés dans les deux maladies, avec une pertinence clinique variable. La phase de distribution présente une élévation ou réduction du débit sanguin intestinale en fonction de l'activité des MICI. L'expression des transporteurs d'efflux au niveau intestinal est altérée possiblement dû aux lésions épithéliales. Pendant la phase de métabolisme, l'expression des cytochromes et notamment des CYP3A4 métabolisant la moitié des médicaments est altérée. Cette diminution de l'expression des CYP3A4 au niveau intestinale et hépatique dans les maladies de Crohn et rectocolite hémorragique, pourrait donc augmenter la concentration plasmatique de nombreux médicaments et être à l'origine de nombreuses interactions médicamenteuses. Par ailleurs, les phases actives de la maladie de Crohn exercent une grande influence sur ces altérations tandis que les phases de rémission se rapproche d'un état physiologique. L'expression de la P-gP diminue dans les tissus inflammés. Concernant la phase d'élimination, l'expression de MDR1 et de la P-gP diminue dans les formes actives des MICI. Une excrétion urinaire anormale de la méthyldopa a été observée mais sans preuves robustes.

Malgré l'augmentation des MICI au cours des dernières décennies, cette thèse a mis en exergue une grande variabilité dans les échantillons de patients, de méthodes, de reproductibilité ainsi qu'un manque d'études portant sur l'impact des MICI sur les étapes de la pharmacocinétique. Plusieurs modifications de ces étapes ont été identifiées, pouvant nécessiter un ajustement des doses médicamenteuses. Cependant, afin d'obtenir des conclusions robustes, des recherches supplémentaires doivent être menées. Dans cette optique et afin de sensibiliser les professionnels de santé, ce travail devrait être publié dans un journal scientifique.

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Table des matières

Table des illustrations

Impact des maladies inflammatoires chroniques de l'intestin sur les étapes de la pharmacocinétique et pertinence clinique

RÉSUMÉ

Les maladies inflammatoires chroniques de l'intestin font partie des pathologies auto-immunes comprenant la maladie de Crohn et la rectocolite hémorragique. Elles se caractérisent par des phases alternantes de rémission et de poussée provoquant diarrhées, crampes abdominales ainsi que de possibles manifestations extra-intestinales quelles soit ostéoarticulaires ou cutanées. Ces pathologies pouvant être associées à une inflammation chronique de l'intestin et du colon, représentant des sites fondamentaux d'absorption et de métabolisation des médicaments, il est pertinent de s'interroger sur l'impact de la maladie de Crohn et de la rectocolite hémorragique sur le devenir des médicaments administrés dans cette population particulière. Ce travail de thèse regroupe et présente les travaux démontrant les impacts de ces pathologies sur les différentes étapes de la pharmacocinétique et les répercussions cliniques associées. Pour la maladie de Crohn, les plus fortes répercussions au niveau clinique concernent un énantiomère du vérapamil et le midazolam, où les concentrations de ces médicaments sont respectivement augmentées par neuf fois et cinq fois, associées de façon paradoxal à une diminution de leur efficacité thérapeutique. Une diminution de l'expression des CYP3A4 et des P-glycoprotéines (P-gP), des modifications du temps de transit intestinal, des sels biliaires et du pH gastrique sont également retrouvés. Dans la rectocolite hémorragique, l'impact est moins documenté, mais des modifications du pH gastro-intestinal, des sels biliaires et du débit sanguin colique ont été identifiées, ainsi qu'une prolongation du temps de transit gastro-intestinal en cas de poussée sévère. Une diminution de l'expression des transporteurs d'efflux (BCRP, P-gP/MDR1) et des cytochromes dans les tissus inflammés a également été rapportée. Toutefois, le faible nombre d'études disponibles limite la portée des conclusions et empêche une évaluation précise de l'impact pharmacocinétique. Les études de ce manuscrit sont également à nuancer par une grande variabilité dans les patients inclus, méthodes et reproductibilité. Des recherches supplémentaires sont indispensables pour mieux comprendre ces altérations et optimiser les traitements des patients atteints de maladies inflammatoires chronique de l'intestin.

Mots-clés : MICI, maladie de Crohn, rectocolite hémorragique, pharmacocinétique

Impact of Inflammatory bowel disease on pharmacokinetics phases and clinical relevance

ABSTRACT

Inflammatory bowel diseases refer to a group of autoimmune diseases including Crohn's disease and ulcerative colitis. Characterized by an alternating of active and quiescent phase often leading to diarrhea, abdominal cramp and extra-intestinal symptoms (osteoarticular, skin problem) can occur. IBD are associated to an intestine and colon chronic inflammation. It is justified to question the fate of the drug in this specific population. This thesis presents studies on the effects of these pathologies on pharmacokinetics and their clinical impacts.

For Crohn's disease, the major clinical impact were concerning one enantiomer of verapamil and midazolam concentration increase respectively by 9 and 5 fold with a paradoxical verapamil inefficacy. A reduction of the expression of CYP3A4, P-gP and alteration of small intestinal transit times, bile salt and gastric pH were identified. Concerning ulcerative colitis, the impact is poorly studied. Documented alteration includes gastro-intestinal pH, bile salt and colonic blood flow along with a prolongation of gastro-intestinal transit times in severe cases. A reduction of expression of CYP3A4, efflux transporter (BCRP/MDR1) were found in inflamed tissue. IBD has significantly increased over the decades, but studies in this review show high variability in patient pools, methods, and reproducibility, with limited data on pharmacokinetics. Several pharmacokinetic alterations may require dose adjustments. Further research are needed to draw reliable conclusions and inform healthcare providers.

Keywords : inflammatory bowel diseases, crohn's disease, ulcerative colitis, pharmacokinetics